2004 International Congress on Natural Products Research

A Joint Meeting of the

American Society of Pharmacognosy (ASP)

Association Francophone pour l'Enseignement et la Recherche en Pharmacognosie (AFERP)

Gesellschaft für Arzneipflanzenforschung (GA) (Society for Medicinal Plant Research)

Phytochemical Society of Europe (PSE)

Program and Abstracts

July 31 – August 4, 2004

Westin Kierland Resort & Spa
Phoenix, Arizona USA

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On behalf of the Organizing Committee of ICNPR – 2004,
we thank the following contributors for their generous support.

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SOCIAL PROGRAM

Member/Non-Member Registrants receive tickets to the three general social functions (Welcoming Reception, Rawhide Western Town and the Closing Banquet).

Postdoctoral/Student Registrants only receive tickets for the Welcoming Reception. Tickets for the Dinner at Rawhide and the Closing Banquet can be purchased at the Registration Desk.

A Light Continental Breakfast will be available Sunday – Wednesday from 7:00 – 8:00 a.m. for all registrants. Additionally there will be afternoon refreshment breaks as appropriate and a Wine and Cheese Reception during Poster Session 1 on Sunday afternoon.

Saturday (7/31):	The Welcoming Reception (Kierland 1 & 2) will feature a variety of foods. Each attendee will receive two drink tickets to be used for the purchase of beer, wine or soft drinks. A cash bar will be available for additional purchases.
Sunday (8/1):	The Younger Members Committee of the ASP invites all younger attendees to a Dessert Reception and Mixer at 9:00 p.m. in Kierland 3. A cash bar will be available. Bio-Botanica, Inc. is the sponsor of this reception.
Monday (8/2):	The ASP is sponsoring a special lunch program for all younger attendees from 12:30 p.m. – 1:45 p.m. in Kierland 1 & 2. The program will feature a panel discussion on grant writing strategies. All student and post-doctoral registrants will receive a ticket for the lunch in their meeting packet. A Western Town Visit and Dinner will be held at Rawhide from 7:15 – 11:00 p.m. Buses will start leaving the hotel at 7:00 pm. Two drink tickets (beer, wine, or soft drinks) will be given to each attendee upon arrival at Rawhide. Country Music and Line-Dancing highlight the evening.
Tuesday (8/3):	The afternoon in on your own with optional excursions available at the Registration Desk. Forty tickets for the Arizona Diamondbacks baseball game against the World Champion, Florida Marlins are available at the registration desk for $20. The cost includes bus transportation to Bank One Ballpark. The bus will depart the hotel at 5:15 p.m.
Wednesday (8/4):	The Closing Reception will be held in the Hall of State starting at 6:00 p.m. Each participant will receive two drink tickets to be used for the purchase of beer, wine, or soft drinks. A cash bar will be available for additional purchases throughout the evening. The Closing Banquet (Kierland 1 & 2) starts at 7:00 pm.

GENERAL PROGRAM

Friday, July 30, 2004

8:00 p.m. – 10:30 p.m. **ASP Foundation Board of Directors Meeting (By Invitation Only)**
Noble Boardroom

2:00 p.m. – 6:00 p.m. **Registration**
Culturekeepers Hall West

Saturday, July 31, 2004

8:00 a.m. – 4:00 p.m. **ASP Executive Committee Meeting**
Noble Boardroom

7:00 a.m. – 8:00 p.m. **Registration**
Culturekeepers Hall West

8:00 a.m. – 11:30 a.m. **Session I. Pharmacognosy – History, Status, and Techniques**
Kierland 1 & 2
Moderator: William Obermeyer

- 8:00 a.m. – 8:10 a.m. **Welcome/Introduction**
  Roy Upton
- 8:10 a.m. – 8:45 a.m. **F:1 Origin & History of Pharmacognosy**
  Wolfgang L. Kubelka
- 8:45 a.m. – 9:20 a.m. **F:2 Classic Techniques of Pharmacognosy**
  Sabine Glasl
- 9:20 a.m. – 9:55 a.m. **F:3 Modernizing Pharmacognosy to a Molecular Science.**
  Lars Bohlin

9:55 a.m. – 10:15.a.m. **Refreshment Break**
Hall of State

- 10:15 a.m. – 10:50 a.m. **F:4 The Decline of Pharmacognosy in the US – A Historical Perspective**
  Norman R. Farnsworth
- 10:50 a.m. – 11:25 a.m. **F:5 Revival of Pharmacognosy**
  Hildebert Wagner

Saturday, July 31, 2004, Contd.

11:30 a.m. – 12:45 p.m. **Lunch (On your own)**

12:45 p.m. – 2:25 p.m. **Classical Pharmacognosy Forum:**
Session II. Pharmacognosy in Quality Control of Herbals
Kierland 1 & 2
Moderator: Marguerite Klein

- 12:45 p.m. – 1:10 p.m. **F:6 Pharmacognosy in Quality Control of Herbals – An Industry Perspective**
  Dean Gray
- 1:10 pm. – 1:35 p.m. **F:7 Pharmacognosy in Quality Control of Herbals – An Academic Perspective**
  Ikhlas Khan
- 1:35 p.m. – 2:00 p.m. **F:8 Perspectives on Global Regulatory Needs for Traditional Medicines**
  Samuel W. Page
- 2:00 p.m. – 2:25 p.m. **F:9 Botanical Product Identity, Quality & Consistency: The Need for Analytical Methods**
  Joseph M. Betz

2:25 p.m. – 2:45 p.m. **Refreshment Break**
Hall of State

2:45 p.m. – 4:00 p.m. **Classical Pharmacognosy Forum:**
Session III. Pharmacognosy in Product Development and Clinical Evaluation
Kierland 1 & 2
Moderator: Peter Houghton

- 2:45 p.m. – 3:10 p.m. **F:10 Novel Plant-Based Pharmaceuticals: A Great Opportunity for Mankind**
  Michael Andreas Karp Popp
- 3:10 p.m. – 3:35 p.m. **F:11 Paclitaxel (Taxol) – A Modern Botanical – Derived Pharmaceutical**
  James D. McChesney
- 3:35 p.m. – 4:00 p.m. **F:12 Pharmacognosy in Clinical Trials**
  Marilyn Barrett

Saturday, July 31, 2004, Contd.

4:00 p.m. – 4:45 p.m. **Classical Pharmacognosy Forum:**
Session IV. Breakout Sessions

A. Educational Program Needs
Kierland 1 & 2
Moderator: Joanne Barnes and Gail Mahady

B. Research Tools and Training
Rainmakers Ballroom
Moderators: Cindy Angerhofer and Steven Dentali

C. Role in Clinical Research, Standard Setting
Greenway
Moderators: Marilyn Barrett and Ray Cooper

4:50 p.m. – 5:30 p.m. **Classical Pharmacognosy Forum:**
Session V: Recommendations and Action Items
Kierland 1 & 2
Moderator: John Cardellina

2:00 p.m. – 5:00 p.m. **Exhibits (Set-up)**
Hall of State

7:00 p.m. – 10:00 p.m. **Exhibits Open**
Hall of State

7:00 p.m. – 10:00 p.m. **Welcome Reception**
Kierland 1 & 2

Sunday, August 1, 2004

7:00 a.m. – 6:00 p.m. **Registration**
Culturekeepers Hall West

7:00 a.m. – 8:00 a.m. **Continental Breakfast**
Hall of State

7:00 a.m. – 5:00 p.m. **Exhibits**
Hall of State

8:00 a.m. – 8:45 a.m. **Opening Ceremonies**
Kierland 1 & 2

Pedro I. Chavez, Chair
ICNPR Scientific Program Committee
(Midwestern University, Glendale USA)

Jon Clardy, President
American Society of Pharmacognosy (ASP)
(Harvard Medical School, USA)

Joël Boustie, Past-General Secretary
Association Francophone pour l'Enseignement et la Recherche en Pharmacognosie (AFERP)
(University of Rennes 1, France)

Rudolf Bauer, President
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University of Graz, Austria

Maike S. Petersen, Honorary Chairperson
Phytochemical Society of Europe (PSE)
(University of Marburg, Germany)

David J. Slatkin, Chair
ICNPR Local Program Committee
(Chicago State University, USA)

Sunday, August 1, 2004, contd.

8:45 a.m. – 12:15 p.m. **Structure-Based Biosynthesis Symposium**
Kierland 1 & 2
Session Chair: Bradley S. Moore (University of Arizona)

8:45 a.m. – 9:30 a.m. **S:1 Intertwining Tails: Unraveling the Wizardry of Terpene Biosynthetic Enzymes for Novel Natural Products.**
Joseph Chappell (University of Kentucky, USA)

9:30 a.m. – 10:15 a.m. **S:2 The Structural, Mechanistic, and Evolutionary Universe of Type III Polyketide Synthases.**
Joseph P. Noel (Salk Institute for Biological Sciences, USA)

10:15 a.m. – 10:45 a.m. **Refreshment Break**
Hall of State

10:45 a.m. – 11:30 a.m. **S:3 Structure-Based Protein Engineering of Polyketide Biosynthesis.**
Chaitan Khosla (Stanford University, USA)

11:30 a.m. – 12:15 a.m. **S:4 Structural Basis for the Synthesis of Macrocyclic Peptides.**
Mohamed A. Marahiel (University of Marburg, Germany)

12:15 p.m. – 1:45 p.m. **Lunch (on your own)**

12:30 p.m. – 1:45 p.m. **Journal of Natural Products Editorial Advisory Board Meeting and Luncheon (By Invitation Only)**
Rainmakers A

Sunday, August 1, 2004, contd.

1:45 p.m. – 3:30 p.m.	**Contributed Oral Presentations** **Session 1 (O:1 – O:7)** – *Kierland 2* (Biosynthesis) **Session Chair:** Rob Verpoorte (IBL, Netherlands) **Session 2 (O:8 – O:14)** – *Kierland 1C* (Herbal Remedies) **Session Chair:** Chaim Ismail (Bionorica AG, Germany) **Session 3 (O:15 – O:21)** – *Kierland 1A & 1B* (Bioactive Natural Products**)** **Session Chair:** Kristín Ingólfsdóttir (University of Iceland, Iceland)
1:45 p.m. – 3:00 p.m.	**Poster Session 1 (Set-up)** **Posters (P:1 – P:187)** *Kierland 3*
3:30 p.m. – 6:00 p.m.	**Poster Session 1:** **Posters (P:1 – P:187)** **Analysis and Herbal Drugs/Neutraceuticals** **(Wine and Cheese Reception)** **Session Chair:** Marie-Aleth Lacaille-Dubois (University of Bourgogne, France) *Kierland 3*
5:00 p.m. – 7:00 p.m.	**GA Board of Directors Meeting (By Invitation Only)** *Noble Boardroom*
6:30 p.m. – 9:00 p.m.	**Poster Session 2 (Set-up)** **Posters (P:188 – P:380)** *Kierland 3*
9:00 p.m. – 12:00 a.m.	**Young Scientists Dessert Reception and Mixer** **Sponsored by Bio-Botanica, Inc.** *Kierland 4*

Monday, August 2, 2004

7:00 a.m. – 6:00 p.m. **Registration**
Culturekeepers Hall West

7:00 a.m. – 8:30 a.m. **Continental Breakfast**
Hall of State

7:00 a.m. – 5:00 p.m. **Exhibits**
Hall of State

7:00 a.m. – 9:30 a.m. **Poster Session 2**
Posters (P:188 – P:380)
Biotechnology, Biosynthesis, Biological Assays, Phytochemistry and Pharmacology
Session Chair: A. Douglas Kinghorn (The Ohio State University, USA)
Kierland 3

9:30 a.m. – 2:45 p.m. **Herbal Symposium Dedicated to Varro (Tip) Tyler**
Session Chair: Rudolf Bauer (University of Graz, Austria)
Kierland 1 & 2

- 9:30 a.m. – 10:00 a.m. **S:5 Current Status and Prospectives for Herbal Preparations as Medicinal Products or Food Supplements in the European Union.**
  A.J. Vlietinck (University of Antwerp, Belgium)
- 10:00 a.m. – 10:30 a.m. **S:6 Physico-Chemical Interactions of Constituents in Plant Extracts and Efficacy.**
  A. Nahrstedt (Westf. Wilhelms University, Germany)

10:30 a.m. – 11:00 a.m. **Refreshment Break**
Hall of State

- 11:00 a.m. – 11:30 a.m. **S:7 Herb–Drug Interactions.**
  Ivar Roots (Humboldt University – Berlin, Germany)
- 11:30 a.m. – 12:00 p.m. **S:8 Herbal Medicinal Products in Clinical Research: Drug Safety – Needs, Trends – and Fashion?**
  Chaim Ismail (Bionorica AG, Germany)

Monday, August 2, 2004, contd.

12:00 a.m. – 12:20 p.m. **S:9 Global Harmonization of Quality Standards for Herbal Medicinal Products (HMP's). Gerhard Franz (University of Regensburg, Germany)** ***(Cancelled and Replaced by Oral Presentation O:49)***

12:30 p.m. – 1:45 p.m. **Lunch (on your own)**

12:30 p.m. – 1:45 p.m. **Panel Discussion on Grant Writing Strategies Special Lunch Program for Younger Attendees**
Kierland 1 & 2

1:45 p.m. – 2:15 p.m. **S:10 Estrogens Versus Phytoestrogens. W. Wuttke (University of Goettingen, Germany)**

2:15 p.m. – 2:45 p.m. **S:11 Lichens: Potentialities and Recent Developments. Joël Boustie (University of Rennes 1, France)**

2:45 p.m. – 4:00 p.m. **The Varro Tyler Prize for Research in Botanical Dietary Supplements (Sponsored by Pharmanex). Award Presentation and Lecture with a Homage to Varro Tyler by Mark Blumenthal (American Botanical Council, USA)**
A:1 Twenty Years Experience in the Botanical Health Food Market
Ezio Bombardelli (Indena S.p.A, Italy)
Kierland 1 & 2

12:00 p.m. – 2:15 p.m. **Poster Session 3 (Set-up)**
Posters (P:381 – P:588)
Kierland 3

4:00 p.m. – 6:30 pm **Poster Session 3**
Posters (P:381 – P:588)
Synthesis, Isolation and Structure Elucidation
Session Chair: Bradley S. Moore (University of Arizona, USA)
Kierland 3

7:00 p.m. – 11:00 p.m. **Theme Party**
Rawhide Western Town

Tuesday, August 3, 2004

7:00 a.m. – 6:00 p.m. **Registration**
Culturekeepers Hall West

7:00 a.m. – 8:00 a.m. **Continental Breakfast**
Hall of State

7:00 a.m. – 12:15 p.m. **Exhibits (Some exhibits may remain open until 5:00 p.m.)**
Hall of State

8:00 a.m. – 12:15 p.m. **Sand and Sea Symposium**
Kierland 1 & 2
Session Chair: Pedro I. Chavez, Scientific Program Chair

- 8:00 a.m. – 8:45 a.m. **S:12 Hot Cuisine as a Source of Drugs: How a Gift from the Sands Triggered Multidisciplinary Research with Unexpected Connections.**
  Giovanni Appendino (University of Piemonte Orientale, Italy)
- 8:45 a.m. – 9:30 a.m. **S:13 Current Research on Medicinal Plants in Mexico: Bioactive Compounds from Selected Mexican Medicinal Plants.**
  Rachel Mata (UNAM, Mexico)
- 9:30 a.m. – 10:15 a.m. **S:14 Plant *In Vitro*-Cultures and Natural Product Research.**
  Maike S. Petersen (University of Marburg, Germany)

10:15 a.m. – 10:45 a.m. **Refreshment Break**
Hall of State

- 10:45 a.m. – 11:30 a.m. **S:15 New Structures from Marine Organisms and their Pharmaceutical Potential.**
  Gabriele M. König (University of Bonn, Germany)
- 11:30 a.m. – 12:15 p.m. **S:16 Natural Products Chemistry and Nature.**
  Koji Nakanishi (Columbia University, USA)

12:15 a.m. **Rest of the day on your own or optional excursions**

Wednesday, August 4, 2004

7:00 a.m. – 6:00 p.m. **Registration**
Culturekeepers Hall West

7:00 a.m. – 8:00 a.m. **Continental Breakfast**
Hall of State

8:00 a.m. – 10:15 a.m. **Contributed Oral Presentations:**

Session 4 (O:22 – O:30) – *Kierland 2*
(Marine-Bacterial Isolation/Synthesis)
Session Chair: Yuzuru Shimizu (University of Rhode Island, USA) and Tawnya C. McKee (NCI, USA)

Session 5 (O:31 – O:39) – *Kierland 1A and 1B*
(Biotechnology and Innovative Natural Products Screening)
Session Chair: James B. Gloer (University of Iowa, USA)

Session 6 (O:40 – O:48) – *Kierland 1C*
(Miscellaneous)
Session Chair: Rogelio Pereda-Miranda (UNAM, Mexico)

10:15 a.m. – 10:45 a.m. **Refreshment Break**
Hall of State

10:45 a.m. – 11:45 a.m. **ASP Matt Suffness Award Lectures**
Session Chair: Tawnya C. McKee (NCI, USA)
Kierland 1 & 2

10:45 a.m. – 11:15 a.m. **A:2 Uncultivated Symbionts: Prospects for the Sustainable Production of Animal-Derived Pharmaceuticals.**
Jörn Piel (Max Planck Institute for Chemical Ecology, Germany)

11:15 a.m. – 11:45 a.m. **A:3 Natural Product Glycorandomization.**
Jon S. Thorson (University of Wisconsin, USA)

11:45 p.m. – 1:00 p.m. **Lunch (on your own)**

Wednesday, August 4, 2004, contd.

1:00 p.m. – 1:45 p.m.	**ASP Research Achievement Award** **A:4 A DNA-Based Approach to Natural Products.** **Jon Clardy (Harvard Medical School, USA)** *Kierland 1 & 2*
1:45 p.m. – 2:30 p.m.	**GA Egon Stahl Award** **A:5 Oligo- and Polysaccharides: Isolation, Characterization and Influence on Human Keratinocytes In Vitro.** **Alexandra M. Deters (University of Erlangen-Nürnberg, Germany)** *Kierland 1 & 2*
2:30 p.m. – 3:30 p.m.	**GA Annual Business Meeting** *Powell*
3:00 p.m. – 5:00 p.m.	**ASP Annual Business Meeting** *Kierland 3*
6:00 p.m. – 7:00 p.m.	**Reception** *Hall of State*
7:00 p.m. – 10:00 p.m.	**Closing Banquet** *Kierland 1 & 2*

Joe Chappell, Ph.D.

Dr. Chappell has been on the faculty at the University of Kentucky since April 1985, where he has developed an internationally recognized research program pioneering the molecular genetics and biochemistry of terpene natural products in plants. Dr. Chappell earned his B.A. degree in Biology from UCSD in 1977, his Ph.D. in Biology in 1981 from UCSC, and pursued postdoctoral studies at the University of Freiburg, Germany and the Max Planck Institute – Cologne, Germany where he worked on the isolation and characterization of genes coding for plant biosynthetic pathways. At the University of Kentucky, Dr. Chappell's research has focused on the mechanisms plants use to defend themselves against microbial pathogens and especially the biosynthesis of anti-microbial terpene-type compounds. During a sabbatical visit in 1994-1995, Dr. Chappell teamed up with Dr. Joe Noel at the Salk Institute in work that led to solving the 3-dimensional structure for one of the key biosynthetic enzymes in terpene biosynthesis, a terpene synthase. This pivotal work has lead to additional collaborative research into the structure and function of these biosynthetic enzymes and the development of a new mechanistic understanding of these enzymological wizards. Work in Dr. Chappell's laboratory has been supported by NSF, NIH and several industrial sponsors.

S:1

INTERTWINING TAILS: UNRAVELING THE WIZARDRY OF TERPENE BIOSYNTHETIC ENZYMES FOR NOVEL NATURAL PRODUCTS

Bryan Thomas Greenhagen[1], Shunji Takahashi[1], Yuxin Zhao[2], Paul O'Maille[3], Joe Noel[3], Robert M Coates[2], **Joe Chappell**[1]
[1]University of Kentucky, Lexington, KY, [2]University of Illinois, Urbana, IL
[3]Salk Institute, La Jolla, CA

Many plants respond to pathogen attack by the synthesis and secretion of anti-microbial compounds. For example, solanaceous plants produce anti-microbial terpenes that inhibit germination and growth of several fungal species. The production of these chemicals has therefore been interpreted as an important defense response. We have also hypothesized that an understanding of the mechanisms responsible for the biosynthesis of the anti-microbial terpenes should provide a means for engineering the generation of novel and more efficacious compounds. Towards that goal, we have elucidated a 2-step biosynthetic pathway for capsidiol, an anti-microbial sesquiterpene di-alcohol. The pathway consists of a terpene synthase that catalyzes the cyclization of farnesyl diphosphate to a bi-cyclic hydrocarbon structure, followed by the action of a P450 hydroxylase that introduces 2 hydroxyl functions with stereo- and regio- specificity. Using a combination of biochemical comparisons, X-ray crystallography, molecular modeling and site-directed mutagenesis, we have mapped functional features of the respective enzymes, and more recently have used this information to evolve novel catalytic activities for the generation of unique chemical entities.

Joseph P. Noel, PhD

Professor Noel was born and raised in rural western Pennsylvania. Upon obtaining a B.S. degree in Natural Sciences with a concentration in Chemistry from the University of Pittsburgh at Johnstown, Joe entered the graduate program in Chemistry at the Ohio State University in the summer of 1985, and graduated from the Chemistry Department in 1990 with a PhD centered on the examination of the mechanistic enzymology of phospholipases with Professor Ming-Daw Tsai. Joe then completed his postdoctoral training with the late Paul B. Sigler in the Department of Molecular Biophysics and Biochemistry at Yale. While at Yale University, he undertook the x-ray crystallographic examination of heterotrimeric G-proteins. Joe and his group are now utilizing a combination of traditional mechanistic enzymology, molecular biology, plant biology, and tools in structural biology including protein x-ray crystallography and NMR to decipher the structure, function, and evolutionary lineage of a large number of enzymes that act in plant cells and many microorganisms to produce biologically active natural products including terpenes, polyketides, and alkaloids. Armed with the three dimensional structure of the enzymes in plant cells responsible for the creation of this diverse array of bioactive compounds, his group is also working to engineer new specificities into these pathways to create novel products using a structurally-guided approach.

S:2

THE STRUCTURAL, MECHANISTIC, AND EVOLUTIONARY UNIVERSE OF TYPE III POLYKETIDE SYNTHASES

Professor Joseph P. Noel, PhD
Structural Biology Laboratory, The Salk Institute for Biological Studies, 10010 N. Torrey Pines Rd., La Jolla, CA 92037

Type III iterative homodimeric polyketide synthases of the chalcone synthase (CHS) superfamily are responsible for the biosynthesis of a number of biologically important compounds in plants and bacteria. While all CHS-like enzymes utilize a handful of absolutely conserved catalytic residues within a single active site to catalyze the iterative addition of acetate units to a starter molecule, family members differ in their choice of starter molecule, number of acetyl additions, and cyclization pathway of the resulting polyketide. Previously in our lab, the structural and functional characterization of CHS from M. sativa (alfalfa) suggested that specificity is modulated in the family by steric constraints provided by a set of variable residues lining the active site. Resveratrol, a beneficial anti-oxidant and anti-aging compound found in red wine, is synthesized by stilbene synthase (STS), a related enzyme thought to have arisen from CHS on at least three independent occasions. Both CHS and STS form the same linear phenylpropanoid tetraketide intermediate via the sequential condensation of three acetyl units derived from decarboxylation of malonyl-CoA with one coumaroyl-CoA starter molecule. However, STS then forms resveratrol via an intramolecular aldol condensation, in contrast to the intramolecular Claisen condensation that CHS utilizes to produce chalcone. Structural elucidation of stilbene synthase from pine and peanut coupled with the structurally guided functional conversion of alfalfa chalcone synthase into an authentic stilbene synthase demonstrates the molecular basis for cyclization specificity in plant type III polyketide synthases.

Chaitan Khosla, Ph.D

Professor of Chemical Engineering, Chemistry and Biochemistry (by courtesy), Wells H. Rauser and Harold M. Petiprin Professor in the School of Engineering

Born on August 14, 1964. Chaitan Khosla received his B. Tech, in Chemical Engineering at the Indian Institute of Technology in Bombay, India. He received his Ph.D. in Chemical Engineering in 1990, from the California Institute of Technology, in Pasadena, California and conducted postdoctoral research in the Department of Genetics, at the John Innes Centre, Norwich, U.K., in 1992.

Professor Khosla began his career as an assistant professor in the Department of Chemical Engineering, Stanford University, in 1992. He became an associate professor of Chemical Engineering and Chemistry, and, Biochemistry (by courtesy) in 1997, before becoming a Professor of Chemical Engineering and Chemistry, and, Biochemistry (by courtesy) in 2001. In 2003 he became the Wells H. Rauser and Harold M. Petiprin Professor in the School of Engineering at Stanford.

Professor Khosla's awards include: Dreyfus New Investigator Award, 1991; NSF Young Investigator Award, 1994-99; Packard Fellowship for Science and Engineering, 1994-99; AIChE Allan P. Colburn Award, 1997; ACS Lilly Award in Biological Chemistry, 1999; NSF Alan T. Waterman Award, 1999; ACS Pure Chemistry Award, 2000; Caltech Distinguished Alumni Award, 2000

Research interests in his laboratory lie at the interface of protein chemistry and medicine.

He has co-authored over 140 publications.

S:3

STRUCTURE-BASED PROTEIN ENGINEERING OF POLYKETIDE BIOSYNTHESIS.

Chaitan Khosla (STANFORD UNIVERSITY, USA)

Polyketide synthases are multifunctional enzymes that make complex natural products of the polyketide family. Over the past few years we have elucidated the structures of key components of these megasynthases.
This presentation will discuss the structures and mechanisms of polyketide synthases, and will present examples of how such insights facilitate the engineered biosynthesis of new natural products.

Mohamed A. Marahiel, Ph.D.

Mohamed A. Marahiel studied chemistry at the Universities of Cairo (Egypt) and Goettingen (Germany). In 1997, he obtained a PhD in biochemistry and microbiology from the University of Goettingen, where he carried out his research work at the Max Planck Institute for Experimental Medicine. Subsequently, he received an assistant professor's position at the Technical University of Berlin, where in 1987 he obtained his Habilitation in biochemistry at the Institute of biochemistry and molecular biology. Three years later he moved to the Philipps-university Marburg as a professor of biochemistry in the chemistry department. He was a DFG fellow in 1978 and 1986 at the John Innes Institute in Norwich (UK) and at the Bioloabs, Harvard University (USA), respectively. His present research focuses on the structure-function relationship and on the elucidation of reaction mechanisms of modular peptide synthetases involved in the nonribosomal synthesis of peptideantibiotics, as well as on the rational design of recombinant enzymes for the synthesis of novel bioactive peptides. His group is also interested in studying the function and regulation of the major cold shock proteins in soil bacteria as well as other stress-induced proteins.

S:4

STRUCTURAL BASIS FOR THE SYNTHESIS OF MACROCYCLIC PEPTIDES

Prof. Mohamed A. Marahiel
Biochemie, Fachbereich Chemie, Philipps-Universität Marburg, Germany
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The ability to synthesize small bioactive peptides nonribosomally that find application in modern medicine is widely spread among microorganisms. As broad as the spectrum of biological activities is the structural diversity of these peptides that are mostly cyclic or branched cyclic in nature, containing unnatural amino acids, small heterocyclic rings and other unusual modification in the peptide backbone. These peptides are synthesized from simple building blocks by multimodular enzymes, the so-called nonribosomal peptide synthetases (NRPSs). Each cycle of chain elongation is carried out by a dedicated NRPS-module that harbors all catalytic units referred to as domains, necessary for substrate activation, covalent binding, and optional modification as well as peptide-bond formation. A terminal domain (thioesterase or cyclase) releases the full-length linear or cyclic peptide and defines its shape in terms of regio- and stereo-selectivity. Recent biochemcial, genetic and structural studies have unveiled the key principles of nonribosomal peptide synthesis allowing the use of NRPS potential for combinatorial biosynthesis.

Sieber, A.S. and Marahiel, M.A. (2003). Learning from nature's drug factories. Nonribosomal synthesis of macrocyclic peptides. J. Bacteriol., 185: 7036-7043.
Schwarzer, D., Finking, R. and Marahiel, M.A. (2003). Nonribosomal peptides: from genes to products. Nat. Prod. Rep., 20: 275-287.
Mootz, H.D., Schwarzer, D. and Marahiel, M.A. (2002). Ways of assembling complex natural products on modular nonribosomal peptide synthetases. ChemBioChem, 3: 490-504.

Arnold J. Vlietinck, Ph. D.

Professor Arnold J. Vlietinck obtained his certifications of pharmacist, industrial pharmacist and clinical biologist from the University of Leuven (KULeuven) in 1968, 1969 and 1972 respectively. At the same university, he graduated as Ph. D. in Pharmaceutical Sciences in 1969 working on the biosynthesis of penicillins and cephalosporins.
He spent a year as research assistant at the School of Pharmacy, University of Wisconsin-Madison working on antimetabolites of vitamin B_{12} under the late professor D. Perlman (1973-1974).
He was appointed in 1974 as lecturer in the Department of Pharmaceutical Sciences of the University of Antwerp (UA) in the field of pharmacognosy and phytochemistry and became full professor at the same university in 1985.
Professor Vlietinck is the author of over 300 scientific papers on the isolation and structure elucidation of pharmacologically active plant components.
He is member of more than 20 scientific societies and over 10 editorial advisory boards of scientific journals. He is an organiser or co-organiser of over 50 research meetings and he represents his country in many commissions on regulatory affairs of herbal medicinal products throughout Europe.
He is currently coordinating two projects on clinical studies of herbal drugs in Africa.
He has been invited as plenary lecturer at many international congresses and as guest-professor in The Netherlands, Italy, Greece, Egypt and Panama.

S:5

CURRENT STATUS AND PROSPECTIVES FOR HERBAL PREPARATIONS AS MEDICINAL PRODUCTS OR FOOD SUPPLEMENTS IN THE EUROPEAN UNION.

Professor Arnold J. VLIETINCK, Ph. D.

The widespread and increasing worldwide use of herbal preparations as herbal medicinal products, dietary supplements, nutraceuticals and functional foods demands that appropriate regulatory actions are undertaken to regulate and harmonise the legal status of these various groups of plant preparations throughout the different Western countries.
At levels of both the European Agency for the Evaluation of Medicinal Products (EMEA) and the European Pharmacopoeia Commission (EP) much effort has recently been made to improve the European legislation and address the specific requirements of herbal medicinal product.
The mutual recognition and bibliographic application for herbal medicinal products has been adopted in the light of the most recent experience gathered by competent national authorities and applications of the European Union. A new legislation (CD 2001/83/EC) has been adopted by the European Parliament and will be implemented in the next coming years by the different European national authorities.
Nevertheless, the distinction between traditional herbal medicinal products and food supplements containing herbal preparations without nutritional value but having physiological effects remains vague and controversial. This problem is not fully resolved as yet by the council directive on food supplements (CD2003/46/EC). Consequently, a regulation at the level of the different EC member states remains appropriate for the time being.
In this lecture the medicines concept and the food concept on herbal preparations throughout the Western world will be discussed especially in the light of the current different situations in the USA and the European Union.
An appreciation will be given on all efforts which are undertaken to ensure quality, safety and efficacy of herbal preparations marketed at both sides of the Atlantic Ocean.

Dr. Adolf Nahrstedt

Professor Dr. rer.nat. Dr. h.c. Adolf Nahrstedt was born 1940; he was educated in Pharmacy and Food Chemistry from 1962 to 1968 at the University of Freiburg, Germany; he obtained his Dr.rer.nat. (Pharmacognosy) there (1971) and passed his habilitation (Pharmaceutical Biology) in Freiburg (1976); he was then appointed Professor (C3, associate) of Pharmaceutical Biology at the Techn. University of Braunschweig, Germany (1977-1986) and finally Full Professor (C4) and Chair of Pharm. Biology and Phytochemistry at the Westfalian Wilhelms-University of Münster (1986-2004). In 1985 he was a visiting scientist at the Univ. of California (Davis) with Prof. E. E. Conn. He was Dean of the Faculty of Chemistry in Münster from 1989 to 1991. In 2004 he received the Dr.h.c. of the Ovidius University at Constanta (Romania). His scientific areas are: Phytochemistry, physiological activity and biopharmaceutical aspects of traditionally used medicinal plants and their constituents. Biochemistry and physiology of secondary constituents of plants and insects, in particular the cyanogenic compounds. He has published some 180 papers in these fields. Dr. Nahrstedt is a Member of the Committee of Experts "Pharmaceutical Biology (Pharmacognosy)" of the German Pharmacopoeia; Member of the Board of Directors of the "Gesellschaft für Arzneipflanzenforschung" and the Board of Directors of the "Gesellschaft für Phytotherapie"; he was a coeditor of "PLANTA MEDICA" from 1983-1992 and is now Editor in Chief of the same journal. He is also a vice-member of the Commission E of the Federal Institute of Medicinal Products and Medical Advices.

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PHYSICO-CHEMICAL INTERACTIONS OF CONSTITUENTS IN PLANT EXTRACTS AND EFFICACY.

Professor Dr. Adolf Nahrstedt
Institute of Pharmaceutical Biology and Phytochemistry, Westf. Wilhelms-University, D-48149 Münster, Germany.

There are some few observations in the literature that the solvation and/or bioavailability of pharmacologically active constituents in plant extracts are strongly influenced by accompanying compounds. Some authors have chosen the term "coeffectors", others the term "cooperative compounds" to describe these properties. Examples are the cardioglycosides from *Digitalis* spec., whose solubility is clearly enhanced when dissolved from an extract preparation, in comparison to the isolated pure glycosides; the kava-lactones (styrylpyrones) of *Piper methysticum*; the pyranochromone khellin of *Ammi visnaga* fruits or ascorbinic acid in the juice of *Citrus* spec. in comparison to pure vitamin C. For all systems the compounds responsible for increased biopharmaceutical properties were not detected. A recently well investigated system is hypericin in extracts of *Hypericum perforatum*; meanwhile not only the compounds are known which increase the solubility of hypericin in St. John's extracts, but it was also shown that such interactions lead to a better bioavailability in rats. Thus, such cooperative effects may indicate some superiority of plant extracts over isolated compounds in a normal therapeutical situation. Interestingly, even new compounds can be produced by mixtures of different dry crude drugs as shown by the example of Prasaplai, a traditional Thai medicine. These effects should find more scientific attention because they may contribute a lot to the pharmaceutical quality of any crude plant extract.

Ivar Roots, MD

Professor Ivar Roots, MD, studied human medicine at the Justus Liebig University, Giessen, and the Freie University, Berlin, Germany (MD in 1972). He started working as a post-doc scientist (Institute of Clinical Pharmacology, Freie Universität Berlin), was appointed assistant professor (1976) and Professor of Clinical Pharmacology (1985). Later he became the institute's interim director (1988-1993). Since 1993, he holds the Chair of Clinical Pharmacology at the Institute of Clinical Pharmacology, University Medical School Charité, Humboldt University of Berlin. His research subjects comprise pharmacogenetics, genetic susceptibility factors, variability of drug metabolism and drug transporters, pharmacokinetics, bioinformatics, and phytomedicine. Roots is the president of the German Society of Clinical Pharmacology and Therapy (since 1998) and founder of Clinical Pharmacogenomics Berlin-Buch Ltd. He was awarded an honorary doctoral degree from Voronesh (2000) and is a member of several national and international committees.

S:7

HERB-DRUG INTERACTIONS

Professor Ivar Roots, MD; Dieter Schwarz PhD; Solveigh Krusekopf, PhD; Andreas Johne, MD
Institute of Clinical Pharmacology, Charité Campus Mitte, Humboldt University of Berlin, 10098 Berlin, Germany

Interactions between herbal drugs and chemically defined drugs are of great clinical importance. Moreover, elucidating the underlying mechanism may unveil how the mammalian organism "interacted" (in the word's true sense) during phylogenesis with specific plant constituents ingested with food. Thus it is not surprising that chemicals which are especially designed to hit those phylogenetically created targets do interfere with constituents of herbal drugs. Interactions of St. John's wort with digoxin (1), ciclosporin (2), amitriptyline (3), and indinavir (4) were among the first to be carefully explored biochemically. Cytochromes P-450 (CYPs) and drug transporters (e.g. p-glycoprotein) turned out to be involved. The wealth of knowledge that has been accumulated about herb-drug interactions has led to the formulation of principal strategies for patient treatment, regulatory processes, drug development, and pharmacovigilance.

When taken for a long time, certain diets containing specific plant components may have beneficial effects by preventing cancer, artherosclerosis or other diseases. Certain herbal drugs can possibly produce the same result. By in-vitro experiments with human CYP1A1, we tested the potential of preparations of St. John's wort and that of some of their constituents (e.g. hypericin, hyperforin, quercetin) for inhibiting ultimate carcinogen formation (benzo[a]pyrene-7,8-dihydrodiol) (5,6). Ki values were 0.6 μM (hypericin), 1.1 μM (hyperforin), and 2.4 μM (quercetin), indicating a hypothetical capacity of these constituents for preventing cancer. Quercetin-mediated inhibition was weaker in those genetic variants of CYP1A1 that are assumed to predispose to bronchial cancer (CYP1A1.2 and CYP1A1.4).

1. Johne A et al. (1999)Clin Pharmacol Ther. 66:338. 2. Ruschitzka F et al. (2000): Lancet 355:548. 3. Johne A et al. (2002). J Clin Psychopharmacol. 22:46. 4. Piscitelli SC et al. (2000): Lancet 355:547. 5. Schwarz D et al.(2003): Cancer Res. 63: 8062. 6. Schwarz D and Roots I (2003): BBRC 303:902.

Dr. med. Chaim Ismail

Dr. med. Ch. Ismail has obtained his medical qualifications on the college of medicine at the Universtiy of Hamburg, Germany (1990). Then he was trained at the Dept. of Dermatology at the same University. Until 1997 he worked at the Hochgebirgsklinik Davos-Wolfgang in Switzerland, Dept. of Pneumology and Allergology. He searched at the Swiss Institue of Asthma & Allergy Research (SIAF), comprising in vivo and in vitro diagnosis with recombinant allergens. In 1997 he changed to the Dept. of Medical Science & Research, responsible for Respiratory Drugs and Drug Safety at Bionorica Arzneimittel GmbH, Neumarkt, Germany. Since 2002 he is head of the Dept. Medical Science & Research, Bionorica AG, Germany.
Awards: Pulmedica Award 1997. Disease specific recombinant allergens for the diagnosis of allergic bronchopulmonary aspergillosis (German Society for Lung and Airways Research); Herbert-Herxheimer-Memorial Award 1998. Humoral and Cell-mediated Autoimmunity in Allergy to Aspergillus fumigatus. (German Society for Allergology and Clinical Immunology**).**
He is a member of the European Respiratory Society, the European Academy Allergy Clinical Immunology, the Gesellschaft für Lungen- und Atmungsforschung e. V. in der Deutschen Gesellschaft für Pneumologie, the ForPaed (Bundesverband für klinische Forschung in der Pädiatrie e.V.), the Deutsche Gesellschaft für Pharmazeutische Medizin e.V. (DGPM) and the GA (Gesellschaft für Arzneipflanzenforschung).

S: 8

HERBAL MEDICINAL PRODUCTS IN CLINICAL RESEARCH: DRUG SAFETY - NEEDS, TRENDS - AND FASHION?

Ismail, Ch., Seffner, B.
Bionorica AG, Neumarkt, Germany

The aim of clinical research is the proof of efficacy and safety and thereby assess the benefit-/ risk ratio of drugs. Herbal preparations have been used since centuries for the treatment of diseases and complaints all over the world. For a long period the so called natural remedies have been assessed to be at least safe. Based on experimental and clinical studies there is an increasing body of evidence that herbal medicinal products are effective and may be alternatives to chemically defined molecules. However, in parallel concerns about the safety increased as well in several parties. In addition it becomes obvious that regulations in different regions may not be sufficient to assess the risk / benefit of herbal medicinal products appropriately. The presentation will give an overview about trends in scientific literature, recent guidelines on drug safety of herbal medicinal products in Europe, the US and Japan and will provide the experience of a phytopharmaceutical company regarding drug safety over the last 15 years exemplary.

1. EMEA, (2003) ICH E2D Note for Guidance on Definitions and Standards for Expedited Reporting (CPMP/ICH/3945/03)
2. EMEA, (2001) Notic to Applicants Volume IX - Pharmacovigilance Guidelines (CPMP/PhVWP/108/99 corr.)
3. Gesetz ueber den Verkehr mit Arzneimitteln (AMG) (German Drug Law), (2000/2004 rev.))
4. FDA, (2000) Guidance for Industry - Botanical Drug Products, 2004
5. FDA, (1999) Guidance for Industry - Statement of Identity, Nutrition Labeling, and Ingredient Labeling of Dietary Supplements - Small Entity Compliance Guide

Prof. Dr. Gerhard Franz

Prof. Dr. Gerhard Franz obtained his Diploma and Approbation as Pharmacist from the University of Karlsruhe/Germany (1963) and his doctoral degree (Dr. rer. nat.) as a fellow of the Deutscher Akademischer Austauschdienst (DAAD) at the University of Fribourg/ Switzerland (1966) in Biology/Analytical Phytochemistry working on structural analysis of high molecular weight polysaccharides. As a postdoctoral fellow with a fellowship of the 'Schweizer Nationalfonds zur Förderung der Wissenschaften' he carried out research at the Department of Biochemistry at the University of California/Berkeley with Professor Dr. Z. Hassid. He was appointed as Assistant Professor at the University of Fribourg/Switzerland (1970) and as Full Professor at the University of Regensburg, Department of Pharmaceutical Sciences, Regensburg/Germany in 1977 until today. He obtained Guest Professorships at he University of Basel/Switzerland and the University of Grenoble/France.
Prof. Franz is author of more than 250 scientific papers in the area of carbohydrate chemistry/biochemistry, natural product analysis, pharmacology of natural products and quality of Herbal Medicinal Products (HMP's). His research was recognised by the award of the first EGON STAHL Medal (1985), the KNEIPP-Award (1994), The H. THOMS Award of the DPhG (2003). He is corresponding member of many scientific Societies such as the Belgian Medical Association and the Académie Francaise de Pharmacie. Prof. Franz is editor and co-editor of several scientific journals. He was appointed as chairman of the Group of Experts (European Council) for the European Pharmacopoeia and the German Pharmacopoeia. From 1994 until 1998 he acted as President of the Gesellschaft für Arzneipflanzenforschung (Society for Medicinal Plant Research) and is still an active member of Commission E of the German Government.

S:9

GLOBAL HARMONISATION OF QUALITY STANDARDS FOR HERBAL MEDICINAL PRODUCTS (HMP's)

Prof. Dr. Gerhard Franz, University of Regensburg, Germany

Our Society has a continuing need for the implementation of recognised common standards for the quality of herbal medicines with the objective, to ensure their quality and to facilitate their free movement Europe- or Worldwide. Specific monographs are addressed to licensing authorities as well as to manufacturers, producing phytopharmaceuticals. The European Directive 2001/03/EC relates to the analytical, pharmacotoxological and clinical standards and provides the general requirements, such as all the test procedures which should correspond to the actual state of scientific progress and should be based on validated procedures. An important feature is the fact that all quality monographs on herbal medicinal products should be drafted with the same overall structure as a monograph on a chemical substance, regardless of the very complex composition of the herbal products in general .
The quality of herbal drug preparations is based upon the quality of the starting material i.e. herbal drugs. However, more and more emphasis is actually given on the implementation of quality standards and monographs for herbal drug preparations such as extracts and tinctures in order to facilitate the licensing procedure and to reach a phytoequivalence of the finished herbal preparations on the market.
This process should include the respective guidelines on Good Agricultural Practice (GAP) and GMP, in-process testing and stability testing. In summary, HMP's should no longer be considered as 'black boxes' of unknown and largely varying quality but as products with well documented and generally accepted quality parameters.

Prof. Dr. med. Wolfgang Wuttke

Prof. Dr. med. Wolfgang Wuttke was born in Berlin, Germany on January 14, 1942. He was educated at the Medical School Free University in Berlin and recognized by the following achievements and accomplishments:

1966 - 1969	Internship and residency
1969 - 1971	Postdoctoral fellowship (Neuroendocrinology) Michigan State University
1971 - 1982	Head of Research Unit at Max-Planck-Institute for Biophysical Chemistry (Göttingen)
1982 - 1985	Head of Department of Reproductive Biology, German Primate Center (Göttingen)
1985 - currently:	Head of Division of Clinical and Experimental Endocrinology, Dept. of OB/GYN, University of Göttingen
1972	Habilitation
1976	Professor
1975 - 1978	Board Member of German Endocrine Society
1984 - 1987	Board Member and Congress President of German Endocrine Society
1984 - 1989	Vice President of International Society of Neuroendocrinology
1984 - 1988	Board Member of European Neuroendocrine Association
1993 - 1996	President of the German Endocrine Society

He has provided service of International Journals including :Section Editor Neuroendocrinology for *Experimental Brain Research* (1979 – 1992), Scientific Editor *Journal of Endocrinology* (1979 – 1985), Editorial Board *Neuroendocrinology* (1979 – 1987), (Life Science Advances: Experimental and Clinical Endocrinology (since 1990), Co-editor of *Experimental and Clinical Endocrinology and Diabetes* (since 1993), Editorial Board of *Neuroendocrinology* (1994 – 2000), Editorial Board of *Clinical Endocrinology* (1996 – 2000), Editorial Board of *Biology of Reproduction*(1999 – 2003)

Dr. Wutte has provided Scientific Services to the German Research Society (Reviewer), Ministry for Science, Ministry for the Environment; Nature Conservation and Nuclear Safety and the National Science Foundation (USA).

He has received several awards including the Schoeller-Junkmann Award of the German Endocrine Society (1972), Carlo Erba Award of the German Society for Cancer Research (1988), and the Rudolf-Fritz-Weiß Award of the Society of Phytotherapy (1990). Since 1991 he is a Corresponding Member of The Argentine Society of Endocrinology and Metabolism.

S:10

ESTROGENS VERSUS PHYTOESTROGENS

Wolfgang Wuttke
Dept. of Clinical and Experimental Endocrinology, University of Goettingen, Germany

The frightening data concerning hormone replacement therapy (HRT) have prompted drug and food additive producing companies to promote plant-derived estrogens. There are only very few placebo-controlled studies to indicate that soy- or red clover-derived isoflavones have beneficial effects on climacteric complaints. The majority of the well controlled studies demonstrated no effect of isoflavones on hot flushes while they may have mild antiosteoporotic effects. In view of putatively dangerous effects of pure isoflavones in the mammary gland a European Consensus Conference held in April 2003 in Greece stated that soy or red clover derived isoflavones are no good alternatives as a replacement for hormone replacement therapy. – Another alternative for HRT are Cimicifuga racemosa (black cohosh) extracts. In several open and two placebo-controlled studies these extracts were shown to alleviate climacteric complaints. In postmenopausal mamma-carcinoma patients a Black cohosh preparation, however, was without effects on hot flushes. The yet unidentified substances, which alleviate climacteric complaints in Black cohosh preparations, do not have an estrogenic effect in the uterus but partially prevent ovx induced osteoporosis in rats. Cell biological and animal experimental data appear to indicate that Black cohosh preparations also do not address the mammary gland.

Pr. Joël Boustie

Pharmacist, Toulouse 1985
PhD Institut National Polytechnique Toulouse 1990
Faculté des Sciences Pharmaceutiques et Biologiques, Univ. RENNES 1
Lecturer 1992
Laboratoire de Pharmacognosie et de Mycologie *Pr. Headmaster 1999*
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http://www.aferp.univ-rennes1.fr/
Topics : phytochemistry**, limonoids, plants, mushrooms, antiviral and cytotoxicity testing,** lichens

General Secretary of AFERP (Association Francophone Pour l'Enseignement et la Recherche en Pharmacognosie)1997-2001

COST Working Group D28/0/03 Coordinator "Bioactive compounds from lichens" nov 2003-http://cost.cordis.lu/src/action_detail.cfm?action=d28
Research Group EA : **Synthèse et extraction de molécules à visée thérapeutique**
http://www.upres2234.univ-rennes1.fr

S:11

LICHENS: POTENTIALITIES AND RECENT DEVELOPMENTS.

Nature, in general, is a valuable source for novel, pharmaceutically relevant compounds. Lichen-forming fungi are unique organisms, producing biologically active metabolites for which a great variety of possible applications, including antibiotic, antiviral, anti-inflammatory, analgesic, antipyretic, antiproliferative and cytotoxic effects have been recognized. It should be emphasized, however, that only a very limited number of lichen substances has been screened for their biological activities and their therapeutic importance in medicine. Certainly, this is due to the difficulties encountered in lichen identification, collection of bulk quantities added to classical difficulties to achieve substantial isolation of pure substances for identification and testing. Hence, only few research teams are involved with lichens, directed towards such a goal. Recently, opportunities for bypassing some of these former difficulties have arisen as new techniques have been introduced for testing (HTS), for cultivation (biotechnological production), for extraction of focused compounds (dereplicative chromatographic techniques), and for synthesis of natural products or their derivatives (classical chemistry or Solid Phase Organic Synthesis).
After a short introduction to lichens and to their metabolites, a focus on the most relevant active compounds along with a presentation of some emerging research works for lichen compounds production and investigation will be presented.

Giovanni Appendino, Ph.D.

Giovanni Appendino was born in Carmagnola (Torino, Italy) on Sept.1, 1955. He graduated in 1979 at the Università di Torino, where he became *Ricercatore* in 1983 and Associated Professor in 1998. In 2000 he became Full Professor or Organic Chemistry at the Università del Piemonte Orientale in Novara (Italy)..
His research activity is documented by over 190 scientific articles, 7 book chapters and over 100 congress communications (plenary lectures, oral communications, poster communications). In 1991 he received the Rhone-Poulenc-Rorer Award of the Phytochemical Society of Europe for his studies on Isoprenoids. His research activity has centred on the chemistry of biologically active organic natural products, and has developed according to three lines, isolation/structural elucidation, chemical modification, and total synthesis. Compounds from different classes and typical of terrestrial organisms, mainly higher plants, were investigated (isoprenoids, alkaloids, coumarins, acetogenins, phenylpropanes). The main research lines have regarded medium-size cyclic compounds, taxoids, phorboids, vanilloids, cannabinoids, coumarins, flavonoids, sesquiterpene lactones, and secondary metabolites from edible plants and spices.

S:12

HOT CUISINE AS A SOURCE OF DRUGS. HOW A GIFT FROM THE SANDS TRIGGERED A MULTIDISCIPLINARY RESEARCH WITH UNEXPECTED CONNECTIONS

G. Appendino
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Nature has invested heavily in terms of DNA to equip our oral cavity with receptors that detect bitter compounds, noxious physical stimuli (hot, cold, electricity), and compounds that mimick them in a process known as chemestesis. While bitternes has traditionally been associated to bioactivity, the pharmacological potential of chemestetic compounds has long gone unrecognized. Pungency is the archetypal chemestetic sensation, though a satisfactory explaination as to why humans like hot cuisine is still lacking. Chili pepper, and other plants as well, are used to induce a fiery trait in the cuisine of various areas of the world. Research in the pungent principles of these plants was long pursued only at a chemical level. A turnming point was the recognition that a constituent of a succulent African *Euphorbia*, the phorboid resiniferatoxin (RTX), behaves as an ultrapotent analogue of capsaicin (CPS), the pungent principle of hot pepper. This discovery set in motion a multidisciplinary research that culminated in the characterization of a series of TRP-type cation channels that act as thermal sensors and respond to a variety of noxious stimula. After a description of the biological potential of RTX and its isolation, the lecture will describe research centered on the synthesis of analogues of capsaicin and ferutinin, two compounds of biomedical relevance isolated from hot plants (chili pepper and various *Ferula* species).

Rachel Mata, Ph.D.

Rachel Mata received her BS in Pharmacy at the Central University of Venezuela, and her graduate education (MS and PhD) in the field of Pharmacognosy at Purdue University, Indiana, under the direction of Professor Jerry McLaughlin. She continued her education as a postdoctoral fellow at the Chemistry Institute of the National University of Mexico (UNAM) under the supervision of Professor Romo de Vivar, and later as a visiting scientist at the University of Rhode Island where she worked with Professor Yuzuru Shimizu. Her research interests include the isolation and characterization of natural bioactive compounds of medicinal and agrochemical interest. She has published over 120 papers in the field of Pharmacognosy, one book on medicinal plants, and several book chapters. In addition, she has graduated 40 BS, 24 MS and 16 PhD students. She received a Distinguished Alumna Award (1998) from the School of Pharmacy and Pharmacal Sciences, Purdue University; The National University Prize in Natural Sciences (2000), UNAM; and The Martín de la Cruz Award (2002), from the Mexican Government. She has served in several important academic administrative positions, evaluation committees and advisory committees in Mexico, and as President of the Phytochemical Society of North America (1996-1997). Currently she is Professor of Pharmacognosy and head of the Department of Pharmacy of the School of Chemistry at UNAM in Mexico City.

S:13

CURRENT RESEARCH ON MEDICINAL PLANTS IN MEXICO: BIOACTIVE COMPOUNDS FROM SELECTED MEXICAN MEDICINAL PLANTS

Rachel Mata
Departamento de Farmacia, Facultad de Química, Universidad Nacional Autónoma de México, Mexico City, 04510, México.

Current research on medicinal plants in México is aimed to the classical ethnobotanical and anthropological investigations, to validate traditional medicinal uses through pharmacological and biological studies and, in a less extent to the search of bioactive compounds, to establish procedures for quality control of herbal remedies and to clinical trials of phytodrugs. Although the potential of Mexican medicinal plants as a source of bioactive compounds remains largely unexplored, the results of our investigations, as well as those of other researchers, clearly indicate that the Mexican medicinal flora shows promise for the discovery of new or known substances with valuable pharmacological activities. On the medicinal area, our efforts have been focused on the discovery of active principles useful for the treatment of gastrointestinal disorders associated with dyspepsia, colic and infectious diarrhea. The reason is very simple, gastrointestinal disorders, regardless of their origin, represent a big health problem in Mexico. Thus, the purpose of this presentation is to illustrate the potential of Mexican medicinal flora as source of bioactive compounds of medicinal interest through examples stemming from our own work. Brief considerations of the botanical sources, isolation, structure elucidation and biological properties of the active principles will be discussed.

Dr. Maike S. Petersen

Professor Maike S. Petersen obtained her Diploma in biology specializing in plant biology from the Eberhard-Karls-Universität Tübingen (Germany) in 1983 and her Dr. rer. nat. in 1986 from the same university. In her doctoral thesis she worked on the 12ß-hydroxylation of digitoxin to digoxin by a cytochrome P450 hydroxylase from *Digitalis lanata*. From 1986 to 1997, she worked as a Research Scientist at the Department for Developmental and Molecular Plant Biology at the Heinrich-Heine-Universität Düsseldorf (Germany); in 1993, she got her "Habilitation". In 1990-1991 she worked as a Postdoctoral Researcher at the Institute for Genetics of the University of Ghent (Belgium) and in 1995 as a Professor for Pharmaceutical Biology at the University of Halle-Wittenberg (Germany). In 1997 she got a full professorship in Pharmaceutical Biology at the Philipps-Universität Marburg (Germany). Since 2001, she is one of the deans of the faculty.
In her research, Professor Petersen is interested in biochemistry and molecular biology of plant secondary metabolism and in the use of plant *in vitro*-techniques for the production of useful natural compounds. Main research topics are phenolic natural compounds, especially rosmarinic acid and lignans. She has published about 70 scientific articles. In 1990, she was rewarded the Research-Prize of Northrhine-Westfalia and in 1995 the Rhône-Poulenc Rorer Award of the Phytochemical Society of Europe. Currently, she is a member of the editorial board of "Phytochemistry Reviews". She is Vice-chairperson of the Section "Natural Compounds" of the German Botanical Society and Chairperson of the Phytochemical Society of Europe (PSE).

S:14

PLANT *IN VITRO*-CULTURES AND NATURAL PRODUCT RESEARCH

Maike S. Petersen
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Plant *in vitro*-cultures are known for more than 100 years now. The use of undifferentiated callus and suspension cultures or differentiated shoot or root cultures for the production of interesting natural products has been intensively explored showing that some natural products are accumulated in quite high amounts in these *in vitro*-systems. Despite these attempts, only a few commercial production systems are known. Rare plant species, however, or plants growing in extreme environments might be saved by using *in vitro*-techniques. These techniques can either be used to micropropagate rare plants or to cultivate plant material under controlled laboratory conditions for the production of natural compounds. As general examples, the accumulation of rosmarinic acid in suspension cultures of *Coleus blumei* (Lamiaceae) and the production of cytotoxic lignans by cell cultures of *Linum* species (Linaceae) as well as investigations on the respective biosynthetic pathways will be presented.

Gabriele M. König (Prof., PD, Ph.D)

Professor König studied pharmacy at the Albert-Ludwigs-Universität, Freiburg/Breisgau, Germany, and graduated in July 1980 with distinctions. She obtained her Ph D from Freiburg University in 1984, and continued with Postdoctoral research in the area of marine natural products chemistry at the Department of Chemistry and Biochemistry, James Cook University of North Queensland, Townsville, Australia (1985-1987: Fellow of the Deutsche Forschungsgemeinschaft, 1987-1988: Australian Postdoctoral Fellow). During 1989-1994 she was Oberassistentin at the Department of Pharmacy, ETH-Zürich, Switzerland. During this time she succeeded in doing her Habilitation on the topic 'Chemical and Biological Investigations of Natural Products derived from Marine and Terrestrial Sources' (Venia legendi, 1993), for which she was honoured with the Egon Stahl Award. From october 1994 till 1999 she was Professor of Pharmacognosy (Pharmaceutical Biology) at the University of Braunschweig, and in october 1999 became Professor and Head of Department of Pharmacognosy (Pharmaceutial Biology) at the University of Bonn, Germany. Her research focuses on the chemistry and pharmacology of marine natural products. She is a member of the Editiorial Advisory Board of Journal of Natural Products.

Research Group: currently 15 members (10 Ph D students, 2 Postdocs, 3 Technicians); Number of Research Publications: 110 original Research Papers (details under: http://www.uni-bonn.de/www/Pharmazeutische_Biologie/Forschung/Koenig/Publikationen.html)Homepage: www.uni-bonn.de/www/Pharmazeutische_Biologie/Forschung/Koenig.html

S:15

NEW STRUCTURES FROM MARINE ORGANISMS AND THEIR PHARMACEUTICAL POTENTIAL

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Marine macro- and microorganisms continue to yield natural products with intriguing structures and potent bioactivity. Investigation of the ascidian *Atriolum robustum* led to new amino acid and nucleoside derived compounds. Some of these contain rare methylthioadenosine and methylsulphinyladenosine moieties and exhibit affinity for A_1 and A_3 adenosine receptors.
In many cases marine macro- and microorganisms live in close association, e.g. cyanobacteria in sponges, or endophytic fungi in algae. Leucamide A, a cytotoxic cyclic heptapeptide containing a unique mixed 4,2-bisheterocycle tandem pair consisting of a methyloxazole and thiazole subunit was isolated from the sponge *Leucetta microraphis* and resembles cyanobacterial peptides. On the other hand the cyanobacterium *Plectonema* sp. was found to produce new and structurally unusual cyclic peptides with protease inhibiting acitities, structurally related to the sponge metabolite mozamide. Based on the idea that algicolous and endophytic fungi may produce new metabolites as a means of dealing with their host plant, algae are proposed as a most valuable source for the isolation of unusual and obligate marine fungal strains. Endophytic fungi isolated from the inner tissue of marine algae provided further new structures, predominantly with antioxidative activity. For some of these metabolites their biogenetic origin was determined by feeding stable isotope labelled precursors.

Koji Nakanishi, Ph.D.

Born in Hong Kong in 1925, and brought up in Lyon, London, and Alexandria, he received his bachelor's degree in chemistry from Nagoya University in 1947 from Fujio Egami. Following two years of post-graduate work with Louis Fieser at Harvard University, he returned to Nagoya University where he completed his Ph.D. in 1954 with Yoshimasa Hirata He was Assistant Professor at Nagoya until 1958 and then appointed Professor of Chemistry at Tokyo Kyoiku University. In 1963 he moved to Tohoku University in Sendai and in 1969 joined Columbia University. In 1980 he became Centennial Professor of Chemistry.

He was a founding member and one of the six Directors of Research at the International Centre of Insect Physiology and Ecology (ICIPE) in Kenya, 1969-1977. In 1978 he was appointed Director of the Suntory Institute for Bioorganic Research (Sunbor), Osaka, and served until 1991. He served as director of the chemistry unit at Biosphere 2, Arizona, operated by Columbia University from April 2001, until its termination in December 2003.

His research covers isolation, structural and bioorganic studies of bioactive compounds, retinal proteins, ligand and neuroreceptor interactions, development of spectroscopic methods, especially circular dichroic spectroscopy. He was also the first to discover and apply NMR NOE in structure determinations during structural studies on ginkgolide (1967), He has determined structures of 200 natural products, published 370 papers, and has received awards from 12 countries. A Nakanishi Prize of the Am. Chem. Society and the Chem. Soc. Japan started in 1996 and is awarded in alternate years in Japan and the U.S.

S:16

NATURAL PRODUCTS CHEMISTRY AND NATURE

Koji Nakanishi.
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Natural products chemistry started with the curiosity regarding odor, taste, color, folk medicinal cures, etc.. In early days what is now known as natural products chemistry was focused in the isolation of the more readily available constituents, structure determination, and if feasible this was followed by synthesis and elucidation of biosynthetic routes. The rapid advancement in isolation techniques and spectroscopy made structure determination increasingly routine; the trend also shifted towards activity-monitored isolation and structural studies. However, in more recent years, it has become possible for organic chemists to direct their attention towards the mode of action, which almost invariably involves the interaction between ligand and its biopolymeric receptor; a decade ago, such studies were impossible to be performed on a molecular structural level. Organic chemists, especially those involved in structural studies have the techniques, imagination, and knowledge with respect to the approach in such studies. However, nature is far more complex, and it is only with multidisciplinary collaborative research encompassing many disciplines that such targets can be successfully investigated. Clarification of the ligand/receptor interaction on a molecular structural basis and in a time-resolved manner is an extremely challenging problems, which at present cannot be answered even with a major multidisciplinary effort. We are at the starting point of a new field which is filled with exciting problems that have an immediate bearing directed towards a better understanding of Nature. In the following, several of our past and ongoing studies in this area will be outlined.

The Varro Tyler Prize for Research in Botanical Dietary Supplements Award Presentation

A:1

TWENTY YEARS EXPERIENCE IN THE BOTANICAL HEALTH FOOD MARKET

Ezio Bombardelli, President of Scientific Board, Indena S.p.A., Milan, Italy

During the last fifteen years we assisted an incredible expansion of formulations containing botanical derivatives, marketed mainly as nutritional supplements (food and dietary) around the world. This rapid and unpredictable development changed several criteria of management for botanical products. The legislators have today the problem to write down new rules to protect the consumers from fraud or dangerous side effects. The tendency around the world is the harmonization of the basic concepts concerning the safety firstly and later the efficacy of a plethora of products. Due to the confusion created by the huge demand and speculation, bad quality products were put on the shelf, destroying step by step the credibility of many preparations. The main problem is the safety: the use of uncontrolled products, prepared from any kind of plant material without biological testing or GMP preparation methods, caused a consistent number of side effects. To gain consumer confidence, we now have to return to the origin for the preparation of botanical extracts, and follow the rigorous concepts of their standardization and biological evaluation of tolerability and efficacy. It is very important to keep in mind that very often by changing the preparation method of a given extract the biological profile of the final product can change dramatically. The presence of unknown substances could play an important role from a biological point of view. For this reason, NMR and NIR spectroscopy have been introduced in the characterization of botanical extracts. As a practical example of how we can manage this, I would like to consider the preparation of the *Ginkgo biloba* extract, *Hypericum perforatum and Serenoa repens* which are very popular products, marketed in several countries, both as prescription drugs and/or as health food products.

Ezio Bombardelli, President of Scientific Board, Indena S.p.A., Milan, Italy.
Valerio Bombardelli, Indena S.p.A., Milan Italy.

ASP Matt Suffness Award Presentations

A:2

UNCULTIVATED SYMBIONTS: PROSPECTS FOR THE SUSTAINABLE PRODUCTION OF ANIMAL-DERIVED PHARMACEUTICALS

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Bacterial symbionts have long been suspected as true source of many bioactive natural products isolated from invertebrates, such as sponges, tunicates and bryozoans. The proof of this symbiont hypothesis could set the stage for the development of renewable supplies of marine drugs based on bacterial fermentation systems. However, the current unculturability of the suspected producers has so far prevented such an approach. An alternative, culture-independent strategy could be the cloning of biosynthetic genes and their expression in bacterial production hosts. To test this approach we have studied the origin of pederin-type antitumor polyketides isolated from *Paederus* rove beetles and marine sponges. We could isolate the entire set of gene candidates for pederin biosynthesis from the metagenomic DNA of *Paederus fuscipes* beetles. Sequence analysis and cell separation studies revealed that the genes belong to the genome of an as-yet unculturable bacterial symbiont that is the next known relative of the opportunistic pathogen *Pseudomonas aeruginosa*. The genes encode a large polyketide synthase system with several unusual architectural features that provided unexpected insights into pederin biosynthesis. In a related study on the biologically extremely complex sponge *Theonella swinhoei*, the source of the pederin-type onnamides and theopederins, a bacterial gene cluster was isolated that is almost identical to the pederin system and should therefore encode biosynthesis of the sponge antitumor compounds. These results suggest that cloning and heterologous expression of symbiont genes could be a general strategy for the sustainable production of many otherwise inaccessible animal-derived drug candidates.

A:3

NATURAL PRODUCT GLYCORANDOMIZATION

Jon S. Thorson, Professor, Pharmaceutical Sciences, Laboratory for Biosynthetic Chemistry, University of Wisconsin, School of Pharmacy, 777 Highland Avenue, Madison, WI 53705, USA

In nature, the attachment of sugars to small molecules is often employed to mediate targeting, mechanism of action, and/or pharmacology. As an alternative to pathway engineering or total synthesis, we report merging three promiscuous enzymes (a sugar kinase - 'E_1', a nucleotidylyltransferase - 'E_2', and a glycosyltransferase) with upstream synthetic chemistry and downstream chemoselective ligation provides a powerful method (*in vitro* glycorandomization or IVG) to diversify the glycosylation patterns of complex natural products. Glycorandomization development via both enzyme evolution and structure-based enzyme engineering, the proof of concept, biological activity of glycorandomized natural product-base drug analogs and the implications for general therapeutic development will be discussed. Progress toward an *in vivo* fermentation-based glycorandomization process and recent developments pertaining to our work on the biosynthesis of enediynes (calicheamicin, dynemicin), *N*-glycosides (indolocarbazoles rebeccamycin and AT2433) and *C*-glycosides (the pluramycins) will also be presented.

ASP Research Achievement Award Presentation
Jon Clardy, Ph.D.

Jon Clardy was born in Washington DC and grew up in that city's Virginia suburbs. He went to Yale University where he received a B.S. in chemistry and to Harvard University, where he received his Ph.D. in organic chemistry. His formal education occurred during a remarkable period of public interest in science: beginning with the launching of Sputnik when he entered high school and ending with the escalation of the Viet Nam War when he was finishing graduate school. His real natural products education began when left Harvard to become an Assistant Professor in the Department of Chemistry at Iowa State University, and he's indebted to Bill Wildman, Gerry Klune, and Orville Chapman for educating him about alkaloids and insects. At Iowa State he began three longstanding collaborations on marine natural products with Bill Fenical, John Faulkner, and Paul Scheuer. In 1978 he moved to the Department of Chemistry at Cornell University. At Cornell he continued to work on natural products, especially structure elucidation. He also served as the Chair of his department for five years and later as an Associate Dean in the College of Arts and Sciences. He also taught large courses in beginning organic chemistry, general chemistry, and chemistry for non-science majors. At Cornell he also began to work on structural problems involving proteins. The first projects were all of natural products bound to proteins, most notably FK506 bound to FKBP12 and fumagillin bound to MetAP-2. At Cornell, his education in natural products continued, and his colleagues Jerry Meinwald and Tom Eisner introduced him to the field of chemical ecology. In late 2002 he moved to Harvard University where he took a position in the Department of Biological Chemistry and Molecular Pharmacology. The move opened up systematic screening efforts, large-scale DNA sequencing, and lots of biomedical collaborators. His new colleague, Chris Walsh, renewed his interest in biosynthesis. Today his lab is working on small signaling molecules from bacteria, fungi, and worms; DNA-based approaches to new natural products; and the introduction of natural products into an academic high-throughput screening environment.

A:4

A DNA-BASED APPROACH TO NATURAL PRODUCTS

Uncultured microorganisms are an attractive source of potentially new natural products. While they cannot be accessed by the traditional approaches used for cultured microbes, it is possible to isolate and express large fragments of microbial DNA extracted directly from environmental samples (eDNA). Heterologous expression of eDNA in a cultured host could provide access to many of the natural products encoded by this previously inaccessible genetic material. We, and others, have worked on a general approach described above. The history of this approach, and its application to antibiotics produced by *P. agglomerans* will be given. In more recent work, environmental DNA is used to prepare large cosmid libraries in *E. coli*, and antibacterial active eDNA clones are found using a double antibiotic selection screen that was developed to identify and recover antibacterial active clones directly from the original library selection plates. New natural product antibiotics and their biosynthetic enzymes that were discovered using this approach will be discussed. Long chain N-acyl amino acid antibiotics along with a thirteen open reading frame biosynthetic gene cluster (*feeA-M*) that codes for the production of long chain N-acyltyrosine as well as two additional families of compounds that are derived from N-acyl amino acids will be described. The biosynthetic pathway that can be inferred from this gene cluster will be discussed. The biosynthetic origin of palmitoyl putrescine, from eDNA isolated from bromeliad tank water in Costa Rica, the cAMP controlled production of N-acyltyrosines, and the likely origin of the cloned eDNA will also be presented.

GA Egon Stahl Award Presentation
Alexandra M. Deters, Ph.D.

1994 – 1996	Basic studies of biology; University of Kassel
1996 - 1998	Main studies; Friedrich-Alexander-University of Erlangen-Nuremberg Center: Pharmaceutical Biology
Jan 1999 - Nov 1999	Diploma Thesis: Influence of Oligo- and Polysaccharides on proliferation and differentiation of human Keratinocytes
Jan 2000 – Feb 2003	Graduation at the Institute for pharmaceutical biology; University of Erlangen-Nuremberg Thesis: Oligo- und Polysaccharides: Isolation, Characterization and Influence on cell physiology of human Keratinocytes

Berufspraxis

March 2003	Scientist at the department of dermatology, Friedrich-Alexander-University of Erlangen-Nuremberg

A:5

OLIGO- AND POLYSACCHARIDES: ISOLATION, CHARACTERIZATION AND INFLUENCE ON HUMAN KERATINOCYTES IN VITRO

Alexandra M. Deters; University of Erlangen-Nürnberg, Department of Dermatology, Glycopharmacy Research Group, Hartmannstr. 43, D-91052 Erlangen, Germany

In traditional medicine a variety of plants with high carbohydrate contents were used for treatment of dermatological diseases and wounds. Within the present study plant derived polysaccharides were characterized concerning monosaccharide composition and structure and were tested under *in vitro* conditions for regulating activities on cell physiology of human keratinocytes.

Treatment of primary keratinocytes (NHK) and HaCaT with the β-glucan from Reed mace seeds resulted in an improved proliferation and differentiation while Blister seaweed fucoidan only induced the cell maturation. Kiwi polysaccharides, identified as galactan and rhamnigalacturonans, increased the cellular proliferation and viability. Rhamnogalacturonans of Heart sease herb reduced the proliferation rates but improved the mitochondrial dehydrogenase activity, too. The watersoluble xylan extracted from Ispaghula seed husks promoted significantly the cell proliferation but the gel-forming xylan showed no influence on keratinocytes. None of the tested polysaccharides had necrotic is promoting activity was not observed.

These results show a structure dependent bioactivity of polysaccharides on keratinocyte cell physiology.

O:1 COMBINATORIAL BIOSYNTHESIS OF NEW AMINOCOUMARIN ANTIBIOTICS

Shu-Ming Li, Lutz Heide*. Pharmaceutical Institute, Tübingen University, 72076 Tübingen, Germany

O:2 IOMYCIN BIOSYNTHESIS IN *STREPTOMYCES VINACEUS* ATCC11861: FORMATION OF THE NONPROTEINOGENIC AMINO ACID 2*S*,3*R*-CAPREOMYCIDINE BY THE TANDEM ACTION OF VioC AND VioD

Xihou Yin and T. Mark Zabriskie*. Department of Pharmaceutical Sciences, Oregon State University, Corvallis, OR 97331.

O:3 BIOCHEMICAL ANALYSIS OF THE "PHENYLACETATE" PRIMING MECHANISM IN CYANOBACTERIAL NON-RIBOSOMAL PEPTIDE SYNTHESIS

Michelle C. Moffitt*, Laura L. Beer, Julie E. Becker, and Bradley S. Moore. University of Arizona, Department of Pharmacology and Toxicology, 1703 E. Mabel St, Tucson, AZ, 85721, USA.

O:4 PHOSPHOPANTETHEINYL TRANSFERASES: AN ESSENTIAL COMPONENT OF SECONDARY METABOLISM IN CYANOBACTERIA.

J.N. Copp and B.A. Neilan* Biotechnology and Biomolecular Sciences, University of New South Wales, Sydney, Australia

O:5 EQUISETIN BIOSYNTHESIS: A MODEL OF TETRAMIC ACID BIOSYNTHESIS

James W. Sims, John P. Fillmore, Douglas W. Warner, Eric W. Schmidt*. Department of Medicinal Chemistry, University of Utah, 20 South 2030 East, 295 BPRB, Salt Lake City, UT, 84094 USA

O:6 A NOVEL SHUNT PATHWAY PROVIDING PRECURSORS FOR ISOFATTY ACID AND SECONDARY METABOLITE BIOSYNTHESES IN MYXOBACTERIA

Taifo Mahmud,[1,3,]* Silke Wenzel,[2] Eva Wan,[1] Kwun Wah Wen,[3] Helge B. Bode,[2] Nikos Gaitatzis,[2,3] and Rolf Müller[2]. [1]College of Pharmacy, Oregon State University, Corvallis, OR 97331-3507, USA, [2]Saarland University, Pharmaceutical Biotechnology, P.O. Box 151150, 66041 Saarbrücken, Germany, and [3]Department of Chemistry, University of Washington, Seattle, WA 98195-1700, USA.

O:7 STRUCTURAL BASIS FOR REGIO-SPECIFICITY OF ISOFLAVANONE 4'-*O*-METHYLTRANSFERASE/6a-HYDROXYMAACKIAIN 3-*O*-METHYLTRANSFERASE

Chang-Jun Liu[1], Stéphane B. Richard[1], Jean-Luc. Ferrer[3], Bettina Deavours[2], Richard A. Dixon[2] and Joseph P. Noel* [1].[1]Structural Biology Laboratory, the Salk Institute for Biological Studies, 10010 North Torrey Pines Road, La Jolla, CA 92037, USA [2]Plant Biology Division, Samuel Roberts Noble Foundation, 2510 Sam Noble Parkway, Ardmore, OK 73401, USA [3]European Synchrotron Radiation Facility, F-38027 Grenoble cedex, France

O:8 ECHINACEA – WHAT CONSTITUENTS ARE THERAPEUTICALLY IMPORTANT?

A.Matthias[1], K.G. Penman[1], K.M. Bone[1,2] and R.P. Lehmann[1*].[1]MediHerb Research Laboratories, The University of Queensland, Brisbane, 4072 Australia; [2]School of Health, University of New England, Armidale, NSW 2351 Australia

O:9 ALKYLAMIDES FROM ECHINACEA PURPUREA POTENTLY MODULATE TNF-ALPHA GENE EXPRESSION: POSSIBLE ROLE OF CANNABINOID RECEPTOR CB2, NF-κB, P38, MAPK AND JNK PATHWAYS

Gertsch Juerg[1,3]*, Schoop Roland[2], Kuenzle Urs[1], Suter Andy[2]. [1]Swiss Federal Institute of Technology, IPW, CH-8057 Zürich, Switzerland; [3]NaproMed GmbH, Wagistr. 32, CH-8952 Schlieren, Switzerland ; [2]Bioforce AG, CH-9325 Roggwil, Switzerland

O:10 PHARMACOKINETICS AND BIOAVAILABILITY OF ALKAMIDES FROM THE ROOTS OF ECHINACEA ANGUSTIFOLIA IN HUMANS AFTER ORAL APPLICATION

Karin Woelkart[1], Christoph Koidl[2], Andrea Grisold[2], J. David Gangemi[3], Ronald B. Turner[4], Egon Marth[2], Rudolf Bauer[1]*. [1]Institute of Pharmaceutical Sciences, Department of Pharmacognosy, Karl-Franzens-University, A-8010 Graz, Austria, [2]Institute of Hygiene, University of Medicine, A-8010 Graz, Austria, [3]Institute for Nutraceutical Research, Clemson University, Clemson, SC 29634, [4]Department of Pediatrics, University of Virginia, School of Medicine, Charlottesville, VA 22908-0386

O:11 ELUSIVE IMMUNOSTIMULATORY COMPOUND DISCOVERED IN *ECHINACEA* AND OTHER IMMUNE ENHANCING BOTANICALS

Nirmal Pugh, Premalatha Balachandran, Hemant Lata, Ebru Bedir, Blamiro Silva, Toshiaki Makino, Erdal Bedir, Ikhlas Khan, Rita Moraes, David S. Pasco*. National Center for Natural Products Research, Research Institute of Pharmaceutical Sciences, School of Pharmacy, University of Mississippi, University, MS 38677 USA

O:12 BIOAVAILABILITY OF ELLAGIC ACID IN HUMAN PLASMA AFTER INGESTION OF ELLAGITANNINS FROM POMEGRANATES (*PUNICA GRANATUM* L.)

Navindra P. Seeram*, Rupo Lee, David Heber. Center for Human Nutrition, David Geffen School of Medicine, UCLA, CA 90095, USA

O:13 PHYLOGENETIC AND CHEMOTAXONOMIC ANALYSIS OF MEDICINAL ZINGIBERACEAE

Hongliang Jiang[1], Zhengzhi Xie[1], Hyunjo Koo[3], Barbara Timmermann[1,2], and David R. Gang[1,3]. [1]Arizona Center for Phytomedicine Research, [2]Department of Pharmacology and Toxicology, and [3]Department of Plant Sciences and Institute for Biomedical Science and Biotechnology, University of Arizona, Tucson, Arizona, 85721

O:14 ^{1}H NMR SPECTRA OF SIMPLE MOLECULES – HYPERCOMPLEX SIGNALS IN ANTIOXIDANT AND ESTROGENIC PHENOLICS FROM *HUMULUS LUPULUS* L.

L. R. Chadwick,[1] B. Jaki,[2] S. Chen,[1] H. H. S. Fong,[1] N. R. Farnsworth,[1] and G. F. Pauli[1,2,*].UIC/NIH Center for Botanical Dietary Supplements Research,[1] and Institute for Tuberculosis Research,[2] University of Illinois at Chicago, Chicago, IL 60612

O:15 NEW CNS ACTIVE LANOSTANE-TYPE TRITERPENOIDS FROM *FOMITOPSIS PINICOLA*

Dongho Lee,[1] Chen Li,[1] Robert J. McGivney,[1] Hernan A. Navarro[2], Keith Warner,[2] Namrata Patel,[2] E. Edward Mena,[3] Mansukh C. Wani,[1] and Nicholas H. Oberlies[1,*].
[1]Natural Products Laboratory and [2]Center for Organic and Medicinal Chemistry, Research Triangle Institute, P.O. Box 12194, Research Triangle Park, North Carolina 27709-2194; [3]LifePharms, Inc., 1084 Shennecossett Rd., Groton, Connecticut 06340.

O:16 HIGHLY CYTOTOXIC SCHWEINFURTHIN-TYPE COMPOUNDS FROM THE FRUIT OF A *MACARANGA* (EUPHORBIACEAE) SPECIES

Brent J. Yoder,[a] Jennifer K. Schilling,[a] Andrew Norris,[a] James S. Miller,[b] Rabodo Andriantsiferana,[c] Vincent E. Rasamison,[c] and David G.I. Kingston*,[a].
[a]Department of Chemistry, M/C 0212, Virginia Polytechnic Institute and State University, Blacksburg, VA 24061, [b]Missouri Botanical Garden, P.O. Box 299, St. Louis, MO 63166, and [c]Centre National d'Application et Recherches Pharmaceutiques, B.P. 702, Antananarivo 101, Madagascar

O:17 STRUCTURE AND STEREOCHEMISTRY OF THE ROCAGLATE DERIVATIVE, SILVESTROL, A CONSTITUENT OF *AGLAIA SILVESTRIS* WITH ANTINEOPLASTIC ACTIVITY

Bang Yeon Hwang,[1,6] Bao-Ning Su,[1,7] Soyoung Kim,[1] Heebyung Chai,[1] Qiuwen Mi,[1] Leonardus B. S. Kardono,[2] Johar J. Afriastini,[3] Soedarsono Riswan,[3] Bernard D. Santarsiero,[4] Andrew D. Mesecar,[4] Robert Wild,[5] Craig R. Fairchild,[5] Gregory D. Vite,[5] William C. Rose,[5] Norman R. Farnsworth,[1] Geoffrey A. Cordell,[1] John M. Pezzuto,[1,8] Steven M. Swanson,[1] and A. Douglas Kinghorn[1,7,*]. [1]Program for Collaborative Research in the Pharmaceutical Sciences, Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, University of Illinois at Chicago, Chicago, IL 60612. [2]Research and Development Chemistry, Indonesian Institute of Science, Serpong, 15310 Tangerang, Indonesia. [3]Herbarium Bogoriense, Research and Development Center for Biology, Indonesian Institute of Science, 16122 Bogor, Indonesia. [4]Center for Pharmaceutical Biotechnology and the Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, University of Illinois at Chicago, IL 60607. [5]Bristol-Myers Squibb, Pharmaceutical Research Institute, P.O. Box 4000, Princeton, New Jersey 08543. [6]Present address: College of Pharmacy, Chungbuk National University, Cheongju, 361-763, Korea. [7]Present address: College of Pharmacy, The Ohio State University, Columbus, OH 43210. [8]Present address: Heine Pharmacy Building, Purdue University, West Lafayette, IN 47907.

O:18 *IN VIVO* BIODISTRIBUTION OF GINKGOLIDE B, A CONSTITUENT OF *GINKGO BILOBA*, IN THE LIVING BODY VISUALIZED BY MICROPET

Makiko Suehiro*, Norman R. Simpson, Mark D. Underwood, John Castrillon, Koji Nakanishi, Ronald van Heertum. Departments of Chemistry, Radiology & Psychiatry, Columbia University, New York, NY 10027 & 10032, USA

O:19 STRUCTURE, BIOSYNTHESIS AND HISTOCHEMICAL ANALYSIS OF PHENYLPHENALENONE-RELATED COMPOUNDS FROM *XIPHIDIUM CAERULEUM* (HAEMODORACEAE)

Stefan Opitz,[1] Jörg-Peter Schnitzler,[2] Bettina Hause,[3] Dirk Hölscher,[1] Bernd Schneider[1*].

[1] Max-Planck-Institute for Chemical Ecology, Hans-Knöll-Str. 8, 07745 Jena, Germany

[2] Institute for Meteorol. and Climate Res., Kreuzeckbahnstr. 19, 82467 Garmisch-P., Germany 3 Institute of Plant Biochemistry, Weinberg 3, 06120 Halle (Saale), Germany

O:20 BIOACTIVE AGENTS FROM SONORAN DESERT PLANT-ASSOCIATED MICROORGANISMS.

A. A. Leslie Gunatilaka,* E. M. Kithsiri Wijeratne, Thomas J. Turbyville, Jian He, Bharat P. Bashyal, Jixun Zhang, Christopher J. Seliga, Libia A. Luevano, Manping X. Liu, Luke Whitesell, Linda Meade-Tollin, Elizabeth E. Pierson, Leland S. Pierson, Hans D. VanEtten, and Stanley Faeth. SW Center for Natural Products Research, Steele Memorial Children's Research Center, and Departments of Surgery, and Plant Sciences, University of Arizona, Tucson, and School of Life Sciences, Arizona State University, Tempe, Arizona, USA

O:21 BIOACTIVE METABOLITES FROM OKINAWAN MARINE-DERIVED FUNGI

Masashi Tsuda, Yuu Kasai, Mai Sasaki, Kazusei Komatsu, Jun'ichi Kobayashi*. Graduate School of Pharmaceutical Sciences, Hokkaido University, Sapporo 060-0812, Japan

O:1

COMBINATORIAL BIOSYNTHESIS OF NEW AMINOCOUMARIN ANTIBIOTICS

Shu-Ming Li, Lutz Heide*
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The aminocoumarin antibiotics novobiocin, clorobiocin and coumermycin A1 are potent inhibitors of DNA gyrase and are produced by different *Streptomyces* strains. Cloning, sequencing and functional analysis of their biosynthetic gene clusters by our group revealed that the structural differences and similarities of these antibiotics are perfectly reflected by the genetic organisation of the clusters.
The function of most of the biosynthetic genes for these antibiotics could be identified by gene inactivation experiments as well as by heterologous expression and biochemical investigations. Using the sequence and the functional information, we have produced more than 50 new aminocoumarin derivatives by combinatorial biosynthesis, by mutasynthesis experiments or by chemoenzymatic synthesis. The biological activities of the new aminocoumarins were evaluated against bacterial gyrase *in vitro* and against various bacterial strains.
Aminocoumarins thereby present a striking example of the potential of genetic engineering for the generation of new antiinfectives.

O:2

IOMYCIN BIOSYNTHESIS IN *STREPTOMYCES VINACEUS* ATCC11861: FORMATION OF THE NONPROTEINOGENIC AMINO ACID 2*S*,3*R*-CAPREOMYCIDINE BY THE TANDEM ACTION OF VioC AND VioD

Xihou Yin and T. Mark Zabriskie*
Department of Pharmaceutical Sciences, Oregon State University, Corvallis, OR 97331.

Viomycin (tuberactinomycin B) is a highly basic, nonribosomal peptide antibiotic characterized by the presence of several unique and nonproteinogenic amino acids. Viomycin is an effective agent in the treatment of multidrug resistant tuberculosis due to its ability to bind RNA and disturb bacterial protein biosynthesis. The gene cluster encoding viomycin biosynthesis was recently cloned and sequenced from *Streptomyces vinaceus* ATCC11861. To fully understand the biochemical mechanisms involved in viomycin precursor construction, we have functionally expressed in *Escherichia coli* many of the genes predicted to function in the biosynthesis of these nonproteinogenic amino acids. In this paper we will describe our investigation of the formation of the unusual arginine-derived capreomycidine residue that is common to all tuberactinomycin peptides. We demonstrate that VioC is a non-heme iron, α-ketoglutarate dependent oxygenase that catalyzes the formation of 3*S*-hydroxy-L-arginine. VioD then promotes the pyridoxal phosphate dependent conversion of the VioC product to 2*S*,3*R*- capreomycidine. The purification and detailed characterization of VioC and VioD, and evidence for the tandem action of these enzymes will be presented.

O:3

BIOCHEMICAL ANALYSIS OF THE "PHENYLACETATE" PRIMING MECHANISM IN CYANOBACTERIAL NON-RIBOSOMAL PEPTIDE SYNTHES

Michelle C. Moffitt*, Laura L. Beer, Julie E. Becker, and Bradley S. Moore
University of Arizona, Department of Pharmacology and Toxicology, 1703 E. Mabel St, Tucson, AZ, 85721, USA.

Cyanobacteria are prolific producers of structurally diverse hybrid peptide-polyketide natural products. The *mcy* gene cluster, encoding the biosynthetic pathway for the hepatotoxin microcystin, has been sequenced in a number of cyanobacteria, including *Microcystis aeruginosa*[1]. *mcyG* encodes a hybrid non-ribosomal peptide synthetase/polyketide synthase (NRPS/PKS) and is thought to be responsible for activation of the starter unit and polyketide extension. The structure of the cyclic heptapeptide microcystin suggests that phenylacetate is the likely biosynthetic starter unit, however, feeding studies verified that although L-phenylalanine is incorporated into microcystin, phenylacetate is not[2]. In this study, biochemical characterization of the McyG protein was performed to analyze the "phenylacetate" priming mechanism. The McyG NRPS protein was expressed heterologously in *E. coli* and characterized *in vitro*. Substrate specificity of the adenylation domain was determined by ATP-PPi exchange assays and acylation of the *holo* peptidyl carrier protein monitored by MALDI-TOF MS. The results of this study were used to propose a novel mechanism for the in trans conversion of phenylalanine to phenylacetate in the biosynthesis of microcystin and structurally related natural products.

[1]Tillet *et al*., 2000. Chem Biol., 7: 753 [2]Moore *et al*., 1991. J. Am Chem Soc., 113: 5083

O:4

PHOSPHOPANTETHEINYL TRANSFERASES: AN ESSENTIAL COMPONENT OF SECONDARY METABOLISM IN CYANOBACTERIA.

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Cyanobacteria produce numerous and structurally diverse secondary metabolites with activities that relate to interesting pharmaceutical applications or potentially fatal toxins. It is predicted that many cyanobacterial bioactive products are synthesised non-ribosomally. This mechanism of synthesis relies on an essential phosphopantetheinyl transferase (PPT) enzyme to convert the inactive (apo-protein) modules into their active (holo-protein) counterparts. Although several cyanobacterial gene clusters have now been characterised, little is known regarding the PPTs that are essential for their synthesis. We present the first detailed analysis of cyanobacterial PPTs. PCR primers were designed and utilized to screen and obtain novel PPTs from a range of cyanobacterial species. Phylogenetic analysis exposed a novel, function-based clade that encompassed a group of PPTs obtained from heterocyst-forming cyanobacteria. The partial PPT fragment amplified from *Nodularia spumigena* was selected, and the full gene sequence was obtained. The surrounding genome revealed other *N. spumigena* heterocyst genes. The investigation of PPTs presents a new approach to the discovery of secondary metabolite gene clusters in cyanobacteria.

O:5

EQUISETIN BIOSYNTHESIS: A MODEL OF TETRAMIC ACID BIOSYNTHESIS

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Tetramic acids form a diverse family of natural products, which are isolated from bacteria, fungi and marine sponges. Many of these compounds are important enzyme inhibitors or toxic to bacteria, fungi or other eukaryotes, making this class of interest for both pharmaceutical and agrochemical purposes. Despite the number of compounds known and their bioactivities, little is known about their biosynthesis. *Fusarium heterosporum* (ATCC 74349) produces the tetramic acid equisetin, a general toxin which has been reported to inhibit mitochondrial ATPase and HIV-1 integrase. Through studies in *F. heterosporum*, we have identified the equisetin biosynthetic gene cluster. The main carbon chain of equisetin is formed by a hybrid polyketide synthase / non-ribosomal peptide synthetase protein of ~3868 aa in size. To the best of our knowledge, this represents the first tetramic acid biosynthetic gene cluster, the first identified hybrid pathway in fungi, and the first iterative PKS-NRPS hybrid.

O:6

A NOVEL SHUNT PATHWAY PROVIDING PRECURSORS FOR ISOFATTY ACID AND SECONDARY METABOLITE BIOSYNTHESES IN MYXOBACTERIA

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A shunt pathway connecting the mevalonate and the pathway providing starter units for branched-chain fatty acid and secondary metabolite biosynthesis has been identified in the myxobacterium *Stigmatella aurantiaca*. This pathway is upregulated when the branched-chain α-keto acid dehydrogenase gene (*bkd*) is inactivated impairing the normal branched-chain amino acid degradation process. In this pathway isovaleryl-CoA (IV-CoA), the starter unit of the antifungal agent myxothiazol, is derived from 3,3-dimethylacrylyl-CoA (DMA-CoA). The latter compound is an isomerization product of 3-methyl-3-butenoyl-CoA (3MB-CoA), which is directly derived from 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) *via* a decarboxylation-dehydration reaction resembling the conversion of mevalonate 5-diphosphate to isopentenyl diphophate (IPP) in the mevalonate pathway. Incubation of cell free extracts of a *bkd* mutant with HMG-CoA gave product(s) with the molecular mass of 3MB-CoA. Incorporation experiments using *S. aurantiaca* Sg a15, the producing strain of the isoprenoid aurachin revealed that the shunt pathway also operates reversibly providing an alternative source for the monomers of isoprenoid biosynthesis in myxobacteria, utilizing L-leucine as precursor.

O:7

STRUCTURAL BASIS FOR REGIO-SPECIFICITY OF ISOFLAVANONE 4'-*O*-METHYLTRANSFERASE/6a-HYDROXYMAACKIAIN 3-*O*-METHYLTRANSFERASE

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Isoflavonoids represent an important and very distinctive subclass of phenylpropanoid metabolites that are distributed primarily in legumes. They are well documented as constitutive or pathogen-inducible antimicrobial compounds in plant-pathogen interactions; as inducers of rhizobial *nod* genes in the rhizobium-legume symbiosis; and interestingly from a human health perspective, as dietary phytoestrogens and antioxidants implicated in human disease prevention including chemoprevention of breast cancer, reducing the risk of cardiovascular heart disease and alleviating postmenopausal symptoms.

Isoflavanone 4'-O-methyltransferase is a key enzyme for the biosynthesis of the central intermediate 4'-methylated formononetine, which subsequently leads to the formation of a variety of isoflavonoid, coumestan and rotenoid natural products. Mining of *M. truncatula* EST databases led to the identification of one isoflavone O-methyltransferase ortholog. *In vitro* assays revealed that the enzyme exhibited unique regio-specificities for two distinct products. In one case, methylation was directed to the 4'-hydroxyl group on the B-ring of 2,7,4'-trihydroxyisoflavanone, a labile intermediate produced by isoflavone synthase at the entry point of the isoflavone biosynthetic pathway, yielding formononetine after hydrolysis. In the second case, methylation was directed to the 3-hydroxy moiety on the A-ring of 6a-hydroxymaackiain leading to the formation of the pterocarpan phytoalexin pisatin. To underlie the regio-specific methylation mechanism of isoflavone 4'/3-O-methyltransferase, the x-ray crystal structure of the enzyme was solved by the MAD approach. The high-resolution crystal structures of the enzyme complexed with the substrates, isoflavanone and 6a-hydroxymaackiain will be presented, and the catalytic mechanism will be discussed.

O:8

ECHINACEA – WHAT CONSTITUENTS ARE THERAPEUTICALLY IMPORTANT?

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Many studies have been done over the years to assess the effectiveness of Echinacea as an immunomodulator with often contradictory results. The major difficulty in comparing these studies has been that the phytochemical profile of the Echinacea used in each study has not been assessed with regards to the bioavailable and therapeutically available components. In a three-tiered study, we have assessed the potential bioavailability of the two main groups of compounds from an ethanolic extract of Echinacea (alkylamides and caffeic acid conjugates), compared it to their actual bioavailability in a Phase I clinical trial and assessed their in vitro immunomodulatory effect both alone and together. Alkylamides but not caffeic acid conjugates were found to be bioavailable using both in vitro (Caco-2) and in vivo (clinical trial) methods and although both alkylamides and caffeic acid conjugates have immunomodulatory activity in vitro, only alkylamides can be expected to have an effect in vivo as they are the only components that are bioavailable.

O:9

ALKYLAMIDES FROM ECHINACEA PURPUREA POTENTLY MODULATE TNF-ALPHA GENE EXPRESSION: POSSIBLE ROLE OF CANNABINOID RECEPTOR CB2, NF-κB, P38, MAPK AND JNK PATHWAYS

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In this study we analyzed the standardized Echinacea purpurea L. extract Echinaforce™ to elucidate its potential biological activity and molecular mechanism of action on human peripheral blood mononuclear cells. Transcriptome analyses showed a potent concentration-dependent and cell-type specific de novo synthesis of tumor necrosis factor alpha (TNF-α) mRNA in primary human CD14+ monocytes/macrophages (Mϕs). No detectable protein was found intracellularly nor in the supernatant. A study of the main constituents of the extract showed that the alkylamides dodeca-2 E,4 E,8 Z,10 E/ Z-tetraenoic acid isobutylamides (1/2) and trienoic and dienoic acid derivatives are in part responsible for this effect. The described effect is mediated cAMP, JNK, p38/MAPK functions and activation of NF-κB, CREB/ATF-2. Due to structural and functional similarities with endocannabinoids we tested the hypothesis that the alkylamides interact with the CB2 receptor on monocytes/Mϕs. Blocking with anti-CB2 polyclonal antibody and the specific antagonist SR144528 inhibited the TNF-alpha mRNA induction. The receptor interaction with the alkylamides are now being investigated by computer simulation. Overall, this study postulates a novel molecular mechanism of action of Echinacea.

O:10

PHARMACOKINETICS AND BIOAVAILABILITY OF ALKAMIDES FROM THE ROOTS OF ECHINACEA ANGUSTIFOLIA IN HUMANS AFTER ORAL APPLICATION

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Alkamides are suspected to contribute to the activity of *Echinacea* preparations. In total, 6 alkamides have been isolated from the roots of *Echinacea angustifolia* as major lipophilic constituents and investigated regarding their bioavailability and pharmacokinetics. They are mainly derived from undeca- and dodecanoic acid, and differ in the degree of unsaturation and the configuration of the double bonds. A sensitive and specific method has been developed for the identification and quantification of these alkamides in human serum using liquid chromatography electrospray ionisation ion-trap mass spectrometry (LC-ESI-IT-MS/MS). The method was applied to analyze plasma samples obtained after oral administration of a 60 % ethanolic extract from the roots of *Echinacea angustifolia* to 12 healthy volunteers. The absorption maximum of dodeca-2E,4E,8Z,10E/Z-tetraenoic acid isobutylamides, the main lipophilic constituents in the roots of *E. angustifolia* appeared already after 30 minutes, and shows that alkamides are rapidly absorbed after oral application.

O:11

ELUSIVE IMMUNOSTIMULATORY COMPOUND DISCOVERED IN *ECHINACEA* AND OTHER IMMUNE ENHANCING BOTANICALS

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We have discovered a previously unrecognized and novel immunostimulatory compound that is a major component within immune enhancing botanicals (5-20% of dry weight). The major reason that this agent has eluded detection is its solvent-specific requirement for extraction / solubility. This class of compounds is a potent activator of monocytes *in vitro* (EC_{50} for most active botanicals is 0.05 to 1.0 microgram/ml) and is also active when taken orally by mice. Interferon gamma production by spleen cells and IgA production by Peyer's patch cells *ex vivo* is substantially enhanced in mice fed this compound for 4 days. Activation of THP-1 human monocytes by this agent requires a member of the pattern recognition receptor family, toll-like receptor 2 (TLR) but not TLR4. We have observed that the wide differences in the potency of botanicals to activate monocytes is largely dependent on this compound and therefore feel that it is a major contributor to their overall immune enhancing properties. This variation is also observed among *in vitro* propagated clones of the three major *Echinacea* species and between the parts of cultivated plants. This agent is present in high levels within botanicals such as ginseng, goldenseal, green tea, alfalfa, astragalus, and licorice. Chemical properties will be presented.

O:12

BIOAVAILABILITY OF ELLAGIC ACID IN HUMAN PLASMA AFTER INGESTION OF ELLAGITANNINS FROM POMEGRANATES (*PUNICA GRANATUM* L.)

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Ellagic acid (EA) and hydrolyzable ellagitannins (ETs) are dietary polyphenols found in fruits (pomegranates, strawberries, raspberries etc.) and implicated with human health benefits. These polyphenols are also widely used as botanical ingredients in dietary supplements and in the food biopreservative and nutraceutical industries. Unfortunately, there are no reports of bioavailability studies of EA or ETs in humans. Therefore we conducted in vivo studies whereby pomegranate concentrate (180 mL) containing EA (25 mg) and ETs (318 mg, as punicalagin, the major fruit tannin) was consumed.
Plasma was obtained before and at 0.5, 1, 2, 3, 4 and 6h post administration. Using HPLC-UV methods, EA was detected and quantified in plasma at a maximum concentration (31.9 ng/mL) after 1h post ingestion but was rapidly eliminated by 4h. Since EA has reportedly strong affinity for proteins and poor absorption in small animals, the detection of free EA in human plasma could be due to its release from the hydrolysis of ETs, facilitated by physiological pH and/or gut microflora action. EA can be considered as a biomarker for future human bioavailability studies involving consumption of ETs from food sources.

O:13

PHYLOGENETIC AND CHEMOTAXONOMIC ANALYSIS OF MEDICINAL ZINGIBERACEAE

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Ginger (*Zingiber officinale*) and turmeric (*Curcuma longa*), family Zingiberaceae, have been widely used as spices and in the treatment of arthritis, liver ailments and other inflammatory diseases in traditional Chinese and Indian medicine for thousands of years. These plants have gained considerable attention as botanical dietary supplements in the USA for these properties as well. However, authentication of ginger and turmeric samples remains a difficult problem, due to the heterogeneity of plant material and also to adulteration in the commercial samples. To help address this problem, we are using phylogenetic and chemotaxonomic analyses to determine the relationships between species closely related to ginger and turmeric. For the phylogenetic studies, variable regions of four conserved genes (trnL, rps16, matK, and ITS) were chosen. ITS and matK were not suitable genes for this analysis, due to multiple copies in the genome (ITS) and high sequence variability (matK). Variable regions from trnL and rps16, however, were successfully sequenced from 112 individuals, belonging to 51 lines and 20 species of 8 genera related to and including *Curcuma* and *Zingiber*. A consensus phylogenetic tree based on the sequences for trnL and rps16 was constructed. Based on the phylogenetic relationships of the analyzed samples, we chose rhizomes from 7 genera, 20 species, and 45 lines to establish the chemotaxonomic relationships. LC/MS- and GC/MS-based metabolic profiling is being used in these chemotaxonomic studies, using rhizome samples (the medicinal part) as the tissue of choice.

O:14

^{1}H NMR SPECTRA OF SIMPLE MOLECULES – HYPERCOMPLEX SIGNALS IN ANTIOXIDANT AND ESTROGENIC PHENOLICS FROM *HUMULUS LUPULUS* L.

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The complexity of the ^{1}H NMR spectra of simple molecules is often surprising, but can open opportunities for rapid dereplication of congeneric analogues. The key to understanding the spectra is a full spin system (SS) analysis. ^{1}H NMR spectra of simple molecules can be precisely analyzed, allowing a complete understanding of complex signals. Once a reference point is established, this was a powerful tool in the structure analysis of chalcones and flavanones that are constituents of estrogenic fractions of *Humulus lupulus* L. A freely rotating prenyl (isopentene) unit is annotated as an $AM_2X_3Y_3$ spin system (SS). Prenyl units in environments where the 1'' methylene protons are anisochronous, ***e.g.***, 8-prenylated flavanones, are $AMNX_3Y_3$. Examples will be given where induced anisochronicity in 1'' methylene protons were used to distinguish isomeric prenylated flavanones. Complex signals that are usually reported as "multiplet" or "broad singlet" may be defined more precisely, ***e.g.*** the case of the olefinic H2'' prenyl proton, as *ddqq* or *tqq*. However, these annotations are invariably first order approximations of a higher-order SS and are meaningful only in the context of the entire, defined SS. The B-ring aromatic and α,β protons in 4-hydroxychalcones were shown to comprise a single spin system that can be annotated as A[B or M][MM'NN' or XX'YY']. Long-range *J*-values for these common natural product structural elements will be discussed.

O:15

NEW CNS ACTIVE LANOSTANE-TYPE TRITERPENOIDS FROM *FOMITOPSIS PINICOLA*

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Our research group has a long history in the isolation and structure elucidation of compounds from plants with cytotoxic anticancer activity. We have expanded our research recently by examining understudied organisms in a variety of CNS pharmacological assays. Accordingly, we screened a library of mushroom samples collected from the wild throughout the continental United States through two GABA A assays shown to identify positive allosteric modulators of this receptor. GABA A regulates chloride permeability and represents the major inhibitory neurotransmitter in the brain. Positive allosteric modulators of this receptor have shown utility as anxiolytics and potential antidepressants. This represents a novel approach to natural products drug discovery because, although the fruiting bodies of a few mushroom species (basidiomycetes) are known to have psychotropic properties, to the best of our knowledge, no one has investigated their potential to effect the CNS via a targeted screening approach. Using these assays we purified a series of eight new lanostane-type triterpenoids from *Fomitopsis pinicola*, and their structures were elucidated via a series of 2D NMR and mass spectral experiments. Three of these compounds were active in both assays and represent novel GABA A modulators. Using this approach in an expanded fashion, mushrooms may represent a new source for CNS drug discovery.

O:16

HIGHLY CYTOTOXIC SCHWEINFURTHIN-TYPE COMPOUNDS FROM THE FRUIT OF A *MACARANGA* (EUPHORBIACEAE) SPECIES

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In the past ten years, a number of prenylated and geranylated stibene compounds have been isolated from various species of *Macaranga* plants. Some of these products from *Macaranga schweinfurthii* have been dubbed the schweinfurthins, and their bioactivity has been examined in the NCI 60-cell line tumor panel. Here we report the isolation and identification of both new and known schweinfurthin-type compounds from a *Macaranga* species obtained in Madagascar through an ICBG program. Our compounds exhibit potent cytotoxicity in the A2780 ovarian cancer cell line assay, with growth inhibition data suggesting that these structures have comparable cytotoxicity to that of Taxol®. Additionally, a few less-active flavanones have also been isolated from similar fractions of the same extract.

O:17

STRUCTURE AND STEREOCHEMISTRY OF THE ROCAGLATE DERIVATIVE, SILVESTROL, A CONSTITUENT OF *AGLAIA SILVESTRIS* WITH ANTINEOPLASTIC ACTIVITY

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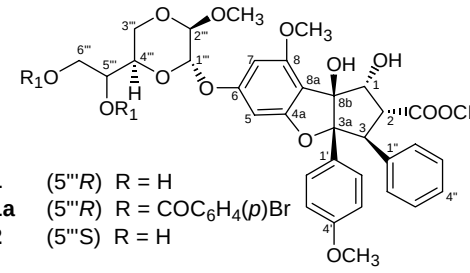
Two new rocaglate derivatives possessing an unusual dioxanyloxy unit, silvestrol (1) and episilvestrol (2), were isolated from both the fruits and twigs of *Aglaia silvestris* by bioassay-guided fractionation monitored with the human oral epidermoid carcinoma (KB) cell line. Additionally, two new baccharane-type triterpenoids, 17,24-epoxy-25-hydroxybaccharan-3-one and 17,24-epoxy-25-hydroxy-3-oxobaccharan-21-oic acid, as well as eleven known compounds, 1□,6□-dihydroxy-4(15)-eudesmene, ferulic acid, grasshopper ketone, apigenin, cabraleone, chrysoeriol, 6□,15□-epoxy-1□,4□-dihydroxyeudesmane, 4-hydroxy-3-methoxyacetophenone, 4-hydroxyphenethyl alcohol, ocotillone, and □-sitosterol glucoside, were also isolated and characterized. The structures of compounds 1 and 2 were elucidated by spectroscopic studies and chemical transformation. The absolute stereochemistry of silvestrol (1) was established by an X-ray diffraction study of its di-*p*-bromobenzoate derivative (1a). Silvestrol (1) and episilvestrol (2) exhibited potent in vitro cytotoxic activity comparable to that of the well-known anticancer drug paclitaxel (Taxol®). Silvestrol (1) was further evaluated in the hollow fiber test, and in the murine P-388 leukemia in vivo model. A mechanism-of-action study indicated that silvestrol induces apoptosis by involvement of the mitochondrial/apoptosome pathway. (Supported by NIH grant U19 CA52956).



1 (5‴*R*) R = H
1a (5‴*R*) R = $COC_6H_4(p)Br$
2 (5‴S) R = H

O:18

IN VIVO BIODISTRIBUTION OF GINKGOLIDE B, A CONSTITUENT OF _GINKGO BILOBA_, IN THE LIVING BODY VISUALIZED BY MICROPET

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Ginkgolides, active ingredients of *Ginkgo biloba* extracts, are believed to act as platelet activating factor (PAF) receptor antagonists, glucocorticoid synthesis regulators, inhibitors of production of inflammatory markers, and/or glycine-gated anion channel blockers. However, their *in vivo* behavior is not well understood.

We labeled gingkolide B (GB) with the positron emitter ^{18}F and visualized the dynamic distribution of the ^{18}F-labeled analog of GB in the living body of a small animal using the positron emission tomographic (PET) technique. The *in vivo* imaging studies, combined with *ex vivo* dissection experiments, have revealed that GB exists in 2 forms in the body; the original GB with its lactone rings closed and a second form with one of the rings open. With time after i.v. injection of the radiolabeled GB, the latter form becomes predominant in plasma, and ^{18}F-GB accumulates into the gastric antrum, the pylorus and the duodenum. On the other hand, the original form of GB is concentrated in the liver and excreted quickly through the bile duct. These observations suggest that the ring-opened form of GB may play an important role when GB is administered as a medication.

O:19

STRUCTURE, BIOSYNTHESIS AND HISTOCHEMICAL ANALYSIS OF PHENYLPHENALENONE-RELATED COMPOUNDS FROM *XIPHIDIUM CAERULEUM* (HAEMODORACEAE)

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Phenylphenalenones are a group of plant-defense secondary metabolites and chemotaxonomic markers of some monocotyledonous plant families. A series of these phenolic compounds were isolated from *Xiphidium caeruleum*, a neotropical plant of the Haemodoraceae. The structures, including diverse oxa-derivatives, an alkaloid and a novel type of allophanyl glucosides, were elucidated by NMR and other spectroscopic methods.
Biosynthetic studies using ^{13}C labeled precursors and NMR analysis demonstrated incorporation of two phenylpropane units into typical phenylphenalenones and oxa-derivatives such as phenylbenzoisochromenones. A biosynthetic mechanism via diarylheptanoids and dioxygenase-catalysed oxidation will be discussed.
Based on intense autofluorescence properties of individual allophanyl glucosides and non-gluco-sidic compounds, their specific cellular localization in root and leaf tissue was studied by confo-cal laser scanning microscopy and microspectral photometry. Accumulation in stomata guard cells and distinct cells of the root (apical meristem, cortex, calyptra and epidermis) was revealed.

O:20

BIOACTIVE AGENTS FROM SONORAN DESERT PLANT-ASSOCIATED MICROORGANISMS.

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Microorganisms represent a valuable resource in the search for bioactive secondary metabolites. The demonstration that plant-associated microbial diversity is strongly influenced by floristic diversity and environmental factors suggests an enhanced potential of isolating unique metabolites from rhizosphere and endophytic microorganisms associated with hitherto unexploited floristically diverse plant communities such as those in the Sonoran desert of the U.S. Southwest. As the first step in our search for bioactive agents from Sonoran desert plant-associated microorganisms, we have constructed a library consisting of over 20,000 bacteria and 3,000 fungi. Extracts derived from over 400 bacteria and 1,500 fungi have been screened for bioactive agents using cancer cell line cytotoxicity, heat shock induction and antiangiogenesis assays. Organisms producing compounds active in these assays have been identified, cultured on large-scale, extracted, and the resulting extracts subjected to bioactivity-guided fractionation to obtain a variety of metabolites with diverse structures and useful biological activities.

O:21

BIOACTIVE METABOLITES FROM OKINAWAN MARINE-DERIVED FUNGI

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Marine microalgae such as dinoflagellates and cyanobacteria have proven to be a rich source of compounds with intriguing structures and interesting bioactivities, while marine-derived fungi have also been an important source of them such as an anthraquinone-derived pentacyclic metabolite enhancing potency of known antifungal agents, a linear dodecapeptide inhibiting cyclin-dependent kinase 4, phenalenone derivatives inhibiting DNA polymerases, ten-membered macrolides with antibacterial activity, and a pentacyclic oxindole alkaloid inhibiting Ca-ATPase, which we have recently isolated.

More recently, a unique pentacyclic oxindole alkaloid has been isolated from *Penicillium citrinum* separated from a marine red alga, while a long chain polyketide is obtained from a fungus *Gliocladium* sp. derived from a seaweed. Furthermore, a pyrrolidine alkaloid has been isolated from another *Penicillium* sp. separated from gastrointestine of a marine fish.

In this symposium the structures and activities of these interesting fungal metabolites will be described.

O:22 SELECTIVE INHIBITION OF HUMAN 15- VERSUS 12-LIPOXYGENASE BY CHRODANGOLS, CHROMANOL FUNCTIONALIZED MERODITERPENES FROM THE MARINE SPONGE *PSAMMOCINIA*.

Robert H. Cichewicz,[†] Victor A. Kenyon,[†] Stephanie Whitman,[†] Nancy M. Morales,[†] Vladimir N. Uversky,[†,‡] Joanne F. Arguello,[†] Maksymilian Chruszcz,[§] Marcin Cymborowski,[§] Wladek Minor,[§] Theodore R. Holman,*[,†] Phillip Crews*[,†,⊥].Department of Chemistry and Biochemistry[†] and Institute for Marine Sciences,[⊥] University of California, Santa Cruz, CA 95064, U.S.A., Institute for Biological Instrumentation, Russian Academy of Sciences, Pushchino, Moscow Region 142290, Russia,[‡] and Department of Molecular Physiology and Biological Physics, University of Virginia, Charlottesville, VA, 22908, U.S.A. [§]

O:23 THE WEWAKPEPTINS, A NEW SERIES OF CYCLIC DEPSIPEPTIDES FROM A PAPUA NEW GUINEA COLLECTION OF THE MARINE CYANOBACTERIUM *LYNGBYA SEMIPLENA*

Bingnan Han,[†] Doug Goeger,[†] Maier, Claudia S.,[‡] William H. Gerwick*[,†]. [†]College of Pharmacy, [‡]Department of Chemistry, Oregon State University, Corvallis,Oregon 97331

O:24 CHEMISTRY AND BIOACTIVITY OF PALMEROLIDE A, A CYTOTOXIC MACROLIDE FROM ANTARCTIC TUNICATE *SYNOICUM ADAREANUM*

Thushara K. Diyabalanage,* Charles D. Amsler, James B. McClintock and Bill J Baker** *Department of Chemistry, University of South Florida, 4202 East Fowler Avenue SCA400, Tampa FL 33620 and Department of Biological Sciences, University of Alabama at Birmingham, Birmingham, AL 33294.

O:25 STRUCTURE-ACTIVITY RELATIONSHIP STUDIES OF THE SELECTIVE
$\tilde{\kappa}$–OPIOID AGONIST, SALVINORIN A

Jeremy Stewart and Jordan K. Zjawiony*. Department of Pharmacognosy and National Center for Natural Product Research, Research Institute of Pharmaceutical Sciences, School of Pharmacy, The University of Mississippi, University, MS 38677, USA.

O:26 STRUCTURE-ACTIVITY RELATIONSHIP STUDIES OF THE MICROTUBULE STABILIZING AGENT (+)-DISCODERMOLIDE

Sarath P. Gunasekera,[1]* Stuart J. Mickel,[2] Robert Daefler,[2] Daniel Niederer,[2] Amy E. Wright,[1] Patricia Linley,[1] and Tara Pitts[1]. [1]Division of Biomedical Marine Research, Harbor Branch Oceanographic Institution, 5600 U.S. 1 North, Fort Pierce, Florida 34946, and [2]Chemical and Analytical Development, Novartis Pharma, AG, Postfach, 4052, Basel, Switzerland.

O:27 TOTAL SYNTHESIS OF MILNAMIDE A AND ITS AUTOXIDATION TO MILNAMIDE D

Chaomin Liu, Makoto N. Masuno, John B. MacMillan, Tadeusz F. Molinski,*.
Department of Chemistry UC Davis, CA 95616

O:28 THUGGACINS – NOVEL HIGHLY ACTIVE ANTIBIOTICS AGAINST MYCOBACTERIA FROM *SORANGIUM CELLULOSUM* AND *CHONDROMYCES CROCATUS*

Rolf Jansen*, Herbert Irschik, Hans Reichenbach, Peter Washausen, Gerhard Höfle.
GBF, German Research Centre for Biotechnology, Mascheroder Weg 1, 38124 Braunschweig, Germany

O:29 MOLECULAR-TARGETED ANTITUMOR AGENTS: LAURENDITERPENOL, A NEW DITERPENE FROM THE TROPICAL MARINE RED ALGA *LAURENCIA INTRICATA* POTENTLY INHIBITS HYPOXIA-ACTIVATED HIF-1

Kaleem A. Mohammed, Chowdhury Faiz Hossain, Yu-Dong Zhou, and Dale G. Nagle*.
Department of Pharmacognosy, National Center for Natural Products Research, RIPS, School of Pharmacy, University of Mississippi, University, MS, 38677-1848.

ASP Student Research Award Presentation

O:30 CHEMICAL INVESTIGATION OF THE HYBRID SOFT CORAL *SINULARIA MAXIMA* X *S. POLYDACTYLA*

Haidy N. Kamel[a], Frank R. Fronczek[b], Nikolaus H. Fischer[a], Daneel Ferreira[a], Marc Slattery[a,*].
[a]Department of Pharmacognosy and National Center for Natural Products Research, RIPS, School of Pharmacy,University of Mississippi, University, MS 38677, USA
[b]Department of Chemistry, Louisiana State University, Baton Rouge, LA 70803-1804, USA

ASP/APhA Kilmer Prize Presentation

O:31 ACETYLCHOLINESTERASE INHIBITORS FROM NATURAL PRODUCTS DISCOVERED BY VIRTUAL SCREENING

Judith M. Rollinger,* Ariane Hornick, Barbara Bergner, Thierry Langer, Helmut Prast, Hermann Stuppner Institute of Pharmacy, University of Innsbruck, Innrain 52, Josef-Moeller Haus, 6020 Innsbruck, Austria

O:32 V-ATPASE INHIBITORS AS ANTICANCER DRUG CANDIDATES

Katherine Hansen, Chand Khanna, Michael Alley, Angie Dull[#], Sherman Stinson, Tawnya McKee, John Porco[^], Xiang Wang[^], Ruichao Shen[^], James Panek[^], Qibin Su[^], and John Beutler*. National Cancer Institute, Frederick, MD 21702, and Bethesda, MD USA [#]SAIC, Inc. [^]Dept. of Chemistry, Boston University, Boston, MA USA

O:33 HIGH-THROUGHPUT NATURAL PRODUCTS CHEMISTRY METHODS AND THE APPLICATION OF THE ADVANCED CAPNMR^{TM} PROBE IN RAPID STRUCTURE ELUCIDATION OF MASS-LIMITED SAMPLES

Jin-Feng Hu,* Mark O'Neil-Johnson, Matt G. Goering, Eliane Garo and Gary R. Eldridge .Sequoia Sciences, Inc., 11199 Sorrento Valley Road, Suite H, San Diego, CA 92121, USA

O:34 AUTOMATED DEREPLICATION - SUPPORT FOR THE HIGH THROUGHPUT SCREENING ANALYST

Rolf Grigat[1]*, Antony N. Davies[1,2]. 1. Waters Informatics, Europaallee 27-29, 50226 Frechen, Germany 2. School of Applied Sciences, University of Glamorgan, CF37 1DL, Wales, UK

O:35 ROBUST SCREENING OF NATURAL PRODUCT EXTRACTS USING MULTI-ARRAY^{TM} TECHNOLOGY

Pankaj Oberoi*.Meso Scale Discovery, 9238 Gaither Road, Gaithersburg, MD 20877, USA

O:36 SUPPRESSION AND OVEREXPRESSION OF DIFFERENT GENES FROM BENZYLISOQUINOLINE BIOSYNTHESIS ALTERS ALKALOID PROFILES IN TRANSGENIC OPIUM POPPY PLANTS

Susanne Frick[1]*, R. Kramell[1], J. Schmidt[1], P.J. Larkin[2] and T.M. Kutchan[1].
[1] Leibniz Institute of Plant Biochemistry, Weinberg 3, D-06120 Halle (Saale), Germany
[2] CSIRO Division of Plant Industry, GPO Box 1600, Canberra ACT 2601, Australia

O:37 A FUNCTIONAL GENOMICS APPROACH TOWARD THE UNDERSTANDING OF PLANT SECONDARY METABOLISM: I. TRANSCRIPTOMICS AND HIGH-THROUGHPUT FUNCTIONAL ANALYSIS OF GENES IN PLANT CELLS

Alain Goossens*[1], Valerie De Sutter[1], Freya Lammertyn[1], Suvi T Häkkinen[2], Heiko Rischer[2], Kirsi-Marja Oksman-Caldentey[2], Dirk Inzé[1]. [1] Department of Plant Systems Biology, VIB-Ghent University, Technologiepark 927, B-9052 Gent, Belgium; [2] VTT Biotechnology, P.O.Box 1500 (Tietotie 2), FIN-02044 VTT, Finland

O:38 GENOMICS AS A TOOL FOR THE DISCOVERY, ISOLATION AND STRUCTURE ELUCIDATION OF NOVEL NATURAL PRODUCTS: ECO-02301 AS AN EXAMPLE.

James McAlpine*, Emmanuel Zazopoulos, Brian Bachmann, Mahmood Piraee, Steve Tremblay, Chris Farnet, Ecopia BioSciences Inc. 7290 Frederick Banting, St-Laurent, Québec, H4S 2A1 Canada

O:39 METABOLOMICS: BACK TO THE FUTURE?

Y.H. Choi, H.K. Kim and R. Verpoorte* .Department of Pharmacognosy, Section Metabolomics, IBL, PO Box 9502, 2300RA Leiden, The Netherlands, Email: VERPOORT@LACDR.LeidenUniv.NL

O:40 ON STRATEGIES OF SELECTION

A. Backlund, S. Larsson and L. Bohlin*. Division of Pharmacognosy, Department of Medicinal Chemistry, Uppsala University, BMC Box 574, S-751 23 Uppsla, Sweden.

O:41 AMINO ACID CHEMOTAXONOMY OF THE GENUS *SOPHORA* (LEGUMINOSEAE)

Mohamad Izaddoost; Department of Pharmacognosy, College of Pharmacy, Tehran University of Med. Sci. Tehran, Iran, IRAN.

O:42 METHODOLOGY IN THE QUALITY CONTROL OF FINGERPRINT CHROMATOGRAMS FOR TRANDICINAL CHINESE MEDICINES

Yuzhu Hu *, Qinghua Meng , Yongsuo Liu, Jiang Shumin. Department of Analytical Chemistry, China Pharmaceutical University, Nanjing 210009, China

O:43 A DISTINCTIVE ISOFLAVONOID CHEMISTRY FOR THE TROPICAL LEGUME, *ATELEIA HERBERT-SMITHII*: TAXONOMIC AND BIOSYNTHETIC IMPLICATIONS

Nigel C. Veitch*, Polly S.E. Sutton, Helen E. Ireland, Geoffrey C. Kite. Royal Botanic Gardens, Kew, Richmond, Surrey, TW9 3AB, U.K.

O:44 ANTIPLASMODIAL ACTIVITY OF ISONEOCRYPTOLEPINE, A NEW SYNTHETIC INDOLOQUINOLINE ALKALOID

Sabine Van Miert[1], Steven Hostyn[2], Bert Maes[2], Roger Dommisse,[2] Guy Lemière[2], Arnold Vlietinck, Luc Pieters[1,*] Departments of [1]Pharmaceutical Sciences and [2]Chemistry, University of Antwerp; [1]Universiteitsplein 1, B-2610, Antwerp, and [2]Groenenborgerlaan 171, B-2020 Antwerp, Belgium

O:45 ANTIPLASMODIAL ACTIVITY OF CHALCONE DERIVATIVES OF HOP (*HUMULUS LUPULUS*) AND THEIR INTERACTION WITH HEME

Sonja Frölich[1], Carola Schubert[1], Ulrich Bienzle[2], Kristina Jenett-Siems[1,*].
[1] Institut für Pharmazie (Pharmazeutische Biologie), Freie Universität Berlin, Königin-Luise-Str. 2-4, D-14195 Berlin, Germany [2] Institut für Tropenmedizin, Medizinische Fakultät der Charité, Humboldt-Universität, D-14050 Berlin, Germany

O:46 RESVERATROL INHIBITS ANGIOTENSIN II-INDUCED VASCULAR SMOOTH MUSCLE CELL HYPERTROPHY BY INTERFERING WITH THE GAB1-PI3K SIGNALING

Thomas U. Roos, Ursula G.B. Haider, Angelika M. Vollmar, and Verena M. Dirsch*.
Department of Pharmacy, University of Munich, Butenandtstr. 5-13, 81377 Munich, Germany

O:47 PODOCARPATES AS LIVER X RECEPTOR AGONISTS, STRUCTURE ACTIVITY RELATIONSHIP

Sheo B. Singh*, Weiguo Liu, Ali Shafiee, Tom Chen, Xiaohua Li, Steve Chen, Aileen Bouffard, Michael Szymonifka, Michael Robbins, Nancy Hayes, Jianhua Wang, Neelam Sharma, Carl Sparrow, Karen MacNaul, John Menke. Merck Research Laboratories, P. O. Box 2000, Rahway, New Jersey, USA

O:48 PRECLINICAL STUDIES OF THE MANZAMINE ALKALOIDS AS TREATMENTS FOR MALARIA.

Mark T. Hamann and Russell Hill. Departments of Pharmacognosy, Pharmacology, Chemistry, Biochemistry & National Center for Natural Product Research, The University of Mississippi, Center for Marine Biotechnology, The University of Maryland Biotechnology Institute.

O:49 PESTICIDE RESIDUES OF HERBAL MEDICINAL DRUGS IN THE PHEUR AND USP - ACTUAL SITUATION AND PROPOSALS FOR AN AMENDMENT OF THE MAXIMUM RESIDUE LEVELS

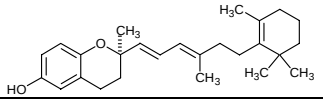
L. Kabelitz*, H. Sievers. PhytoLab GmbH & Co. KG, Vestenbergsgreuth, Germany

O:22

SELECTIVE INHIBITION OF HUMAN 15- VERSUS 12-LIPOXYGENASE BY CHRODANGOLS, CHROMANOL FUNCTIONALIZED MERODITERPENES FROM THE MARINE SPONGE *PSAMMOCINIA*.

Robert H. Cichewicz,[†] Victor A. Kenyon,[†] Stephanie Whitman,[†] Nancy M. Morales,[†] Vladimir N. Uversky,[†,‡] Joanne F. Arguello,[†] Maksymilian Chruszcz,[§] Marcin Cymborowski,[§] Wladek Minor,[§] Theodore R. Holman,*[,†] Phillip Crews*[,†,⊥] Department of Chemistry and Biochemistry[†] and Institute for Marine Sciences,[⊥] University of California, Santa Cruz, CA 95064, U.S.A., Institute for Biological Instrumentation, Russian Academy of Sciences, Pushchino, Moscow Region 142290, Russia,[‡] and Department of Molecular Physiology and Biological Physics, University of Virginia, Charlottesville, VA, 22908, U.S.A. [§]

Atherosclerosis is a progressive disease that results in vascular occlusion and subsequent infarction of myocardial tissues. In vitro and in vivo studies indicate that the non-heme iron-containing oxygenase, human 15-lipoxygenase (hLO-15), plays a critical role in the process of atherogenesis. It is proposed that selective inhibition of hLO-15 could serve as a promising therapeutic modality for the prevention of atherosclerotic lesion formation. We observed that crude extracts of the marine sponge *Psammocinia* sp. exhibited potent hLO-15 inhibitory activity. Bioassay-guided fractionation led to the isolation of chrodangols A-E, chromanol meroditerpenoids, that are potent and selective inhibitors of 15-hLO. An additional 22 structurally related compounds including meroterpenes from *Psammocinia* and *Strongylophora* species, tocopherols, and synthetic chromanes, were further evaluated as 15-hLO antagonists. Our results demonstrate that the 6-hydroxychromanol is essential for selective 15-hLO inhibition. These data further define the structure activity requirements for the selective inhibition of 15-hLO as a therapeutic target in the treatment and prevention of atherosclerotic coronary artery disease.



Chrodangol A

IC_{50} (μM) hLO-15 = 0.6±0.1

O:23

THE WEWAKPEPTINS, A NEW SERIES OF CYCLIC DEPSIPEPTIDES FROM A PAPUA NEW GUINEA COLLECTION OF THE MARINE CYANOBACTERIUM *LYNGBYA SEMIPLENA*

Bingnan Han,[†] Doug Goeger,[†] Maier, Claudia S.,[‡] William H. Gerwick*[,†]
[†]College of Pharmacy, [‡]Department of Chemistry, Oregon State University, Corvallis,Oregon 97331

Five new depsipeptides have been isolated from the marine cyanobacterium *Lyngbya semiplena* collected from Papua New Guinea. The partial structures of wewakpeptin A-E were elucidated through extensive spectroscopic techniques, including HRFABMS, 1D ^{1}H, ^{13}C, 2D COSY, HSQC, HSQC-TOCSY, and HMBC NMR spectra. The sequence of the amino acids was determined and confirmed through a combination of multifaceted approaches including standard 2D HMBC, ESPI MS/MS, ROESY, and a modified 1D HMBC experiment. The absolute stereochemistry of most of the amino acids and carboxylic acid units were determined by chiral HPLC and chial GC-MS methods. Wewakpeptin A and B are the most active natural products among these five depsipeptides, with IC_{50} values of 0.5 μg/mL to the NCI H-460 lung tumor cell line, and 0.2 μg/mL to the mouse Neuro-2a neurablastoma cell line.

O:24

CHEMISTRY AND BIOACTIVITY OF PALMEROLIDE A, A CYTOTOXIC MACROLIDE FROM ANTARCTIC TUNICATE *SYNOICUM ADAREANUM*

Thushara K. Diyabalanage,* Charles D. Amsler, James B. McClintock and Bill J Baker**
*Department of Chemistry, University of South Florida, 4202 East Fowler Avenue SCA400, Tampa FL 33620 and Department of Biological Sciences, University of Alabama at Birmingham, Birmingham, AL 33294.

The colonial tunicate *Synoicum adareanum* found commonly on the benthos around Palmer Station on Anvers Island Antarctica elaborates a series of polyketides, the palmerolides, bearing an unusual 20-membered macrolide. These macrolides display functionality more commonly found in sponges or cyanobacteria. Palmerolide A, the major natural product, showed potent *in vitro* cytotoxicity and three log-orders of selectivity against melanoma in the NCI human tumor cell line panel. In this paper we wish to report the isolation, structure elucidation and bioactivity of palmerolide A.

O:25

STRUCTURE-ACTIVITY RELATIONSHIP STUDIES OF THE SELECTIVE κ–OPIOID AGONIST, SALVINORIN A

Jeremy Stewart and Jordan K. Zjawiony*
Department of Pharmacognosy and National Center for Natural Product Research, Research Institute of Pharmaceutical Sciences, School of Pharmacy, The University of Mississippi, University, MS 38677, USA.

Selective κ-opioid receptor ligands are a pharmaceutical curiosity due to their ability to block pain without the euphoric effects of μ– and δ– stimulation. Salvinorin A, a non-nitrogenous neoclerodane diterpene, has demonstrated a level of selectivity and potency for the κ-opioid receptor that approaches the endogenous ligand, dynorphin. We will report on several semisynthetic salvinorin derivatives and the pharmacological consequences of these modifications.

O:26

STRUCTURE-ACTIVITY RELATIONSHIP STUDIES OF THE MICROTUBULE STABILIZING AGENT (+)-DISCODERMOLIDE

Sarath P. Gunasekera,[1]* Stuart J. Mickel,[2] Robert Daefler,[2] Daniel Niederer,[2] Amy E. Wright,[1] Patricia Linley,[1] and Tara Pitts[1]

[1]Division of Biomedical Marine Research, Harbor Branch Oceanographic Institution, 5600 U.S. 1 North, Fort Pierce, Florida 34946, and [2]Chemical and Analytical Development, Novartis Pharma, AG, Postfach, 4052, Basel, Switzerland.

In 1990, we reported the isolation, structure determination and preliminary biological activities of the marine sponge derived anticancer compound (+)-discodermolide. (+)-Discodermolide has shown strong microtubule stabilizing properties and excellent activity against multiple drug resistant tumors. Currently, synthetic (+)-discodermolide is undergoing Phase I clinical trials for solid tumor malignancies at the Cancer Therapy and Research Center in San Antonio, Texas.

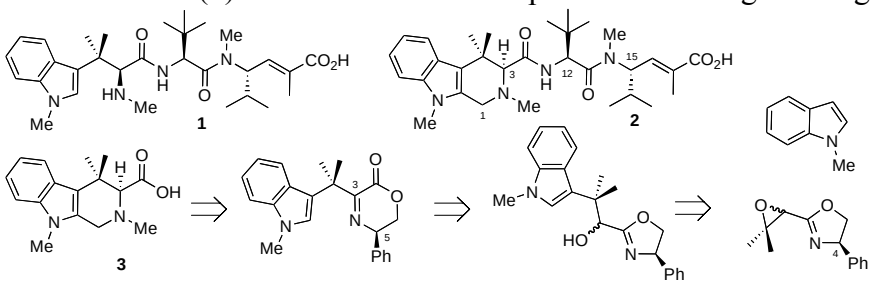
A series of new synthetic (+)-discodermolide analogues that are minor side products generated during the final stages in the synthesis of (+)-discodermolide have been purified and evaluated for in vitro cytotoxicity against A549, P388, MFC-7, NCI/ADR, PANC-1 and VERO cell lines, and their effects on microtubule architecture on A549 cells. The separation of these analogues and their structure-activity studies towards the identification of the pharmacophore of (+)-discodermolide will be presented.

O:27

TOTAL SYNTHESIS OF MILNAMIDE A AND ITS AUTOXIDATION TO MILNAMIDE D

Chaomin Liu, Makoto N. Masuno, John B. MacMillan, Tadeusz F. Molinski,* Department of Chemistry UC Davis, CA 95616

Hemiasterlin (1)[1] and the milnamide A (2)[2] are representive of a family of tubulin binding peptides, derived from the marine sponges *Hemiasterella*, *Cymbastella* and *Auletta constricta*, among others. We present here the first total synthesis and stereochemical elucidation of milnamide A (2). A novel oxidative oxazoline-dihydrooxazinone rearrangement, discovered in our labs in 1996,[3] provided a highly efficient route to the tetra-methylated β-carboline amino acid (3) with exceptional stereoselectivity. We also present evidence for the rapid autoxidation of milnamide A (2) to milnamide D and a possible non-biogenic origin of the latter peptide.



(1) Coleman, J. E.; de Silva, E. D.; Kong, F.; Anderson, R. J; Allen, T. M. *Tetrahedron* 1995, *51*, 10653

(2) Crews, P.; Farias, J. J.; Emrich, R.; Keifer, P. A. *J. Org. Chem.* 1994, *59*, 2932.

(3) Shafer, C. M.; Molinski, T. F. *J. Org. Chem.* 1996, *61*, 2044.

O:28

THUGGACINS – NOVEL HIGHLY ACTIVE ANTIBIOTICS AGAINST MYCOBACTERIA FROM *SORANGIUM CELLULOSUM* AND *CHONDROMYCES CROCATUS*

Rolf Jansen*, Herbert Irschik, Brigitte Kunze, Hans Reichenbach, Gerhard Höfle
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In our ongoing screening of Myxobacteria the genera *Sorangium* and *Chondromyces* consistently proved to be very rich sources of most diverse secondary metabolites and biologically active compounds. Currently the epothilones are their most prominent representatives. The group of thuggacin antibiotics presents a rare example of a structural type, which is produced by strains of two different Myxobacteria genera.
The thuggacins are complex polyketide-derived antibiotics containing a thiazole in their macro- lactone ring, which is provide by two side chains. The products of both genera differ in the length of the aliphatic side chain. Remarkably the size of the lactone ring is not fixed. Under aqueous or protic conditions the ring is enlarged by lactone group migration to the hydroxy groups of the second side chain. However, the antibiotic activity is retained in the resulting equilibrium mixture.
Thuggacin A proved to be highly active against reference and hospital strains of *Mycobacterium tuberculosis*.
Isolation, structure elucidation, and biological data of thuggacins will be presented.

O:29

MOLECULAR-TARGETED ANTITUMOR AGENTS: LAURENDITERPENOL, A NEW DITERPENE FROM THE TROPICAL MARINE RED ALGA *LAURENCIA INTRICATA* POTENTLY INHIBITS HYPOXIA-ACTIVATED HIF-1

Kaleem A. Mohammed, Chowdhury Faiz Hossain, Yu-Dong Zhou, and Dale G. Nagle*
Department of Pharmacognosy, National Center for Natural Products Research, RIPS, School of Pharmacy, University of Mississippi, University, MS, 38677-1848.

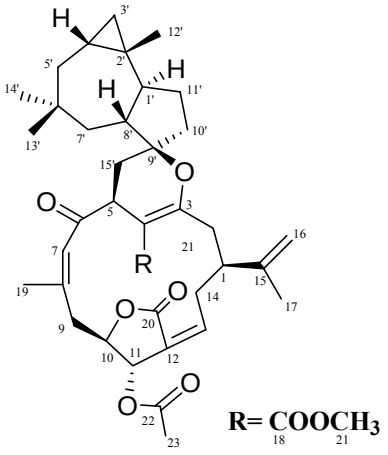
The transcription factor hypoxia-inducible factor- 1 (HIF-1) is a key regulator of tumor cell adaptation and survival under hypoxic conditions. Selective HIF-1 inhibitors represent an important new class of potential molecular-targeted antitumor therapeutic agents. Extracts of plants and marine organisms were evaluated using a cell-based reporter assay for inhibitors of HIF-1 activation in T47D human breast tumor cells. Bioassay-guided fractionation of the lipid extract of red alga *Laurencia intricata* resulted in the isolation of structurally novel diterpene laurenditerpenol (1). The structure of 1 was determined spectroscopically. The relative configurations of both ring systems were assigned based on NOESY correlations. The absolute configurations of C-1, C-6, C-7 were determined by a combination of modified Mosher ester method and NOESY correlations. Compound 1 was also shown to inhibit the hypoxic induction of the angiogenic factor VEGF. Further study revealed that 1 selectively blocks the induction of HIF-1α protein, the oxygen regulated HIF-1 subunit that determines HIF-1 activity.

O:30

CHEMICAL INVESTIGATION OF THE HYBRID SOFT CORAL *SINULARIA MAXIMA* X *S. POLYDACTYLA*

Haidy N. Kamel[a], Frank R. Fronczek[b], Nikolaus H. Fischer[a], Daneel Ferreira[a], Marc Slattery[a,*]
[a]Department of Pharmacognosy and National Center for Natural Products Research, RIPS, School of Pharmacy,University of Mississippi, University, MS 38677, USA
[b]Department of Chemistry, Louisiana State University, Baton Rouge, LA 70803-1804, USA

Hybridization and its consequences have attracted scientists for centuries. An important effect of hybridization is the generation of qualitative and quantitative variation in secondary metabolite chemistry. Chemical studies of the extract of the hybrid soft coral *Sinularia maxima* x *S. polydactyla* resulted in the isolation of 8 compounds. Five of these are new compounds. The structure and stereochemistry were determined using spectroscopic methods and X-ray diffraction analysis. Compound **8** which we named polymaxenolide represents a novel metabolite with a biosynthetically mixed skeleton linking a cembrane-type diterpene and an africanane-type sesquiterpene. Compound **5** showed moderate cytotoxic properties while compounds **6** and **7** showed antituberculosis activity.



8- Polymaxenolide

O:31

ACETYLCHOLINESTERASE INHIBITORS FROM NATURAL PRODUCTS DISCOVERED BY VIRTUAL SCREENING

Judith M. Rollinger,* Ariane Hornick, Barbara Bergner, Thierry Langer, Helmut Prast, Hermann Stuppner
Institute of Pharmacy, University of Innsbruck, Innrain 52, Josef-Moeller Haus, 6020 Innsbruck, Austria

At present, the cholinesterase inhibition is the mainstay of treatment for Alzheimer's disease (AD) and other forms of neurological impairment. Acetylcholinesterase (AChE) inhibitory drugs increase the effectiveness of cholinergic transmissions by inhibiting the metabolic hydrolysis of acetylcholine. Some of these successful drug substances originate from natural sources, e.g. galanthamine, and are already marked for the treatment of AD.
The aim of this project was to discover secondary plant metabolites with AChE inhibiting activity. For a targeted selection of promising compounds out of the natural products multitude we used an *in silico* filtering experiment, which is described in detail. Based on this information, the coumarins scopoletin and scopolin were isolated from the medicinal plant *Scopolia carniolica* Jaqc. and chosen for an exploratory study. In an enzyme assay using Ellman's reagent they showed moderate, but significant and long-lasting inhibitory activities. From the *in vivo* experiments both coumarins emerged as highly active natural compounds able to elevate significantly the extracellular acetylcholine in rat brain.

O:32

V-ATPASE INHIBITORS AS ANTICANCER DRUG CANDIDATES

Katherine Hansen, Chand Khanna, Michael Alley, Angie Dull[#], Sherman Stinson, Tawnya McKee, John Porco[^], Xiang Wang[^], Ruichao Shen[^], James Panek[^], Qibin Su[^], and John Beutler* National Cancer Institute, Frederick, MD 21702, and Bethesda, MD USA [#]SAIC, Inc. [^]Dept. of Chemistry, Boston University, Boston, MA USA

The potently cytotoxic marine metabolites salicylihalamide A and lobatamides A-F and the structurally related oximidines and apicularens have been shown to inhibit mammalian vacuolar ATPase at low nanomolar concentrations. Recent data indicates that salicylihalamide A binds to a distinct site from the bafilomycins and concanamycins, and may operate through a distinctly different mechanism. Difficulty in obtaining the compounds from natural sources has required chemical synthesis to support preclinical development as anticancer agents.
This series of macrolides display strongly differential cytotoxicity in the NCI 60-cell assay, with the melanoma cell lines being the most sensitive. We have recently found that these compounds also are potent inhibitors of human and murine osteosarcoma cell growth in vitro, which has prompted us to investigate their pharmacokinetics and activity in animal models of osteosarcoma. Other opportunities for development which are under investigation include effects on bone metastasis and invasion.
Funded in part through DHHS contract #NO1-CO-12400

O:33

HIGH-THROUGHPUT NATURAL PRODUCTS CHEMISTRY METHODS AND THE APPLICATION OF THE ADVANCED CAPNMR™ PROBE IN RAPID STRUCTURE ELUCIDATION OF MASS-LIMITED SAMPLES

Jin-Feng Hu,* Mark O'Neil-Johnson, Matt G. Goering, Eliane Garo and Gary R. Eldridge Sequoia Sciences, Inc., 11199 Sorrento Valley Road, Suite H, San Diego, CA 92121, USA

Our high-throughput purification methods applied to the production and analysis of natural products libraries is described, which can highly increase the rate of discovery of novel, bioactive compounds from plants in various drug discovery collaborations.
Utilizing the advanced CapNMR™ probe for structure elucidation enables the identification of purified natural products with 5 to 100 micrograms of material. Approximately 5 micrograms is needed to perform 1D proton and 2D homonuclear (COSY and NOESY) NMR experiments, approximately 30 micrograms is needed to acquire HMQC or HSQC NMR spectra, and approximately 70 micrograms is needed to acquire HMBC NMR spectra. Approximately 200 micrograms of a compound is needed to perform ^{13}C and DEPT NMR experiments.
A natural products library was generated from *Penstemon centranthifolius*. The NMR spectra of six iridoid glycosides isolated from *P. centranthifolius* were acquired using the CapNMR™ probe on a Bruker Avance 600 MHz NMR spectrometer and performed on 25 to 300 micrograms of materials. The structures were identified using a combination of NMR experiments and the data of LR-/HR-ESIMS.

O:34

AUTOMATED DEREPLICATION - SUPPORT FOR THE HIGH THROUGHPUT SCREENING ANALYST

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Natural product research can generate vast numbers of possible pharmaceutical lead compounds. The job of the analyst to identify the compounds of interest can be a nightmare due to the volumes of analytical data needing assessment.

The Marlin Project is a collaboration between the scientists in Bayer Healthcare and Waters Informatics aiming to lighten the workload of the research scientist with novel automated analytical tools to pre-screen primarily liquid-chromatography/mass spectrometry and associated molecular spectroscopy data sets. Known or otherwise uninteresting substances are automatically sorted out from the analytical separation allowing the new candidate compounds of interest to be focussed on.

Additionally new data visualisation tools have been developed hand-in-hand with the analytical scientists to support the rapid assessment of the new candidate substances. Together a powerful new tool has been produced to help cope with the flood of data threatening to overwhelm the High Throughput Screening analysts.

O:35

ROBUST SCREENING OF NATURAL PRODUCT EXTRACTS USING MULTI-ARRAY™ TECHNOLOGY

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Screening natural products for inhibitors of complex biological processes is well known to be fraught with interferences and false positives resulting in a general perception that these materials are difficult to use. We present a high-throughput technology platform based on electrochemiluminescent detection that is robust to traditional interferences observed with natural product screens that thus improves the probability of finding real therapeutics. The technology platform is fast (1 minute read time per plate) and highly sensitive (~ 10 attomole detection) while maintaining the ability to measure 5 logs of dynamic range. A subset of extracts from the NCI natural products library, including materials derived from marine, plant, and fungal sources, along with a priori known, promiscuous extracts (i.e. those extracts generally observed to inhibit biochemical assays) tested the performance of the technology platform in several different assays. These assays included searches for inhibitors of E3-ubiquitin ligases, modulators of receptor-ligand interactions, and simple binding assays. We screened the extracts at the relatively high concentration of 75ug/ml to exaggerate the potential effects of general assay interferences. We observed that the appearance of non-specific inhibitors (materials showing apparent inhibition in at least two different types of biochemcial assays) was significantly and simply reduced by the addition of 0.5% BSA. The multiplexing capability of the Multi-Array technology provided additional criteria that facilitated the rapid identification of specific and selective inhibitors**.**
We present results from a primary screen of the whole NCI natural products library (~145,000 extracts) for inhibitors of MDM2 self-ubiquitinylation. The inhibition profiles from the screen were distinct for the different source materials, with many of the samples reconfirming in both the aqueous and organic fractions. The hits from the primary screen were highly reproducible with a reconfirmation rate of about 80%. The selectivity screens revealed profiles of extracts that classified them into Ring-specific, E3-specific, or promiscuous E3 inhibitors. We identified approximately 100 extracts that are highly specific inhibitors of MDM2 self-ubiquitinylation. These extracts are now being further characterized in cell based assays on the MSD Multi-Array platform.

O:36

SUPPRESSION AND OVEREXPRESSION OF DIFFERENT GENES FROM BENZYLISOQUINOLINE BIOSYNTHESIS ALTERS ALKALOID PROFILES IN TRANSGENIC OPIUM POPPY PLANTS

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Opium poppy (*Papaver somniferum* L.) produces a large variety of benzylisoquinoline alkaloids including the analgesic and narcotic drugs morphine and codeine, the muscle relaxant papaverine, the antitumoric agent noscapine and the antimicrobial sanguinarine. The aim of our investigation is to understand the regulation of biosynthesis and the ecological function of the alkaloids in the plant. Additionally, the metabolic engineering of alkaloid metabolism in opium poppy is being approached.
An *Agrobacterium*-mediated approach has been used to introduce different cDNAs encoding enzymes of benzylisoquinoline biosynthesis in sense or antisense orientation into explants to attempt to alter the alkaloid profiles. Plants were regenerated via somatic embryogenesis.
Data will be presented from transgenic plants containing genes from the biosynthetic pathways for reticuline and morphine. The alkaloid content in latex and roots of these plants was determined with HPLC and LC-MS. The altered alkaloid profiles are heritable at least to the T_2 generation.

O:37

A FUNCTIONAL GENOMICS APPROACH TOWARD THE UNDERSTANDING OF PLANT SECONDARY METABOLISM: I. TRANSCRIPTOMICS AND HIGH-THROUGHPUT FUNCTIONAL ANALYSIS OF GENES IN PLANT CELLS

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Genetic knowledge on biosynthetic pathways and the regulation thereof is of crucial importance to bypass the low-product yield of various secondary metabolites in plant cells. To facilitate gene discovery in plant secondary metabolism, we have developed a comprehensive profiling approach that is based on functional genomics and can be applied on any plant system, without a need for prior sequence knowledge. Thus far, we have monitored jasmonate-induced changes on the transcript and alkaloid profiles of tobacco BY-2 and *Catharanthus roseus* cell cultures. Using cDNA-AFLP based transcript profiling, an inventory of hundreds of genes, potentially involved in plant secondary metabolism, has been built. A technology platform, especially driven towards the exploitation of plant cell suspension cultures, for high-throughput isolation and functional analysis of these genes has been established. This platform will allow creating a novel toolbox for metabolic engineering of plant cells. At present, more than 50 tobacco BY-2 full-length open reading frames have been isolated and are currently subjected to functional analysis in transgenic tobacco, *Hyoscyamus muticus* and *C. roseus* cell or hairy root lines.

O:38

GENOMICS AS A TOOL FOR THE DISCOVERY, ISOLATION AND STRUCTURE ELUCIDATION OF NOVEL NATURAL PRODUCTS: ECO-02301 AS AN EXAMPLE.

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The biosynthesis of secondary metabolites is now sufficiently well understood at the genomics level, to provide the natural product scientist with a new and exciting tool to discover NCEs, guide their isolation, and add to the battery of methods available for structure determination. The clustering of genes into a single locus, coding for all of the enzymes involved in the biosynthetic pathway for a single metabolite, allows for *in silico* examination of the biosynthetic capabilities of an organism.
Deconvolution of a biosynthetic locus, enables the researcher to ascertain, with a high level of certainty, the novelty of a metabolite, even before isolating it. Moreover, the chemist can use the structural characteristics to assist in the isolation and purification of the desired metabolite and to complement the spectral data analysis in the determination of structure.
These advances will be demonstrated with a description of the discovery of ECO-02301, a novel linear type I polyketide of MW 1297, with potent antifungal activity. The entire structure of this complex antibiotic was initially deduced from the genome of the producing streptomycete.

O:39

METABOLOMICS: BACK TO THE FUTURE?

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Functional genomics requires characterization of phenotypes by means of morphological observations and (bio)chemical characterization (proteomics and metabolomics). Some definitions: - Metabolic profiling: measuring a selected group of metabolites; - Metabolomics: measuring all metabolites; - Metabolic fingerprinting: measuring fingerprints of metabolites, without identification. The difference is the choice to qualitatively and quantitatively analyze (all) compounds, or to use a differential display approach to identify differences. The methods for metabolomics in plants are known phytochemical methods, e.g. chromatography, MS and NMR. ^{1}HNMR is not very sensitive, but very reproducible and allows direct comparison of quantities. For large numbers of data multivariate and principle component analysis are suitable to find patterns for similarities or differences. Metabolomics can be applied to study safety of GMOs and in quality control of food and medicinal plants. In studies of activity of medicinal plants metabolomic data on extracts and activity in an organism, mulivariate analysis may identify (a) compound(s) that correlate with activity (e.g. also find pro-drugs or synergism). One may find new modes of action. This systems biology approach is a totally new approach to drug discovery, which may replace the present single compound – single target approach.

O:40

ON STRATEGIES OF SELECTION

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Among the most important and critical decisions made in virtually any scientific endeavour is the selection of the objects to study. In the field of pharmacognosy this often end up in the selection of living organisms or chemical substances originating from such. Traditionally has the application of ethnopharmacological data in these selection processes been of uttermost importance, but with the increasing knowledge regarding the origins and development of life, as well as with mathematical and technological breakthroughs, a new set of data is at hand to assist us in making intelligent choices in the vast diversity presented by nature.

Some principles and practical issues in applying phylogenetic and chemometric data in selection strategies, as demonstrated in recent work at the division of pharmacognosy will be discussed. Examples will include chemometric and phylogenetic implications for the study of COX-inhibitors[1, 2], the utility of phylogenies in search for plant polypeptides on familial levels from Violaceae[3] and Viscaceae[4], as well as in interpreting neutrophil bioassay response from plant extracts[5].

Acknowledgements: Ulf Göransson, Ulrika Huss, Therese Ringbom, Senia Johansson, Josefin Larsson, and Christoffer Nellåker, all at the Division of Pharmacognosy, which contributed with parts of the primary data to be analysed. *References:* 1. Larsson, J., Gottfries, J., Huss, U., and Backlund, A. (2002) Navigating chemical space – ChemGPS and COX-inhibitors. Masters thesis in Pharmaceutical Sciences. Div. of Pharmacognosy. 2. Nellåker, C., and Backlund, A. (2002) Phylogenetic implications on naturally occurring COX-inhibitors. Masters thesis in Pharmaceutical Sciences. Div. of Pharmacognosy. 3. Broussalis, A. M., Göransson, U., et al. (2001) Phytochemistry, 58: 47-51. 4. Larsson, S., and Backlund, A. (2002) Mistletoe toxins revisited. *manuscript* 5. Johansson, S., et al. (2002) A neutrophil multitarget functional bioassay to detect anti-inflammatory natural products. J Nat Prod. 65: 32-41.

O:41

AMINO ACID CHEMOTAXONOMY OF THE GENUS *SOPHORA* (LEGUMINOSEAE)

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Since the time of taxonomy of the genus, the polyphyly of the genus was noticed. The alkaloid chemotaxomy of the genus in *phytochemistry*, 1975, did not solve the problem. At the present the argue is still continuing. Since the alkaloid content of the seeds varies from time to time, therefore, we investigated the free amino acid content of the seeds of some 23 species of the genus, by ion-exchange separation and amino acid analysis comparison. These components are precursors of alkaloids and are more stable, as a chemotaxonomic marker. According to these studies some species contain 4-OH- pipocolic acid, some do not . In addition, some contain γ-glutamyl tyrosine, some do not. Also some contain γ – amino – n-butyric acid, and some do not. Therefore, a classification based on these findings are proposed and a phylogenetic tree is drawn which is presented by convincing slides. At the same time, two species (*S. allopecuroides* and *S. gypsophylla*) belong to different parts of the world were compared by amino acid analyzer to confirm their amino acid chemotaxonomic relationships.

O:42

METHODOLOGY IN THE QUALITY CONTROL OF FINGERPRINT CHROMATOGRAMS FOR TRADITIONAL CHINESE MEDICINES

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The chromatographic fingerprint technology was proposed as an identification and quality evaluation tool for herbal medicines in the 80's of last century. For the near future, fingerprint chromatograms seem to become the standard technique for the quality evaluation of herbal medicines. The importance of methodology in the quality control of fingerprint chromatograms for Traditional Chinese Medicines is stressed.

Our study was focused on how to determine and evaluate the similarity of different chromatograms with reasonable solution, as well as how to match the peaks of two chromatographic fingerprints automatically with computer.

The several algorithms for the similarity evaluation of the fingerprints were proposed. Matching peaks of chromatographic fingerprints is necessary for the similarity in many cases which use meaningful peaks, area or height, not full curves. Based on the simple linear relationship, selecting n pairs of mutual peaks as standards, the retention vectors for two curves are designed and used for the identification of matching peaks. The proposed algorithms were validated with samples Yinzhihuang Injections, Xiangdan Injections, Flos Lonicerae and Extracts of Ginkgo leafs. The results confirmed the above algorithms perform well for evaluating the similarity between two fingerprints which is helpful in quality control of TCM.

O:43

A DISTINCTIVE ISOFLAVONOID CHEMISTRY FOR THE TROPICAL LEGUME, *ATELEIA HERBERT-SMITHII*: TAXONOMIC AND BIOSYNTHETIC IMPLICATIONS

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Ateleia herbert-smithii (Leguminosae) is an uncommon tree of seasonally dry tropical forests in Columbia, Costa Rica and Nicaragua best known for the unusual cyclic non-protein amino acids found in its seeds. Recent studies of the chemical constituents of the leaves of this plant have revealed a rich diversity of isoflavones, chalcones and flavonol glycosides, including a new 5-deoxyflavonol rutinoside and six new isoflavones (Veitch, N.C. et al., *J. Nat. Prod.* 2003, *66*, 210–216). Among the latter are four derivatives with a unique bis(methylenedioxy) substitution pattern. LC-NMR, direct NMR of isoflavone-rich fractions, and LC-MS analysis of fragments of plant material sourced from herbarium specimens are techniques used to characterise *Ateleia* flavonoids in addition to classical methods of isolation and structure determination.

Chemical profiles of *A. herbert-smithii* and related taxa are contributing new data towards resolution of the current debate about the systematic position of *Ateleia*, one of several basal genera of the Leguminosae considered to be transitional between the subfamilies Papilionoideae and Caesalpinioideae. In particular, consideration of the biosynthetic relationships among *A. herbert-smithii* isoflavones offers new insight into different patterns of chemical diversity found in some closely related genera such as *Aldina*, *Swartzia* and *Zollernia*.

O:44

ANTIPLASMODIAL ACTIVITY OF ISONEOCRYPTOLEPINE, A NEW SYNTHETIC INDOLOQUINOLINE ALKALOID

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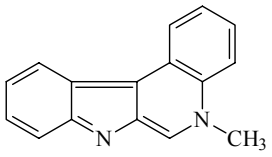
Cryptolepine, neocryptolepine and isocryptolepine are isomeric indoloquinoline alkaloids with antiplasmodial and cytotoxic properties, originally isolated from *Cryptolepis sanguinolenta*. The 'missing alkaloid' in this series, not isolated before from nature, is the corresponding indolo[2,3-c]quinoline, for which we propose the name isoneocryptolepine (1). It was synthesised by a Suzuki arylation of 4-chloroquinoline with a protected 2-aminophenylboronic acid, followed by a nitrene C-H insertion reaction and methylation. Of all 4 isomers, isoneocryptolepine showed the highest selectivity against chloroquine-resistant *Plasmodium falciparum* (IC_{50} 0.061 µg/ml, cytotoxicity (L6 cells) IC_{50} 1.16 µg/ml.

1



O:45

ANTIPLASMODIAL ACTIVITY OF CHALCONE DERIVATIVES OF HOP (*HUMULUS LUPULUS*) AND THEIR INTERACTION WITH HEME

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Hop cones, derived from female hop plants (*Humulus lupulus* L., Cannabaceae), have a long tradition in European folk medicine as mild sedatives. Recently, also anti-viral and cancer chemopreventive properties were reported. In addition, 8-prenylnaringenin has been identified as a potent phytoestrogen. We now evaluated the antiplasmodial activity of the main hop chalcone, xanthohumol, and seven further prenylated derivatives against *Plasmodium falciparum* (strain poW).
The best antiplasmodial activity with an IC_{50} value of 2.9 µg/ml was observed for xanthohumol itself. Whereas further C-5-methoxylated derivatives also showed reasonable inhibition of P. falciparum, demethylation in position 5 caused a dramatic decrease in activity. In order to evaluate a possible mode of action, the ability of the compounds to interact with the GSH-dependent polymerization of heme was measured.

O:46

RESVERATROL INHIBITS ANGIOTENSIN II-INDUCED VASCULAR SMOOTH MUSCLE CELL HYPERTROPHY BY INTERFERING WITH THE GAB1-PI3K SIGNALING

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Angiotensin II (Ang II) plays a critical role in the development of atherosclerosis and hypertension by inducing vascular smooth muscle cell (VSMC) growth. Our group has previously shown that resveratrol (RV), a polyphenolic stilbene derivative found in grape skin, inhibits Ang II-induced VSMC hypertrophy by interfering with the PI3K/Akt signaling pathway (Haider et al. Mol Pharmacol 2002). Aiming at the identification of the molecular target affected by resveratrol we show here that RV mediates its effect not by inhibiting the Ang II-induced transactivation of the epidermal growth factor receptor (EGF-R) but rather by an interference with the EGF-R signaling to the PI3K. We found that RV reduces the EGF-induced phosphorylation of the adapter molecule Gab1 which leads to a reduced binding and activation of the regulatory subunit p85 of the PI3K. Moreover, studies in fibroblasts expressing a hypomorphic mutant of the phosphotyrosin phosphatase Shp2 support the hypothesis that RV keeps Gab1 hypophosphorylated by activation of Shp2.
Thus, RV inhibits Ang II-induced VSMC hypertrophy most likely by activating Shp2.

O:47

PODOCARPATES AS LIVER X RECEPTOR AGONISTS, STRUCTURE ACTIVITY RELATIONSHIP

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Liver X Receptors (LXR) are members of a superfamily of nuclear hormone receptors represented by two subtypes, LXRα and LXRβ. The α-subtype is predominantly present in liver whereas the β-subtype is ubiquitously expressed. Oxysterols have been identified as endogenous ligands for both subtypes. These receptors have been shown to play a role in cholesterol homeostasis. LXRs form heterodimers with the retinoid X receptor, RXR, to regulate the expression, either directly or indirectly, of a number of genes involved in cholesterol and fatty acid metabolism. It has been shown that a nonsteroidal LXR agonist causes increased expression of ABCA1 and raises the HDL levels in mice. ABCA1 mediates the efflux of cholesterol out of the cells and onto the ApoAI protein of a HDL particle. Therefore, LXR agonists are expected to provide an opportunity for the development of drugs to increase reverse cholesterol transport and thus decrease the burden of atherosclerosis. Recently, we identified podocarpic acid anhydride as a potent agonist of LXRα. We have synthesized a series of derivatives of podocarpic acid by chemical, enzymatic and biotransformation methods leading to the identification of key amide derivatives with better biological and physical profiles. In this presentation, the rationale, synthesis and structure activity relationship of podocarpate will be discussed.

O:48

PRECLINICAL STUDIES OF THE MANZAMINE ALKALOIDS AS TREATMENTS FOR MALARIA.

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Center for Marine Biotechnology, The University of Maryland Biotechnology Institute**.**

The manzamine alkaloids have emerged as an exciting new class of antimalarial leads from Indo-Pacific sponges from a variety of genera. These metabolites exhibit activity in animal models which is significantly better then the clinically used drugs chloroquine and artemisinin. In addition, these metabolites represent a unique example in which a sponge derived metabolite can be successfully produced through the fermentation of a sponge associate Actinomycete. Our results regarding the antimalarial activity, pharmacokinetics, oral availability, improvements in fermentation methods as well as gram to kilogram scale isolation of the drug-lead will be presented. Some of the relatively simple but very significant improvements in cost-effective production have been through the use of supercritical fluids and generation of the freebase of the alkaloid under aqueous conditions.

O:49

PESTICIDE RESIDUES OF HERBAL MEDICINAL DRUGS IN THE PHEUR AND USP - ACTUAL SITUATION AND PROPOSALS FOR AN AMENDMENT OF THE MAXIMUM RESIDUE LEVELS

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Regulations for pesticide residues in herbal medicinal drugs are included in the Monograph "Pesticide Residues" of the European Pharmacopoeia (Ph. Eur.). According to the monograph limits applying to pesticides not listed in the table of the monograph comply with the limits set by the EC directives 76/895 and 90/642 including their annexes and successive updates. The limits indicated in the mentioned EC directives that have been adopted in German legislation within the Maximum Residue Level Regulation (Rückstands-Höchstmengenverordnung, RHmV) are not appropriate. They refer to certain product groups only they are too low and therefore they are not practicable.
According to the Contaminants Working Group of the Federal Association of Pharmaceutical Product Manufacturers (BAH) 67 pesticides respectively substance groups are relevant to selected medicinal plants which were given a positive assessment by the E Commission or ESCOP. The table of substances and limits in the Ph. Eur. monograph should be amended Maximum limits for 70 pesticides, calculated on the positive findings and the 90th percentile should be adopted to the Ph. Eur and quantification limits for a number of pesticides should be adopted as maximum levels of the Ph. Eur if the actual limit is not strict.
As the analytical method provided by the Ph. Eur. is not suitable to check the limit of these pesticides the DFG S 19 procedure, which has been adopted in ³ 35 of the LMBG (German Food and Commodities Act) as procedure L 00.00-34 is proposed for adoption into the Ph. Eur. Monograph "Pesticide Residues"

P:1 GC/MS FINGERPRINT PROFILING OF *IOSTEPHANE HETEROPHYLLA* ROOTS AND QUANTITATIVE ANALYSIS OF XANTHORRHIZOL IN AN ALCOHOLIC EXTRACT.

María Isabel Aguilar[1*], Roberto Castro[1], Georgina Duarte[2] and Margarita Guzmán[2]
[1]Departamento de Farmacia, [2]Laboratorio de Espectrometría de Masas, USAI. Facultad de Química. Universidad Nacional Autónoma de México, Coyoacán D. F.,04510. México.

P:2 RAPID AND EASY IDENTIFICATION OF THE ADULTERANT *ILLICIUM ANISATUM* L. IN THE POWDER OF *I. VERUM* HOOK. F.

Srinivas V. Pullela[1], Vaishali Joshi[1] and Ikhlas A. Khan[1,2]* [1]National Center for Natural Products Research, Research Institute of Pharmaceutical Sciences, [2]Department of Pharmacognosy, School of Pharmacy, The University of Missisippi, MS 38677, USA

P:3 ANALYSIS OF POLYPHENOLIC ANTIOXIDANTS FROM THE FRUITS OF THREE *POUTERIA* SPECIES BY SIM LC-MS

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P:4 COMPARATIVE ANALYSIS OF FLAVONOIDS FROM DIFFERENT EDIBLE ORGANS OF *SECHIUM EDULE* (JACQ) SWARTZ (CUCURBITACEAE) BY HPLC-PDA-ESI-MS

Tiziana Siciliano[1,]*, Nunziatina De Tommasi[2], Alessandra Braca[1], Ivano Morelli[1], [1]Dipartimento di Chimica Bioorganica e Biofarmacia, Via Bonanno 33, 56126 Pisa, Italy; [2]Dipartimento di Scienze Farmaceutiche, Università di Salerno, Via Ponte Don Melillo, 84084 Fisciano (SA), Italy

P:5 IDENTIFICATION AND MEASUREMENT OF THE MAJOR FATTY ACIDS IN *IRVINGIA GABONENSIS* (O'RORKE) BAILL SEED OIL USING MALDI-TOFMS AND HPLC.

Enwerem N.M[1*], Kumar K[1] and Ayorinde F[2] [1]School of Pharmacy and [2]Department of Chemistry, Howard University, College of Pharmacy, 2300 4th Street, NW, Washington DC, 20059-0001

P:6 DEREPLICATION OF CYTOTOXIC CUCURBITACINS IN PLANT EXTRACTS

William P. Jones,[1,4] Heebyung Chai,[1] Leonardus B. S. Kardono,[2] Soedarsono Riswan,[3] Norman R. Farnsworth,[1] Geoffrey A. Cordell,[1] Steven M. Swanson,[1] and A. Douglas Kinghorn[1,4,]* [1]Program for Collaborative Research in the Pharmaceutical Sciences, Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, University of Illinois at Chicago, Chicago,

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P:7 A NEW HOLISTIC GINKGO FRESH PLANT EXTRACT INCREASES THE MICROCIRCULATION IN ELDERLY PATIENTS

A. Suter[a]*, S.Bommer[a], R. Schoop[a], R. Klopp[b] *[a]A. Vogel Bioforce AG, CH-9325 Roggwil, Switzerland [b]Institute for Microcirculation, Wolfener Strasse 32-34, 12681 Berlin, Germany

P:8 A VALIDATED METHOD FOR THE QUANTIFICATION OF TRACHYLOBANE AND PIMARANE DITERPENES IN THE LEAVES OF *CROTON ZAMBESICUS* BY CAPILLARY GAS CHROMATOGRAPHY

S. Block[1], P. Hubert[2], J. Quetin-Leclercq[1(*)] [1]Laboratoire de pharmacognosie, UCL-CHAM, Av E. Mounier, 72, B-1200 Brussels, Belgium. [2]Laboratoire d'Analyse des Médicaments, ULg, CHU, B36, B-4000 Liège, Belgium

P:9 COMPREHENSIVE 2-DIMENSIONAL HPLC (LCxLC)

Teris A. van Beek*, Frederique van Holthoon and Elbert van der Klift Natural Products Chemistry Group, Laboratory of Organic Chemistry, Wageningen University, Dreijenplein 8, 6703 HB Wageningen, The Netherlands

P:10 ANTIPLATELET ACTIVITY OF ISOMALTOL AND SULFURETIN FROM THE BARK OF *RHUS VERNICIFLUCA*

Won Kyung Jeon*, Ju Hyun Lee, A Yeong Lee, Byoung Seop Ko and Ho Kyoung Kim
Department of Quality Control of Herbal Medicine, Korea Institute of Oriental Medicine, Daejeon, South Korea

P:11 PRELIMINARY MICROBIOLOGICAL INVESTIGATION OF NIGERIAN TUBERCULOSIS ETHNOMEDICINE.

Oladosu, Peters[1]; Orisadipe, Abayomi T.[1] ; Ibrahim Kolo[1]*; Okogun Joseph I. [1]; Inyang Uford S. [1]; Helena Boshoff[2] ; Cynthia Dowd [2] and Clifton Barry, 111 [2]. 1.National Institute for Pharmaceutical Research and Development P.M.B.21, Garki, Abuja, Nigeria. 2.TB Research Section, National Institute for Allergy and Infectious Disease, National Institute of Health, Rockville, Md., USA.

P:12 CARDIOPROTECTIVE ACTIONS OF *SCOPARIA DULCIS* IN PERCHLORATE ADMINISTERED RATS

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P:13 STRUCTURE DETERMINATION OF SENNOSIDES A AND C FROM SENNA (*CASSIA ANGUSITFOLIA*) PODS

Nam-Cheol Kim,[1,3*] Tyler N. Graf,[1] Nicholas H. Oberlies,[1] Charles M. Sparacino,[2] Mansukh C. Wani[1]
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P:14 GASTROINTESTINAL ABSORPTION OF THE TWO COMPONENT EXTRACTS OF A COMBINED VALERIAN/HOPS PREPARATION (ZE91019) IN HUMANS – A PRELIMINARY STUDY

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P:15 ENZYME INHIBITION TESTS ON *GRINDELIA ROBUSTA* NUTT. HERB EXTRACTS

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P:16 A SYSTEMATIC REVIEW AND META-ANALYSIS ON CLINICAL DATA OF PADMA, A TIBETAN HERBAL MULTI-COMPOUND FORMULA, IN THE TREATMENT OF PERIPHERAL ARTERIAL OCCLUSIVE DISEASE (PAOD)

Melzer J* [1], Brignoli R [2], Diehm C [3], Reichling J [4], Do Dai-Do [5], Saller R [1 1] University Hospital Zurich Department of Internal Medicine, Complementary Medicine, Zurich, Switzerland [2]Tradyser GmbH, Rueschlikon, Switzerland [3]Clinic Karlsbad-Langensteinback, Internal Medicine/Angiology, Karlsbad, Germany [4]University of Heidelberg, Institute of Pharmacy and Molecular Biotechnology, Heidelberg, Germany [5]Insel hospital of the University of Berne, Department of Angiology, Berne, Switzerland

P:17 RED GRAPE POLYPHENOLICS PREVENT APOPTOSIS AND OXIDATIVE DNA- DAMAGE IN HUMAN PBMC AND INFLUENCE THE ANTIOXIDANT POTENTIAL IN PLASMA AFTER ACUTE CONSUMPTION OF RED WINES AND GRAPE JUICE.

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P:18 BIOCHEMICAL AND HAEMATOLOGICAL EVALUATION OF (CUCURBITACEAE) *CUCUBITA MAXIMA* IN ALBINO RATS

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of pharmaceutical chemistry, Faculty of pharmacy, University of Lagos, Idi-Araba, Lagos.

P:19 ANTI-TUMOR PROMOTING EFFECTS AND CYTOTOXIC ACTIVITIES AGAINST HUMAN CANCER CELL LINES OF TRITERPENE GLYCOSIDES AND FLAVONOL GLYCOSIDES FROM MARIGOLD (*CALENDULA OFFICINALIS L.*) FLOWERS

Motohiko Ukiya[‡], Toshihiro Akihisa*[, ‡], Harukuni Tokuda[§], Yumiko Kimura[⊥], Takashi Suzuki[⊥], Hoyoku Nishino[§ ‡]College of Science and Technology, Nihon University, 1-8 Kanda Surugadai, Chiyoda-ku, Tokyo 101-8308, Japan, [§]Department of Biochemistry, Kyoto Prefectural University of Medicine, Kamigyo-ku, Kyoto 602-0814, Japan, [⊥]College of Pharmacy, Nihon University, 7-7-1 Narashinodai, Funabashi-shi, Chiba 274-8555, Japan

P:20 CHARACTERIZATION OF *RADIX ASTRAGALI* BY LC/APCI/MS

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P:21 STABILITY OF *ECHINACEA PURPUREA* SAMPLES AND EXTRACTS

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P:22 USE OF ECHINILIN IN THE TREATMENT OF COLDS

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[2] University of British Columbia, Dept of Biochemistry and Molecular Bilogy. Vancouver, BC V6T 1Z3 Canadian Center for Functional Medicine. 1550 United Blvd Coquitlam, BC. V3K 6Y2

P:23 PROTECTIVE EFFECT OF RED GRAPE SEEDS PROANTHOCYANIDINS IN ALLOXAN-INDUCED DIABETES IN RATS.

Abir T. El-Alfy*, Amani A.E. Ahmed, Amal J. Fatani. Pharmacology Department, Faculty of Pharmacy, King Saud University, Riyadh 11495, Saudi Arabia

P:24 STUDIES ON ANTIFUNGAL FLAVONOIDS FROM *ALLIUM* SPECIES

Sook Lim, Ji-Hyun Kim, Youn Sim, Mi-Sun Pyun, Seungwon Shin Duksung Women's University, College of Pharmacy, Seoul 132-714 Korea

P:25 INDUCTIONS OF PITUITARY HORMONE RELEASE BY *Anemarrhena asphodeloides* B_{UNGE} (Liliaceae) AND ITS INGREDIENT

C. Kim.*, D.Y. Jung., H.Y. Lee., H. Ha., D.Y. Jung., H. Y. J., J.S. Choi., J. H Lee.[1], K. H. Son.[2] and S. S. Kang.[3] *Department of Herbal Medicine, Korea

Institute of Oriental Medicine, Daejeon, 305-811, [1]Kyunghee Univ., [2]Andong National Univ., [3]Natural Products Research Institute, Seoul National Univ., KOREA.

P:26 MEDICINAL PLANTS OF THE PRAIRIE AS SOURCES OF NEW PHARMACEUTICALS.

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P:27 VIRTUAL SCREENING FOR NUTRACEUTICALS IN TYPE 2 DIABETES PREVENTION

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P:28 NUTRACEUTICALS – FROM PLANT EXTRACT TO FUNCTIONAL FOOD. A DISCOVERY HIGH THROUGHPUT APPROACH

Goede Schueler, Vincent Acker, Katharina Arnosti, Elvira Calabek, Biagio Colletto, Daniel D'Orazio, Ann Fowler, Claus Kilpert, Laure Morisset, Benno Mueller, Albine Sorlet, Greet van Loon, Karin Wernli-Kuratli, Antoine de Saizieu* DSM Nutritional Products, P.O. Box 3255, Bldg 203/132a, 4002 Basel, Switzerland

P:29 COMPONENTS AND BIOLOGICAL ACTIVITY OF YACON

Jitka Ulrichová*, Kateřina Valentová, Nina Škottová, Jitka Psotová, Rostislav Večeřa, Vladimír Křen, Vilím Šimánek Institutes of Medical Chemistry and Pharmacology, Faculty of Medicine, Palacký University, Hněvotínská 3, 775 15 Olomouc, Czech Republic

P:30 EVALUATION OF TWENTY HIGH-GRADE TRADITIONAL CHINESE MEDICINE DUE TO THEIR ANTI-HIV, ANTIBACTERIAL, AND ANTICANCER BIOACTIVITIES

Jin-Feng Hu,[1,2,*] Kelli Kuhen,[1] Doris Hafenbradl,[1] Jun Li,[1] Teresa Chen,[1] Jennifer Harris,[1]Nathanael Gray,[1] and Peter Schultz[1,2*] [1]Genomics Institute of the Novartis Research Foundation, 10675 John Jay Hopkins Drive, San Diego, CA 92121. [2]Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037

P:31 HERBAL REMEDIES FOR MENOPAUSAL HOT FLASHES WHICH INTERACT WITH SEROTONIN RECEPTORS

Rachel L. Ruhlen*, Birgit Dietz, Joanna E. Burdette, Daniel S. Fabricant, Shixin Deng, Norman R. Farnsworth, Judy L. Bolton. Dept of Med Chem and Pharmacognosy, 833 S Wood MC 781, UIC, Chicago, IL 60612.

P:32 DIETARY SUPPLEMENTS AND THEIR IN VITRO EFFICACY RELATED TO HUMAN HEALTH

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P:33 A CROSS-SECTIONAL STUDY OF PHARMACY UNDERGRADUATE STUDENTS' VIEWS ON INCLUSION OF PHARMACOGNOSY AND COMPLEMENTARY MEDICINE IN UNDERGRADUATE PHARMACY PROGRAMMES IN THE UK

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P:34 ANALYSIS OF TRITERPENOID SAPONINS IN *BACOPA MONNIERI* (BRAHMI) BY HPLC AND HPLC-MS

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P:35 A CROSS-SECTIONAL STUDY OF TEACHING IN PHARMACOGNOSY AND RELATED AREAS ON UNDERGRADUATE PHARMACY PROGRAMMES AT UK SCHOOLS OF PHARMACY

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P:36 SIMULTANEOUS DETERMINATION OF THE ALKALIODS FROM *EPHEDRA SINICA* AND *CITRUS AURANTIUM* BY IONPAIRCHROMATOGRAPHY

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P:37 INHIBITORY EFFECTS OF CHAMOMILE (*MATRICARIA RECUTITA* L.) ESSENTIAL OIL AND ITS MAJOR CONSTITUENTS ON HUMAN CYTOCHROME P450 ENZYMES

Markus Ganzera *, Peter Schneider, Hermann Stuppner Institute of Pharmacy, Department of Pharmacognosy, University of Innsbruck, 6020 Innsbruck, Austria

P:38 HYPOGLYCEMIC ACTIVITY OF A STANDARDIZED EXTRACT OF *TRIGONELLA FOENUM GRAECUM L* SEEDS GROWING IN EGYPT

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Belbeis road PO Box1535, Egypt National Cancer Institute [2]Pharmacology department, Kasr El- Aini Cairo 11562,Egypt

P:39 MARKER PROFILING OF TRIPHALA - AN AYURVEDIC FORMULATION USED IN INDIAN SYSTEM OF MEDICINE

Sujay Rai*, K. Mukherjee, A. Wahile, Nazeer Ahmed, S. Raja, K. Maiti, S. Bhattacharya, A. Gantait, V. Kumar, B. P. Saha, Pulok K. Mukherjee School of Natural Product Studies, Department of Pharmaceutical Technology, Jadavpur University, Kolkata - 700 032, India

P:40 ROLE OF OLIGOSACCHARIDE SIDE CHAINS IN INTESTINAL IMMUNE SYSTEM MODULATING ARABINOGALACTAN FROM RHIZOMES OF *ATRACTYLODES LANCEA* DC.

Haruki Yamada*, Hiroaki Kiyohara, Ikue Taguchi, Tsukasa Matumoto Kitasato Institute for Life Sciences, Kitasato University & Oriental Medicine Research Center, The Kitasato Institute, Tokyo 108—8641, Japan

P:41 FREE RADICAL-SCAVENGING ABILITY OF THE CHEMICAL CONSTITUENTS OF THE FRUITS OF *MORINDA CITRIFOLIA* L. (NONI)

Bao-Ning Su,[1,3] Alison D. Pawlus,[1,3] William J. Keller,[2] Jerry L. McLaughlin,[2] and A. Douglas Kinghorn[1,3,*] [1]Program for Collaborative Research in the Pharmaceutical Sciences, Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, University of Illinois at Chicago, Chicago, IL 60612. [2]Nature's Sunshine Products, Inc., 1655 N. Main St., Spanish Fork, UT 84660. [3]Present address: College of Pharmacy, The Ohio State University, Columbus, OH 43210.

P:42 COUMARINS IN RED CLOVER? EXAMINATION OF A PHASE II CLINICAL *TRIFOLIUM PRATENSE* L. EXTRACT FOR ANTICOAGULANT COUMARINS

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P:43 PREVENTION OF VENOUS THROMBOSIS IN LONG-HAUL FLIGHTS WITH FLITE TABS: THE LONFLIT-FLITE RANDOMIZED, CONTROLLED TRIAL

M.R. Cesarone, MD, G. Belcaro PhD, A.N. Nicolaides, MS, A. Ricci, MD, G. Geroulakos, PhD, E. Ippolito, MD, R. Brandolini, MD, G. Vinciguerra, PhD, M. Dugall, MD, M. Griffin, PhD, I Ruffini, MD, G. Acerbi, MD, M. Corsi, MD, N.H. Riordan, MS, S. Stuard, MD, P. Bavera, MD, A. Di Renzon, MD, J. Kenyon, MD, and B. M. Errichi, MD, *Pescara, Italy and London, UK,Angiology* Volume 54, Number 5, 2005 pp. 531-539.

P:44 ZEAXANTHIN AND LUTEIN PROTECT A2E-LADEN HUMAN RETINAL PIGMENT EPITHERIUM CELLS FROM PHOTOTOXOCITY

So Ra Kim[1,2,*], Jilin Zhou[1], Koji Nakanishi[2], Janet Sparrow[1]Department of Ophthalmology[1] and Chemistry[2], Columbia University, New York, NY 10032, USA

P:45 *VALERIAN* EXTRACT AND VALERENIC ACID ARE PARTIAL AGONISTS OF THE 5HT-5a RECEPTOR

Birgit Dietz, G. Pauli, N.R. Farnsworth and G.B. Mahady* UIC/NIH Center for Botanical Dietary Supplements Research in Women's Health College of Pharmacy, University of Illinois at Chicago

P:46 ANALYSIS OF THE AERIAL PARTS OF *VERBENA OFFICINALIS* L. BY MICELLAR ELECTROKINETIC CAPILLARY CHROMATOGRAPHY

Andrea Müller*, Markus Ganzera, Hermann Stuppner Institute of Pharmacy, Department of Pharmacognosy, University of Innsbruck, Innrain 52, 6020 Innsbruck, Austria

P:47 MALARIA TREATMENT BY PREPARATIONS OF *ARTEMISIA ANNUA* L. (ANNUAL WORMWOOD): A PHARMACOKINETIC STUDY IN HUMAN VOLUNTEERS AND A RANDOMIZED, CONTROLLED CLINICAL TRIAL IN MALARIA PATIENTS

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P:49 LOCAL FOOD – NUTRACEUTICALS OF THE MEDITERRANEAN

Marco Leonti, Sabine Nebel, Michael Heinrich* Centre for Pharmacognosy and Phytotherapy, The School of Pharmacy, Univ. London 29-39 Brunswick Sq., London, WC1N 1AX, UK

P:48 PROTECTIVE EFFECTS OF FLAVONOIDS FROM CRANBERRY (*VACCINIUM MACROCARPON*) ON RAT NEURONS AND VASCULAR CELLS

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P:50 *ARGEMONE PLATYCERAS* ETHYLACETATE FRACTION ANTAGONIZES LTD_4-INDUCED CONTRACTIONS IN GUINEA PIG AIRWAYS.

Jacquelina Fernández, Héctor Ponce, Ricardo Reyes-Chilpa, Maria G. Campos*Unidad de Investigación Médica en Farmacología, Centro Médico Nacional Siglo XXI, Instituto Mexicano del Seguro Social; San Franciso 350, Col. Del Valle, 03100 México D.F.

P:51 *IN VITRO* BINDING OF THE FIXED VALERIAN-HOPS COMBINATION EXTRACT (ZE91019) TO MELATONIN AND SEROTONIN RECEPTORS

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P:52 DETERMINATION OF CAFFEINE IN STIMULANT HERBAL PRODUCTS AND POWER DRINKS BY HIGH PERFORMANCE THIN LAYER CHROMATOGRAPHY

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P:53 SEPARATION, IDENTIFICATION AND QUANTIFICATION OF THE BENEFICIAL NUTRIENTS OF ROSEMARY BY HPLC.

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P:54 QUALITATIVE AND QUANTITATIVE EVALUATION OF CITRUS BIOFLAVONOIDS IN CITRUS FRUITS AND EXTRACTS USED AS NUTRACEUTICALS

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P:55 QUANTITATIVE ESTIMATION OF EMODIN & PHYSCION FORMED IN *IN VITRO* PROPAGATED SHOOTS AND PLANTS OF *POLYGONUM MULTIFLORUM* THUNB.

Li-Chang Lin, Satish Manohar Nalawade , Vanisree Mulabagal and Hsin-Sheng Tsay* Institute of Biotechnology, Chaoyang University of Technology, Taichung, 413, Taiwan.

P:56 PERMEABILITY STUDIES OF ALKYLAMIDES AND CAFFEIC ACID CONJUGATES FROM ECHINACEA USING A CACO-2 CELL MONOLAYER MODEL

A. Matthias[1*], J.T. Blanchfield[3], K.G. Penman[1], I. Toth[2,3], C.-S. Lang[3], J.J. De Voss[3]and R.P. Lehmann[1] [1]MediHerb Research Laboratories, University of Queensland, Brisbane, 4072 Australia; [2]School of Pharmacy, University of Queensland, Brisbane, 4072 Australia; [3]School of Molecular and Microbial Sciences, University of Queensland, Brisbane, 4072 Australia

P:57 BIOAVAILABILITY AND PHARMACOKINETICS OF ALKYLAMIDES FROM *ECHINACEA*

A. Matthias[1*], K.G. Penman[1], R.S. Addison[3], R.G. Dickinson[3], K.M. Bone[1,2] and R.P. Lehmann[1] [1]MediHerb Research Laboratories, The University of Queensland, Brisbane, 4072 Australia; [2]School of Health, University of New England, Armidale, NSW 2351 AUstralia; [3]Centre for Studies in Drug Disposition, The University of Queensland, Clinical Sciences Building, Royal Brisbane Hospital, Brisbane, QLD 4072 Australia

P:58 *ECHINACEA* EFFECTIVELY MODULATES IMMUNE RESPONSES

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P:59 IN VITRO ANXIOLYTIC ACTIVITY OF CALIFORNIA POPPY

(*Eschscholtzia californica* Cham.) *C*hantal Bergeron[1]*, Megan McCollom[1], Ian Scott[2], Jan A. Glinsky[3], John T. Arnason[2], Brian Foster[2], Stefan Gafner[1] [1]Tom's of Maine, Lafayette Center, Kennebunk, ME 04043, USA [2]University of Ottawa, 150 Louis Pasteur Priv, ON, Canada K1N 6N5 [3]Planta Analytica, 8 Warwick Rd, New Fairfield, CT 06812, USA

P:60 EVALUATION OF THE ANTI-INFLAMMATORY PROPERTIES OF SKULLCAP (*SCUTELLARIA LATERIFLORA* L.) EXTRACTS IN DIFFERENT *IN-VITRO* MODELS

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P:61 ACTIVITIES RELEVANT TO ALZHEIMERS DISEASE OF SOME CHINESE MEDICINAL PLANTS

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P:62 ACTIVITIES RELEVANT TO WOUND HEALING OF SOME PLANTS USED TRADITIONALLY IN GHANA PLANTS

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P:63 SELECTION AND DEVELOPMENT OF TREE NUTS AS SOURCES OF ESSENTIAL FATTY ACIDS FOR NUTRACEUTICAL AND COSMETICEUTICAL INDUSTRIES

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P:64 SOME SPECIES OF THE GENUS *SAUSSUREA* DC AS PERSPECTIVE SOURCES OF PHARMACOLOGICAL RAW MATERIAL FROM THE RUSSIAN ALTAI

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P:65 PLANTS WITH ADAPTOGENIC AND IMMUNOPOTENTIATING ACTIVITIES ENDEMIC TO THE RUSSIAN ALTAI

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P:66 STUDIES ON ESSENTIAL OILS OF THE HERBAL PLANTS FROM *MENTHA* SPECIES IN KOREA

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P:67 SAFETY PROFILE OF PURIFIED LARREA TRIDENTATA LEAF RESIN EXTRACT ALONE AND IN COMBINATION WITH ASCORBIC ACID

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P:68 UTILITY OF PURIFIED *LARREA TRIDENTATA* LEAF RESIN FORMULATIONS FOR VIRAL AND INFLAMMATORY CONDITIONS

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P:69 STANDARDIZED GINGER EXTRACT REDUCES BACTERIAL LOAD AND SUPRESSES ACUTE AND CHRONIC INFLAMMATION IN MONGOLIAN GERBILS

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P:70 CRANBERRY INHIBITS TRANSCRIPTIONAL FACTOR NF-κB ACTIVATION, CYTOKINE RELEASE AND COX II ACTIVITY IN VITRO.

Susan Pendland, Allison Turner, Sutatip Bhamarapravati, Jundee Rabablert and G.B. Mahady* College of Pharmacy, University of Illinois at Chicago and College of Medicine, Thammasat University, Bangkok, Thailand.

P:71 MICROSCOPIC DIFFERENTIATION BETWEEN *ARISTOLOCHIA* SPECIES AND *AKEBIA TRIFOLIATA, CLEMATIS ARMANDII, C. CHINENSIS,* AND *STEPHANIA TETRANDRA*

Karin Herzog, Reinhard Laenger*Inst. of Pharmacognosy, Univ. Vienna, Vienna Pharma Center, Althanstr. 14, A-1090 Vienna, Austria

P:72 INVESTIGATING THE MOLECULAR BASIS OF NEUROPROTECTIVE ACTIONS OF TRADITIONAL CHINESE MEDICINE (TCM) STROKE DRUGS

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P:73 PHYTOCHEMICAL SCREENING AND *INVITRO* ANTIBACTERIAL EFFECT OF LEAF EXTRACT ON *PAULINIA PINNATA*

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P:74 BOTANICAL AND CHEMICAL CHARACTERIZATION OF *GUIERA SENEGALENSIS,* A WELL KNOWN WEST AFRICAN MEDICINAL PLANT

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P:75 COMPARISON OF *IN VITRO* RELAXANT PROPERTIES OF RASPBERRY LEAF EXTRACTS IN DIFFERENT SMOOTH MUSCLE PREPARATIONS

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P:76 ISOLATION OF ANISATIN AS REFERENCE SUBSTANCE FOR THE DETERMINATION OF TOXIC ADULTERATIONS IN ILLICIUM VERUM BY HPLC-MS/MS

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P:77 AN IMPROVED ELECTROSPRAY INTERFACE FOR COUPLING OF NORMAL-PHASE LIQUID CHROMATOGRAPHY TO MASS SPECTROMETRY: APPLICATION TO NEOFLAVONOID SCREENING IN *CALOPHYLLUM INOPHYLLUM* FROM FRENCH POLYNESIA.

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P:78 SUBSTRATE SUITABILITY FOR FUNCTIONAL ASSAYS WITH REGARD TO THE INFLUENCE OF GREEN TEA EXTRACT ON ABC-TRANSPORTERS

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P:79 EFFECT OF POLYSACCHARIDES FROM DIASCOREA AS DANGER SIGNALS: IMPLICATION FOR REGULATING IMMUNE RESPONSES AND USE AS VACCINE ADJUVANT

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P:80 ESCIN INHIBITS THE ACUTE INFLAMMATION OF LING IN BOH RATS AND MICE

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P:81 PLANT POLYSACCHARIDES STIMULATE HUMAN PERIPHERAL MONOCYTES TO EXPRESSION INTERLEUKIN 8 AND TUMOR NECROSIS FACTOR-ALPHA VIA TOLL-LIKE RECEPTOR-MEDIATED SIGNALING PATHWAY

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P:82 OMNI (AN ENDOGENOUS INTERFERON INDUCER): AN EMERGING DRUG FOR TREATMENT OF HEPATITIS

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P:83 CYTOPROTECTIVE ACTIVITY OF SOLIDAGENONE BIOTRANSFORMATION DERIVATIVES IN CELL CULTURES

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P:84 MICROPROPAGATION AND EFECTS OF CROPING AREA ON GROWTH OF *KAEMPFERIA PARVIFLORA*

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P:85 GASTROPROTECTIVE ACTIVITY OF THE DITERPENE FERRUGINOL

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P:86 NEOPEIN® AND IMPROVED BIOPEIN® AS NATURAL PRESERVATIVES

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P:87 SEEDS OF *MILLETTIA THONNINGII* POSSESS SEDATIVE AND ANTICONVULSANT PROPERTIES IN MICE

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P:88 SEDATIVE AND ANTICONVULSANT PROPERTIES OF *PASSIFLORA EDULIS* IN MICE

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P:89 IMMUNOMODULATORY ACTIVITIES OF EXTRACTS AND CONSTITUENTS FROM ECHINACEA PLANTS

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P:90 AMINO ACID CHEMOTAXONOMY OF THE GENUS *SOPHORA* (LEGUMINOSEAE)

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P:91 STEVIOSIDE IN COMBINATION WITH SOY-BASED DIETARY SUPPLEMENT EXERTS A BENEFICIAL EFFECT ON TYPE 2 DIABETIC GK-RATS – MULTIFACTORIAL TREATMENT OF TYPE 2 DIABETES AND THE METABOLIC SYNDROME.

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P:92 ANALGESIC EFFECTS OF THE EXTRACT OF *RAUVOLFIA VOMITORIA* (AFZEL)

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P:93 ANTIMALARIAL AND ANTIPYRETIC EFFECTS OF *RAUVOLFIA VOMITORIA* (AFZEL)

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P:94 TANNIC ACID AS A SAFE AND EFFECTIVE HEMOSTATIC AGENT IN PERIRADICULAR SURGERY

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P:95 PROTECTIVE EFFECT OF FLAVONOIDS FROM *GARCINIA KOLA* SEED ON GALACTOSAMINE- INDUCED HEPATOTOXICITY IN MICE.

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P:96 THE ROLE OF MARKER COMPOUNDS IN HERBAL PHARMACEUTICAL PREPRATIONS:

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P:97 HAWTHORN EVOKES A POTENT ANTI-HYPERGLYCEMIC CAPACITY IN STREPTOZOTOCIN-INDUCED DIABETIC RATS.

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P:98 INHIBITION OF ENDOGENOUS GLUCOSE PRODUCTION ACCOUNTS FOR HYPOGLYCAEMIC EFFECT OF *SPERGULARIA PURPUREA* IN STREPTOZOTOCIN MICE.

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P:99 EFFECT OF THE DESERT PLANT *RETAMA RAETAM* ON GLYCAEMIA IN NORMAL AND STREPTOZOTOCIN-INDUCED DIABETIC RATS.

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P:100 CHOLESTEROL LOWERING ACTIVITY OF AQUEOUS EXTRACT OF *SPERGULARIA PURPUREA* IN NORMAL AND RECENT-ONSET DIABETIC.

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P:101 ASSESSMENT ON APPLICATIONS AND ANALITYCAL METHODS OF COPPER IN TRADITIONAL CHINESE MEDICINES

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P:102 HYDROXY-1-ARYLISOCHROMANS: A NEW CLASS OF NATURAL ANTIOXYDANTS AND FREE RADICAL SCAVENGERS

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P:103 GAS CHROMATOGRAPHIC ANALYSIS FOR SUGAR COMPOSITIONS OF CRUDE POLYSACCHARIDE FRACTIONS FROM SOME *PHELLINUS* SPECIES

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P:104 THE ADVANCES RESEARCH IN MARINE NATURAL PRODUCTS FOR ANTI-ALZHEIMER'S DISEASE

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P:105 ANALYSIS ON COMPOSITION AND ANTIFUNGAL ACTIVITIES OF ESSENTIAL OILS FROM *ALLIUM MONANTHUM* MAX.

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P:106 CLINICAL STUDY OF SHAKLEE IMMUNE BUILDING COMPLEX® IN MENOPAUSAL PATIENTS

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P:107 DETERMINATION OF ARISTOLOCHIC ACID IN ASARI HERBA BY LIQUID CHROMATOGRAPHY/TANDEM MASS SPECTROMETRY

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P:108 HERBAL PREPARATION – GINSENG AND DANG GUI TEN COMBINATION (PS10) AND IMMUNE RESPONSE IN HUMANS

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P:109 INHIBITION OF MENADIONE-INDUCED DNA DAMAGE THROUGH INDUCTION OF QUINONE REDUCTASE BY XANTHOHUMOL ISOLATED FROM HOPS

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P:110 ANTIOXIDANT EFFECT OF MILK THISTLE EXTRACTS ON AVIAN MACROPHAGE CELL LINES

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P:111 GARLIC IS EFFECTIVE WITHOUT ALLICIN. (1) CURRENT MARKER COMPOUND FOR HERBS IS NOT MARKER.

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P:112 GARLIC IS EFFECTIVE WITHOUT ALLICIN. (2) MULTIPLE RISK FACTORS OF CARDIOVASCULAR DISEASES AND ANTIATHELOSCEROTIC EFFECT OF AGED GARLIC EXTRACT (KYOLIC) AS A COMPLEMENTARY MEDICATION.

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P:113 GARLIC IS EFFECTIVE WITHOUT ALLICIN. (3) AGED GARLIC EXTRACT (KYOLIC) HAS BEEN CONFIRMED NO CONTRA-INDICATION WITH DRUGS AS A COMPLEMENTARY MEDICATION.

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P:114 THE USE OF COLORED PRINCIPLES IN *HIBISCUS SABDARIFA* AND *SORGHUM BICOLOR* AS NATURAL COLORANTS

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P:115 EFFECT OF GRADED CONCENTRATIONS OF THE AQUEOUS AND ETHANOLIC EXTRACTS OF THE RIPE PLUCKED AND RIPE FALLEN LEAVES OF *TERMINALIA CATAPPA* ON CALCIUM INDUCED BLOOD CLOTTING OF HbAA AND HbSS GENOTYPES.

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P:116 CATIONIC EVALUATION OF SOME TRADITIONAL ANTI SICKLING HERBAL DRUGS USED IN NIGERIA AND THEIR POSSIBLE EFFECTS ON THE EFFICACY OF THE DRUGS

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P:117 QUALITATIVE DETERMINATION OF ARISTOLOCHIC ACIDS IN *ARISTOLOCHIA* PLANTS AND IN COMMERCIAL PRODUCTS BY HPLC-UV-ESI/MS METHODS.

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P:118 HERBAL PRODUCTS FROM THE INTERNET: EVALUATION OF NEPHROTOXICITY AND ARISTOLOCHIC ACID CONTENT

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P:119 STRUCTURE-ACTIVITY RELATIONSHIPS OF ARISTOLOCHIC ACID ANALOGUES. TOXICITY IN CULTURED RENAL TUBULAR EPITHELIAL CELLS

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P:120 COMPARATIVE FATTY ACID CONTENT OF SEEDS OF FOUR *CUCURBITA* SPECIES GROWN IN A COMMON GARDEN.

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P:121 SINGLE LAB VALIDATION FOR THE DETERMINATION OF COMPONENTS IN ST. JOHN'S WORT RAW AND FINISHED PRODUCTS BY HIGH PERFORMANCE LIQUID CHROMATOGRAPHY WITH PHOTODIODE ARRAY DETECTION

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P:122 DETERMINATION OF ADRENERGIC AMINES AND FLAVONOIDS IN CITRUS PEEL/FRUIT EXTRACTS AND IN PRODUCTS BY REVERSED-PHASE HPLC.

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P:123 ENANTIOMERIC SEPARATION OF BIOGENIC AMINES IN CITRUS EXTRACTS/PRODUCTS BY HIGH PERFORMANCE CAPILLARY ELECTROPHORESIS.

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P:124 QUANTITATIVE DETERMINATION OF LIGNAN CONSTITUENTS FROM *SCHISANDRA CHINENSIS* BY HIGH PERFORMANCE LIQUID CHROMATOGRAPHY.

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P:125 CHEMICAL CONSTITUENT STUDY ON *VITEX AGNUS-CASTUS*

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P:126 AUTHENTICATION OF *STEPHANIA TETRANDRA* S. MOOR AND ITS TOXIC ADULTERANT ARISTOLOCHIA FANGCHI WU. USING MICROSCOPY.

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P:127 MACROSCOPIC AND MICROSCOPIC AUTHENTICATION OF *ILLICIUM VERUM* HOOK. F. AND ITS ADULTERANT ILLICIUM ANISATUM L.

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P:128 AUTHENTICATION OF *EPHEDRA* SPECIES FROM OLD WORLD AND NEW WORLD

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P:129 QUANTITATIVE DETERMINATION OF USNIC ACID FROM *USNEA* LICHEN AND IN PRODUCTS BY REVERSED PHASE HPLC.

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P:130 ANALYZING THE YIELD OF ISOQUINOLINE ALKALOIDS IN CULTIVATED AND WILD CRAFTED BLOODROOT (Sanguinaria canadensis) GROWN IN NORTH CAROLINA

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P:131 ANTI-INFLAMMATORY AND CYTOTOXIC ACTIVITIES OF CYCLOARTANES PRESENTS IN *P. ARGENTATUM*.

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P:132 BIOPROSPECTING HISTORIC HERBAL TEXTS WITH BIOINFORMATICS

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P:133 ESSENTIAL OIL ANALYSIS OF *BRICKELLIA VERONICAEFOLIA* (ASTERACEAE)

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P:134 PROANTHOCYANIDINS AND TRITERPENES FROM CRANBERRY FRUITS: ANTITUMOR ACTIVITY AND EFFECTS ON MATRIX METALLOPROTEINASE EXPRESSION

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P:135 THE EFFECTS OF TERPENOIDS ISOLATED FROM LEAVES OF *DIOSPYROS KAKI ON* CARBON TETRACHLORIDE INDUCED HEPATOTOXICITY IN RATS

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P:136 ANTI-INFLAMMATORY AND ANTINOCICEPTIVE EFFECTS OF THE EXTRACT FROM *KALOPANAX PICTUS, PUERARIA THUNBERGIANA* AND *RHUS VERNICIFLUA*

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P:137 PROTECTIVE MECHANISM OF FLAVONOIDS ISOLATED FROM *RHUS VERNICIFLUA* STOKES ON THE PARAQUAT TOXICITY

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P:138 IN VITRO ANTIINFLAMMATORY ACTIVITY OF 23-HYDROXYURSOLIC ACID ISOLATED FROM CUSSONIA BANCOENSIS IN MURINE MACROPHAGE RAW 264.7 CELLS

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P:139 NEW ALKAMIDES FROM *LEPIDIUM MEYENII* (MACA)

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P:140 ANTI-INFLAMMATORY AND ANTI-ARTHRITIC EFFECT OF A DIET-SUPPLEMENT CONTAINING RED GINSENG EXTRACT AND GLUCOSAMINE COMPLEX

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P:141 ANTI-INFLAMMATORY AND ANTI-NOCICEPTIVE EFFECTS BY THE BRANCHES OF *CINNAMOMUM CASSIA* IN RAT ARTHRITIS

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P:142 ANTIOXIDANT COMPONENT OF SIAMESE NEEM TREE LEAF EXTRACT

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P:143 ETHYL CAFFEATE, A NOVEL ANTIOXIDANT ISOLATED FROM *BIDENS PILOSA*, SUPPRESSES ACTIVATION OF NUCLEAR FACTOR-kB BY INHIBITING ITS ABILITY TO BIND DNA IN MACROPHAGE RAW 264.7 CELLS

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P:144 DIFFERENTIAL EFFECTS OF *ECHINACEA PURPUREA* EXTRACTIONS ON TNF PRODUCTION IN HUMAN IMMUNE CELLS

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P:145 NEW TOXINS FROM ARTHROPODS OF ISLAND MADAGASCAR

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P:146 QUALITY EVALUATION OF TEN COMMERCIALLY AVAILABLE BLACK COHOSH PRODUCTS

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P:147 CHEMOPREVENTIVE EFFECT OF OXYPHENBUTAZONE, A NONSTEROIDAL ANTI-INFLAMMATORY DRUG ON EPSTEIN-BARR VIRUS ACTIVATION AND TWO-STAGE MOUSE SKIN CARCINOGENESIS

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P:148 A CASE STUDY OF AN 85-YEAR-OLD BLACK COHOSH (ACTAEA RACEMOSA L.) SAMPLE

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P:149 COMPARATIVE CYTOTOXIC EFFECTS OF BETANIN AND ADRIAMYCIN IN PC-3 AND MCF-7 HUMAN CANCER CELL LINES

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P:150 EFFECTS OF CRAMP BARK (VIBURNUM PRUNIFOLIUM) AND BLACK COHOSH (*ACTAEA RACEMOSA* L.) ON MAMMALIAN UTERINE CONTRACTILITY

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P:151 ISOLATION AND IDENTIFICATION OF INGREDIENTS IN CRUDE EXTRACTS OF *BOSWELLIA CARTERII* BIRDW AND THEIR APOPTOTIC EFFECT IN HUMAN LEUKEMIA CELLS.

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P:152 HPLC CHROMATOGRAPHIC FINGERPRINT OF ASHMI, A CHINESE HERBAL FORMULA AGAINST ALLERGY ASTHMA

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P:153 WHO PUT EPHEDRINE IN *PINELLIA* & WHERE IS THE ARISTOLOCHIC ACID?

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P:154 ANALYTICAL METHODS FOR THE ANALYSIS OF HYPERICIN IN PLASMA TO SUPPORT A CLINICAL TRIAL OF ST. JOHN'S WORT (*HYPERICUM PERFORATUM*) FOR ANXIETY

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P:155 COMPARISON OF THE ESTROGENIC PROPERTIES OF *TRIFOLIUM PRATENSE* AND *HUMULUS LUPULUS*

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P:156 PRODUCTION OF PYRROCIDINES BY THE MAIZE ENDOPHYTE *ACREMONIUM ZEAE* AND THEIR OCCURRENCE IN INFECTED KERNELS

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P:157 OPTIMIZATION OF IN VIVO AND IN VITRO MODELS FOR THE EVALUATION OF SEXUAL AROUSAL AND ERECTILE FUNCTION IN MALE RATS

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P:158 TOXICITY STUDIES OF *TEUCRIUM STOCKSIANUM* BOISS., USED IN TRADITIONAL MEDICINE IN THE ARABIAN GULF

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P:159 EFFECTS OF 10% ETHANOLIC EXTRACT OF *ALPINIA GALANGA* ON THE SEXUAL ACTIVITY IN EXPERIMENTAL ANIMALS

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P:160 SELECTIVE INHIBITION OF COX-2 BY CO2 EXTRACTS FROM BUTTERBUR ROOTS (*PETASITES HYBRIDUS*)

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P:161 CHEMISTRY OF KAVA RHIZOME AND ITS POTENTIAL ADULTERANTS

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P:162 TRAGANTH AS A CONDITIONING AGENT IN SHAMPOO FORMULATION

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P:163 EXTRACTION, IDENTIFICATION, DOSE, AND CLINICAL APPLICATIONS OF MEDICINAL MUSHROOMS

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P:164 PROFILING SAPONINS AND OTHER PHYTOCHEMICALS IN COW COCKLE (*SAPONARIA VACCARIA* L.) BY LC-DAD-MS. EXAMINATION OF FRACTIONS FOR CYTOXICITY AGAINST SOME HUMAN CANCER CELL LINES.

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P:165 MULTIVARIATE STATISTICAL ANALYSIS OF AGRICULTURAL, MORPHOLOGICAL AND PHYTOCHEMICAL CHARACTERISTICS OF *ECHINACEA PURPUREA* PLANTS

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P:167 THE VASODILATIATION EFFECT OF DECURSIN AND DECURSINOL ANGELATE FROM ANGELICA GIGAS

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P:168 THE EFFECT OF *ACANTHOPANACIS SENTICOSI* RADIX ON ALLERGIC IMMUNE REACTION

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P:169 VASODILATION EFFECTS OF DECURSIN MIXTURES ON 5-HT-INDUCED CONSTRICTION IN RAT THORACIC AORTA

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P:170 AN HPLC METHOD WITH PRE-COLUMN DERIVATIZATION FOR QUANTIFICATION OF HEXACOSANOL AND OCTACOSANOL-CONTAINING PRODUCTS

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P:171 ALKALOIDS ISOLATED FROM RHIZOMA *CORYDALIS DECUMBENTIS* HAVE STRONG ANTI-ARRHYTHMIA EFFECT

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P:172 EXTRACTION OF TOTAL FLAVONOID FROM *FLOS ABELMOSCHI* AND ITS ANTI-ULCER EFFECT

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P:173 ANTI DIABETIC ACTIVITY OF STEMS OF *TINOSPORA CORDIFOLIA*

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P:174 ANTIMICROBIAL ACTIVITIES OF ESSENTIAL OILS FROM Oenanthe javanica DC

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P:175 ANTIANGIOGENIC ACTIVITY OF OLEIC ACID FROM SAW PALMETTO (SERENOA REPENS) BERRIES AND A STRUCTURE-ACTIVITY RELATIONSHIP (SAR) STUDY ON RELATED FATTY ACIDS

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P:176 ANTI-INFLAMMATORY AND ANALGESIC PROPERTIES OF *POTHOMORPHE UMBELLATA* AERIAL PARTS ETHANOLIC EXTRACT.

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P:177 ANTI-INFLAMMATORY ACTIVITY OF *POTHOMORPHE UMBELLATA* AERIAL PARTS ETHANOLIC EXTRACT AGAINST HISTAMINE INDUCED *IN VIVO* MODELS.

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P:178 INCREASING THE RATE OF THROUGHPUT IN NATURAL PRODUCT CHARACTERISATION USING EXACT MASS MEASUREMENT WITH POLARITY SWITCHING AND PARALLEL ANALYIS.

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P:179 QUANTIFICATION AND CHARACTERISATION OF C-GLYCOSIDIC FLAVONOIDS FROM NATURAL PRODUCTS USING Oa-TOF-MS.
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P:180 BOTANICAL DRUG DEVELOPMENT IN THE US-AN UPDATE ON BOTANICAL DRUG SUBMISSION AND REVIEW FROM CENTER FOR DRUG EVALUATION AND RESEARCH, FDA
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P:181 ORGANIC ACIDS ISOLATED FROM OLIBANUM ARE POTENT ANTI-ARTHRITIS AGENTS.
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P:182 QUANTITATIVE DETERMINATION OF APORPHINES IN *CASSYTHA FILIFORMIS* L.: METHODOLOGY AND VALIDATION.
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P:183 STANDARDS OF EVIDENCE FOR SAFETY, EFFICACY, AND QUALITY TO OBTAIN A CANADIAN NATURAL HEALTH PRODUCT LICENCE FOR SALE
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P:184 CHARACTERIZATION OF MEDICINAL ZINGIBERACEAE USING ISSR
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P:185 ISOLATION OF ANTIPLASMODIAL COMPOUNDS FROM *CASSIA SIAMEA* STEMBARK EXTRACT
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P:186 *ARGEMONE PLATYCERAS* ETHYLACETATE FRACTION ANTAGONIZES LTD$_4$-INDUCED CONTRACTIONS IN GUINEA PIG AIRWAYS.

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P:187 PHYTOCHEMICAL VARIATION IN STINGING NETTLE (*URTICA DIOICA*) EXTRACTS PROCESSED WITH DIFFERENT SOLVENT EXTRACTION RATIOS.

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P:1

GC/MS FINGERPRINT PROFILING OF *IOSTEPHANE HETEROPHYLLA* ROOTS AND QUANTITATIVE ANALYSIS OF XANTHORRHIZOL IN AN ALCOHOLIC EXTRACT.

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Iostephane heterophylla (Cav.)Benth (Asteraceae) is an appreciated plant in Mexican traditional medicine. Chemical and biological studies on the roots have identified sesquiterpenes, diterpenes and glycosides as bioactive constituents. In this study, a GC/MS method was developed and validated to examine the chromatographic fingerprint profile of *Iostephane heterophylla* roots. Diterpenic acids as trachyloban-19-oic, *ent*-kaur-16-en-19-oic, and 16□-hydroxy-*ent*-kaurane and the sesquiterpene 2-methyl-5-(1,5-dimethyl-4,5-epoxyhexyl)-phenol were selected because they constitute major compounds found in the roots. A selective and sensitive GC/MS method for quantitation of xanthorrhyzol as the major compound in the ethanol extract was developed, and provides a rapid and sensitive method for identification of *Iostephane heterophylla* species, and could be used for quality control in the manufacture of its products.

P:2

RAPID AND EASY IDENTIFICATION OF THE ADULTERANT *Illicium anisatum* L. IN THE POWDER OF *I. verum* Hook. f.

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The fruit of *Illicium verum* Hook. f. (Star anise) has stimulant, diuretic and digestive properties and is known to be an effective remedy for gas and indigestion. In the TCM (Traditional Chinese Medicine) it is particularly given as herbal tea to infants suffering from colic pain. Due to its success in the TCM in treating colic pain in infants, it is now being preferred by growing number of consumers even in the Western countries. Unfortunately in the recent years increasing number of cases of infants suffering from acute neurological effects such as seizures, vomiting, jitteriness and rapid eyeball movement were reported from Western countries after the consumption of Star anise herbal tea. These adverse cases are believed to be due to the possible adulteration of Chinese star anise with the Japanese or the Bastard anise *Illicium anisatum* L. So a rapid and easy Gas chromatographic method has been developed for the ready identification of the possible adulterant *Illicium anisatum* in the powder of *I. verum*. Also the GC fingerprints of various *Illicium* species were developed.

P:3

ANALYSIS OF POLYPHENOLIC ANTIOXIDANTS FROM THE FRUITS OF THREE *POUTERIA* SPECIES BY SIM LC-MS

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Pouteria campechiana, *Pouteria sapota*, and *Pouteria viridis* are tropical plants in the Sapotaceae family that bear edible fruits. The fresh fruits of these three *Pouteria* species were each extracted and activity-guided fractionations were performed to identify the antioxidant constituents. Seven polyphenolic antioxidants, gallic acid (1), (+)-gallocatechin (2), (+)-catechin (3), (-)-epicatechin (4), dihydromyricetin (5), (+)-catechin-3-*O*-gallate (6), and myricitrin (7), were isolated and identified. Extracts of the three *Pouteria* fruits were analyzed by a selected ion monitoring liquid chromatography-mass spectrometry (SIM LC-MS) method to quantify their polyphenolic antioxidants. The fruits of *P. sapota* contain the highest level of total polyphenolic antioxidants; the fruits of *P. viridis* contain the medium level of total polyphenolic antioxidants, the fruits of *P. campechiana* contain the lowest level of total polyphenolic antioxidants. This work is supported by NIH-NIGMS award S06GM008225 and the Professional Staff Congress of The City University of New York (PSC-CUNY) award 669662.

P:4

COMPARATIVE ANALYSIS OF FLAVONOIDS FROM DIFFERENT EDIBLE ORGANS OF *SECHIUM EDULE* (JACQ) SWARTZ (CUCURBITACEAE) BY HPLC-PDA-ESI-MS

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Sechium edule (Jacq.) Swartz (Cucurbitaceae), a herbaceous climbing plant, has been cultivated since pre-Colombian times in Mexico, where the edible fruit is commonly called "chayote". In addition to the fruits, also stems, tender leaves, and the tuberous part of the adventitious roots are eaten. Medicinal use of *S. edule* has also been documented in the literature. The leaves decoction dissolves kidney stones, and it's useful as complementary treatment for arteriosclerosis and hypertension.[1] Few previous phytochemical studies on *S. edule* led to the isolation of sterols, alkaloids, and saponins,[2] while there are no reports on the flavonoidic composition of the edible organs of the plant. The aim of the present study was to promote the conservation and the use of *S. edule* as food, evaluating the profile of flavonoids of roots, leaves, stems, and fruits by LC-PDA-MS. Eight flavonoids, including three *C*-glycosyl and five *O*-glycosyl flavones, were detected, characterized by NMR spectral data, and quantified.
[1]Flores, E. *Rev.Biol.Trop.* 1989, *37*, 1-54. [2]Salama, A.M.; Polo, N.A.; Enrique, M.; Contreras, C.R.; Maldonado, R.L. *Rev. Colombiana Cien. Quim. Farmac*. 1986, 15, 79-82.

P:5

IDENTIFICATION AND MEASUREMENT OF THE MAJOR FATTY ACIDS IN *IRVINGIA GABONENSIS* (O'RORKE) BAILL SEED OIL USING MALDI-TOFMS AND HPLC.

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Consumption of excessive dietary fats via dietary supplements/foods is becoming a major public health concern linked to coronary heart disease. Theseeds of *Irvingia gabonensis* (Irvingiaceae-), locally known in Nigeria as 'agbono' are used as soup thickener and seasoner in many native dishes. Agbono is a choice ingredient in fufu, a major staple of Nigeria, consumed by over 120 million people regularly. The main objective of this study is to analyze the fatty acid content of agbono.
The major fatty acids in the heptane extract of the dried seeds of the edible species of *I.gabonensis* was identified and measured by a combination of matrix-assisted laser desorption/ionization time-of-flight mass spectrometry [MALDI-TOFMS] and HPLC.
The MALDI-TOF mass spectrum of saponified heptane extract of *I.gabonensis* showed the presence of sodiated sodium salts of lauric acid (m/z 245), myristic acid (m/z 273), palmitic acid (m/z 301) and oleic acid (m/z 327). The HPLC analysis was carried out on the compounds derivatized with phenacyl bromide/triethylamine/acetic acid in acetone. These were eluted with methanol/water and detected at 244 nm. The presence of lauric acid, myristic acid, palmitic acid and oleic acid were confirmed by MALDI-TOFMS. The extraction efficiency in heptane was 91 % for myristic acid, 90 % for Lauric acid, 88 % for oleic acid and 81 % for palmitic acid respectively. The percentage content of these four acids and their concentration in a100 mg powdered seed were lauric acid (0.21 M; 39.6 %), Myristic acid (0.26 M, 47.95 %), Palmitic acid (0.033 M, 6.31 %) and Oleic acid (0.032 M, 6.10%).
Lauric, myristic and palmitic acids are considered to be cholesterol-raising saturated fatty acids. The labeling regulations in the United States and Canada allow oils with less than 7.1% of these acids to be considered as low in saturated fatty acids. The data presented in this study suggests that *Irvingia gabonensis* seed oil is high in saturated fatty acids.

Keywords: Identification, fatty acids, *Irvingia gabonensis*, HPLC, MALDI-TOFMS

P:6

DEREPLICATION OF CYTOTOXIC CUCURBITACINS IN PLANT EXTRACTS

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In the course of the LC-MS dereplication of cytotoxic plant extracts in anticancer drug discovery, a number of extracts have been predicted to contain cucurbitacins as the cytotoxic principles. Several potently cytotoxic cucurbitacins have been studied *in vivo* and found to have poor therapeutic indexes and little potential for further development.[1] Thus, in cell-based screening for potential anticancer leads, cucurbitacin-containing plants may be seen as potential false-positive hits. LC-MS dereplication provides a chemical rationale for prioritizing samples for bioassay-guided isolation, based on whether a known active compound is associated with the bioactivity. However, extremely potent cucurbitacins may show bioactivity, but be present in amounts below the detection limit of the standard sample-preparation and LC-MS method used for dereplication in our laboratory. A method using solid-phase extraction sample enrichment and LC-MS/MS analysis for the isolation and rapid identification of selected cucurbitacins from plant extracts is presented. (Supported by grant U19 CA52956 from NCI, NIH, Bethesda, MD).

[1] Cassady, J. M.; Suffness, M. In *Anticancer Agents Based on Natural Product Models*; Cassady, J. M.; Douros, J. D., Eds.; Academic Press; New York, 1980; Chapter 7, pp 201-269.

P:7

A NEW HOLISTIC GINKGO FRESH PLANT EXTRACT INCREASES THE MICROCIRCULATION IN ELDERLY PATIENTS

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We developed a new holistic Ginkgo fresh plant extract, which is free of ginkgolic acids (<5 ppm). In a controlled clinical trial we investigated in 32 elderly ambulatory patients the influence of the Ginkgo preparation on parameters of microcirculation, blood flow and immune function. We examined two tissues (derma and gingiva) with intravital microscopy, vitalmicroscopic reflection spectrometry and combined Laser-Doppler-flowmetry. Participants received either 2 x 270 mg Ginkgo extract per day or no treatment (reference group) during 30 days.

After a treatment duration of 20-30 days all investigated microcirculatory parameters such as number of nodal points, venular streaming (Qven) and the tube hematocrit, as well as the number of adhering white blood cells and the number of ICAMs were statistically significant in favour for the Ginkgo group.

The results show that administration of 2 x 270mg Ginkgo fresh plant extract leads after a treatment duration of 30 days in elderly patients to clinically relevant changes of their microcirculation and may improve their immunological response.

P:8

A VALIDATED METHOD FOR THE QUANTIFICATION OF TRACHYLOBANE AND PIMARANE DITERPENES IN THE LEAVES OF *CROTON ZAMBESICUS* BY CAPILLARY GAS CHROMATOGRAPHY

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Croton zambesicus is a small tree widespread in Tropical and Central Africa. The leaves decoction is used in African folk medicine to treat hypertension, microbial infections or fever. Recently, several new trachylobane and pimarane diterpenes have been isolated from the leaves (1, 2). In order to quantify these compounds (*ent*-trachyloban-3β-ol, *ent*-18-hydroxy-trachyloban-3-one, *ent*-trachyloban-3-one and isopimaran-7,15-dien-3β-ol) in the leaves, a sensitive and accurate method, combining soxhlet extraction, solid-phase extraction and gas chromatography has been developed. This method has been fully validated and it demonstrates that *C. zambesicus* could become an interesting source of trachylobane diterpenes in order to screen their biological activities.

1. Block *et al*., Planta Medica 2002; 68: 647-649.
2. Block *et al*., Phytochemistry 2004; 65: 1165-1171.

P:9

COMPREHENSIVE 2-DIMENSIONAL HPLC (LCxLC)

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Due to an increasing need for improved chromatographic resolution of complex mixtures, in recent years much attention has been given to 2-dimensional (2D) chromatography. So called comprehensive techniques (GCxGC, LCxGC or LCxLC) appear very promising. These techniques involve a slow separation on a first column that is cut into many small parts each of which is transferred and then rapidly separated on a short second column with different properties. For the analysis of volatiles and proteins comprehensive techniques are becoming routine. LCxLC of natural products is still in its infancy mainly because columns generally applicable for secondary metabolites and possessing good orthogonality are hard to find.
To explore the possibilities of LCxLC for the separation of complex mixtures of similar secondary metabolites, we have attempted to separate a mixture of 52 benzoic and cinnamic acid derivatives. As a first step the compounds were separated individually on different columns with various solvents to find two columns providing sufficient orthogonality. In a next step the optimal combination was combined in a true LCxLC system and evaluated with different mixtures of the 52 compounds. Some initial results will be shown and some problems and plans for improving the system will be discussed.

P:10

ANTIPLATELET ACTIVITY OF ISOMALTOL AND SULFURETIN FROM THE BARK OF *RHUS VERNICIFLUCA*

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Antiplatelet activity has been identified in a methanolic extract of *Rhus vernicifluca*, a herbal medicine in Korea for treatment of blood stasis. Bioassay-guided fractionation using ADP-, arachidonic acid-, collage-induced human platelet aggregation by whole blood aggregometer for thrombosis yielded the active components, isomaltol and sulfuretin, with significant more inhibition of platelet aggregation than aspirin at nearly equivalent concentrations. In addition, we evaluated platelet activation on the surface expression of glycoprotein IIb/IIIa (CD41), P-selectin (CD62), PAC-1 binding to the activated conformation of the GPIIb/IIIa receptor, and intracellular calcium mobilization responses by flow cytometry. Dose-dependent inhibition of platelet aggregation and reduction of platelet receptor expression were observed in the isomaltol and sulfuretin- treated, respectively. These results showed that isomaltol and sulfuretin form *Rhus vernicifluca* have potent antiplatelet activity.

P:11

PRELIMINARY MICROBIOLOGICAL INVESTIGATION OF NIGERIAN TUBERCULOSIS ETHNOMEDICINE.

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In a preliminary survey, eighteen extracts of seven plants KP1-KP7 used in Nigerian ethnomedicine in the treatment of Tuberculosis were tested in vitro against a number of bacteria viz.: *Mycobacterium tuberculosis*, *Mycobacterium smegmatis, Pseudomonas aeruginosa, Escherichia coli, Staphylococcus aureus* and *Candida albicans* using broth micro dilution and agar diffusion technique.
The significance of these organisms in HIV/AIDS endemic settings will be discussed.
Thirteen of the plant extracts from six plants showed antibacterial activity with Minimum Inhibitory effects ranging from 250µg/ml-1250µg/ml. Three of the plant extracts were specific for *M. tuberculosis* with MIC of 625µg/ml.
This work lends credibility to the tuberculosis ethnomedicine practice in Nigeria.

P:12

CARDIOPROTECTIVE ACTIONS OF *SCOPARIA DULCIS* IN PERCHLORATE ADMINISTERED RATS

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Antioxidant and hypolipidemic activities of Flavonoid Rich Fraction (FRF) from the medicinal plant Scoparia dulcis was studied in perchlorate administered rats. Administration of perchlorate significantly raised the concentrations of all lipid components in serum, liver and heart of the experimental animals. Lipid peroxidation was also enhanced to highly significant rate as evidenced by the elevated levels of Malondialdehyde, Hydroperoxides and Diene conjugates. Antioxidant machinery was defective to meet the increased demands. Administration of FRF compensated for the decrease in activity of the antioxidant and anti lipid peroxidative enzymes like superoxide dismutase, catalase, glutathione reductase, glutathione peroxidase and glutathione –s-transferase. The results thus show an alteration in the metabolism of lipids and lipid peroxides in different tissues during oxidative stress. *In –vitro* studies also support this view and provide evidence for the inhibition of superoxide production by Scoparia dulcis FRF. Antioxidant activities assessed by *in vitro* assay indicate inhibition of *in-vitro* lipoprotein diene formation in a concentration dependent manner. The above results provide valuable information on the potential cardioprotective effects of flavonoid compounds from Scoparia dulcis

P:13

STRUCTURE DETERMINATION OF SENNOSIDES A AND C FROM SENNA (*CASSIA ANGUSITFOLIA*) PODS

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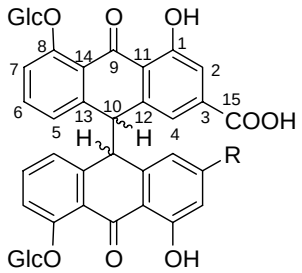
The leaves and pods of senna (*Cassia angustifolia* Vahl., Fabaceae) are used traditionally for their laxative effects. Several dianthrone glycosides, sennosides A through G, have been isolated as the laxative principles. However, the structure elucidation of these has been accomplished largely without the use of NMR; the only exception being sennoside A, where ^{13}C NMR data are available in the literature. In the present study, sennosides A and C were isolated from senna pods by successive chromatographies followed by prep-HPLC. Structures of sennosides A and C were confirmed using 1D and 2D NMR spectroscopy and mass spectrometry, and their stereochemistries were determined using circular dichroism (CD) via comparisons with the CD data of other sennosides. This is the first report of determining the structure of sennoside C using NMR (supported by contract No. NO1-ES-05455).



Sennoside A R = COOH
Sennoside C R = OH

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GASTROINTESTINAL ABSORPTION OF THE TWO COMPONENT EXTRACTS OF A COMBINED VALERIAN/HOPS PREPARATION (ZE91019) IN HUMANS – A PRELIMINARY STUDY

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The fixed extract combination of valerian and hops, known as Ze91019, has been on the European and North American market for a number of years. Its efficacy as a natural sleep aid remedy has been substantiated by previous and ongoing studies. Beside pharmcodynamics, the need for a full understanding of pharmacokinetics is essential to enhance the potential of herbal products as reliable phytopharmaceuticals. In this study, a human volunteer was orally administered characterized extracts of valerian and hops (components of Ze91019) in separate sessions. Plasma samples were analyzed by LC-MS to detect the presence of the characteristic marker(s) of each extract. Two components of the valerian extract and three of the hops extract were identified in human plasma within 15 minutes of administration. The valerian components were identified as hydroxy- and acetoxyvalerenolic acid; while those of hops were hulupone, cohulupone and hulupinic acid.

P:15

ENZYME INHIBITION TESTS ON *GRINDELIA ROBUSTA* NUTT. HERB EXTRACTS

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Gum plant, *Grindelia robusta* NUTT., is indigenous in Southwestern United States, Central America, and in parts of South America. The perennial asteraceae has been used in folk medicine as anti-spasmodic and expectorant. Additionally positive effects on inflammatory arthritis are described (references cumulated in [1]).
In continuation to our previous studies [e. g. 2, 3] on grindelia differently prepared gum plant extracts (extraction solvents of different polarities, CO_2) were quickly checked by a rapid TLC applying the DESAGA H-chamber and furthermore submitted to enzyme inhibition tests (inhibition of neutrophil elastase and thrombin activity). In both cases an acetone extract (1 g plant material/ 10 ml) of grindelia herb showed higher inhibitory effects at diverse extract concentrations, e. g.
- neutrophil elastase activity: acetone extract $IC_{50} \approx 1$ µg/ml vs. EtOH extract $IC_{50} \approx 100$ µg/ml, - thrombin activity: acetone extract $IC_{50} \approx 330$ µg/ml vs. CO_2 extract $IC_{50} \approx 500$ µg/ml.

References: [1] A. Menghini et al. (1995) Grindelia. *Aboca*. GRAPHOS s.r.l. [2] B. Gehrmann, M. F. Melzig (2003) Congress Issue 44th ASP-Meeting, P 141. [3] B. Gehrmann, M. F. Melzig (2002) Revista de Fitoterapia 2 (S1): 91.

P:16

A SYSTEMATIC REVIEW AND META-ANALYSIS ON CLINICAL DATA OF PADMA, A TIBETAN HERBAL MULTI-COMPOUND FORMULA, IN THE TREATMENT OF PERIPHERAL ARTERIAL OCCLUSIVE DISEASE (PAOD)

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Where as in Western Medicine treatment of peripheral arterial occlusive diseases (PAOD) is rather based on drugs containing a single compound (i.e. pentoxifylline, naftidrofuryl), in Tibetan Medicine drugs consisting of multi compounds are used. One of these is known for about 30 years in Switzerland and registred as PADMA 28® (22 compounds: 20 herbal drugs, Camphora and Calcium Sulphate).

Method: A systematic review was performed searching the databases Medline, Embase, Amed, Cochrane Collaboration, Cancerlit, Toxline, Healthstar using the seach terms Tibetan, herbal medicine, phytotherapy, PADMA, peripheral arterial occlusive disease, clinical study/trial. Including additional handsearching of relevant medical magazines, contacting experts, disclosure of the product documentations of the manufacturer and without any language restrictions, up to June 2003, 19 studies were found. Trials with an identical design (double-blind, placebo-controlled) on PAOD could be pooled for a meta-analysis.

Result: Out of 19 studies with PADMA 28® eight studies contained data on PAOD. Six studies with the primary end point of the maximum treadmill walking distance were pooled for a meta-analysis according to Peto Mantel Haenszel. The data of 444 patients (mean age 63 years, 64 % males) with stable PAOD stage IIb, according Fontaine, were included in the efficiacy analysis. After 4 month of treatment 23,5% of the verum group showed an increase in treadmill walking distance by at least 100 m versus 2,1 % in the the placebo group. The mean increase in walking distance was 92,7 m ± 118,5 m under verum and 21,2 m ± 85.9 m under placebo ($p < 0,001$). Pain free treadmill walking distance also increased significantly with the the active tratment in 2 trials reporting on it. As in the different studies there were reports of side effects, adverse events and intercurrent disease all these data were considered to be undesired events for the safety evaluation. The preparation was well tolerated. None of the four serious adverse events (1 death due to myocardial infarct, 3 cases of neoplasm) could be related to the drug. In the analysis per body system only dermatological symptoms (i.e. exanthem, dermatosis) were more frequent yet, not significant in the verum group with 1,4 % versus 0,5 % in the placebo group.

Conclusion: The existing data indicate that PADMA 28 significantly increases walking distance in patients with PAOD Fontaine stage II b in a clinical relevant manner and is well tolerated.

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RED GRAPE POLYPHENOLICS PREVENT APOPTOSIS AND OXIDATIVE DNA-DAMAGE IN HUMAN PBMC AND INFLUENCE THE ANTIOXIDANT POTENTIAL IN PLASMA AFTER ACUTE CONSUMPTION OF RED WINES AND GRAPE JUICE.

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The beneficial effects of red wine consumption have been reported in context with potential risk factors for many diseases, such as coronary heart disease and cancer. More specifically, several of the disease-preventive features of red wine such as antioxidant effects and protective effects against chemical-induced DNA damage and apoptosis have been ascribed to red wine-polyphenolics.

The objective of this study was to compare the antioxidant effects of acute consumption of a moderate amount of the polyphenol-rich red muscadine wine (*Vitis rotundifolia*) to red cabernet sauvignon wine (*Vitis vinifera*), red muscadine juice- and an ethanol-control beverage.

Hydrogen peroxide-induced DNA damage, generation of reactive oxygen species, etoposide-induced apoptosis in peripheral blood mononuclear cells (PBMC) and antioxidant potential in plasma from 37 subjects were determined before, 1 and 2h after the consumption. Overall, results demonstrate the antioxidant and cell-protective effects of an acute consumption of both wines and the juice, whereas the consumption of ethanol induced a pro-oxidant response.

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BIOCHEMICAL AND HAEMATOLOGICAL EVALUATION OF (CUCURBITACEAE) *Cucubita Maxima* IN ALBINO RATS

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Leaves of C*ucurbita Maxima* (Cucurbitaceae), an edible plant was evaluated in albino rats. Hot and cold water extracts were prepared with percentage yields of 10.34 and 12.61 % respectively. Animals were fed with two different doses of both preparations. Control animals were allowed H_2O only. Normal rat diet was used throughout the period of study. Total protein, cholesterol, hematological profile, food intake and weight gain were measured. Doses of 75g/kg and 150g/kg were used for both preparations. Results showed significant increase ($P<0.01$) in PCV, platelet count, RBC, Hb for the cold water extracts preparations. 75g/kg of the hot water extract also showed a significant difference ($P<0.001$) in RBC, platelet, Hb and PCV, while the 150g/kg dose only gave a significant difference for RBC, Platelet and PCV (compared with the control group). Total protein was significant increased ($P<0.001$) for only the cold water extracts. Cholesterol levels were also high and very significant in both cold and hot water extracts. Food intake was higher in controls but percentage weight increase was particularly significant in the cold-water extract treatment groups. Study show that leaf extracts of *cucurbita maxima* could be use as food supplements.

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ANTI-TUMOR PROMOTING EFFECTS AND CYTOTOXIC ACTIVITIES AGAINST HUMAN CANCER CELL LINES OF TRITERPENE GLYCOSIDES AND FLAVONOL GLYCOSIDES FROM MARIGOLD (CALENDULA OFFICINALIS L.) FLOWERS

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Marigold (*Calendula officinalis* L., Compositae) is a popular medicinal plant and cosmetic herb in Europe and in the US. In the course of our study, we found that the triterpene diols and triols isolated from the methanol extract of some Compositae plants showed the inhibitory effect on Epstein-Barr virus early antigen (EBV-EA) induced by the tumor promoter 12-*O*-tetradecanoylphorbol 13-acetate (TPA) in Raji cells. In this study, we will report anti-tumor promoting effects and cytotoxic activities of triterpene glycosides and flavonol glycosides isolated from marigold flowers.

Marigold flowers were extracted with MeOH, and the extract was partitioned with *n*-hexane, MeOH-H_2O, *n*-BuOH, and H_2O. The *n*-BuOH layer was subjected to column chromatography on Diaion HP-20 and ODS, followed by HPLC, which yielded 10 triterpene glycosides and 4 flavonol glycosides. They were evaluated for their anti-tumor promoting activity and cytotoxic activity.

P:20

CHARACTERIZATION OF *Radix Astragali* BY LC/APCI/MS

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Radix Astragali, known as “Huang-Qi” in Chinese medicine, is widely used as a tonic to replenish vital energy, particularly treating symptoms of “Qi-deficiency” and “Yang-weakness”. Botanically, the herbal drug is derived from the roots of *Astragalus membranceous* (Fisch.) Bunge or *A. membranceous* var. *mongolicus* (Bunge) Hsiao (Family Leguminosae). Major ingredients of *Radix Astragali* include triterpene saponins (such as astragalosides) and flavonoids. Polysaccharides have also been found.
As part of the work to establish fingerprint chromatograms for commonly used Chinese medicinal materials, we have examined the two species of *Astraglus* and report here an HPLC/MS method for the analysis of nine marker components, calycosin-7-O-β-D-glucoside, ononin, 9-methoxy-nissolin-3-O-β-D-glucoside, isomucronulatol-7-O-β-D-glucoside, calycosin, astragaloside IV, formononetin, 9-methoxynissolin, and isomucronulatol.

(This work is part of a project on the study of some common Chinese materia medica in Hong Kong, being undertaken by the Department of Health, Hong Kong Special Administrative Region Government, People’s Republic of China.)

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STABILITY OF *ECHINACEA PURPUREA* SAMPLES AND EXTRACTS

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Echinacea purpurea (L.) MOENCH (Asteraceae) is indigeneous to North America, but has been cultivated in Europe since app. 1900. Preparations of *E. purpurea* are used as herbal medicine to cure/prevent the common cold and to ”boost” the immune system. But proper standardisation of the preparations is still needed. In the search for biologically active substances in *E. purpurea,* three classes of compounds have received special attention: Alkamides, cichoric acid and polysaccharides. We have developed an HPLC method for quantitative analysis of the alkamides and cichoric acid (Mølgaard *et al.* 2003).
The aim of this study was to test the stability of cichoric acid and alkamides in *E. purpurea* samples and extracts in order to make recommendations concerning storage.
Plant material from *E.purpurea* grown in Denmark was air dried at 40°C and milled. The amount of alkamides and cichoric acid present before storage was determined by HPLC. At regular time intervals i.e. weeks or months new extracts was made from the dry, milled plant material and analysed together with the extracts made before storage.
The alkamides and cichoric acid decay rapidly in the dried milled plant material, while in methanolic extracts they are stable for at least five months. The stability in ethanolic extracts is being determined at the moment and will be presented at the congress.

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USE OF ECHINILIN IN THE TREATMENT OF COLDS

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282 subjects were recruited for a randomized, double-blind, placebo-controlled study conducted to evaluate the efficacy of Echinilin for the treatment of a common cold. Echinilin, a proprietary extract of Echinacea purpurea, is chemically standardized to contain alkylamides, cichoric acid, and polysaccharides at concentrations of 0.25/2.5/25.5 mg/mL, respectively. At the onset of initial symptoms of a common cold, subjects commenced Echinilin/placebo treatment for a period of 7 days. During this period, using a 10-point scale, subjects also self evaluated the following 13 symptoms: sore throat, runny nose, stuffy nose, sneeze, watery eyes, chills, malaise, fever, headache, sore muscles, hoarseness, shortness of breath and cough. Self-assessed total daily symptom scores were found to be significantly lower in the Echinilin group ($p<0.05$) compared to the placebo group. This is true both on an intention-to-treat and per protocol basis. Echinilin treatment also reduced the duration of a common cold. No significant differences in the incidences of reported side effects were found between the Echinilin and placebo group.

P:23

PROTECTIVE EFFECT OF RED GRAPE SEEDS PROANTHOCYANIDINS IN ALLOXAN-INDUCED DIABETES IN RATS.

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It has been documented that impaired homeostasis in diabetes mellitus is associated with increased production of reactive oxygen species and depletion of the antioxidant defense systems. Such high oxidative stress promotes lipid peroxidation and subsequent tissue damage. Natural grape seed proanthocyanidins (GSP) are potent free radical scavengers and hence provide significant protection against lipid peroxidation. Accordingly, the present study focused on investigating the possible protective role of GSP against oxidative stress damage in pancreatic tissues of alloxan-induced diabetes in rats. The results revealed that oral administration of 50 and 100 mg/kg (body weight) of GSP for 72 hours significantly ($p<0.001$) increased pancreatic glutathione (GSH) levels and inhibited the increase in lipid peroxidation caused by alloxan. Furthermore, GSP caused significant decline in the sustained increment in serum glucose as well as nitric oxide (NO) release induced by alloxan ($p<0.001$, $p<0.005$, respectively). In conclusion, the study suggests that GSP are effective in ameliorating the damage to pancreatic tissue in experimental diabetes mellitus. Such effect may be related to their potent antioxidant properties as evidenced by the increase in pancreatic GSH and reduction of lipid peroxidation as well as NO production.

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STUDIES ON ANTIFUNGAL FLAVONOIDS FROM *ALLIUM* SPECIES

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Allium species have been recognized as the rich sources of flavor and fragrant compounds as well as the various interesting pharmacological activity. Allicin is the well-known fungistatic component of *Allium* spp. However, this compound is so unstable, once it is generated it readily changes into other compounds. Thus allicin has not been conclusively proven to be responsible for garlic's known health benefits. Moreover, recent scientific findings have revealed that allicin itself is not biologically active form inside of the body. Therefore, it is strongly possible that compounds in *Allium* spp. other than allicin are also responsible for the activities.
To develop the stable and safe antifungal agents from natural products, especially from the daily foodstuffs, the antifungal activities of the flavonoids in *Allium sativum* (bulbs), *A. cepa* (bulbs), *A. fistulosum* and *A. tuberosum* (whole plant part) were studied. The extracted fractions of *Allium* species were analyzed and compared by thin layer chromatography and the corresponding phytochemical reactions. The antifungal activity of the flavonoid factions and the isolated compounds by column chromatography were investigated by broth dilution method and disk diffusion test on Sabouraud"s agar plates against *Aspergillus, Trichophyton* and *Candida* species. Among the tested fungi, *Trichphyton* species showed especially high susceptibility to flavonoids from *Allium* species.

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INDUCTIONS OF PITUITARY HORMONE RELEASE BY *Anemarrhena asphodeloides* BUNGE (Liliaceae) AND ITS INGREDIENT

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Anemarrhena asphodeloides B_{UNGE} (AA) has been used as a traditional anti-inflammatory drug in Asia. Hormonal releases by herbal extracts were not studied seriously, yet. Pituitary Hormones are Growth Hormone (GH), Luteinizing Hormone (LH), Prolatin, FSH, Thyroid stimulating hormone and Adrenocorticotrophin. Induction of pituitary hormones release by the AA extract and its gradients were determined using rat pituitary primary cell culture method to develop a new drug and improve bioavaliablity. Concentrations of hormones were analyzed using RIA kits.
In results, one of its ingredients (TA) was isolated from the rootstock of AA and its structure was identified. The methanol extract of AA and TA induced rat GH 18 times and 17 times of the control, respectively. The release of rat LH of AA and TA were 11 fold and 2.7×10^5 fold as high as the control, respectively. However, plasma concentrations of both hormones after an i.v. administration of AA and TA, each, were not significantly different from those of the control. These results suggest that methanol extracts of AA and TA stimulated both rGH and rLH releases from pituitary somatotrophs. Further studies on reaction mechanism of TA are in progress.
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MEDICINAL PLANTS OF THE PRAIRIE AS SOURCES OF NEW PHARMACEUTICALS.

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For the past eleven years this laboratory has been investigating the chemistry of native North American prairie plants with a history of medicinal uses by Native Americans and early European immigrants to the plains. Investigative literature searches have identified over 200 different species with documented medicinal and ceremonial uses. Over 50 species of these plants have been collected and bioassayed for activity against HIV-1, human tumor cell lines and cytotoxicity against *M.tuberculosis* . These assays have been done in collaboration with the US National Institutes of Health (NIH) pilot program for the development of AIDS-related therapeutics. Of the 50 species assayed , eight have shown sufficient activity to warrant further investigation by our laboratory. This presentation will discuss the current research on four of these species (*I.leptophylla, E. pallida, S. laciniatum* and *G. lepidota).*

P:27

VIRTUAL SCREENING FOR NUTRACEUTICALS IN TYPE 2 DIABETES PREVENTION

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Obesity and diabetes have become global health epidemics. High percentages of the American and Western Europe population are obese. As a result more and more young people are affected by type 2 diabetes. Special nutraceuticals consumed with the normal food could increase insulin sensitivity and lower blood glucose level in the long-term and therefor help to prevent type 2 diabetes.
Virtual Screening (VS) can be an effective tool to select the best set of natural compounds for this indication. Based on publicly available crystal structures we developed a VS method based on GLIDE (Schrödinger Software). Of the approximately 3000 natural compounds that Interbioscreen is selling we screened *in silico* about 1200 with suitable physical and chemical properties. The result was a list of less than 400 compounds ranked by their "docking score". Looking for non-toxicity, food-chain origin, and diversity we selected the 80 most promising structures. These compounds were tested in a series of *in vitro* assays (e.g. glucose uptake, adipocyte differentiation). In the end about 18 times more natural compounds were selected from this target-focussed selection than out of a previous random substance library.

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NUTRACEUTICALS – FROM PLANT EXTRACT TO FUNCTIONAL FOOD. A DISCOVERY HIGH THROUGHPUT APPROACH

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Functional food is an emerging market. Nutraceuticals as food supplements should have a long-term effect in preventing a wide range of medical conditions, but many products lack efficacy and cannot deliver what they promise. DSM Nutritional Products as the world's leading vitamins supplier follows a scientific and target-based discovery approach to find and develop new products for this field.
Plant extracts, mostly from food chain and often selected based on ethnobotanical information are prepared for high throughput screening (HTS). This includes extraction, lyophylization, and fractionation onto microtiter plates. In contrast to other companies our extracts are fractionated before the screening process. This allows higher accuracy by reducing the effects of inhibitory or cell toxic compounds and speeds-up up the dereplication process. Usually the peak containing the active principle can be determined without further fractionation. After HT screening with primary and secondary assays the active compound is identified. This substance is then further profiled using additional *in vitro* assays.

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COMPONENTS AND BIOLOGICAL ACTIVITY OF YACON

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Yacon (Smallanthus sonchifolius Poepp.& Endl.) is a native Andean plant, cultivated for its tubers, which are common as food in South America. The leaves contain polyphenolics and terpenoids, the tubers mainly β-oligosaccharides of a low degree of polymerization. Traditionally, yacon tubers and dried leaves are recommended to people suffering from diabetes, various digestive and/or renal disorders.
In leaves, we identified and determined the spectrum of phenolics, in the tubers saccharides. The cytoprotective (hepatocyte, HUVEC) and antioxidant activities of leaf and tuber extracts were assessed in vitro. Rats fed a diet supplemented with aerial parts of yacon (10%, w/w) and 1% of tubers had significantly increased antioxidant blood capacity, decreased plasma TAG level and nonsignificantly decreased VLDL (cholesterol and TAG), resp.
The antioxidant effect of leaves and hypolipidemic effect of tubers are promising for application of yacon as a dietary supplement. This research was financially supported by grants MSM 151100003 and FD-K/096.

P:30

EVALUATION OF TWENTY HIGH-GRADE TRADITIONAL CHINESE MEDICINE DUE TO THEIR ANTI-HIV, ANTIBACTERIAL, AND ANTICANCER BIOACTIVITIES

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The ethanol extracts of 20 high-grade Traditional Chinese Medicines were assayed for their biological activities of anti-HIV, antibacterial, and anticancer. *Artemisia capilllaris (Yin-Chen-Hao)*, *Lonicera japonica (Jin-Yin-Hua)*, *Paeonia lactiflora (Bai-Shao)* and *Panax ginseng (Ren-Shen)* showed anti-HIV activity at concentrations of 10 □M, 10 □M, 10 □M and 1 □M, respectively.
Glycyrrhiza uralensis (Gan-Cao), *Artemisia capillaries*, *Cassia tora (Jue-Ming-Zi)*, *Lonicera japonica*, *Schizandra chinensis (Wu-Wei-Zi)*, *Astragalus membranaceus (Huang-Qi)*, *Coptis chinensis (Huang-Lian)*, *Rehmannia glutinosa (Shou-Di-Huang)*, *Zea mays (Yu-Mi-Xu)*, *Lycium barbarum (Gou-Qi-Zi)* and *Aquilaria sinensis (Chen-Xiang)* displayed antibacterial activity against Gram-positive and/or Gram-negative bacteria.
Angelica sinensis (Dang-Gui) and *Coptis chinensis* exhibited 57% and 42% inhibition of Kallikrein 6 (an ovarian cancer model) at a concentration of 2 □M, respectively. 15 pure components were isolated from the EtOH extract of the very high-grade herb *Glycyrrhiza uralensis*. Their structures were determined by NMR and MS spectroscopic methods. Some of them were found to have unreported anti-HIV and antibacterial activities.

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HERBAL REMEDIES FOR MENOPAUSAL HOT FLASHES WHICH INTERACT WITH SEROTONIN RECEPTORS

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Traditional hormone therapy (HT) has been used for the numerous benefits it provides to post-menopausal women, but unfortunately brings with it uncommon but adverse side effects. The search for remedies of menopausal hot flashes has been hampered by lack of relevant and practical animal models. Because inhibitors of the serotonin transporter (SSRIs) were recently found to alleviate menopausal hot flashes, the focus for hot flash remedies has expanded from estrogenic compounds to neurotransmitter systems that are indirectly influenced by estrogen, such as serotonergic neurons involved in thermoregulation. Herbal remedies provide a promising source of potential selective estrogen receptor modulators (SERMs) and/or serotonergic ligands. We identified three herbal hot flash remedies, black cohosh, valerian, and dong quai, which interact with the serotonin receptor 5-HT_7, but not estrogen receptors. To further investigate efficacy of these and other hot flash remedies, we developed a novel model of hot flashes by implanting thermosensors subcutaneously in ovariectomized rats to measure peripheral temperature fluctuations.
This study investigates the interaction of herbal hot flash remedies with serotonin receptors.
NIH Grant P50 AT00155 to UIC/NIH Center for Botanical Dietary Supplements Research.

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DIETARY SUPPLEMENTS AND THEIR IN VITRO EFFICACY RELATED TO HUMAN HEALTH

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Lipid peroxidation is one of the major causes of free radical generation in vivo. It is implicated in many of the chronic diseases. Prevention of free radical generation or its removal can be helpful in maintaining a good health. Cyclooxygenase enzymes (COX) are responsible for mediating inflammation and cancer. Inhibitors of COX-2 enzyme are therefore significant in preventing both inflammation and cancer.
Several dietary supplements in the market indirectly claim antioxidant and COX inhibitory activities. Therefore, we have analyzed several brands of echinacea, garlic, ginkgo, ginseng, grape seed, kava kava, saw palmetto and St. John's Wort dietary supplements for lipid peroxidation and COX-1 and COX-2 enzyme inhibitory activities. The supplements were extracted with acidic water at pH=2 and at 37°C to mimic human stomach conditions. Based on the recommended per day dose of the supplements studied, we have tested the extracts at 25 ppm. Extracts of echinacea, ginkgo, ginseng, grape seed, saw palmetto and St. John's Wort demonstrated 60 to 80 % inhibition of lipid peroxidation. Grape seed was found to be a potent inhibitor of lipid peroxidation. Results from COX enzymes and lipid peroxidation inhibitory assays will be presented.

P:33

A CROSS-SECTIONAL STUDY OF PHARMACY UNDERGRADUATE STUDENTS' VIEWS ON INCLUSION OF PHARMACOGNOSY AND COMPLEMENTARY MEDICINE IN UNDERGRADUATE PHARMACY PROGRAMMES IN THE UK

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For several reasons, pharmacists are likely to encounter users of herbal (botanical) and complementary medicines (CMs). Most pharmacies sell these types of products, and many pharmacists are asked for information and advice on their use, including potential interactions with conventional medicines. Also, in the UK, pharmacists have a role in monitoring the safety of herbal medicines. Against this background, there is a clear need for pharmacists to be knowledgeable about herbal and CMs and their quality, safety and efficacy. However, previous work has shown that the extent of teaching in pharmacognosy and related areas on pharmacy undergraduate programmes varies. As today's undergraduates are future pharmacists, we explored their experiences of, and views on, teaching in pharmacognosy and complementary medicine (CM) in undergraduate pharmacy programmes at UK Schools of Pharmacy (SOPs). We conducted a cross-sectional study using a structured questionnaire given to cohorts of final-year undergraduate students at 3 SOPs in April 2001. Response rates were 93, 89 and 41% from the 3 SOPs, respectively (total number of responses = 183). The majority of respondents (>50%) supported teaching of pharmacognosy/natural products, herbal medicines, homoeopathy and vitamins/minerals/dietary supplements on the core curriculum. Other results will be presented.

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ANALYSIS OF TRITERPENOID SAPONINS IN BACOPA MONNIERI (BRAHMI) BY HPLC AND HPLC-MS

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The first analytical procedure permitting the analysis of individual bioactive saponins (bacosides) in *B. monnieri* is described. By using 3 µm C-8 column material (Luna C-8) and a mobile phase comprising of water and methanol the developed HPLC method enabled the baseline separation of seven major saponins within less than 30 min. Flow-rate, detection wavelength, and temperature were adjusted to 0.5 ml/min, 205 nm, and 40 °C, respectively. Identity of the analytes was confirmed in an LC-MS experiment, with all compounds being clearly assignable in negative ESI mode. Furthermore, the method was validated for limit of detection, linearity, precision, accuracy, and intra- / inter-day variation.
Several *B. monnieri* samples (extract, plant material, commercial products) were successfully analyzed, each of them containing at least four of the seven reference compounds. Main components were either bacoside A_3 or bacopaside II, least dominant showed to be bacopasides IV and V. The total saponin content in the samples varied from 1.1 to 13.0 %.

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A CROSS-SECTIONAL STUDY OF TEACHING IN PHARMACOGNOSY AND RELATED AREAS ON UNDERGRADUATE PHARMACY PROGRAMMES AT UK SCHOOLS OF PHARMACY

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The use of herbal (botanical) medicines among patients and the general public for use in the prevention and treatment of minor and chronic medical conditions is widespread. As pharmacies are an important source of herbal medicines for consumers, pharmacists are likely to encounter people who wish to purchase such products and/or who require information and advice on their use. Also, in the UK, pharmacists have a role in monitoring the safety of herbal medicines, and are encouraged to submit reports of suspected adverse drug reactions (ADRs) associated with the use of these products to the Committee on Safety of Medicines. Against this background, there is a clear need for pharmacists to be knowledgeable about herbal medicines and their quality, safety and efficacy.
To explore the extent of teaching and learning in pharmacognosy and related areas on under-graduate pharmacy programmes at UK Schools of Pharmacy (SOPs), we conducted a cross-sectional study using a structured questionnaire sent to all 16 SOPs in April 2000. In total, 15 responses (94%) were received. Of these, 13 SOPs include teaching in pharmacognosy and related areas on the core curriculum, and 9 (including the two that do not teach pharmacognosy on the core curriculum) offer an elective in a relevant area. Other results will be presented.

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SIMULTANEOUS DETERMINATION OF THE ALKALIODS FROM EPHEDRA SINICA AND CITRUS AURANTIUM BY IONPAIRCHROMATOGRAPHY

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The use of *Ephedra sinica* (Ma Huang) and its major alkaloid ephedrine in dietary supplements for weight loss was banned by FDA recently due to serious side effects associated with their consumption. Most of the products now contain *Citrus aurantium* extracts instead; alkaloids (e.g. synephine, octopamine) found in this plant are structurally and pharmacologically very similar to those of Ma Huang.
We have developed the first HPLC method for the simultaneous determination of the major alkaloids in *E. sinica* and *C. aurantium*. By means of 3 µm C-18 column material, addition of the ionpairreagent SDS to the mobile phase and application of a pH-gradient for elution, six alkaloids and two amino acids (constituents of many commercial products and usually overlapping with the alkaloids) could be separated within 26 min.
The method was validated in accordance to USP requirements and it is applicable for the analysis of plant material and products containing *E. sinica* and / or *C. aurantium*, without the need of a time consuming sample preparation. It allowed a reliable and fast detection of possible adulterations of samples with ephedrine; the obtained results will be discussed.

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INHIBITORY EFFECTS OF CHAMOMILE (MATRICARIA RECUTITA L.) ESSENTIAL OIL AND ITS MAJOR CONSTITUENTS ON HUMAN CYTOCHROME P450 ENZYMES

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Chamomile extracts and tea are widely used in Europe to treat all kinds of minor illnesses (e.g. indigestion, inflammation). In this study the inhibitory effect of chamomile essential oil and seven of its major constituents on human cytochrome P450 enzymes (CYP1A2, CYP2C9, CYP2D6 and CYP3A4) was studied. Increasing concentrations of the test compounds were incubated with individual, recombinant CYP isoforms, and their effect on the conversion of surrogate substances was measured fluorometrically in 96-well plates.
Essential oil inhibited each of the enzymes, with CYP1A2 being more sensitive than the other isoforms. Three constituents of the oil, namely chamazulene (IC_{50} = 4.41 μM), cis-spiroether (IC_{50} = 2.01 μM) and trans-spiroether (IC_{50} = 0.47 μM) showed to be potent inhibitors of this enzyme, also being active towards CYP3A4. CYP2C9 and CYP2D6 were much less inhibited, only α-bisabolol (IC_{50} = 2.28 μM) revealed a significant inhibition of the latter. As indicated by these *in vitro* data, chamomile preparations contain constituents potently inhibiting the activities of major human drug metabolizing enzymes. Interactions with drugs whose route of elimination is mainly via cytochromes (especially CYP1A2) are therefore possible and probable.

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HYPOGLYCEMIC ACTIVITY OF A STANDARDIZED EXTRACT OF *Trigonella foenum graecum L* SEEDS GROWING IN EGYPT

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Trigonella foenum-graecum L (fenugreek) is a member of the Leguminosae (Fabaceae) family and is commonly cultivated in Egypt and Middle East. The seeds of the plant are used in the Egyptian folk medicine as lactagogue and as antidiabetic drug. 30% defatted alcoholic extract of the Egyptian seeds were standardized to contain 32%total saponins. We perform an HPLC analytical procedure for the determination of diosgenin as a marker component. The diosgenin content was 0.04%. This extract was subjected to in vivo antidiabetic activity at a dose of 1g/kg both in normal and in streptozotocin-diabetic rats. Glucose level remains unchanged in normoglycemic rats. The hypoglycemic effect of the orally administered extract over a period of 1h was (18%), and reaches its maximum after 3 hrs (27%) in diabetic induced rats. The antihyperglycemic effect was studied over a period of 3 weeks with daily administration of the extract. A significant decrease in blood glucose level was detected after 14 days (38%), which was comparable to that of Gliclazide. A 7-day acute toxicity study in rats did not produce any apparent adverse effects at doses as high as 5g/kg orally. Activity-guided fractionation of *Trigonella foenum-graecum L.* defatted alcoholic extract showed that the saponin fraction elicited a marked hypoglycemic effect in the streptozotocin-induced model.

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MARKER PROFILING OF TRIPHALA - AN AYURVEDIC FORMULATION USED IN INDIAN SYSTEM OF MEDICINE

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'Triphala' is an age old commonly used Ayurvedic powdered preparation in Indian system of medicine. This well known formulation is made in combination with *Terminalia chebula*, *Terminalia belarica* and *Emblica officinalis,* in equal proportions based on the observation of Ayurvedic Formulary of India (AFI). The formulation is prescribed in the first line treatment of many aliments as laxative, detoxifying agent and rejuvenator. The individual herbs, used in the formulation are reported to have several other health benefits. Quality evaluation of herbal formulation is a fundamental requirement of Industries and organizations dealing with nutraceuticals to ensure the therapeutic efficacy. Adequate standards using biological, chemical, instrumental and physiochemical methods required to be developed. The present studies are based on fingerprint profiling of individual components of Triphala as well as in formulations, by High Performance Thin Layer Chromatography (HPTLC), using Gallic acid as a marker compound.
Raw materials used to prepare in-house standard, were screened on the basis of quality control protocol prescribed by WHO. Further we compared in-house standard and marketed samples to evaluate gallic acid and tannin content in the therapeutic dose. Marker profiling of the extracts of individual component as well as for the formulation were made with HPTLC method using suitable solvent system and scanned at 254 nm, with respect to standard gallic acid. Fingerprint profile of in-house standard and marketed products also has been performed. This study helps to develop the quality control profile of marketed 'Triphala', which can be utilized further for developing standardization parameter for such formulations used in various system of medicine.

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ROLE OF OLIGOSACCHARIDE SIDE CHAINS IN INTESTINAL IMMUNE SYSTEM MODULATING ARABINOGALACTAN FROM RHIZOMES OF *ATRACTYLODES LANCEA* DC.

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Because herbal medicines, are generally administrated orally, there is a possibility that these medicines express their chinical effects through the intestinal immune system. The intestinal immune system modulating arabinogalactan (ALR-5IIa-1-1), which consists mainly of arabino-3, 6-galactan structure, has been isolated from hot water extract of rhizomes of *Atractylodes lances* DC.[1)] Degradation of galactosyl side chains in Ara*f*-side chain-trimmed ALR-5IIa-1-1(AF-ALR-5IIa-1-1) by endo-β-D-(1→6)-galactanase digestion remarkably decreased the enhancing activity of AF-ALR-5IIa-1-1 on cytokine production from Peyer's patch cells. Structural analysis indicated that major endo-β-D-(1→6)-galactanase-digestable side chains in ALR-5IIa-1-1 are composed ofβ-D-(1→6)-galactopyranosyl oligosaccharides having d.p.1-8. Because degradation ofβ-D-(1→3)-galactan backbone in AF-ALR-5IIa-1-1 also significantly reduced the enhancing activity, these galactosyl side chains, which are attached to ofβ-D-(1→3)-galactan backbone are suggested to be responsible for expression of the activity ALR-5IIa-1-12.

1) Yu *et al*., *Planta Medica*, 64, 714-719(1998); *Carbohydr.Polyms*., 46, 147-156(2001)
2) Taguchi et al., *Carbohydr. Res*. 339, 763-770(2004)

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FREE RADICAL-SCAVENGING ABILITY OF THE CHEMICAL CONSTITUENTS OF THE FRUITS OF *MORINDA CITRIFOLIA* L. (NONI)

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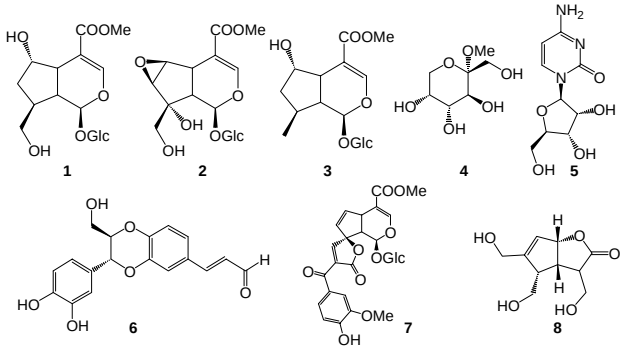
Morinda citrifolia L., commonly known as noni, is a small evergreen tree growing in open coastal regions and in forest areas up to about 1300 feet above sea level. It is also known as Indian mulberry or "Mengkudu", and it was considered to have originated from tropical Asia or Polynesia. The bark, stem, roots, leaves, and fruits have been used traditionally for many diseases, including diabetes, hypertension, and cancer, and noni is considered one of the most important Hawaiian herbal remedies. The purification of the *n*-BuOH soluble partition part of the MeOH extract of noni fruits led to the isolation of a total of twenty compounds. Among the isolates, compounds **1**-**8** were isolated for the first time from noni, compound **1** is a new iridoid glucoside, and compound **2** was previously characterized only as its pentaacetate. The free radical-scavenging activity of all isolates was evaluated using a DPPH assay. The neolignan, isoamericanin A (**6**), was demonstrated to be as potent as the positive control used in this assay, gallic acid.



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COUMARINS IN RED CLOVER? EXAMINATION OF A PHASE II CLINICAL *TRIFOLIUM PRATENSE* L. EXTRACT FOR ANTICOAGULANT COUMARINS

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Herbal remedies and dietary supplements are consumed by 14% of the United States population and approximately 16% of prescription drug users concurrently use herbal products. As a result, herb-drug interactions and herbal toxicities are receiving more attention than ever in the clinical literature. However, some misconceptions exist concerning terminology and the presence of "coumarins" in botanical dietary supplements and their anticoagulant effects. In 1941 the natural product dicoumarol was found to be responsible for hemorrhagic death of livestock consuming moldy hay made from *Melilotus alba* Med. and/or *M. officinalis* (L.) Pall. (Fabaceae) which are commonly known as "sweet clover." Although distinct from *Melilotus* species, red clover, *Trifolium pratense* L. (Fabaceae), is sometimes called "sweet clover," too. Because of redundancy with respect to common names, some researchers and clinicians believe that red clover is a potential source of natural dicoumarol, and that consumption of red clover supplements presents a risk to patients taking warfarin or other synthetic anticoagulants. This error is reported regularly in the current clinical literature despite the lack of clinical, botanical or analytical evidence to substantiate the occurrence of dicoumarol or other natural anticoagulants in red clover supplements. We report results of LC-MS analyses of a Phase II clinical red clover extract for 17 coumarins, some of which are known anticoagulants.

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PREVENTION OF VENOUS THROMBOSIS IN LONG-HAUL FLIGHTS WITH FLITE TABS: *THE LONFLIT-FLITE* RANDOMIZED, CONTROLLED TRIAL

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The aim of this study was to evaluate the development of edema, and superficial and deep vein thrombosis (DVT) prophylaxis with an oral profibrinolytic agent (Flite Tabs, 150 mg pinokinase, Aidan, Tempe, AZ, USA) in long-haul flights (7-8 hours), in high-risk subjects. A group of 300 subjects was included; 76 were excluded for several problems including concomitant treatments; 204 were randomized into 2 groups (active treatment or placebo) to evaluate the effects of prophlyaxis with Flite Tabs. An exercise program was used in both groups. The femoral, popliteal, tibial, and superficial veins were scanned with ultrasound before and within 90 minutes after flights. Of the included subjects, 92 of 103 controls and 94 of 101 treated subjects completed the study. Dropouts were due to connection problems. Age, gender, and risk distribution were comparable in the groups. In the treatment group, no DVT was observed. In the control group, 5 subjects (5.4%) had a DVT and there were 2 superficial thromboses (7 events in 92 subjects; 7.6%). At inclusion, edema was comparable in the 2 groups. After flights there was an increase in score in controls (+12%) in comparison with a decrease (-15%) in the Flite Tabs group (the difference in variation was statistically significant). Intention-to-treat analysis for thrombotic events shows 18 failures in controls (11 lost to follow-up + 7 thrombotic events) of 92 subjects (19.6%) in comparison with 7 failures (of 94 subjects, equivalent to 7.4%) in the treatment group ($p<0.05$). Events were asymptomatic. In conclusion, Flite Tabs were effective in reducing thrombotic events and in controlling edema in high-risk subjects in long flights.

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ZEAXANTHIN AND LUTEIN PROTECT A2E-LADEN HUMAN RETINAL PIGMENT EPITHERIUM CELLS FROM PHOTOTOXOCITY

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The accumulation of A2E, a fluorescent pigment, in retinal pigment epithelial (RPE) cells of older adults is implicated in the onset of certain eye diseases, especially Age-Related Macular Degeneration (AMD). When A2E is exposed to blue light, A2E itself generates singlet oxygen with the latter being added to carbon-carbon double bonds of the side-arms of the molecule to generate reactive epoxides (photooxidized A2E). Photooxidized A2E causes cellular injury, including damage to DNA, and can lead to the death of RPE.

In in vitro studies, we have observed that zeaxanthin and lutein, two carotenoids present in human eyes, inhibit blue light induced epoxidation of A2E and A2PE, the latter being a precursor of A2E. Furthermore, the death of A2E-laden RPE cells in culture was protected with treatment of lutein and zeaxanthin. The protective activity of zeaxanthin and lutein was superior to that of vitamin E, a well known antioxidant. Studies in which singlet oxygen was generated by endoperoxide in the presence of A2E revealed that the carotenoids reduced A2E photooxidation by quenching singlet oxygen. These studies suggest mechanisms by which zeaxanthin and lutein serve as natural antioxidants in human eyes.

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VALERIAN EXTRACT AND VALERENIC ACID ARE PARTIAL AGONISTS OF THE 5HT-5a RECEPTOR

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Insomnia is the most frequently encountered sleep disorder worldwide. While many prescription drugs are used to treat insomnia, herbal medicines including extracts of valerian (*Valeriana officinalis* L., Valerianaceae) are widely used for the treatment of insomnia and restlessness. To determine novel mechanisms of action, radioligand binding studies were performed with valerian extracts (100% methanol, 50% methanol, dichloromethane and petroleum ether) at the melatonin, glutamate, and $GABA_A$ receptors, and 8 serotonin receptor subtypes. The results revealed that only the petroleum ether extract contained compounds with strong binding affinity to the 5-HT2b and 5-HT5a subtypes, as well as the serotonin transporter. Subsequent binding studies were performed using 5-HT5a receptor due of its distribution in areas of the brain, including the suprachiasmatic nucleus, which has been implicated in the sleep-wake cycle. The PE extract inhibited [3H]lysergic acid diethylamide (LSD) binding to the human 5-HT5a receptor (86% at 50 μg/ml). Generation of an IC_{50} curve for the PE extract produced a biphasic curve, thus GTP shift experiments were also performed. In the absence of GTP, the competition curve was biphasic (two affinity sites) with an IC_{50} of 15.7 ng/mL for the high affinity state and 27.7 μg/ml for the low affinity state. The addition of GTP (100 μM) resulted in a righthand shift of the binding curve with an IC_{50} of 11.4 μg/ml. Bioassay-guided fractionation of the PE extract revealed that valerenic acid was the active constituent with an IC_{50} of 17.2 μM. These results indicate that valerian and valerenic acid are partial agonists of the 5-HT5a receptor.

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ANALYSIS OF THE AERIAL PARTS OF *VERBENA OFFICINALIS* L. BY MICELLAR ELECTROKINETIC CAPILLARY CHROMATOGRAPHY

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A micellar electrokinetic capillary chromatography (MECC) method was developed for the qualitative and quantitative determination of five marker compounds (iridoid glycosides, flavonoids and phenylethanoids) in *Verbena officinalis*.
Optimum separation was achieved using a 50 mM sodium borate solution (pH 9.3), containing 50 mM sodium dodecylsulfate (SDS) as surfactant, at an applied voltage of 25 kV and a temperature of 30 °C, respectively. Because of their different absorption maxima, the compounds were detected either at 205 or 235 nm.
Calibration data confirmed linearity of the detector response within the concentration range injected (R^2 from 0.997 to 0.999), and revealed detection limits ranging form 5.0 $\mu g \cdot mL^{-1}$ (verbascoside) to 13.6 $\mu g \cdot mL^{-1}$ (hastatoside). The five markers were readily assignable in several samples of *Verbena*.

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MALARIA TREATMENT BY PREPARATIONS OF *ARTEMISIA ANNUA* L. (ANNUAL WORMWOOD): A PHARMACOKINETIC STUDY IN HUMAN VOLUNTEERS AND A RANDOMIZED, CONTROLLED CLINICAL TRIAL IN MALARIA PATIENTS

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The Chinese medicinal plant *Artemisia annua* L. (Annual Wormwood) contains the antimalarial compound artemisinin. The locally grown herb may offer an additional tool in the control of malaria, especially in poor countries. Aqueous preparations of the dried herb are included in the pharmacopoeia of the People's Republic of China for treatment of fever and malaria.
14 healthy male volunteers received 1 liter of tea, prepared from 9 g *Artemisia annua* leaves. Blood samples were taken and artemisinin was determined by HPLC. Mean maximum plasma concentration was 240 ng/mL artemisinin (SD ±75 ng/mL). This concentration is sufficient to potentially result in clinical effects (MIC = 9 ng/mL).
In an open, randomized, controlled trial in malaria patients, we investigated the efficacy and safety of these tea preparations in the treatment of uncomplicated malaria. Treatment resulted in a quick resolution of parasitaemia and of clinical symptoms. Cure rates were on average 74% for the *Artemisia* preparations compared with 91% for quinine. However, recrudescence rates were high in the *Artemisia* groups. Therefore, *Artemisia annua* L. preparations can presently not be recommended as a monotherapy, but may deserve further investigation.

Räth *et al.*, Am J Trop Med Hyg 70: 128-132 (2004); Müller *et al.*, Trans R Soc Trop Med Hyg 98: 318-321 (2004)

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LOCAL FOOD – NUTRACEUTICALS OF THE MEDITERRANEAN

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The Consortium "Local Food – Nutaceuticals" with seven partners funded by the EU was created to study the role of local dietary plants with a special focus on wild gathered greens used in selected rural communities of Southern Italy, Greece and Spain. The aim is to select plants and plant material with potential health promoting activities focusing on chronic diseases and ageing processes and the pharmacological screening in the search of new nutraceuticals. From the ca. 250 documented wild food species 127 plants were extracted, their polyphenol content and the HPLC-MS profile assessed and screened for antioxidant activity, xanthin oxidase inhibition, the protection of induced DNA damage, serotonin reuptake inhibition and the PPAR gamma binding assay (relevant in diabetes II). An example is plant '3007' which shows high anti-oxidant effects in the guaiacol assay (95% at 0.2 µg/ml), it stimulates eNOS activity to a level 5x the control's (at a concentration of 10^5 M gallic equivalents, ca. 0.2 mg/µl) and acts as a scavenger of HOCl (28%). Plants showing interesting activity like *Reichardia picroides*, *Urospermum picroides*, (Asteraceae), *Thymus piperella* (Lamiaceae) and *Scandix pecten-veneris* (Apiaceae) were selected for further investigations and are included in a mice feeding trial and a clinical intervention study with humans focusing on acute/post-prandial effects.

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PROTECTIVE EFFECTS OF FLAVONOIDS FROM CRANBERRY (*Vaccinium macrocarpon*) ON RAT NEURONS AND VASCULAR CELLS

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Extracts and fractions from the fruit of the North American Cranberry (*Vaccinium macrocarpon*) were evaluated for their ability to protect rat neurons from the effects of simulated stroke and for their ability to influence the expression of genes related to migration and proliferation of vascular smooth muscle cells associated with atherosclerosis. A phenolics-rich extract of whole fruit was fractionated using a combination of Diaion HP-20, C18 and Sephadex LH-20 media to produce flavonol, anthocyanin and proanthocyanidin fractions. A crude triterpene fraction was also produced by ethyl acetate extraction. The ability of these fractions to protect brain cells from necrosis and apoptosis induced by oxidative stress or ischemia was evaluated using a rat neuron tissue culture model. Treatment with whole cranberry extract at 300 □g/mL produced a 43% decrease in necrosis and a 36% decrease in apoptosis induced by oxidative stress. A 50% decrease in both necrosis and apoptosis induced by oxygen and glucose deprivation (simulated ischemic stroke conditions) was observed. Among the fractions, a combined anthocyanin-flavonol fraction was the most effective at protecting cultured neurons against oxidatively-induced necrosis. Tested separately, both anthocyanins (AN) and flavonols (FL) protected against necrosis and apoptosis induced by oxidative stress but less protection was observed under conditions of oxygen and glucose deprivation. At lower concentrations (30 □g/mL), anthocyanins were more effective than whole cranberry extract at protecting rat neurons against apoptosis induced by conditions of oxidative stress. The protective effects of cranberry under conditions of reperfusion may largely be attributed to the anthocyanins. Tissue culture experiments in A10 thoracic aorta smooth muscle cells found that whole cranberry extract inhibited the expression of matrix metalloproteinases associated with vascular cell migration and proliferation. Of the fractions, only the proanthocyanidins completely inhibited expression of MMP-2 and MMP-9 at the lowest concentration tested, suggesting that they play the major role in the inhibition of matrix metalloproteinases by cranberry.

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ARGEMONE PLATYCERAS ETHYLACETATE FRACTION ANTAGONIZES LTD_4-INDUCED CONTRACTIONS IN GUINEA PIG AIRWAYS.

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Argemone platyceras Link & Otto (papaveraceae) is traditionally used to treat asthma, cough and bronchitis in Mexican traditional medicine. The methanol extract of the flowers was assayed for bronchoconstriction induced by antigen and by several agonists in guinea pig trachea. The methanol extract significantly inhibited (10 □g/mL, $p < 0.01$) the contractile response to ovalbumin in trachea from sensitized guinea pigs and the bronchoconstriction response to carbachol (100 □g/mL, $p< 0.01$) and histamine (100 □g/mL, $p < 0.05$). A bioassay-guided fractionation of the extract was performed by partitioning with dichloromethane/ethylacetate/metanol-water. Only the ethylacetate fraction produced a significant inhibition of the contractile response to ovalbumin in trachea from sensitized guinea pigs and of the bronchoconstriction induced by leukotriene D_4 (LTD_4). The results of this study suggest a competitive antagonistic effect of the ethylacetate fraction. A phytochemical screening has showed the presence of glycosylated flavonoids in the ethylacetate fraction.

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***IN VITRO* BINDING OF THE FIXED VALERIAN-HOPS COMBINATION EXTRACT (ZE91019) TO MELATONIN AND SEROTONIN RECEPTORS**

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Ze91019 is a fixed combination of valerian and hops extracts that has been available on the European and USA markets as a natural sleep aid. In order to achieve a better understanding of the mechanism of action of such combination, the affinity of Ze91019 and its component valerian and hops extracts was assessed via the inhibition of specific radioligand binding to 14 subtypes of 5 classes of central receptors (dopamine, serotonin, melatonin, MCH and neuropeptide-Y). Binding affinities could be demonstrated at some of the screened receptor subtypes, mainly melatonin (ML_1 & ML_2) and serotonin ($5\text{-}HT_{4e}$, $5\text{-}HT_6$ & $5\text{-}HT_7$). Ze91019 exhibited an IC_{50} of 97 and 180 □g/ml on ML_1 and $5\text{-}HT_6$, respectively. The nature of the affinity (agonist/antagonist) of Ze91019 to the respective receptors is yet to be determined.

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DETERMINATION OF CAFFEINE IN STIMULANT HERBAL PRODUCTS AND POWER DRINKS BY HIGH PERFORMANCE THIN LAYER CHROMATOGRAPHY

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The caffeine content of nine herbal products and energy drinks available in the Saudi market was determined by high performance thin layer chromatography (HPTLC) coupled with UV densitometric detection. Pre-coated HPTLC silica gel plates (20 x 10 cm) were used for the analysis. The solvent system consisted of ethyl acetate-methanol (85:15, v/v) and caffeine was detected at 275 nm. The developed method was validated for recovery, accuracy and precision. The levels of caffeine were 4.76-13.29 % w/w and 0.011-0.032 % w/v, in the herbal products and the energy drinks, respectively.

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SEPARATION, IDENTIFICATION AND QUANTIFICATION OF THE BENEFICIAL NUTRIENTS OF ROSEMARY BY HPLC.

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Beneficial phytochemicals present in Rosemary include phenolic diterpenes (carnosol and carnosic acid) and rosmarinic acid. These compounds are beneficial to health due to their anti-oxidant properties that scavenge free radicals and hence have lately gained significant popularity as herbal supplements. However, the available analytical methodologies for qualitative and quantitative evaluation of these compounds may not adequately test for them in botanical supplement matrices. These methods are imperative for substantiating the health promoting benefits of the phytochemicals present in Rosemary. We report qualitative and quantitative determination of carnosol, carnosic acid and rosmarinic acids in dietary supplement raw materials and finished products. Precision and accuracy between multiple labs and analysts is also discussed.

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QUALITATIVE AND QUANTITATIVE EVALUATION OF CITRUS BIOFLAVONOIDS IN CITRUS FRUITS AND EXTRACTS USED AS NUTRACEUTICALS

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Citrus fruits have gained a significant place as popular botanicals supplement due to their anti-oxidant, anti-carcinogenic and antitumor activities. Flavanone glycosides constitute the major class of the beneficial phytonutrients that are present in the edible parts of these fruits. In this study we report analytical methods for : A) Qualitative fingerprint / ID profiles for the separation , identification and relative distribution of the major flavanone glycosides such as eriocitrin, narirutin, naringin, hesperidin, nobiletin and tangeretin in fresh citrus fruits by HPLC.; B) Quantitative estimation of total citrus bioflavonoids by HPLC on fresh fruit and supplement extract matrices. The information derived from these studies provides a simple and accurate analytical method customized for botanical supplement matrices leading to: a clear differentiation between lemon, grapefruit and mandarin orange based on their typical flavanone-glycoside fingerprint profiles; qualitative evaluation of the actives / markers during various processing steps in the manufacturing process, optimization of the harvest times based on levels of beneficial phytonutrients, precision and accuracy of the analytical methods in fresh fruit and extract matrices between multiple labs and analysts.

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QUANTITATIVE ESTIMATION OF EMODIN & PHYSCION FORMED IN *IN VITRO* PROPAGATED SHOOTS AND PLANTS OF POLYGONUM *MULTIFLORUM* THUNB.

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Polygonum multiflorum Thunb. a perennial vine like herb, is one of the most important and widely used Chinese medicinal herbs of the family Polygonaceae. The vine is called Ye-Jiao and the root tubers are called Ho-shou-wu, which are used as tonic and in many remedies in traditional Chinese medicine

Nodal explants were grown *in vitro* on Murashige and Skoog's (MS) basal medium containing different concentrations of α-naphthaleneacetic acid (NAA) and benzyladenine (BA). The nodal explants (97%) produced multiple shoots (4.7 shoots/explants) on MS basal medium supplemented with 0.2 mg/l NAA and 2.0 mg/l BA after six weeks of culture. Eighty eight to hundred percentage of the shoot (1.0 cm in length) elongated (about 3.02–4.28 cm) and rooted on MS basal medium containing NAA or indole-3-butyric acid (IBA). All the rooted shoots were transferred to pots having autoclaved soil, vermiculite and peat moss (1:1:1). The anthraquinones contents were determined by high performance liquid chromatography (HPLC). Significantly higher amount of emodin and physcion were observed in the *in vitro* propagated shoots and plants than the marketed crude drug (stem or underground parts of *P. multiflorum*). The content of emodin and physcion were higher in the three months old greenhouse grown plants (emodin – 0.392 mg/g dry wt. Physcion – 0.413 mg/g dry wt.) than six weeks cultured *in vitro* propagated shoots (emodin – 0.318 mg/g dry wt. Physcion – 0.277 mg/g dry wt.).

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PERMEABILITY STUDIES OF ALKYLAMIDES AND CAFFEIC ACID CONJUGATES FROM ECHINACEA USING A CACO-2 CELL MONOLAYER MODEL

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The bioavailability of alkylamides and caffeic acid conjugates from echinacea was investigated using Caco-2 monolayers, which are a model of the intestinal epithelial barrier. The caffeic acid conjugates (caftaric acid, echinacoside and cichoric acid) permeated poorly through the Caco-2 monolayers although one potential metabolite, cinnamic acid, diffused readily. Alkylamides were found to diffuse rapidly through Caco-2 monolayers at different rates. This diversity in diffusion rates for the different alkylamides correlates to structural variations, with saturation and N-terminal methylation contributing to decreases in diffusion rates. The transport of the alkylamides is not affected by the presence of other constituents and the results for synthetic alkylamides were in line with those for the alkylamides in the echinacea preparation. These data suggest that alkylamides but not caffeic acid conjugates are likely to cross the intestinal barrier and thus be available to influence an immune response.

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BIOAVAILABILITY AND PHARMACOKINETICS OF ALKYLAMIDES FROM ECHINACEA

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Relatively little is still known about the bioavailability and pharmacokinetics of the alkylamides and caffeic acid conjugates found in echinacea. The major tetraene alkylamide (mw = 247) has previously been shown to be present in plasma 1 hour after ingestion of an echinacea ethanolic liquid but nothing is known about the bioavailability of caffeic acid conjugates. In this investigation, we have examined plasma from healthy volunteers for 12 hours after ingestion of echinacea tablets manufactured from an ethanolic liquid extract. Caffeic acid conjugates could not be identified in any plasma sample at any time after tablet ingestion. Alkylamides were detected in plasma 20 minutes after tablet ingestion and for each alkylamide, plasma clearance rates have been calculated. The data are consistent with the dosing regimen for Echinacea Tablets already recommended – that of 1 tablet three times daily.

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ECHINACEA EFFECTIVELY MODULATES IMMUNE RESPONSES

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Evidence of immune regulatory activity of individual constituents in Echinacea including alklyamides and cichoric acid is lacking.. Activity of an ethanolic Echinacea extract and key constituents have been examined using three *in vitro* measures of immune function - NF□B, TNF□ and nitric oxide (NO). NF□B stimulates the expression of several genes including key mediators of the inflammatory response such as TNF□ which help mount an immune response. In cultured macrophages, all constituents decreased LPS stimulated NF□B levels. The inflammatory cytokine TNF□ is involved in the immune response including the induction of iNOS that generates NO. All constituents were found to decrease TNF□ production under either basal or LPS stimulated conditions in macrophages. NO exerts multiple modulating effects on inflammation and plays a key role in the regulation of the immune response. In macrophages, all constituents decreased LPS stimulated NO production. The mixture of alklyamides in the Echinacea extract was more efficacious than the individual alkylamides investigated. While cichoric acid has been shown to initiate an immune response, it is unlikely to be relevant *in vivo* due to its non-bioavailability – i.e. no demonstrated absorption across the intestinal barrier and no detectable levels in plasma. These results demonstrate that Echinacea is an effective modulator of immune responses.

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IN VITRO ANXIOLYTIC ACTIVITY OF CALIFORNIA POPPY (*Eschscholtzia californica* Cham.)

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California poppy, *Eschscholtzia californica* Cham.(Syn. *Escholtzia californica, Eschscholzia californica*), is an annual or short-lived perennial of the Southwestern United States and Northern Mexico. It has golden orange blooms and attains a height of 60 cm (Griffith, 1994). Orally, California poppy is used for insomnia, sedation, aches, nervous agitation, enuresis in children, and disease of the bladder and the liver.
In vitro studies on extracts or isolated alkaloids demonstrated interactions with enzymes and brain receptors, suggesting sedative and anxiolytic properties. Recently, research has demonstrated that the inhibition of aromatase (cytochrome P450 CYP19) by *Passiflora incarnata* was linked with a decrease in anxiety. We report here the inhibition of aromatase by ethanolic extract of California poppy.
The aromatase assay was done in 96 wells using a fluorometric detector in order to evaluate the percentage of inhibition.
The activity of the crude extract and the major alkaloids (californidine, protopine and escholtzine) isolated from California poppy on aromatase will be discussed.

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EVALUATION OF THE ANTI-INFLAMMATORY PROPERTIES OF SKULLCAP (*SCUTELLARIA LATERIFLORA* L.) EXTRACTS IN DIFFERENT *IN-VITRO* MODELS

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Inflammatory processes are responsible for some of the major problems related to oral and skin health. In our screening to evaluate the anti-inflammatory potential of herbal extracts, *Scutellaria lateriflora* demonstrated *in-vitro* activities against cyclooxygenase-1 (COX-1), COX-2, 5-lipoxygenase (5-LOX) and elastase.

An additional screening in a human keratinocyte cell culture system was performed, which included a cytotoxicity evaluation as well as an assay of the inflammation markers interleukin 1□ (IL1□), IL8, tumor necrosis factor a (TNF□) and production of PGE_2. A hot water extract of skullcap showed little cytotoxic effects in this cell line and was able to decrease the production of PGE_2 by 68% at 80 □g/mL. A 60% alcohol extract was tested at a lower level (5 □g/mL) due to increased cytotoxicity, but was also able to significantly inhibit PGE_2 production. Both extracts were able to decrease the production of TNF□, but the difference was not statistically significant. None of the interleukin levels were influenced by the treatment with *S. lateriflora* extracts.

Recent data [1, 2] showed that extracts and isolates from Baikal skullcap (*S. baicalensis* GEORGI), which contains compounds similar to *S. lateriflora*, were able to suppress the expression of the inducible enzyme COX-2. Due to the fact that the *S. lateriflora* extracts showed only moderate COX-1 and COX-2 inhibitory activities, it is likely that the PGE_2 reduction in the cell culture assay is due to a decrease of COX-2 expression in the keratinocytes.

[1] Zhang DY et al. *Cancer Res*. 2003, **63** : 4037-4043. [2] Chen YC et al. *Biochem. Pharm*. 2001, 61 : 1417-1427.

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ACTIVITIES RELEVANT TO ALZHEIMERS DISEASE OF SOME CHINESE MEDICINAL PLANTS

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Alzheimers disease (AD) is associated with cognitive decline and symptoms are relieved to some extent by acetylcholinesterase (AChE) inhibitors. In addition, there is some evidence that anti-inflammatory and antioxidant substances reduce the risk of AD developing.
Seven Chinese medicinal herbs were selected on the basis of literature reports and interviews with Chinese herbal practitioners in London and were *Salvia miltiorrhiza* roots (SM) , *Alisma orientalis* root (AO), *Apocynum lancifolium* leaf (AL), *Polygonum multiflorum* root (PM), *Codonopsis pilulosa* root (CP), *Polygala tenuifolia* root (PT) and *Ziziphus jujuba* seed (ZJ) . Ethanolic extracts were tested for their ability to inhibit AChE, for antioxidant activity using DPPH, for inhibitory effects on 5-lipoxygenase (5-LOX) and cycloxygenase (COX), two enzymes involved in the inflammatory response. The diterpenes, e.g. dihydrotanshinone, present in SM were shown to be mainly responsible for the cholinesterase effect of this plant.
SM and AL gave significant inhibition of AChE and SM also inhibited 5-LOX and COX and showed a strong antioxidant effect. *Salvia miltiorrhiza* root therefore appears to display a range of activities which might help in prevention or symptomatic relief of AD.

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ACTIVITIES RELEVANT TO WOUND HEALING OF SOME PLANTS USED TRADITIONALLY IN GHANA PLANTS

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A survey of the literature and of traditional healers in the Ashanti region of Ghana revealed that the bark of *Spathodea campanulata* (Bignoniaceae), the leafy stems of *Secamone afzelii* (Asclepiadaceae) and the aerial parts of *Commelina diffusa* (Commelinaceae) are used to aid healing of wounds. Alcoholic extracts of the plants were subjected to tests for antibacterial and antifungal activity using serial dilution of extracts in agar suspensions of microorganisms in microtitre well plates. The extracts were also tested for antioxidant activity using thiobarbituric acid determination of malonaldehyde produced by free radical attack on liposomes. *S. campanulata* extract showed high antibacterial activity and *C. diffusa* exhibited some antibacterial and selective antifungal activity.
S. afzelii showed little antimicrobial activity but demonstrated a significant antioxidant effect. Bioassay-guided fractionation revealed that this was mainly due to a high level (0.12%w/w) of α-tocopherol present in the plant material. All three species examined show some activity which is relevant to wound-healing properties.

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SELECTION AND DEVELOPMENT OF TREE NUTS AS SOURCES OF ESSENTIAL FATTY ACIDS FOR NUTRACEUTICAL AND COSMETICEUTICAL INDUSTRIES

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For successful introduction, development and commercialization of new nut crops or products thereof, development of superior more widely adapted cultivars is a crucial factor. The potentials of tree nuts are that they can produce high quality food and other useful products for human use on marginal soils that are too rough for field crops, as well as on prime agricultural lands. Nut trees have multipurpose applications, providing food, fiber, fuel, shade, and environmental enhancement. Though agronomic data is available for tree nuts, published information on the variations within each species and opportunities for genetic improvement of the content of essential fatty acids (EFA) is inadequate. The United States FDA approved health claims for almonds, hazelnuts, pecan, pistachios, walnuts and peanuts to reduce the risk of heart disease in 2003.
The objective of our research is to identify and introduce genetically improved cultivars of tree nuts (black walnuts, Persian walnuts, almonds, hazelnuts, pecans), as well as sea berry (*Hippophae rhmnoides*) suitable for commercial cultivation and processing for the nutraceutical, veterinary, and personal care industry. GC based comparative studies of EFA of some tree nuts of various origins, including the former Soviet Union are presented. Germplasm of these species are being introduced to the U.S.A., and cultivars with novel desirable traits will be developed.

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SOME SPECIES OF THE GENUS SAUSSUREA DC AS PERSPECTIVE SOURCES OF PHARMACOLOGICAL RAW MATERIAL FROM THE RUSSIAN ALTAI

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The *Genus Saussurea* DC embraces about 400 species, where 11 of them are endemic to the Russian Alatai. *S. frolovii* Ledeb.; *S. salicifolia* (L). DC.; *S. baicalensis* (Adams) *Robins.*; *S. schanginiana* (Wydl.) Fisch. ex Herd.; *S. alpina* (L.) DC.; *S. controversa* DC.; *S. foliosa* Ledeb.; *S. latifolia* Ledeb.; *S. parviflora subsp. parviflora*; *S. pseudoalpina* Simps.; *S. tilesii* (Ledeb.) Ledeb., Nekratova. Many of the Sausssurea spp. have long been used in traditional medicine of Tibet, China, Mongolia, Buryatia, Transbaikalia, and Siberia.
The chemical and pharmacological traits of *Saussurea spp*. are still poorly investigated. The objectives of our study were to find the spectrum of biological activities of some of the locally available species, screen for bioactivity, identify and improve the plant for field cultivation, and processing. The majority of them had antibacterial, haemostatic and febrifugal activities. 8 of them contained flavonoids, tannins, coumarins, sesquiterpene lactones, bitter substances, essential oil, and saponins. Few species contained terpenoids, phenol carbonic acids, anthraglycosides, lignans, phytoechdysteroids, sterins, glycosides, organic acids, polyacethylenes, and vitamin C. *S. latifolia* and *S. controversa* responded well to field cultivation with wide range of ecological adaptation and high seed germination rate. New data is presented.

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PLANTS WITH ADAPTOGENIC AND IMMUNOPOTENTIATING ACTIVITIES ENDEMIC TO THE RUSSIAN ALTAI

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Few endemic plant species, such as *Rhodiola rosea*, L, *Rhaponticum carthamoides,* (Willd) Iljin, *Eleutherococcus senticosus*, Max., *Schizandra chinensis*, Turkz, Baill, *Scutellaria baikalensis*, Georgi., with adaptogenic, immunopotentiating and stimulative activities have been studied. While optimizing arterial pressure, some of them were found to have general tonic stimulating, hormone regulating, hepatoprotective, and anticarcinogenic activities.
In addition to the popular *R. rosea*, and *R. carthamoides* in Altai mountains, we found many species with adaptogenic and immunopotentiating properties, though the majority of them still needing modern chemical, pharmacological and agronomic investigations. We found that some plants under our study may have good potentials as alternatives to over-exploited and genetically endangered plant species.
Our program focuses on identifying alternative and reliable sources of adaptogenic botanicals with desirable chemical and morphological traits, while finding optimum cultivation, harvesting and processing methods to increase productivity and quality of the raw materials of the major adaptogens, including *Rhodiola rosea, Rhaponticum carthamoides* and other species that are traditionally used in Russian nutraceutical, pharmacological and personal care applications.

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STUDIES ON ESSENTIAL OILS OF THE HERBAL PLANTS FROM MENTHA SPECIES IN KOREA

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The essential oils of *Mentha piperita* (peppermint), *M. spicata* (spearmint), *M. piperita* var. *citrata* (eaude-cologne mint), *M. pulegium* (pennyroyal mint), *M. rotundifolia* (applemint) and *M. suaveolens* "Variegata" (pineapplemint) were extracted by steam distillation, and analyzed by GC-MS.
Antifungal activities of the oils were investigated by broth dilution method against *Aspergillus niger*, *Candida utilis* and *C. tropicalis*. As the results, it was found there was tremendous diversity in composition of essential oils according to the species of *Mentha*. The tested essential oils significantly inhibited the growth of *C. tropicalis* and to a lesser extent that of *A. flavus* and *C. utilis*, with MICs (minimal inhibitory concentrations) in the range 0.31- 5.00 mg/ml.

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SAFETY PROFILE OF PURIFIED LARREA TRIDENTATA LEAF RESIN EXTRACT ALONE AND IN COMBINATION WITH ASCORBIC ACID

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Desert creosote bush, *Larrea tridentata* (Cov.), is a shrubby plant that dominates desert areas of the Southwest U.S. This plant has long been used in folk medicine by Native Americans and European settlers to treat various health conditions.
Employing an *in vitro* hepatotoxicity model based on precision cut rat liver slices, Larrea leaf resin extract processed with ascorbic acid was no more toxic to liver tissue than other generally recognized as safe (GRAS) food substances such as cinnamon oil and clove oil. Additionally, when the processed Larrea leaf resin extract is formulated in a 1:5 ratio with ascorbic acid, this combination is substantially safer than cinnamon oil or clove oil and may actually be hepatoprotective.
An acute toxicity study, compliant with the principles of the Good Laboratory Practice Regulations of the United States Food and Drug Administration, further confirmed the safety of purified Larrea leaf resin formulated in a 1:5 ratio with ascorbic acid. No adverse effects such as, toxic symptoms, illness, deaths, weight changes or toxic gross pathological changes to liver or kidneys were noted following a 2,000 milligram/kilogram dose of a dietary supplement formulation containing this mixture of Larrea leaf resin extract and ascorbic acid. This experimental dosage represents the highest dose that can be given to rats safely and is the limit dose suggested in the international guidelines for acute toxicity testing.
These studies support a good safety profile for purified Larrea leaf resin when processed and formulated with ascorbic acid. This type of processing and formulation may have implications for enhancing the safety of other natural products and pharmaceuticals.

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UTILITY OF PURIFIED LARREA TRIDENTATA LEAF RESIN FORMULATIONS FOR VIRAL AND INFLAMMATORY CONDITIONS

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Larrea tridentata (Cov.) is commonly known as Larrea or creosote bush and formerly described as *Larrea divaricata* (Cav.). Larrea is a shrubby plant that dominates some areas of the hot, dry deserts of the Southwest in California, Nevada, Arizona, Utah, New Mexico and Texas. This plant has long been used in folk medicine by Native Americans and European settlers to treat many conditions including, skin disorders, arthritis, rheumatism, painful joints, headache, fever, infections, asthma, bowel disorders, colds, neuritis, sciatica, venereal disease, cancer, and inflammation of the respiratory and intestinal tract.
Dietary supplement and topical formulations containing purified *Larrea tridentata* leaf resin formulated with ascorbic acid have been shown to have a good safety profile. These formulations have also shown promising results in an open clinical study and during seven years of test marketing. The results presented here focus primarily on viral and inflammatory indications.

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STANDARDIZED GINGER EXTRACT REDUCES BACTERIAL LOAD AND SUPRESSES ACUTE AND CHRONIC INFLAMMATION IN MONGOLIAN GERBILS

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Previously, we have demonstrated that a methanol extract of ginger rhizome inhibited the growth of *Helicobacter pylori* in vitro with a minimum inhibitory concentration range of 0.78 to 12.5 μg/ml. The gingerols were the active constituents, and inhibited the growth of all HP strains with an MIC range of 0.78 to 12.5 μg/ml. This extract was tested in a rodent model of *H. pylori*-induced disease, the Mongolian gerbil, to examine the effects of extract on both prevention and eradication of infection. The animals were administered 100 mg/kg body weight/day of the ginger extract in rations either 3 weeks prior to infection or six weeks post-infection. Bacterial load and chronic and acute levels of inflammation were assessed four weeks after treatment. As compared with controls, a significant reduction in bacterial load, as well as chronic and acute inflammation scores was observed in gerbils treated with the ginger extract (containing 6-, 8-, 10-gingerols and 6-shoagol, in a ratio of 7.5:1:13:2% w/w) and these changes were paralleled by reductions in the severity of epithelial cell degeneration and erosions. Importantly, the extract did not increase morbidity or mortality. Treatment with the standardized ginger extract reduced HP load as compared with controls and significantly ($P<0.05$) reduced both acute and chronic muscosal and submucosal inflammation, cryptitis, as well as epithelial cell degeneration and erosion induced by HP. In an attempt to determine the mechanism of action, our in vitro studies demonstrated that the ginger extract also inhibited the activity of COX II, with an IC50 of 8.5 μg/ml. Furthermore, the ginger extract also inhibited the NF-κB transcriptional response in kBZ Jurkat cells (human T lymphocytes) with an EC50 of 24.6 μg/ml, and significantly inhibited the release of IL-1b, IL-6, IL-8 and TNF-a from LPS-stimulated human peripheral blood mononuclear cells in vitro, with an EC50 of 3.89, 7.7, 8.5 and 8.37 μg/ml, respectively.

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CRANBERRY INHIBITS TRANSCRIPTIONAL FACTOR NF-κB ACTIVATION, CYTOKINE RELEASE AND COX II ACTIVITY IN VITRO.

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Cranberry, the fresh or dried ripe fruit of *Vaccinium macrocarpon* Ait., Ericaceae, is currently used as adjunct therapy for the prevention and symptomatic treatment of urinary tract infections. Data from clinical trials indicates that cranberry may reduce the bacterial load of *E. coli* and also suppress the inflammatory symptoms caused by the bacteria. A methanol extract prepared from 2 kg of dehydrated cranberries (Ocean Spray) did not inhibit the growth of *E coli* strains ATCC 700336 or ATCC 25922 at concentrations up to 256 μg/ml in vitro. However, further investigation showed that the extract inhibited the activity of COX II, with an IC50 of 12.8 μg/ml. Moreover, the cranberry extract also inhibited the NF-κβ transcriptional response in Jurkat cells (human T lymphocytes) with an EC50 of 19.4 μg/ml, and significantly inhibited the release of IL-1β, IL-6, IL-8 and TNF-α from lipopolysaccharide (LPS)-stimulated human peripheral blood mononuclear cells in vitro, at a concentration of 50 μg/ml. The extract had no effect on iNOS activity. The attachment of gram negative bacteria to human cells induces the release of LPS which in turn activates pro-inflammatory signaling pathways needed for the process of infection. These pathways include NF-κβ, pro-inflammatory cytokines, iNOS and COX II. Our data suggests that cranberry extract does not have a direct antibacterial effect on *E. coli*, but appears to the pro-inflammatory signally pathway involved in the infection process. Thus, cranberry may reduce the inflammatory symptoms associated with urinary tract infections, as well as prevent *E. coli* from infecting human cells through a mechanism that involves the suppression of intracellular signaling.

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MICROSCOPIC DIFFERENTIATION BETWEEN ARISTOLOCHIA SPECIES AND AKEBIA TRIFOLIATA, CLEMATIS ARMANDII, C. CHINENSIS, AND STEPHANIA TETRANDRA

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Aristolochic acid-containing herbal drugs are toxic and have occasionally been confused with safe TCM botanicals, resulting in serious health consequences. Such confusion is often due to similarities between species in morphology and nomenclature.
The microscopic examination of authenticated plant material revealed diagnostic anatomical characters useful for the identification of crude drugs as well as powders. Aristolochia fangchi root and A. manshuriensis stem contain cluster crystals of calcium oxalate, which are absent in the non-toxic Akebia, Clematis, and Stephania. Crystals are entirely absent in Clematis root and stem, while Stephania tetrandra root contains small oxalate prisms in parenchyma cells, and Akebia stem is characterized by small prisms embedded in fibers. Thus the presence of cluster crystals in powdered plant material indicates the presence of a potentially risky adulteration. Preferably, proof of identity should occur prior to comminution, since the species in question each have a highly characteristic arrangement of tissues when viewed in transverse section, allowing for reliable identification.

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INVESTIGATING THE MOLECULAR BASIS OF NEUROPROTECTIVE ACTIONS OF TRADITIONAL CHINESE MEDICINE (TCM) STROKE DRUGS

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Excessive activation of N-methyl-D-aspartate receptors (NMDARs) is a critical first step in a cascade of molecular events leading to stroke-induced neuronal damage. We screened TCM drugs for their ability to block NMDA-induced currents in cultures of mouse cortical neurons. Extracts of Radix scutellariae baicalensis, Radix stephaniae tetrandrae, and Radix salviae miltiorrhizae blocked NMDA-evoked currents. The block was voltage-dependent and showed the negative slope conductance similar to the effect of Mg^{2+}. In contrast, Ramulus uncariae cum uncis extract produced a voltage-independent block of NMDA-evoked currents.
Production of nitric oxide by neuronal nitric oxide synthase (nNOS) is a major factor contributing to NMDAR-mediated toxicity. We used NMR spectroscopy to screen the TCM drugs for components that bind to postsynaptic density 95(PSD-95), the scaffold protein linking nNOS and NMDARs at the postsynaptic membrane of neurons. It was shown previously that disruption of the association of PSD-95 and nNOS suppressed NMDAR-induced toxicity. Radix scutellariae baicalensis extract showed significant binding to PSD-95. Four flavones, baicalin, norwogonoside, oroxylin A-glucuronide, and wogonoside were isolated by activity-guided assay and found to account for the PDZ-binding activity of the extract.

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PHYTOCHEMICAL SCREENING AND *INVITRO* ANTIBACTERIAL EFFECT OF LEAF EXTRACT ON *PAULINIA PINNATA*

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Paulinia pinnata D.C. is a wood climber plant belonging to the family of *Sapindaceae.* This plant which is widespread in Tropical Africa and America is used in Nigeria for the treatment of pile and bloody diarrhoae. We report here, the antibacterial activity of defatted methanolic and acetone extracts of the leaves of the herbal plant on *Staphylococcus aureus* NCTC6571, *Bacillus subtilis* NCTC8263 and *Escherichia coli* NCTC10418 as well as clinical strains of *Shigella sonnei*, Salmonella typhi and Enterobacter aerogenes. Phytochemical screening of the crude extracts revealed the presence of phenols, flavones, coumarins alkaloids and saponins. Three fractions obtained from colum chromatograph eluted with n-Hexane: ethylacetate (3:1)exhibited bacterial growth inhibition. The significance of the use of the crude extract of *Paulinia pinnata* as a potential herbal medicine for the treatment of bacterial infections will be discussed.

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BOTANICAL AND CHEMICAL CHARACTERIZATION OF *GUIERA SENEGALENSIS*, A WELL KNOWN WEST AFRICAN MEDICINAL PLANT

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Moshi medicine. *Guiera senegalensis* J. F. Gmel is a medicinal plant used by traditional healers in several West African countries to treat venereal, diarrhoeal and fungal diseases. Biological studies performed with an ethanol extract of dried leaves of this medicinal plant showed *in vitro* activity against *Neisseria gonorrhoeae*, *Shigella dysenteriae*, *Vibrio cholerae*, *Giardia lamblia* and *Cladosporium cucumerinum* corroborant the traditional use. Flavonoids, gallic tannins, naphthalene derivatives (a naphthyl butenone and naphthopyrans) and terpenoids are present in the extract. A bioassay guided fractionation of this extract allowed the localization of the activity on *n*-hexane and diethyl ether fractions.

We report here the botanical characters and chemical markers useful to the identification of the dried leaves of this medicinal plant. Additionally we present the LC/MS chemical profile of the most active fraction (diethyl ether).

Botanical analysis includes macroscopic and microscopic characters**.**
Chemical characterization was focused on the classes of the major compounds on the active fractions and was performed by TLC and LC/UV-DAD.

By means of LC/MS-ESI miricitrin, quercetin, rhamnetin, 5-methyldihydroflavasperone, 5-methylflavasperone and guieranona A were identified as main constituents. At our knowledge this is the first LC/MS method developed for *G. senegalensis* extracts and for naphthalene derivatives identified on this medicinal plant.

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COMPARISON OF *IN VITRO* RELAXANT PROPERTIES OF RASPBERRY LEAF EXTRACTS IN DIFFERENT SMOOTH MUSCLE PREPARATIONS

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Tea made from raspberry (*Rubus idaeus*) leaves has been used for centuries to treat diarrhoea, colic and as a uterine relaxant during parturition. We have partially purified and characterised relaxant activities from methanolic extracts of dried raspberry leaves, using transmurally stimulated Guinea pig ileum assays *in vitro* in which the active fractions exhibit dose-dependent relaxant activity, with relaxant responses being initiated within approximately 30 seconds of extract addition. The present study examines potential relaxant activities of raspberry leaf extracts in bronchial and pregnant uterine smooth muscle. Raspberry leaf extracts at increasing doses which had previously been shown to relax transmurally stimulated G. pig ileum had no effect in a carbachol pre-contracted G. pig *in vitro* tracheal strip preparation. Salbutamol however showed expected dose-related relaxation in this preparation. Addition of the extracts to an *in vitro* 4-day pregnant mouse endometrial tissue preparation caused similar relaxations to those in the ileum; but of more prolongued duration. These responses were not inhibited by nitric oxide synthase inhibitors. We conclude that relaxant responses to raspberry leaf extracts may be selective for different smooth muscle preparations, suggesting a specific receptor mediated mechanism which appears to be independent of a nitric oxide mediated mechanism.

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ISOLATION OF ANISATIN AS REFERENCE SUBSTANCE FOR THE DETERMINATION OF TOXIC ADULTERATIONS IN ILLICIUM VERUM BY HPLC-MS/MS

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Star anise (*Illicium verum*) is a plant which is commonly used as spice and in traditional herbal medicine. While cultivation of the plant is carried out in Indochine, Japan or Philippines, the import also takes place from China and Vietnam. This fact traditionally makes the drug susceptible for adulteration by other Illicium species. Especially mixing with Shikimi fruits (*I. anisatum* L.) caused severe intoxications in the past, because of the presence of highly toxic sesquiterpene lactones anisatin and neo-anisatin [1].

The differentiation between Star anise and Shikimi which show a very similar macroscopic appearance is described by microscopic methods as well as by DC and GC. These methods are not specific to Shikimi nor do they allow the detection and quantification of minor adulterations of Shikimi in Star anise fruits [2]. Therefore we isolated Anisatin from Shikimi as reference substance. Furthermore we developed a selective HPLC-MS/MS-method for the determination of anisatin in star anise with a detection limit of 1,1 ppb. The assay shows good repeatability for intra- and inter-day precision as well as good linearity of calibration curve (r^2 0.999). The recovery from spiked Shikimi was 98% at levels of 600 ppb and 3000 ppb. The method allows the determination of adulterations of Shikimi in Star anise less than 0,05% [3].

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AN IMPROVED ELECTROSPRAY INTERFACE FOR COUPLING OF NORMAL-PHASE LIQUID CHROMATOGRAPHY TO MASS SPECTROMETRY: APPLICATION TO NEOFLAVONOID SCREENING IN *CALOPHYLLUM INOPHYLLUM* FROM FRENCH POLYNESIA.

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Calophyllum inophyllum is an evergreen tree mainly found in tropical parts of the indo-pacific area. Different parts of this plant have been widely used in folk medicines, suggesting a rich source of bioactive secondary metabolites. Recently, neoflavonoïds from *Calophyllum inophyllum* have been shown to exhibit significant biological effects, particularly anti-HIV activities.

The screening of these molecules in crude extracts requires a robust and performant analytical method to establish the composition of the samples according to their geographical origin.

We report here the development of a new analytical method that allows the separation of targeted compounds in crude extracts and their characterization by mass spectrometry. HPLC analyses were performed on a normal-phase column and a special design of the ionisation source was implemented to circumvent the drawbacks induced by the use of non polar solvents in electrospray.

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SUBSTRATE SUITABILITY FOR FUNCTIONAL ASSAYS WITH REGARD TO THE INFLUENCE OF GREEN TEA EXTRACT ON ABC-TRANSPORTERS

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Green tea is one of the most popular beverages worldwide and several beneficial/protective effects on life-style related diseases, including antioxidative [1] and anticarcinogenic [2] activities, are being attributed to its consumption. Due to the increasing use of green tea preparations as food supplements or drugs, safety aspects regarding possible interactions with other medications have to be assessed.

Transmembrane transport proteins play a crucial role for the disposition as well as for the cytotoxicity of xenobiotics. Multidrug resistance-associated protein 2 (MRP2), a secretory transport protein of the ATP binding cassette (ABC) superfamily, is localized in the apical membrane of polarized cells and transports various glutathione S-conjugates and several anticancer drugs including methotrexate (MTX) [3,4]. Recently, inhibitory effects of green tea components on the function of another ABC transport protein, namely P-glycoprotein, have been reported in the literature [5].

We investigated the influence of the green tea extract EFLA®942 (GTE) on the functional activity of MRP2 in Madin-Darby canine kidney cells (MDCK) stably overexpressing human MRP2 (MDCK-MRP2). As substrate 5-chloro-methyl fluorescein diacetate was used, which intracellularly becomes metabolized to glutathion-conjugated methyl-fluorescein. Concentration-dependend significant autofluorescence activity of GTE were observed at concentrations of 0.01, 0.1, and 1 mg/ml GTE. However, GTE autofluorescence was very weak at 0.01 mg/ml. Additionally, GTE at concentrations of 0.1 and 1 mg/ml exerted significant quenching activity against methyl-fluorescein. The green tea components (-)-epigallocatechin gallate (EGCG), (-)-epigallocatechin (EGC), theanin, and caffeine did neither show autofluorescence activities nor quenching effects against methyl-fluorescein. These autofluorescence and quenching activities of GTE lead to false positive results with regard to an inhibition of MRP2 functional activity. This was demonstrated with functional assays in MDCK-MRP2 cells using [^{3}H]MTX as substrate, where the influence of 0.1 and 1 mg/ml GTE, or corresponding concentrations of EGCG, was examined. The cellular accumulation of the MRP2-specific substrate [^{3}H]MTX was significantly increased with the MRP2-specific inhibitor MK-571 or with 1 mg/ml GTE, but not with 0.1 mg/ml. The inhibition of MRP2 functional activity with 1 mg/ml GTE due to GTE-mediated cytotoxicity was excluded by preliminary colorimetric cytotoxicity experiments.

These observations result in the conclusion that for the prevention of artifacts during experiments using green tea preparations, possible interactions of the substance of interest with the respective marker substance or autoactivities of the substance of interest have to be assessed preliminary. As shown, in particular the use of fluorescent chromophore coupled marker substances requires these preliminary investigations.

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EFFECT OF POLYSACCHARIDES FROM DIASCOREA AS DANGER SIGNALS: IMPLICATION FOR REGULATING IMMUNE RESPONSES AND USE AS VACCINE ADJUVANT

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Dendritic cells (DCs) could sense the presence of a potential pathogen via detection of PAMPs (exogenous signals) or infection-induced alterations in self-markers (endogenous signals). Either type of signal may be detected by DCs directly or indirectly. Toll-like receptors (TLRs) are belong to pattern-recognition receptors that known to play an important role in binding of various PAMPs or non-PAMPs, signalizing the perception of stimuli from pathogens or specific endogenous cellular components of the host, and resulting in subsequent immune responses. It is not clear whether these molecular mechanisms are also responsive to the interaction with macromolecules (e.g., polysaccharides) of higher plant components, leading to promotion of host defense systems. We hypothesized that specific plant cell polysaccharides might mimic the functions of exogenous danger signals to mammalian immune cells and confer multiple effects in stimulating a spectrum of cellular activities in various immune cell systems. We observed in this study that human monocytes-derived immature dendritic cells could be effectively activated by a polysaccharide rich fraction, Dx-I, extracted from yam tuber (Dioscorea) via the TLR4-mediated NF-kappaB signaling pathway. Furthermore, we show that co-treatment of mice with ovalbumin protein or transgenic hAAT specific antigen and Dx-I as adjuvant drastically enhanced the antigen-specific antibody production responses and splenocyte proliferation in two mouse vaccine models. These results thus reveal an apparently unrecognized strong interactive activity between the higher plant polysaccharide compounds and the mammalian defense system. The finding may provide rational and implications for appropriate use of specific medicinal herbs as food supplements or remedies to enhance the immune system, and as adjuvants for vaccination.

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ESCIN INHIBITS THE ACUTE INFLAMMATION OF LING IN BOH RATS AND MICE

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Objective To investigate the effects of escin (sodium aescinate) on acute inflammation of lung resulted from lipopolysacchairde (LPS). **Methods** The time-effects curve of escin inhibiting the capillary permeability in mice was made firstly and the protective effects of escin by iv on the acute pulmonary edema induced by epinephrine in rats or the pneumonia resulting from LPS in mice were observed. **Results** After given 5 h escin displayed to inhibit the permeability of capillary vessel in mice and could maintain for 24 h. Both the mortality of rat with pulmonary edema and the weight of lungs in mice with acute pneumonia were decreased significantly by administrating escin. **Conclusion** Escin may be an effective drug for both preventing and treating of acute inflammation of lung.

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PLANT POLYSACCHARIDES STIMULATE HUMAN PERIPHERAL MONOCYTES TO EXPRESSION INTERLEUKIN 8 AND TUMOR NECROSIS FACTOR-ALPHA VIA TOLL-LIKE RECEPTOR-MEDIATED SIGNALING PATHWAY

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The initiation of immune or inflammatory reactions is a complex process involving the coordinated expression of co-stimulatory molecules, adhesion molecules, cytokines, and chemokines. Interleukin (IL)-8 and TNF-alpha are two important pro-inflammatory chemokine and cytokine, respectively, involved in the initiation and maintenance of a spectrum of immune and inflammatory reactions. In response to specific phyto-compounds, the Dx-I and Dx-II fractions of Dioscorea tuber tissue, human monocyte primary cultures were assayed for their activity in production of IL-8 and TNF-alpha, as an indication modulating of immune cell activities by candidate medicinal herbs. Using flow cytometry analysis, the protein expression levels of intracellular IL-8 and TNF-alpha were determined in test with Dexamethasone (negative control) or with lipopolysaccharide (LPS) (positive control), Dx-I or Dx-II. As compared to untreated or LPS-treated cultures, Dx-I and -II elicited a low level but significant pro-inflammatory response in test cells. We then further demonstrate that innate immune system activities are likely to involve the signaling pathway mediated by toll-like receptor (TLR) 4. Dx-I and Dx-II also showed a counter-balancing effect of LPS on secretion of these cytokines when monocytes are pre-treated with Dx-I or Dx-II. We thus conclude that Dx-I and Dx-II can modulate the immune cell system by increasing the production of pro-inflammatory chemokines & cytokines, and this information may contribute to the immune-modulation activities of test phyto-compounds.

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OMNI (AN ENDOGENOUS INTERFERON INDUCER): AN EMERGING DRUG FOR TREATMENT OF HEPATITIS

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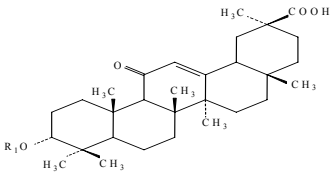
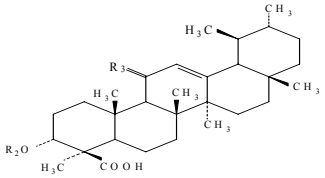
Omni has both oleanene-type triterpenes (B-Boswellic acid and B-glycyrrhitinic acid) which



R_1= D-glucuronic acid-D-glucuronic acid

Glycyrrhizin



1 R_2= H R_3= H_2 β-boswellic acid.
2 R_2= Ac R_3= H_2 3-O-acetyl-β-boswellic acid.
3 R_2= H R_3= O 11-keto-β-boswellic acid.
4 R_2= Ac R_3= O 3-O-acetyl-11-keto-β-boswellic acid.

Boswellic acids

proved the capability to protect rats against CCl_4-induced hepatotoxicity in subchronic CCl_4 exposure. ***Omni*** is pure plant constituents with antihepatotoxic potential, glycyrrhizin, curcumin and Boswellia carterii (BC) proved to exhibit a protective effect against (CCl_4)-induced hepatotoxicity. Glycyrrhizin (Glz), an Oleanene triterpenoid glycoside obtained from the roots of Glycyrrhiza glabra, was known with its preventive effect against several forms of experimental liver injury in animals. Glz is widely used to treat hepatocellular injury especially hepatitis. Moreover, it was noticed that glycyrrhizin treatment blunts ALT elevations and impedes fibrosis in animals. The therapeutic effect of ***Omni*** against chronic hepatitis has been confirmed by conducting a double-blind test on 375 patients.

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CYTOPROTECTIVE ACTIVITY OF SOLIDAGENONE BIOTRANSFORMATION DERIVATIVES IN CELL CULTURES

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Solidagenone is a gastroprotective diterpene occurring in *Solidago chilensis* rhizomes. Three derivatives were obtained by biotransformation of solidagenone with *Aspergillus niger* ATCC 16404. 3ß-Hydroxysolidagenone (**4**), 3ß-acetylsolidagenone (**5**) and 19-hydroxysolidagenone (**6**) were assessed for cytoprotective activity and cytotoxicity in human gastric cell cultures (AGS, ATCC CRL 1739) and human lung fibroblasts (MRC-5, ATCC CCL-171). A 60 min pretreatment with compounds **4** and **6** at concentrations of 50 and 200 μM, respectively, showed cytoprotective effect on AGS cells subsequently damaged with sodium taurocholate. Pretreatment (4 h) with compound **6** enhanced the total sulfhydryl content in the AGS cells but **4** and **5** were inactive. Proliferation of the AGS cells was stimulated with compound **4** treating the cells during 5 days at concentrations of 8, 16, 32 and 64 μM. The cytotoxicity was assessed by the neutral red uptake test and the IC_{50} values (μM) obtained were **4**: 744, **5**: 381, **6**: 335 for MRC-5 and **4**: > 1000, **5**:189, **6**: 192 for the AGS cells, respectively. The results suggest that different mechanisms are involved in the gastroprotective activity of the solidagenone biotransformation derivatives.
Supported by FONDECYT 1030792 and Programa de Investigación "Desarrollo de Productos Bioactivos", Universidad de Talca, Chile.

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MICROPROPAGATION AND EFECTS OF CROPING AREA ON GROWTH OF KAEMPFERIA PARVIFLORA

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Rhizome of *Kaempferia parviflora***,** Thai traditional herb, has been known as health promoting and also used for the treatment of colic disorder, peptic and duodenal ulcers. It contained several flavonoids, which exhibited antiplasmodial, antifungal and antimycobacterial activity. Due to the dormancy of rhizome in winter, *in vitro* culture was needed for mass propagatoin in short time. The surface sterilized *Kaempferia parviflora* shoot tips were cultured on Murashige and Skoog (MS) medium supplemented with 16 factorial combinations of NAA (0, 0.25, 0.5, and 1mg/l) and BA (0, 1.0, 2.0, and 3.0 mg/l) for 4 weeks. It was found that the MS medium with 0.5 mg/l of NAA and 3.0 mg/l of BA could induce the maximum shoot formation (2.4 shoots /explant) and the highest percentage of shoot formation (80%). The plantlets were transplanted to pots containing 1:1:1 of sand, charred rice hull and coir dust at different times (May, July and September 2002). The transplant was done to acclimatize the young plants in the greenhouse before planting. They were then planted in two different areas in Thailand: Muang District, Chiang Mai Province (360 meters above sea level) and Mae Tha District, Lumphun Province (450 meters above sea level). It was shown that the different transplanting times result in insignificant differences in fresh weight of rhizomes. However, the average weight of fresh rhizomes grown in Chiang Mai were significantly lighter than those grown in Lumphun.

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GASTROPROTECTIVE ACTIVITY OF THE DITERPENE FERRUGINOL

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Some abietane diterpenes have been shown to display gastroprotective effect in animal models. The abietane diterpene ferruginol is a main bark and wood constituent of *Prumnopitys andina* (Poepp. Ex Endl.) de Laub (Podocarpaceae), known as "Lleuque" in Chile. We now report the gastroprotective effect of ferruginol in the EtOH:HCl-induced ulcer model in mice as well as its activity on cell proliferation, red blood cell lipoperoxidation and cytotoxicity. Cell proliferation as well as cytotoxicity were assessed by means of the neutral red uptake method. Oral administration of ferruginol at 100 mg/kg showed a gastroprotective effect of 83.4 % while the reference compound lansoprazole at 20 mg/kg inhibited lesions by 59.6 %. Ferruginol prevented lipoperoxidation in red blood cells at 100 µg/ml. At concentrations of 1 up to 16 µM, the compound significantly increased proliferation of human lung fibroblasts (MRC-5, ATCC CCL 171) and epithelial gastric cells (AGS, ATCC CRL 1739). Cytotoxicity, expressed as $IC_{50,}$ ranged from 23 µM to 27 µM in MRC-5 and AGS cells, respectively. Further studies are in progress to assess the gastroprotection mechanism(s) of ferruginol.
Supported by FONDECYT 1030792 and Programa de Investigación en Productos Bioactivos, Universidad de Talca.

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NEOPEIN® AND IMPROVED BIOPEIN® AS NATURAL PRESERVATIVES

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The antimicrobial activity of improved "Biopein" and "Neopein®" (Biopein® from which the Cinnamon bark fraction was omitted) were tested against an array of microorganisms with different spectral susceptibilities. The organisms included gram positive *Staphylococcus aureus*, gram negative *Escherichia coli, Salmonella typhimurium*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*, acid-fast bacterium *Mycobacterium smegmatis*, the Yeast *Candida albicans* and the filamentous mold *Aspergillus niger*. For comparison the following well-known synthetic preservatives were used viz. Phenoxyethanol (PE), Phenyl Ethyl alcohol (PEA), and a combination of Methyl/Propylparabens (MP) in ratio 5:4. The Minimum Inhibitory Concentration (MIC) was determined for each agent. It was found that improved Biopein® has the lowest MIC (0.2%) followed in increasing order by "Neopein®" (0.55%), PEA (0.60%), PE (1.00%), and MP (2.16%) according to their capability of inhibiting all the tested organisms. "Biopein®" and "Neopein®" can therefore, be used as effective natural alternatives to commonly used synthetic ingredients in appropriate formulations for product preservation. Their composition and use are patent pending.

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SEEDS OF *MILLETTIA THONNINGII* POSSESS SEDATIVE AND ANTICONVULSANT PROPERTIES IN MICE

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Millettia thonningii trees are find in Democratic Congo, Ghana, Nigeria, etc. Bark and seeds of *Millettia thonningii* have been reported to possess molluscicidal and insecticidal activities. In these studies, the methanolic extract of *Millettia thonningii* potentiated in a dose dependent manner sodium thiopental-induced sleep in mice. At a dose of 1000 mg/kg, the total sleep time of control mice (42 min) was multiply by a factor of three (133 min). The extract protected also mice against maximal electroshock-, pentylenetetrazol- and strychnine- induced seizures in mice. The percentages of protection of mice against STR, PTZ- and MES-induced seizures at a dose of 1000 mg/kg were 70, 90 and 30% respectively. The ED_{50} for protection against seizures was 572 mg/kg (i.p.) for the PTZ test and 1790 mg/kg (i.p.) for MES test. The potentiation of sodium thiopental-induced sleep and the antagonism of electrical and chemical -induced seizures suggest that *Millettia thonningii* extract possess sedative and anticonvulsant properties in mice.

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SEDATIVE AND ANTICONVULSANT PROPERTIES OF *PASSIFLORA EDULIS* IN MICE

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Passiflora edulis is a plant used in traditional medicine in Africa to treat many diseases (anxiety, convulsions, headache, insomnia, etc). Very few pharmacological studies are done with this plant. In these studies, the decoction of *Passiflora edulis* potentiated in a dose dependent manner sodium thiopental-induced sleep in mice. The total sleep time increased from 31 min in mice of control group to 63 min in mice treated with extract at the dose of 1000 mg/kg. The decoction protected also mice against strychnine (STR)- induced seizures and N-methyl-D-aspartate-(NMDA)-induced turning behavior. The percentage of mice protected against STR -induced seizures at a dose of 1000 mg/kg was the same as clonazepam: 83.33%, (ED_{50} = 235mg/kg, ip). The decoction at a dose of 3000 mg/kg protected 100% of mice against NMDA-induced turning behavior (ED_{50} = 300 mg/kg (ip). The potentiation of sodium thiopental-induced sleep and the antagonism of chemical -induced seizures suggest that *Passiflora edulis* possess sedative and anticonvulsant properties in mice. These properties could explain its use in traditional medicinal.

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IMMUNOMODULATORY ACTIVITIES OF EXTRACTS AND CONSTITUENTS FROM ECHINACEA PLANTS

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Echinacea angustifolia, *E. Purpurea*, and *E. pallida*, the native North American plants, have been used for non specific immunostimulatory function in prevention and treatment of cold, flu and respiratory track infection for centuries. However, some of the pharmacological studies and clinic trials are contradictory, and as a result, varied *Echinacea* products on the naturopathic product market consistently confuse the customers. We have conducted a systematical study in *Echinacea* species identification, cultivation development, bioassay screening of extracts, fractions and isolated components, stability and bioactivities vs. material treatment and storage methodology, as well as toxicities of extracts and constituents. With bioassay of Raw 271 mouse microphage cell lines, both the immunostimulatory and immunosuppressive activities of extracts, fractions and components from three *Echinacea* species have been evaluated for the first time. A survey of immunomodulatory activities of *Echinacea* products on US market has been conducted. The results of the finding are being reported here.
Acknowledgements: This work was supported by a grant from National Center for Complementary and Alternative Medicine, National Institute of Health, Bethesda, Maryland, USA

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AMINO ACID CHEMOTAXONOMY OF THE GENUS *SOPHORA* (LEGUMINOSEAE)

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Since the time of taxonomy of the genus, the polyphyly of the genus was noticed. The alkaloid chemotaxomy of the genus in *phytochemistry*, 1975, did not solve the problem. At the present the argue is still continuing. Since the alkaloid content of the seeds varies from time to time, therefore, we investigated the free amino acid content of the seeds of some 23 species of the genus, by ion-exchange separation and amino acid analysis comparison. These components are precursors of alkaloids and are more stable, as a chemotaxonomic marker. According to these studies some species contain 4-OH- pipocolic acid, some do not . In addition, some contain γ-glutamyl tyrosine, some do not. Also some contain γ – amino – n-butyric acid, and some do not. Therefore, a classification based on these findings are proposed and a phylogenetic tree is drawn which is presented by convincing slides.
At the same time, two species (*S. allopecuroides* and *S. gypsophylla*) belong to different parts of the world were compared by amino acid analyzer to confirm their amino acid chemotaxonomic relationships.

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STEVIOSIDE IN COMBINATION WITH SOY-BASED DIETARY SUPPLEMENT EXERTS A BENEFICIAL EFFECT ON TYPE 2 DIABETIC GK-RATS – MULTIFACTORIAL TREATMENT OF TYPE 2 DIABETES AND THE METABOLIC SYNDROME.

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Background: The Stevia rebaudiana Bertoni (SrB) plant has been used in traditional medicine by the Guarani Indians in Paraguay and Brazil in the treatment of diabetes. Dietary supplement of soy protein (Abalon®) has shown to have beneficial effects on CV risk markers in type 2 diabetes. Aims: To investigate if the combination of stevioside and a dietary supplement of soy protein possesses beneficial qualities in the treatment of type 2 diabetes and the metabolic syndrome. Materials and Methods: Diabetic GK rats were fed for 4 weeks with 4 different test diets. A) Standard carbohydrate rich lab diet (Chow), B) Chow + stevioside (0.03 g/kg BW/day), C) 80 % soy (Abalon®) + 20 % Chow and D) 80 % soy (Abalon®) + 20 % Chow + stevioside 0.03 g/kg BW/day. An intra-arterial catheter was inserted in the carotic artery of rats after 3 weeks and at week 4 the conscious rats underwent an intra-arterial glucose tolerance test (GTT) (2.0 g/kg BW). Results: Stevioside exerts beneficial effects in the mild type 2 diabetic GK rat i.e.: 1) lowers blood glucose (IAUGC)) (group A vs. B a 31 % reduction and group C vs. D a 86 % reduction, $p<0.00005$), respectively; 2) Increase of the first phase insulin secretion (IAUIC) (0-30 min): (group A vs. B a 80 % increase and C vs. D a 163 % increase; $p<0.003$), respectively; 3) Suppresses glucagon (IAUGC): (group A vs. B by 28% and group C vs. D by 49 %, $p< 0.0004$), respectively; 4) After 2 weeks of treatment with stevioside a 12 % suppression of the systolic blood pressure was observed ($p<0.0002$). Abalon® had a beneficial effects on CV risk markers i.e : 1) Lowers total-cholesterol (group A vs. C by 15%, $p<0.0043$); 2) Reduces Triglycerides (group A vs. C by 47%, $p< 0.0028$); 3) Reduces FFA : (group A vs. C by 13 %, $p<0.02$). Conclusion: The combination of stevioside and Abalon® appears to possess the potential as effective treatment of a number of the characteristic features of the metabolic syndrome i.e. hyperglycaemia, hypertension and dyslipidaemia. However a long-term proof of concept study in type 2 diabetic subjects is needed to verify these promising results.

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ANALGESIC EFFECTS OF THE EXTRACT OF *RAUVOLFIA VOMITORIA* (AFZEL)

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Aqueous leaf extract of *Rauvolfia vomitoria* (Afzel), a Nigerian traditional medicinal plant has been evaluated for its analgesic potential in mice. The analgesic potential of the plant extract was studied using the thermic (hot-plate) test stimuli. A dose of the herbal plant extract corresponding to 2g/kg given orally to mice was found to raise the pain threshold. The plant extract was found effective in elevating pain threshold.
Phytochemical screening of the plant reveals the presence of alkaloids, flavonoids, saponins, tannins and reducing sugars and the LD_{50} was calculated to be 6.45 g/kg
Keywords Analgesic effect, *Rauvolfia vomitoria,* thermic test stimuli

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ANTIMALARIAL AND ANTIPYRETIC EFFECTS OF *RAUVOLFIA VOMITORIA* (AFZEL)

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The antimalarial effect of an aqueous extract of *Rauvolfia vomitoria* (family, Apocynaceace), a Nigerian traditional medicinal plant was found efficacious in suppressing infections due to *Plasmodium yoelli nigeriensis* in mice. Infected animals were orally given the extract three times daily in doses of 0.004 – 0.034 g kg^{-1} for four consecutive days after the disease had been well established.
These animals were observed to be cleared of the malarial parasites about 72 hours post-therapy. On the other hand, the antipyretic effect of the plant drug was also investigated in pyrexial – induced rabbits. Pyresis was induced by infecting rabbits with *Klebsiella aerogenes.* The animals were orally given the plant extract in a dose range of 1.1-1.2 g kg^{-1} and these produced a fall in body temperature of the animals 2 h post–therapy from 42.0± 0.01 to 40.5± 0.0^{o}C almost to the basal temperature (40.0 ±0.01oc) which was statistically significant ($P< 0.05$). Body temperature was recorded every 15 min for over 120 min. The plant drug extract was found effective in suppressing malaria infections and pyrexia, which is usual occurrence in plasmodial infections. Phytochemical analysis of the extract revealed the presence of alkaloids,saponins and tannins
Keywords: Rauvolfia vomitoria, antipyretic, antimalarial, Klebsiella aerogenes, Plasmodium yoelli nigeriensis

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TANNIC ACID AS A SAFE AND EFFECTIVE HEMOSTATIC AGENT IN PERIRADICULAR SURGERY

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Hemostasis during periradicular surgery is important for successful case management. Excessive bleeding obscures visualization of the surgical field and interferes with the placement of root-end filling materials. Thus, the use of hemostatic agents may be crucial during surgical procedure. Ferric sulfate has been used as a hemostatic agent for a long time; however, it is known to be cytotoxic and may cause tissue necrosis and tattooing. Tannic acid is a natural compound isolated from many plants and has been used for centuries as a safe hemostatic agent for treatment of hemorrhoids and gingival bleeding. This study was designed to investigate the effect of tannic acid (15%) versus ferric sulfate (21%) on osseous wound healing. Standardized size osseous defects were created bilaterally in the mandible of fourteen rabbits. Tannic acid was placed in the oseou bone of the right mandible defects until hemostasis was obtained and ferric sulfate was used for the contralateral defect of twelve rabbits, after five minutes both defects were curetted, irrigated and finally closed with sutures. The defects of the remaining two rabbits' mandibles were used as control and were sutured immediately after clot formation. The repair of the defects was evaluated histologically at 18 and 46 days and scored for healing. This study revealed that tannic acid is a tolerable and effective hemostatic agent in periradicular surgery.

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PROTECTIVE EFFECT OF FLAVONOIDS FROM *Garcinia kola* SEED ON GALACTOSAMINE- INDUCED HEPATOTOXICITY IN MICE.

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The protective effects of four flavonoids from *Garcinia Kola* seed (family; Guttiferae) namely, kolaviron (KV), Garcinia biflavanone (GB) 1, GB 2 and kolaflavanone (KF) on galactosamine ($GalNH_2$) – induced hepatotoxicity and the possible mechanisms involved in this protection were investigated in experimental animals.
Pretreatment with KV, GB1, GB2, and KF for seven consecutive days before challenged with a single dose of $GalNH_2$ (800 $mgKg^{-1}$) significantly ($P < 0.05$) decrease serum alanine and aspartate aminotransferases by 67, 71, 77, 36% and 39, 46, 35, 7% respectively over $GalNH_2$ -intoxicated mice. In addition, pretreatment with KV, GB1, GB2 and KF significantly ($P < 0.05$) decrease the $GalNH_2$ – mediated increase in the activity of microsomal gamma glutamyl transferase by 42, 64, 18 and 22% respectively. Furthermore pretreatment with KV, GB1, GB2, and KF also significantly ($P < 0.05$) prevented the elevation of hepatic malondialdehyde formation and the depletion of reduced glutathione content in the liver of $GalNH_2$- intoxicated mice.
The effects of these flavonoids on the cytochrome P450 2E1 (a major isozyme involved in drug biotransformation), aniline hydroxylase activity (AH), and mitochondrial bcl_2 (an apoptotic protein) were also investigated. Treatment of mice with KV, GB1, GB2, and KF caused insignificant ($p<0.05$) decrease of P450 2EI and bcl_2 protein by 67, 31, 24, 41% and 2, 17, 14, 10% respectively over controls. Similarly, AH activity was insignificantly decreased ($p< 0.05$) by 3, 4, 11.3 and 5.1% following pretreatments with KV, GB1, GB2 and KF, respectively.
$GalNH_2$- induced hepatotoxicity was also essentially prevented, as indicated by a liver histopathologic study.
Our results suggest that the protective effects of flavonoids from *Garcinia kola* seeds against $GalNH_2$- induced hepatotoxicity probably do not relate to its ability to block the expression of phase I enzymes.

Keywords: *Garcinia kola*, Galactosamine, Western blotting, Cytochrome P450, Hepatotoxicity.

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THE ROLE OF MARKER COMPOUNDS IN HERBAL PHARMACEUTICAL PREPRATIONS:

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Medicinal herbs are significant source of synthetic and herbal drugs. In the commercial market, medicinal herbs are used as raw drugs, extracts or tinctures. Isolated active constituents are used for applied research. The systematic investigations of plant material for its phytochemical behavior involve following steps: - (i) Procurement of raw material and quality control. (ii) Extraction, purification and characterization of the active constituents of pharmaceutical interest. (iii) Probe into the biosynthetic pathways applicable to particular compounds. (iv) Quantitative evaluation.

The commonly employed technique for removal of active substance from the crude medicinal plant is called extraction. Standardization helps in adjusting the herbal drug formulation to a defined content of a constituent or constituents with therapeutic activity. The active constituents are usually secondary metabolites, and are responsible for pharmacological activity of herbal formulations/extracts. A constituent of a medicinal herb, which is used for quality control and assurance of herbal product, is known as marker compound. The paper reviews the applications for markers for better quality control and assurance of herbal preparations.

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HAWTHORN EVOKES A POTENT ANTI-HYPERGLYCEMIC CAPACITY IN STREPTOZOTOCIN-INDUCED DIABETIC RATS

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In this study, the effect of aqueous extract of hawthorn leaves at two oral doses on blood glucose in normal and streptozotocin (STZ) diabetic rats was investigated. The effect of the extract on blood glucose levels was tested in severely streptozotocin diabetic rats after acute and chronic treatments at two doses. Oral administration of the aqueous extract produced significant and dose-dependent decrease in blood glucose levels in STZ diabetic rats ($P<0.001$), but had no effect in normal rats. No remarkable changes were observed in basal plasma insulin concentrations after hawthorn treatment in both normal and STZ rats. In addition, the acute toxicity study of hawthorn was investigated in mice. The results obtained showed that the aqueous extract had minimal adverse effects and a high LD_{50} value.

We conclude that aqueous extract of hawthorn leaves exhibited a potent anti-hyperglycaemic activity in STZ rats, but not in normal rats, without affecting basal plasma insulin concentrations.

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INHIBITION OF ENDOGENOUS GLUCOSE PRODUCTION ACCOUNTS FOR HYPOGLYCEMIC EFFECT OF SPERGULARIA PUPUREA IN STREPTOZOTOCIN MICE.

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The purpose of this study was to determine the underlying mechanism of the hypoglycaemic activity of the aqueous extract perfusion of *Spergularia purpurea* (SP) in diabetic mice and streptozotocin-induced diabetic rats. The aqueous extract was administered intravenously and the blood glucose levels were determined within 4 hours after starting the treatment. Plasma insulin concentrations and endogenous glucose production were also determined.
The aqueous extract at a dose of 10 mg/kg produced a significant decrease in blood glucose levels in normal rats ($P<0.05$), and even more in diabetic rats ($P<0.001$). This hypoglycaemic effect might be due to an extra-pancreatic action of the aqueous extract of SP, since the basal plasma insulin concentrations were unchanged after SP treatment. In diabetic mice, a similar effect was observed and the results showed that aqueous extract of SP caused a potent inhibitor effect on basal endogenous glucose production ($p<0.001$).
We conclude that aqueous extract perfusion of SP inhibits endogenous glucose production in mice. This inhibition is at least one mechanism explaining the observed hypoglycaemic activity of this plant in diabetic animals.

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EFFECT OF THE DESERT PLANT RETAMA RARTAM ON GLYCAEMIA IN NORMAL AND STREPTOZOTOCIN-INDUCED DIABETIC RATS.

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The effect of the aqueous extract of *Retama raetam* (RR) on blood glucose levels was investigated in fasting normal and streptozotocin-induced diabetic rats after single and repeated oral administration. The aqueous extract of RR at a dose of 20 mg/Kg significantly reduced the blood glucose in normal rats six hours after a single oral administration ($p<0.005$) and two weeks after repeated oral administration ($P<0.05$). This hypoglycaemic effect is more pronounced in streptozotocin (STZ) diabetic rats ($P<0.001$).
The aqueous extract of RR had no effect on basal plasma insulin levels indicating that the underlying mechanism of RR activity is extra-pancreatic.
These findings suggest that the aqueous extract of RR possess significant hypoglycaemic effect in both normal and STZ diabetic rats.

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CHOLESTEROL LOWERING ACTIVITY OF AQUEOUS EXTRACT OF SPERGULARIA PUPUREA IN NORMAL AND RECENT-ONSET DIABETIC.

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The purpose of this study was to examine the effect of single and repeated oral administration of the aqueous extract of *Spergularia purpurea* (SP) at a dose of 10 mg/kg in normal and streptozotocin-induced diabetic rats. In normal rats, the aqueous extract of SP induced a significant decrease of the plasma cholesterol concentrations six hours after a single oral administration ($p<0.05$) and two weeks after repeated oral administration ($p<0.05$). The plasma triglycerides levels increased significantly six hours after a single oral administration ($p<0.05$) and decreased two weeks after repeated oral administration ($p<0.05$).
In diabetic rats, SP treatment caused a significant decrease of plasma cholesterol levels after a single ($p<0.01$) and repeated ($p<0.01$) oral administration. A significant increase of triglycerides levels was observed six hours after a single oral administration of the SP aqueous extract ($p<0.01$). One week after repeated oral administration of SP aqueous extract, the plasma triglycerides levels were significantly decreased ($p<0.005$) and still dropped after two weeks ($p<0.01$).
On other hand, the repeated oral administration of SP aqueous extract caused a significant decrease of body weight after two weeks of treatment in both normal ($p<0.001$) and diabetic ($p<0.01$) rats.

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ASSESSMENT ON APPLICATIONS AND ANALITYCAL METHODS OF COPPER IN TRADITIONAL CHINESE MEDICINES

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Recently many studies on trace elements in Traditional Chinese Medicines (TCM) have been reported, but very rare about copper. Copper is an essential micronutrient to all aerobic organisms including plants, animals and humans, metabolic disorder results in a broad spectrum of diseases. The assessment on applications and analytical methods of copper in TCM was emphatically summarized in our study.

Syndrome of yin-yang and picture of the tongue are essential theories of bianzheng-lunzhi. In the patients of deficiency of yin-yang, trace elements in serum were characterized by ascent of the amount of copper and ratio of copper to zinc. Another example is picture of the tongue, according to the statistical data of primary carcinoma of liver, the amount of copper and ratio of copper to zinc in hair were likewise higher from patients of yellowish and greasy tongue fur.

The speciation analysis of copper in TCM, namely the dissoluble species, suspended solid, soluble inorganic and organic species, was also explored. Coordination chemistry is a new theory that concerns the interactions of organic composition with trace elements. All in all, it is to be hoped that the findings of any future research will aid our comprehension of the connection between copper and traditional Chinese medicine and herbal medicine.

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HYDROXY-1-ARYLISOCHROMANS: A NEW CLASS OF NATURAL ANTIOXYDANTS AND FREE RADICAL SCAVENGERS

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Hydroxyisochromans are a class of polyphenols, recently identified as natural constituents from olive oil. Here we investigated the antioxidant and free radical scavenging activity of the natural isochroman 1-(3‘-methoxy-4‘-hydroxy)phenyl-6,7-dihydroxyisochroman (ISO-3) and that of three other newly synthesized derivatives (ISO-4, ISO-2 and ISO-0). These isochromans differ from the natural compound by their degree of hydroxylation. Our *in vitro* studies show that ISO-4 (4 OH groups) is an better scavenger for the artificial radical 1,1-diphenyl-2-picrylhydrazyl (DPPH), superoxide ($O_2^{\cdot -}$) and peroxynitrite ($ONOO^-$) as compared to ISO-3 (3 OH groups) and ISO-2 (2 OH groups), while ISO-0 (no OH) was inactive.
In C6 rat glioma cell cultures and also in isolated rat brain mitochondria the hydroxyisochromans (ISO-2, -3 and -4) were more protective against H_2O_2/ $^{\cdot}OH$-derived oxidative stress than the well known antioxidant trolox. The excellent radical scavenging and antioxidant features of the hydroxyisochromans and their easy availability via synthesis make these compounds interesting as candidates for protection against reactive oxygen/nitrogen species (ROS/RNS).

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GAS CHROMATOGRAPHIC ANALYSIS FOR SUGAR COMPOSITIONS OF CRUDE POLYSACCHARIDE FRACTIONS FROM SOME *PHELLINUS* SPECIES

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The Extracts of *Phellinu*s spp. have been used as immunostimulating agents in folk medicine and their major active fractions were recently known to be polysaccharide fractions.
The active polysaccharide fractions of some *Phellinus* spp. including *P. linteus*, *P. baumii*, *P. pini* and *P. igniarius* were examined for their sugar compositions. The crude polysaccharide fractions made by the ethanol precipitation method were hydrolyzed, reduced and acetylated to the corresponding alditol acetate derivatives to be analyzed by gas chromatograpy. The sugar composition analysis revealed that glucose, galactose and mannose were main hexoses and the pentoses part was composed of ribose, arabinose, xylose and rhamnose. Uronic acid was also identified as glucuronic acid.

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THE ADVANCES RESEARCH IN MARINE NATURAL PRODUCTS FOR ANTI-ALZHEIMER'S DISEASE

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Alzheimer's Disease (AD) is the most common cause of dementia in older people. At present, the cause of the disease is unknown and there is no cure. Researchers continue to look for new treatments to alter the course of the disease. Marine organisms are new sources to find active products for anti-Alzheimer's disease. Lots of active constituents have been extracted from marine organisms and showed good anti-Alzheimer activity. Compound GTS-21 (**1**) from Nemertea (*Amphiponus lactifloreus*) has passed phase I clinical trial and displayed promising result. Some other compounds from marine organisms such as TDB (2,3,6-tribromo-4, 5-dihydroxybenzyl methyl ether) (**2**), Hymenialdisine (HD) (**3**), Omega-3 fatty acids (n -3 fatty acids) (**4**), serotonin sulfate (**5**), Xestospongine B (**6**), sceptrine (**7**) and ageliferine (**8**) are also effective in anti-Alzheimer's disease in the preclinical development research. Herein we will review the advances research in marine natural products for anti-Alzheimer's disease.

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ANALYSIS ON COMPOSITION AND ANTIFUNGAL ACTIVITIES OF ESSENTIAL OILS FROM *ALLIUM MONANTHUM* MAX.

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Essential oils from plants are a promising source for novel natural antifungal drugs, though their activity against human pathogenic fungi is generally milder than commercial synthetic antifungal drugs. *Allium monanthum* is one of the favorite wild vegetables, which has a unique fragrance. This has been collected in the early spring on the field in Korea. The whole plant parts including bulbs and roots are used as condiments and vegetables. It has anti-microbial, anti-cathartic, hematinic, and sedative activities. Therefore it has been sometimes indicated in gastro-intestinal catharsis and insect stings.
In this study we analyzed the essential oil from *A. monanthum* and evaluated its antifungal activity by the broth dilution method and disk diffusion test against five *Trichophyton* species. On the basis of these results, checkerboard micro titer tests were performed and isobolograms were constructed to determine the combined effect of the essential oils and ketoconazole in order to develop more effective and safer anti-catharsis therapy.
As the results, the essential oil of *A. monanthum* showed high susceptibility against the tested fungi .The antifungal activities were dose dependent. It exhibited significant synergism in combination with ketoconazole.

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CLINICAL STUDY OF SHAKLEE IMMUNE BUILDING COMPLEX® IN MENOPAUSAL PATIENTS

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Shaklee Immune Building Complex® (IBC) is a patented herbal blend developed by Yamanouchi Pharmaceutical Company. *In vitro* and *in vivo* studies of IBC demonstrate pronounced stimulation of macrophage, interferon, and cytokine activities. Recent menopause studies have indicated a beneficial influence of cytokines upon associated symptoms. In this study, the effects of IBC on 32 menopausal women (age = 53.0 ± 5.1) are examined. IBC was administered 500mg TID p.o. for 6 months, and menopausal symptoms were evaluated using both the Green's climacteric scale and visual analogue scale (VAS). Blood pressure, body fat, facial skin blood flow, plasma lipids, IL-6, IL-6R, TNF-α, GM-CSF, G-CSF, LH and FSH concentrations were compared. IBC significantly decreased Green's climacteric scores ($P<0.01$), VAS scores ($P<0.01$), and plasma FSH levels ($P<0.05$). IBC significantly increased blood GM-CSF ($P<0.05$), and tended to decrease TNF-α and G-CSF. Of interest, TNF-α levels increased in patients with low baseline levels. These data indicate that IBC significantly improves menopause symptoms, apparently through homeostatic actions on the immune and endocrine systems.

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DETERMINATION OF ARISTOLOCHIC ACID IN ASARI HERBA BY LIQUID CHROMATOGRAPHY/TANDEM MASS SPECTROMETRY

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Aristolochic acid I (AA-I) is a potent carcinogen and nephrotoxin existing in *Aristolochiaceae* family. Asari Herba ("Xixin" in Chinese) is categorized in this family and contains traces of AA-I. The distribution of AA-I in whole plant and the amounts of AA-I in water extracts were properly evaluated in this study. The amounts of AA-I were determined by liquid chromatography/tandem mass spectrometry with electrospray positive ion detection. Piromidic acid (PA) was used as an internal standard. The chromatographic analysis was carried out using a C_{18} column (2.1×150 mm) and a mixture of 0.1% formic acid (containing 0.1% ammonium acetate) and acetonitrile (65:35; v/v) as the mobile phase at a flow rate of 0.3 mL/min. The precursor and the daughter ions of AA-I and PA for the quantitation were set at m/z 359.1, 289.1 and m/z 298.0, 270.9, respectively. The limit of quantitation of AA-I was about 10 ng/mL and the calibration curves of AA-I showed a good correlation ($r^2 > 0.9995$) at the concentration from 0.01 to 5 μg/mL. The results revealed the amounts of AA-I in 70% methanol extracts of root, rhizome, petiole and leaf were 0.48-2.90 ppm, 0.19-4.89 ppm, 1.89-18.41 ppm and 8.01-89.78 ppm, respectively. In addition, the amounts of AA-I in water extracts of root, rhizome, petiole and leaf were 0.03-1.34 ppm, 0.04-1.87 ppm, 0.79-15.23 ppm and 0.69-40.42 ppm, respectively. In conclusion, the amounts of AA-I in root and rhizome were less than those in petiole and leaf; and the amounts of AA-I in water extract were less than those in 70% methanol extract.

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HERBAL PREPARATION – GINSENG AND DANG GUI TEN COMBINATION (PS10) AND IMMUNE RESPONSE IN HUMANS

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The severe debility and immune dysfunction associated with serious disease may respond well to treatment with the tonic formulas from **T**raditional **C**hinese **M**edicine (TCM). One of these, Ginseng and Dang Gui Ten Combination has gained prominence as the formula most suitable to assist convalescence after chemotherapy and radiotherapy.

We have investigated the specific immunomodulatory effects of the PS10 combination in 10 healthy volunteers, of which there were 7 males and 3 females aged 43 to 58 years. The study was a longitudinal study (28 days), using a repeated measures design to investigate the pre and then post intervention changes in Natural Killer (NK) cell activity as well as total and differentiated lymphocyte counts. Further liver function tests (LFT) were included to assess any adverse effects on the liver. It was envisaged that NK cells or other white blood cell subset variation could indicate an immunomodulatory effect of the herbal formulation, PS10.

Investigative methodologies included NK cell function assessment via the ability of peripheral blood lymphocytes (PBL) to lyse the human erythro-leukemia cell line K562.[1] Tumour target cells were labelled with ^{51}Cr, which was released from cells following membrane damage (lysis) and measured in a gamma-counter. Several effector to target cell ratios (E:T) were used in the 4-hour micro-cytotoxicity assay and the results were plotted as %Cr release versus E:T ratio.

The gradient of the line of best fit through the plotted points was recorded as the measure of cytotoxicity or killing.[2] The higher the number and steeper the gradient the greater the cytotoxicity.

To increase the accuracy of detecting a change in immune function, both the effects of NK cell cytotoxicity and number of mononuclear cells were combined and expressed as *lytic units*.

The following trends were observed:

- **Day 0 to day 14:**
  - NK cell activity: 3 patients reduced, 3 no change, 4 increased activity
  - Lytic unit: 5 patients reduced, 1 no change, 4 increased activity
- **Day 0 to day 28:**
  - NK cell activity: 3 patients reduced, 1 no change, 6 increased activity
  - Lytic unit: 2 patients reduced, 1 no change, 7 increased activity

The herbal combination of PS10 appears to synergistically provide a broad range of pharmacological activity with very low level of toxicity. The herbs may have haemopoietic, antimutagenic, antitumor, immunomodulatory and anticomplement activities. They promote lymphocyte activation, interleukin production, protect various organs against toxicity, inflammation and ulceration, and promote drug delivery and radiation sensitising while protecting healthy tissue. The results will be further discussed.

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INHIBITION OF MENADIONE-INDUCED DNA DAMAGE THROUGH INDUCTION OF QUINONE REDUCTASE BY XANTHOHUMOL ISOLATED FROM HOPS

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The quinone reductase assay using murine hepatoma (Hepa 1clc7) cells and the DPPH antioxidative assay were performed to assess the chemopreventive effect of hops (*Humulus lupulus* L.). The detoxification enzyme quinone reductase [NAD(P)H:quinone oxidoreductase] (QR) plays an important role in protecting against quinone-induced carcinogenesis in particular, and has been used as a marker in cancer chemoprevention studies. While the methanol extract of hops showed only weak antioxidant effects as measured by the DPPH assay, it demonstrated strong QR induction activity. In addition, a variety of compounds isolated from hops, such as xanthohumol and 8-prenylnaringenin were tested for QR induction. Among the prenylated compounds, xanthohumol (CD value: 0.85 □M) was the most effective at inducing QR. In addition, xanthohumol significantly inhibited menadione-induced DNA single strand breaks and oxidative DNA damage as measured by the alkaline single-cell gel electrophoresis (comet) and the FLARE (fragment length associated repair enzyme) assays. The QR inhibitor dicumarol reversed the protective activity of xanthohumol against menadione induced-DNA damage. These data suggest that xanthohumol inhibits DNA damage induced by menadione through the induction of QR, and has promise as chemopreventive agent in vivo. (Supported by NIH Grant P50 AT00155 from the Office of Dietary Supplements, NCAM, and NIGMS).

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ANTIOXIDANT EFFECT OF MILK THISTLE EXTRACTS ON AVIAN MACROPHAGE CELL LINES

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Milk thistle extracts contain compounds known as flavanoids, which are collectively referred to as silymarin. The silymarin complex consists of the dihydroflavanol taxifolin, and the flavanolignans silychristin, silydianin, and the diastereomers silybinin A and B and isosilybinin A and B. Their liver-stimulating properties and inhibitory effects on cancer cell growth are well documented. Milk thistle extract also is shown to increase the levels of oxidative stress markers, whereby administration of the extract to rats increased glutathione in liver, intestine, and stomach tissues. The silymarin complex may be beneficial for preventing glutathione depletion in macrophage cells. Most studies devoted to define the health benefits of milk thistle extract were conducted using either a highly processed silymarin complex or the isolated component, silybinin. Although silybinin is claimed by many researchers to be the most active member of the silymarin complex, side by side testing of the various components of the silymarin complex on levels of oxidative stress markers has not been conducted. The test system consists of an avian macrophage cell line (MQ-NCSU cultures), which is cultured in 24-well-plates in LM-Hahn medium. Lipopolysaccharide (LPS) is used to activate the macrophages. Oxidative stress is induced by inhibiting intracellular glutathione synthesis using tert-butylhydroperoxide (t-BHP). The cells are cultured with combinations of LPS, t-BHP, and silymarin components. Preliminary results of glutathione levels will be presented based on data from cells cultured with the silybinin diastereomers and silychristin at various concentrations.

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GARLIC IS EFFECTIVE WITHOUT ALLICIN. (1) CURRENT MARKER COMPOUND FOR HERBS IS NOT MARKER.

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While the herbal supplement market has grown rapidly in recent years, the quality of available products is being heavily scrutinized by the public. Although the quality of products should be well-controlled by reasonable quality control systems, including standardization with marker compounds based upon legitimate science to ensure consistent high quality as well as valid efficacy and safety, there is still a great deal either unknown or misunderstood regarding the real active compounds of herbs. Bioavailability is one of the issues often ignored for standardization of herbs due to the complexity of chemicals, even though it is essential for the utility of active ingredient(s) and is critical for assuring product quality. It is also beneficial for confirming the compliance of the subjects in clinical trials.

In fact, in the case of garlic, allicin has long been believed to be the active compound since it bears the specific odor of garlic. However, several recent studies have shown that allicin is not present in any of the garlic products on the market, nor is it found in human blood even after consumption of a large amount of garlic/garlic supplements. This might be the reason for inconsistent cholesterol-lowering effects demonstrated from dehydrated garlic powder products standardized with allicin potential or yield.

Since herbal supplements are different from synthesized medicines that usually contain a single chemical entity with a clear mechanism of action, they need to be assessed from a different viewpoint. Various constituents are present in herbs and work synergistically, but in most cases it is not known exactly which one(s) is the real active compound. To assure the quality of products, more studies are needed to clarify the bioavailability of the chemical compounds in the herbs and to specify the actives for appropriate standardization.

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GARLIC IS EFFECTIVE WITHOUT ALLICIN. (2) MULTIPLE RISK FACTORS OF CARDIOVASCULAR DISEASES AND ANTIATHELOSCEROTIC EFFECT OF AGED GARLIC EXTRACT (KYOLIC) AS A COMPLEMENTARY MEDICATION.

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Objective: To review the efficacy of Aged Garlic Extract (AGE, Kyolic) on the atherosclerosis in cardiac patients, AGE has been tested in several clinical studies to determine whether the significant benefits are obtained under the influence of AGE.
Design: All of the clinical studies were performed in placebo-controlled, double-blind, randomized manner. The numbers of the subjects were varied between 19 through 80 in these studies. AGE 4 ml or 1.2-3.6 g/day with the equivalent amount of placebo was given subjects individually. Duration of study was also varied from 3 months to 1 year. S-allyl cystine (SAC), one of the active compounds of AGE was measured in the blood as a compliance marker. The measured indications were atherosclerotic plaque burden detected by electron beam tomography (EBT), blood pressure, platelet aggregation, LDL-oxidation and other various biomarkers.
Results: More than 65% of significant inhibition of the plaque formation indicated by calcium score (Volumetric method) for the AGE group ($n = 9$) was detected by EBT over one year compared to placebo ($n = 10$) ($p < 0.05$). The significant reductions of the various risk factors caused by consumption of AGE are 6-9% in blood pressure, 10-25% in platelet aggregation and 38% in LDL oxidation ($p < 0.05$). In AGE patients, there was favorable trend to improving the homocysteine level ($p = 0.08$). The patient compliance was confirmed by significantly high SAC level in the blood in the AGE group compared to the placebo.
Conclusions: These clinical studies have clearly demonstrated the various abilities of AGE to inhibit the rate of progression of coronary calcium, as compared to placebo over one year, by the reduction of multiple risk factors related with cardiovascular diseases. It suggests that AGE may be useful and beneficial for the treatment and prevention of cardiac atherosclerosis.

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GARLIC IS EFFECTIVE WITHOUT ALLICIN. (3)
AGED GARLIC EXTRACT (KYOLIC) HAS BEEN CONFIRMED NO CONTRA-INDICATION WITH DRUGS AS A COMPLEMENTARY MEDICATION.

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Background: Garlic has been shown to be useful in many areas of health maintenance. However, due to its anti-platelets property, the use of garlic has been cautioned when patient are on anticoagulation therapy. As there is no major clinical data on safety regarding concomitant use of garlic and anticoagulant, we have proceeded to evaluate the safety of using garlic along with oral anti-coagulation. For this project, Aged Garlic Extract (AGE, Kyolic) was tested with Coumadin. AGE is one of garlic formulations and since it is well-researched to reduce many risk factors of cardiovascular diseases including anti-platelets property and has been shown solid safety data, it would be a suitable material for this clinical test purpose. We have evaluated its safety on patients taking oral anticoagulation (Coumadin) therapy.
Methods: Sixty-six (66) deep vein thrombosis (DVT) patients were screened for the study. Fifty-two (52) patients were randomized to the project. Forty-eight patients (30 men and 18 women, mean age 56 ± 10 years) completed study. Eighteen patients (14 before randomization, 4 after randomization) were dropped from the study. Study medication (AGE or placebo) was administered at a dose of 5 ml twice a day for 12 weeks. Potential bleeding and thromboembolic episodes were monitored.
Results: There was no evidence of increased hemorrhage in either placebo or medication group. Some of the adverse events included headache, fatigue, colds and dizziness. However, there was no significant difference in incidence of these minor adverse events between the groups. Thus, they are unlikely to be attributable to AGE.
Conclusion: Aged Garlic Extract is relatively safe and poses no serious hemorrhagic risk for patients on oral anticoagulation (Coumadin) therapy with close monitoring. Risk benefit ratio of AGE use need to be considered carefully when Coumadin therapy becomes necessary.

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THE USE OF COLORED PRINCIPLES IN *HIBISCUS SABDARIFA* AND *SORGHUM BICOLOR* AS NATURAL COLORANTS

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Hibiscus sabdarifa Linn. (Malvaceae) and *Sorghum bicolor* (Linn.) Moench (Gramineae) are two plants grown in abundance in Northern Nigeria as a source of beverage and food respectively. These plants are rich in anthocyanins the color giving compounds widely found in plants with antioxidant activities and no history of reported toxicity.
The ground dried calyces of *H. sabdarifa* and ground dried leaf sheaths of *S. bicolor* were extracted using acidified alcohol. TLC achieved separation of anthocyanins while Ultra-Violet spectroscopy analysis was used for tinctoral power (concentration of colored principles) with amaranth as a standard.
Results showed *S. bicolor* extract as a potential source of abundant cheap natural colorant due to the high content of uncommon stable anthocyanins apigenin (over 20%) while *H. sabdarifa* showed high susceptibility to loss of color intensity in light as a result of the instability of its constituent anthocyanins.

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EFFECT OF GRADED CONCENTRATIONS OF THE AQUEOUS AND ETHANOLIC EXTRACTS OF THE RIPE PLUCKED AND RIPE FALLEN LEAVES OF *TERMINALIA CATAPPA* ON CALCIUM INDUCED BLOOD CLOTTING OF HbAA AND HbSS GENOTYPES.

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The effect of the graded concentrations of both aqueous and ethanolic extracts of ripe plucked leaves and ripe fallen leaves of *Terminalia catappa*, a fruit bearing tree reported for its anti sickling activities were assessed on calcium induced blood clotting on normal human hemoglobin HbAA and sickled hemoglobin HbSS in a comparative study.
Clotting time of the normal human hemoglobin HbAA was found to be greatly prolonged by the ethanolic extracts of the ripe fallen leaves as earlier recorded by Mgbemene and Ohiri. A clotting time of 13 minutes at extract concentration of 4mg/ml was recorded against the 9 minutes of the 5.0µg/ml para hydroxyl benzoic acid positive control employed. Drastic fall in clotting time was observed with the HbSS genotype which attained clotting at a minimum time of one minute (aqueous extract of the plucked ripe leaves 1.0mg/ml) as against the positive control clotting time of 3.8 minutes.
The very low clotting time observed for HbSS blood may not be unrelated to the changes in cell membrane permeability to Ca^{++} during sickling.

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CATIONIC EVALUATION OF SOME TRADITIONAL ANTI SICKLING HERBAL DRUGS USED IN NIGERIA AND THEIR POSSIBLE EFFECTS ON THE EFFICACY OF THE DRUGS

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Eleven aqueous plant extracts from 8 traditionally used medicinal plants, (*Terminalia catappa*, *Perquetina negriscence, Adasonia digitata, Cissus populnea, Zanthoxyllum xanthoxyloides*, *Cajanus cajan, Bryophyllum pinnatum* and *Carica papaya*), were evaluated for their cationic constituents as a measure of their efficacy in sickle cell anemia disorder.
Extracts were subjected to dry ash digestion and the resultant supernatants were used for macro and micronutrients determination using the emission flame photometer and the absorption spectrophotometer. K^+ was found to be relatively high (> 1.5%) in most cases, Na^+ was low (< 1.0%) and Ca^{++} was significantly low, (< 0.5%) in some. The magnesium content was in most cases less than 1%. The presence of these cations, K^+, Na^+, Ca^{++} which are implicated in the process of sickling and are involved in electrolytes movement in the physiological system of the body may be an important parameter in sickle cell anemia management.
The data of the cationic evaluation and the claim to the possible effect on the efficacy of these herbal medicines will be presented.

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QUALITATIVE DETERMINATION OF ARISTOLOCHIC ACIDS IN ARISTOLOCHIA PLANTS AND IN COMMERCIAL PRODUCTS BY HPLC-UV-ESI/MS METHODS.

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The development and validation of a rapid qualitative method based on an HPLC-UV-MS technique with electrospray ionization for the simultaneous analysis of six aristolochic acids suah as Aristolochic Acid A, Aristolochic Acid B, Aristolochic Acid C, Aristolochic Acid D, 7-OH Aristolochic Acid A, and Aristolic Acids in a number of aristolochia medicinal plants and some commercial products is reported. HPLC with DAD and ESI/MS detection allowed the identification of target compounds and increased the selectivity of complex analysis such as those involved with multi-botanical preparations. The optimized experimental conditions allowed a considerable reduction of analysis time and simplified the sample preparation procedure. The HPLC-MS method proved to be more sensitive than HPLC-UV, and the selectivity could be improved greatly by the joint use of two detectors.

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HERBAL PRODUCTS FROM THE INTERNET: EVALUATION OF NEPHROTOXICITY AND ARISTOLOCHIC ACID CONTENT

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Aristolochia species have been administered by those trained in Traditional Chinese Medicine for centuries. After determining *A. fangchi* was an adulterant that caused death due to renal failure in a number of patients at a Belgium weight loss clinic, many countries took steps to regulate products containing *Aristolochia species*. The USFDA issued a Consumer Advisory stating the appropriate regulatory action would take place against products known and suspected to contain *Aristolochia* and *Asarum* Spp. An Internet search conducted in our laboratory has identified a few websites that sell herbal products from US merchants containing either *Aristolochia* or *Asarum* as one of their ingredients. These products (25 nos.) were purchased and screened for their nephrotoxic effects by neutral red assay on LLC-PK_1 cell lines and also analyzed for the presence of renal toxins aristolochic acid I and II (AA-I & II) content by HPLC. Four out of 25 products were found to be cytotoxic with IC_{50} values ≤ 100 □g/mL when tested on this cell line. Two of these nephrotoxic products contained detectable amounts of AA I and II. Four more products were also found to contain AA I and II but didn't show considerable toxicity *in vitro*. The lack of relevant correlation between toxicity and analytical data suggest that ingredients other than AA-I and II, could also a play a significant role on the overall toxicity of these products.

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STRUCTURE-ACTIVITY RELATIONSHIPS OF ARISTOLOCHIC ACID ANALOGUES. TOXICITY IN CULTURED RENAL TUBULAR EPITHELIAL CELLS

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Recent studies showed that Aristolochic acid (AA) could induce acute renal failure and tubular lesions in several species and demonstrated the unequivocal role of AA in so called Chinese herbs nephropathy. Inasmuch as AA nephrotoxicity and carcinogenicity represents a serious health risk, there exists increasing demand to understand the structural requirements of various AA compounds for their nephrotoxicity. A series of twenty-two AA derivatives isolated from Aristolochia Spp. were screened for their nephrotoxic potential using the neutral red assay *in vitro* in cultures of LLC-PK_1 cell line. The relationships between their structure and nephrotoxicity were analyzed to predict cytotoxic levels of AA-I and its analogues. Further, caspase-3 activity assay was performed on toxic compounds to determine if capsases, the enzymes that are involved in cell death pathway called apoptosis are involved in AA induced nephrotoxicity. AA-I was found to be most toxic followed by AA-II, AA –VIIIa and AA-Ia in decreasing sequence of toxicity. The other compounds from Aristolochia spp. viz., nitrophenanthrene carboxylic acid analogues of AA-I, Aristolactum derivatives and few other benzoic acid derivatives have not exhibited considerable cytotoxicity. The results from caspase 3-activity assay suggested the involvement of caspases in AA induced apoptosis. The critical structural determinants for nephrotoxicological potency of AA compounds will be discussed.

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COMPARATIVE FATTY ACID CONTENT OF SEEDS OF FOUR *CUCURBITA* SPECIES GROWN IN A COMMON GARDEN.

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The seeds of pumpkin (primarily *Cucurbita pepo* L. and *C. maxima* Duch.) are a common snack food in several cultures, and oil is processed from the hull-less variety *C. pepo* var. *styriaca* Grebenščikov for culinary and pharmaceutical uses. Pumpkin seeds have also been used in traditional medicine as a vermifuge, and are among several food plants and herbs containing fatty acids and phytosterols that are used for the treatment of benign prostatic hyperplasia. Great variation has been observed in fatty acid content of pumpkin seeds from *Cucurbita pepo*, while other pumpkin or winter squash species, including *C. moschata*, *C. maxima*, and *C. mixta* (aka *C. argyrosperma*), have been inadequately studied. Varieties of these four species were grown in a common garden; percent free fatty acids and relative content of palmitic, stearic, oleic and linoleic acids were determined by GC-FID. *C. moschata* and *C. maxima* had higher free fatty acids on average than *C. pepo*, and the former species had the highest observed concentrations of linoleic acid. *C. mixta* had high total lipid content, but high saturated fatty acid and low linoleic acid content. All species were variable, and hybridization in open-pollinated fruits affected seed lipid phenotype.

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SINGLE LAB VALIDATION FOR THE DETERMINATION OF COMPONENTS IN ST. JOHN'S WORT RAW AND FINISHED PRODUCTS BY HIGH PERFORMANCE LIQUID CHROMATOGRAPHY WITH PHOTODIODE ARRAY DETECTION

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St. John's Wort (SJW), *Hypericum perforatum* L. (Clusiaceae), also known as goatweed, has gained notoriety as an antidepressant. The reported antidepressant nature of SJW has led to large scale clinical trials on SJW extracts and finished products in the United States. Due to the complex matrix of plant material, obtaining a uniform product can be difficult. The source of the plant material, the location the plant material was grown, when the plant material was harvested, and preparation of the plant material are a few factors that can affect the quality and activity of the dietary supplement. Therefore, the development of a method for quality control becomes a priority. The use of analytical methods is one way to aid in the quality control of the test material. The method uses high performance liquid chromatography with photodiode array detection for the quantitation of nine analytes in SJW: I3,II8-biapigenin (1), hyperforin (2), hypericin (3), hyperoside (4), isoquercitrin (5), pseudohypericin (6), quercetin (7), quercitrin (8), and rutin (9). The method was validated for the quantitation of these compounds in raw SJW herb, SJW extracts (solid and liquid form), SJW capsules and tablets, and teabags containing a mixture of plants including SJW.

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DETERMINATION OF ADRENERGIC AMINES AND FLAVONOIDS IN CITRUS PEEL/FRUIT EXTRACTS AND IN PRODUCTS BY REVERSED-PHASE HPLC.

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Citrus aurantium L. (Rutaceae), commonly known as sour orange is used in traditional folk medicine to treat anxiety, insomnia and as an anticonvulsant, suggesting depressive action upon the central nervous system (CNS), among other properties. Citrus species are known to produce coumarins, flavanones, flavones, flavonols, which occur in the free form and/ or as glycosides, and limonoids. A large number of natural compounds have potent anticarcinogenic or antimutagenic activity against environmental carcinogen and mutagen. Differences between varieties in terms of the flavanone glycoside content, particularly hesperidin and naringin, were observed. It is becoming important to evaluate the *Citrus aurantium* for its adrenergic amine as well for phenolic content due to popularity of synephrine as a substitute for ephedrine. Twelve flavonoids (rutin, neoeriocitrin, naringin, hesperidin, neohesperidin, naringenin, narirutin, hesperetin, nobiletin, 5-O-demeth-nobiletin, tangeretin) and four amines (synephrine, octopamine, hordenine, tyramine) in the peel of citrus species were analyzed with HPLC with a C18 reversed phase column using gradient mobile phase of sodium acetate buffer (pH 5.5) and acetonitrile at a flow rate of 1.0 mL per minute with detection at 224 and 280 nm.

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ENANTIOMERIC SEPARATION OF BIOGENIC AMINES IN CITRUS EXTRACTS/PRODUCTS BY HIGH PERFORMANCE CAPILLARY ELECTROPHORESIS.

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C aurantium L. (Rutaceae) fruit extracts have recently been used for weight loss. The most important active constituent of the plant is the sympathomimetic compound synephrine and commercially available extracts are standardized for their content of this active principle. *C aurantium* contains a rare composition of adrenergic amines - synephrine, hordenine, octopamine and tyramine. While synephrine is best known, the others have demonstrated equally powerful thermogenic properties. The amines (nitrogen-containing compounds) in *Citrus aurantium* are not as lipophilic (fat-soluble) as those in *Ma Huang*, so do not readily cross the blood-barrier. A new capillary electrophoresis method was developed for the quantitative determination of d-synephrine, l-synephrine, d-octopamine, l-octopamine, tyramine and hordenine. The electrophoretic separation is performed using a 75 cm x 50 µm ID (66.5 cm effective length). The samples are injected by pressure for 5 seconds at 50 mbar and the running voltage is 30 kV at the injector end of the capillary. The method is successively applied to the determination of the adrenergic amines in dietary supplement products and in citrus peel/fruits.

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QUANTITATIVE DETERMINATION OF LIGNAN CONSTITUENTS FROM SCHISANDRA CHINENSIS BY HIGH PERFORMANCE LIQUID CHROMATOGRAPHY.

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The fruits of *Schisandra chinensis* (Schisandraceae/Magnoliaceae) are a traditional Oriental medicine possessing diverse activities such as adaptogenic, antitussive, anti-asthmatic, sedative, insecticidal, antioxidant, PAF antagonist, antitumour, antiviral against human immunodeficiency virus and antihepatotoxic activities. A simple, specific analytical method for the quantitative determination of eight lignan constituents from the methanolic extract of the fruits of *Schisandra chinensis* was developed. The lignan content present in the fruits of *Schisandra chinensis* were separated with an Acetonitrile-Water-Reagent alcohol gradient at a flow rate of 1.0 mL per minute. The HPLC separation was performed on a Phenomenex Luna C18(2) (150 x 4.6 mm I.D., particle size 5 μm) reversed phase column with detection at 215 nm. The limit of detection was in the range from 0.2 to 1.5 μg/mL. The relative standard deviation (RSD) values for the determination of lignan constituents in fruits of *Schisandra chinensis* were less than 3.0 %. The method was successfully used to analyze different *Schisandra chinensis* market products as well as to distinguish between other *Schisandra* samples from Korea. This analytical method developed for the lignan constituents present in *S chinensis* dried fruit having multiple biological activities.

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CHEMICAL CONSTITUENT STUDY ON *VITEX AGNUS-CASTUS*

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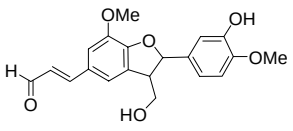
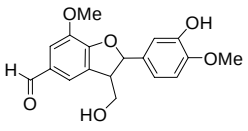
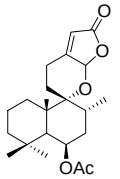
An extract of chaste berry (*Vitex agnus-castus* L.) has long been used in Western countries as a remedy for the relief of symptoms of premenstrual syndrome (PMS). As part of our Center's efforts to chemically characterize and standardize defatted MeOH extracts of *V. agnus-castus* fruits, two new lignans named vitagnusin A and B, the new diterpene agnolide A, the new triterpene vitexolic acid A, and 21 known compounds were isolated from bioactive fractions under activity guided fractionation using opioid δ_2 and μ bioassay models. Structural elucidation and identification of all compounds were accomplished by detailed NMR spectral analysis.



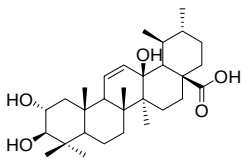
Vitagnusin A



Vitagnusin B



Agnolide A



Vitexolic acid A

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AUTHENTICATION OF *Stephania tetrandra* S. Moor AND ITS TOXIC ADULTERANT *Aristolochia fangchi* Wu. USING MICROSCOPY.

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Aristolochia fangchi Wu. contains Aristolochic acids, which is a know nephrotoxic and carcinogenic. In 1993 few young women in Belgium developed renal fibrosis, which was attributed to a slimming preparation containing the herb *Aristolochia fangchi* Wu. instead of *Stephania tetrandra* S. Moore. These cases are indicative of lack of quality control especially authentication aspect. Both species *Stephania tetrandra* S. Moore and *A. fangchi* Wu. are officially listed in the Chinese Pharmacopoeia. *S. tetrandra* is used as an analgesic, anti-inflammatory and diuretic agent and for the treatment of hypertension. *Stephania tetrandra* S. Moore and *Aristolochia fangchi* Wu. are commonly know as " Han Fang Ji" and "Guang Fang Ji" respectively in the Traditional Chinese Medicine. Roots of both the species look very much alike and have almost similar vernacular name. As a result *Stephania tetrandra* S. Moore is often adulterated with *Aristolochia fangchi* Wu. A microscopic and macroscopic method has been developed to differentiate these two species.

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MACROSCOPIC AND MICROSCOPIC AUTHENTICATION OF *Illicium verum* Hook. f. AND ITS ADULTERANT *Illicium anisatum* L.

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The fruits of *Illicium verum* Hook. f. (Star anise) has stimulant, diuretic and digestive properties and is known to be an effective remedy for gas and indigestion. In the TCM (Traditional Chinese Medicine) it is given as herbal tea to infants suffering from colic pain. Due to its success in the TCM in treating colic pain in infants, it is now being preferred by growing number of consumers even in the Western countries. Unfortunately in the recent years increasing number of cases of infants suffering from acute neurological effects such as seizures, vomiting, jitteriness and rapid eyeball movement were reported from Western countries after the consumption of Star anise herbal tea. These adverse cases are believed to be due to the possible adulteration of Chinese star anise with the Japanese or the Bastard anise *Illicium anisatum* L. A macroscopic and microscopic authentication for the two species has been developed using Stereo scope and Fluorescent microscopy. These differences were further confirmed using SEM (Scanning Electron Microscopy).

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AUTHENTICATION OF *Ephedra* SPECIES FROM OLD WORLD AND NEW WORLD

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Ephedra sinica Stapf or Ma Hung is used in the traditional Chinese medicine for over 5000 years as bronchodilating and stimulatory. In the West, it was popularly used as dietary supplements for weight loss and athletic performance enhancement. There are 50 known species of *Ephedra*. *Ephedra* contain six optically active alkaloids. The ratio of ephedrine to other alkaloids depends on the species used; however the North American species lack alkaloids. A lot of adverse cases have been reported due to consumption of dietary supplements containing *Ephedrine* alkaloid and is thus banned by the FDA. Method commonly used in the dietary supplement industry for authentication of botanical is to analyse the product for the presence of chemical markers known to be present in the specific herb. However this method does not ensure the product contains actual herb, especially if it's spiked with chemical markers. The other problems associated with authentication of the drug in the dietary supplement industry is that the manufactures receive *Ephedra* sample in the form of cut bits or powders without any vouchers, so identification of the species is difficult. In the present study a macroscopic and microscopic authentication of *Ephedra* in cut bit as well as in powdered form is developed using light microscopy and stereoscope. The present study will assist in authentication the presence or absence of *Ephedra* herb in the dietary supplements and to a certain extent the region of its occurrence.

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QUANTITATIVE DETERMINATION OF USNIC ACID FROM *Usnea lichen* AND IN PRODUCTS BY REVERSED PHASE HPLC.

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Usnic acid, a lichen substance have a wide range of pharmaceutical applications; it reported to have antibiotic, antimycotic, antifeedant, phytotoxic, antitubercular, antitumor, and enzyme-inhibiting activities and also used in cosmetics. The products containing usnic acid were marketed as a weight control supplement. While on the market heptatoxicity and acute liver failures were reported as a result of the products containing usnic acid. The usnic acid present in the plant material and products were separated with an 0.1 % acetic acid and acetonitrile gradient at a flow rate of 1.0 mL/min. A Waters XTerra RP18 (150 x 4.6 mm; 5 □m particle size) column was the stationary phase with the detection performed at 233 nm. The limit of detection was 0.7 µg/mL. The raw material of *Usnea lichen* and products were analyzed for the content of usnic acid.

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ANALYZING THE YEILD OF ISOQUINOLINE ALKALOIDS IN CULTIVATED AND WILD CRAFTED BLOODROOT (Sanguinaria Canadensis) GROWN IN NORTH CAROLINA

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Bloodroot (*Sanguinaria canadensis*) has been utilized as an herbal remedy for inhibiting oral bacterial growth and for treating various skin and systemic infections. Populations of this plant can be found along the eastern coast of the United States, with particular abundance in the southern Appalachian mountains. Recently, its use is growing in Europe as a non-antibiotic animal feed supplement to promote weight gain. For this, it is being harvested from the wild throughout western North Carolina, and some fear that rising demand could result in bloodroot becoming a threatened or endangered species. Moreover, it is difficult to predict the volume of material that will be available from year to year relying solely on wild crafting. As efforts to develop economical ways to grow and cultivate this herb are underway, there is an ever-pressing need to understand how various permutations affect the yield of isoquinoline alkaloids in bloodroot. Towards this end, we studied the month to month variability of the concentration of these alkaloids in both cultivated and wild crafted samples. We developed and applied extraction and HPLC procedures to determine the concentration of the isoquinoline alkaloids sanguinarine and chelerythrine in rhizomes of bloodroot collected from two different locations once a month for seven months. The alkaloid yield was consistently higher, but more variable, in wild crafted plants. We also determined the concentration of a suite of heavy metals and trace elements in soil samples collected simultaneously with each plant sample. Differences in the element profiles for the soil samples were compared against alkaloid yields, and these results may be useful in the development of a production system for high alkaloid yielding bloodroot.

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ANTI-INFLAMMATORY AND CYTOTOXIC ACTIVITIES OF CYCLOARTANES PRESENTS IN P. ARGENTATUM.

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Derivatives of naturally occurring substances are important therapeutic agents for many types of cancer, thus natural products continue to be important starting materials for drug development[1]. On the other hand, our systematic study on the resin of *P. argentatum* (guayule), shrub endemic to the Chihuahua desert, has revealed the presence of large quantities of cycloartane-type triterpenes[2]. Since significant evidence indicates that the processes of inflammation and carcinogenesis share common mechanisms[3], we wish to report the cytotoxic and anti-inflammatory activities of 26 derivatives of argentatins A and B, main cycloartane-type triterpenes present in *P. argentatum*. The anti-inflammatory activity was evaluated by means of the TPA-induce edema in mice, while the cytotoxic activity was determined by means of the sulphorrodamine B assay. Our results showed that 2α-bromo argentatina A was the most active anti-inflammatory compound, while 1-en-2-formyl-argentatine B was the most cytotoxic among all the tested compounds.
[1] Place A. E. *et al*. Clinical Cancer Research 9, 2798-2806, 2003, [2] Céspedes C. L. *et al*., Z. Naturforsch. 56c, 95-105, 2001. [3] Steinbach G., *et al*., N. Engl. J. Med. 342, 1946-1952, 2000.

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BIOPROSPECTING HISTORIC HERBAL TEXTS WITH BIOINFORMATICS

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Ethnobotany has lead to the identification of novel pharmacologic agents, but there remain many challenges to using ethnobotany as a research tool. Particularly, the loss of traditional knowledge in concert with the advent of high-throughput screening has made ethnobotanical techniques laborious and potentially unnecessary. However, historic herbal texts provide a pre-existing resource documenting the traditional uses of various species as medicines. As generational losses of traditional knowledge accrue, these herbal texts therefore become increasingly valuable. Methodology for leveraging the information contained in these resources had previously been cumbersome and consuming, however through utilizing a novel new bioinformatics data mining system we are able to extract leads from historic herbal texts and identify candidate species that hold promise for revealing unassessed pharmacotherapeutic leads to bioactive compounds.

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ESSENTIAL OIL ANALYSIS OF *BRICKELLIA VERONICAEFOLIA* (ASTERACEAE)

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The analysis of the essential oil of the species *Brickellia veroniceafolia* (Kunth) Gray (Asteraceae) prepared from the fresh aerial parts by hydrodistillation has been conducted. HPLC separation allowed the isolation of the major constituents characterized as chamazulene, germacrene D, and caryophyllene. In addition, the oil was analyzed by GC/MS and HPLC in order to establish the chromatographic "fingerprint profiles" of the species. In addition, quantitative analyses using HPLC, GC/MS, and NMR have been developed for the quantification of chamazulene These methods proved to be valuable tools (rapid and sensitive) for quality control of the herb and commercial products containing *B. veronicaefolia*.
This work was supported by a grant of CONACyT C01-018.

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PROANTHOCYANIDINS AND TRITERPENES FROM CRANBERRY FRUITS: ANTITUMOR ACTIVITY AND EFFECTS ON MATRIX METALLOPROTEINASE EXPRESSION

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Cranberry fruit (*Vaccinium macrocarpon*) is rich in several classes of compounds with potential anticancer activity. Our goal is to investigate this activity in two areas: tumor cytotoxicity *in vitro*, and effects on the expression of matrix metalloprotinases (MMPs) linked to tumor proliferation in DU145. Proanthocyanidins (PACs) from whole cranberries and blueberries were prepared by gel chromatography. Red cranberry PACs were further fractionated using Toyopearl HW40. Several proanthocyanidin-rich extracts selectively inhibited tumor cell growth, with the strongest cytotoxicity occurring in lung (H460) colon (HT-29) and leukemia (K562) cell lines with GI_{50} below 100 μg/mL. Two triterpene hydroxycinnamate esters were isolated from cranberry fruits (cis- and trans-3-*O*-*p*-hydroxycinnamoyl ursolic acid) and tested at NCI for cytotoxicity on 60 tumor-cell lines. Several cancer cells were inhibited by cis isomers with the concentration (GI_{50}) of less than 10 μM in all of leukemia, lung cancer, breast cancer, and prostate cancer cell lines. Trans isomers inhibited in GI_{50} of less than 10 μM all of leukemia, non-small cell lung cancers, colon cancers, CNS cancers, ovarian cancers, renal cancers, prostate cancers, and breast cancers. Crude cranberry extract, crude triterpene and crude PAC fractions inhibited the expression of MMP-2 and MMP-9 in DU-145 human prostate metastatic carcinoma. Cis hydroxycinnamoyl ursolic acid inhibited expression of both MMPs by 50 % at a concentration of 1 μg/mL in both MMP-2 and MMP-9. The trans isomer was only slightly effective at a concentration of 1 μg/mL in MMP-2 but inhibited both MMPs at 10 μg/mL. Further characterization of bioactive PAC fractions and investigation of additional possible mechanisms is underway.

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THE EFFECTS OF TERPENOIDS ISOLATED FROM LEAVES OF DIOSPYROS KAKI ON CARBON TETRACHLORIDE INDUCED HEPATOTOXICITY IN RATS

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This study was performed to investigate the protective effect of terpenoids isolated from leaves of Diospyros kaki on Carbon Terachloride induced hepatotoxicity in rats. The isolated compounds, 19α-hydroxy ursolic acid (**I**), α-amylin (**II**), Uvanol (**III**), Ursolic acid (**IV**), and 19α, 24-dihydroxy ursolic acid (**V**) were obtained and injected in rats during 3days before CCl_4 treatment. The group treated with **V** showed the decreased activities of ALT, AST, ALP, γ-GT, LDH, CAT and GSH-Px, and decreased the contents of cholesterol and TG compared to the only CCl_4 treated group. The compound, **V** not only significantly increased the content of GSH but also increased the activity of GST. On the other hand, the compound, **I** decreased the content of MDA and the activity of SOD. On the microscopic examination for liver tissues treated with the compounds, the tissue of the compound, **V** showed scantly mononuclear cell infiltration and necrosis.

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ANTI-INFLAMMATORY AND ANTINOCICEPTIVE EFFECTS OF THE EXTRACT FROM *Kalopanax pictus, Pueraria thunbergiana* AND *Rhus verniciflua*

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The combined extracts obtained from three Chinese herb medicine, *Kalopanax pictus*, *Pueraria thunbergiana* and *Rhus verniciflua*, have been used as therapeutics for *diabetes mellitus* in Korea. In the present study, we have investigated their possible anti-inflammatory effects by comparing the potency of individual extracts with that of the combined extracts. An individual water extract prepared from*K. pictus*, *P. thunbergiana*, and *R. verniciflua* was named K-1, P-1, andR-1, respectively. Simultaneously, we also prepared the combined extracts from above three plant materials by identical methodsand named KPR-1. These four extracts were further fractionated into the EtOAc extracts, and these were designated as K-2, P-2, R-2, and KPR-2, respectively. These eight samples were subjected to the nitrite assays in LPS-induced macrophage 264.7 cells. KPR-2 exhibited the most pronounced effect on the inhibition of NO production among all the extracts. KPR-2 also significantly decreased PGE2, and TNF- release. In addition, KPR-2 showed in vivo anti-inflammatory activity against acute paw edema induced by carrageenan in rats. When analgesic activity was measured by the acetic acid-induced abdominal constriction and hot plate test, KPR-2 showed a dose-dependent inhibition in animal models. These results suggested that the mixture extract and successive fractionation could lead to the betteruse of anti-inflammatory medicinal crude drugs.

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PROTECTIVE MECHANISM OF FLAVONOIDS ISOLATED FROM *Rhus verniciflua* STOKES ON THE PARAQUAT TOXICITY

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The Rhus verniciflua Stokes has been used as a medicine in China for expellingso-called abdominal pain, hyperacidity, constipation, diabetes mellitus, destroying intestinal parasites, promoting blood circulation and treating paralysis caused by wind and damp, pain along the knee and spine and anticalcinogen. In the presnet study, we conducted this study to examine new pharmacological activity of flavonoids(fustin, sulfuretin) which were isolated from Rhus verniciflua Stokes on the toxicity of paraquat in rats. Flavonoid reduced the elevated serum enzyme activities of biological liver function test and the formation of hepatic and lung malondialdehyde induced by paraquat. Flavonoid also significantly restored towards normalization the decreased activity of hepatic microsomal enzymes and lung tissue enzymes induced by paraquat. Fustin and sulfuretin were potent inhibitor of NO production and it also significantly decreased PGEs and TNF-α release. The protein and mRNA expression level of inducible NO synthase and cyclooxygenase-2 was inhibited by fustin and sulfuretin in a dose-dependent manner.

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IN VITRO ANTIINFLAMMATORY ACTIVITY OF 23-HYDROXYURSOLIC ACID ISOLATED FROM *Cussonia bancoensis* IN MURINE MACROPHAGE RAW 264.7 CELLS

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In the present study, the effects of various triterpenoids isolated from the stem bark of *Cussonia bancoensis*, namely, ursolic acid (**1**), 23-hydroxyursolic acid (**2**), 3-*O*-α-L-arabinopyranosyl-23-hydroxyursolic acid (**3**), and 3-*O*-β-D-glucopyranosyl-23-hydro-xyursolic acid (**4**) were evaluated on lipopolysaccharide (LPS)-induced nitric oxide (NO) and prostaglandin E_2 (PGE_2) release by the macrophage cell line RAW 264.7. Of the tested triterpenoids, 23-hydroxyursolic acid (**2**) was found to be the most potent inhibitor of NO production, and also significantly reduced PGE_2 release. Consistent with these observations, the protein and mRNA expression levels of inducible NO synthase (iNOS) and cyclooxygenase (COX)-2 enzymes were inhibited by 23-hydroxyursolic acid (**2**) in a concentration-dependent manner. Furthermore, 23-hydroxyursolic acid (**2**) inhibited the LPS-induced DNA binding activity of nuclear factor-*κ*B (NF-*κ*B), which was associated with decrease p65 protein levels in nucleus. These results suggest that the 23-hydroxyursolic acid-mediated inhibition of iNOS and COX-2 expression, by blocking NF-*κ*B activation, may mechanistically responsible for the anti-inflammatory effects of *Cussonia bancoensis* stem bark.

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NEW ALKAMIDES FROM *LEPIDIUM MEYENII* (MACA)

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Maca (*Lepidium meyenii*) has been used for increasing fertility and stamina in Peru and elsewhere for thousands of years. Nowadays a wide array of commercial maca products is gaining popularity as dietary supplement, with claims of anabolic and aphrodisiac effects. Chemical investigations of Maca led to the isolation of characteristic macaenes and macamides (unsaturated fatty acids and their amides). Even though the biologically active principles of maca are not fully known, extracts rich in macamides and macaenes showed promising pharmacological activities. These kinds of compounds are unique, only found from *L. meyenii*, and they can be used as markers for quality control. We have reported the isolation of two new macamides, a novel macaene and a new N-hydroxypyridine derivative macaridine in the previous study. In this study, three additional new alkamides, N-benzyl-9-oxo-12*E*-octadecenamide, N-(3-methoxybenzyl) palmitamide and N-benzyltetracos-15*Z*-enamide were isolated and identified based on the 2D NMR experiments, as well as ^{1}H-^{15}N NMR HMBC correlations. In addition, the structure of N-benzyltetracos-15*Z*-enamide was confirmed by synthesis.

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ANTI-INFLAMMATORY AND ANTI-ARTHRITIC EFFECT OF A DIET-SUPPLEMENT CONTAINING RED GINSENG EXTRACT AND GLUCOSAMINE COMPLEX

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We evaluated the anti-arthritic effect of a new diet-supplement product containing red ginseng. glucosamine, shark cartilage, ascorbic acid and manganese chloride for the relieving arthritic symptoms. Anti-inflammatory activities of the aqueous extract of red ginseng (250 and 500 mg/kg), glucosamine (240 mg/kg) and shark cartilage (240 mg/kg) were tested individually on vascular permeability and carrageenan-induced paw edema. Glucosamine and shark cartilage showed the inhibition of vascular permeability by 29.6 and 32.9%, respectively. Red ginseng (500 mg/kg) and shark cartilage showed the inhibition of carrageenan-induced paw edema at 0.5, 1, 2 and 3 hr. The supplement (red ginseng mixture:RGM) composed of red ginseng (43.5%), glucosamine (25.0%), shark cartilage (25.0%), ascorbic acid (5.0%) and manganese chloride (1.5%) was prepared and its inhibitory activities including vascular permeability and carrageenan-induced paw edema were comparable to anti-inflammatory drugs such as diclofenac and ibupofen. It was also tested on adjuvant-induced arthritis in rats as one of chronic arthritic tests and Randall Selitto assay as an analgesic test. RGM showed the inhibition against the swelling of rat paws induced *by Mycobacterium tuberculosis* at a dose of 1,500 mg/kg. Determination of cytokines of the sera sampled from arthritis-induced animals indicated that RGM increased the levels of interferon-γ and interferon-6, representing the immunostimulatory effect by red ginseng. RGM treatment moderately reduced the production of NO in RAW 264.7 cells in a dose-dependent manner. Taken together, these results support that RGM can be applicable for the improvement of arthritic symptoms as a new diet-supplement.

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ANTI-INFLAMMATORY AND ANTI-NOCICEPTIVE EFFECTS BY THE BRANCHES OF *CINNAMOMUM CASSIA* IN RAT ARTHRITIS

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Rheumatoid arthritis is an autoimmune disorder of unknown etiology that is characterized by progressive joint destruction, deformity, disability and premature death in most patients. In the screening of inflammatory effects of herbal medicines, it found that 80%-EtOH extracts of *Cinnamomum cassia* Blume (Lauraceae) rhizomes exhibited anti-inflammatory effects in carrageenan-induced paw edema in rats. In addition, this extracts also showed chronic anti-inflammatory and anti-nociceptive effects against primary and secondary hind paw swelling in Freund's complete adjuvant–induced rheumatoid rat model. Its EtOAc, *n*-BuOH, and H_2O extracts from the 80% ethanolic extract of *C. cassia* were tested anti-inflammatory effects on the carrageenan models *in vivo*. Plus, its anti-inflammatory effect *in vitro*, were examined through inhibitory activities of nitric oxide (NO) and prostaglandin E_2 (PGE_2) production, and expression of COX-2 and iNOS by lipopolysaccaride (LPS) on Raw 264.7 macrophage cell *in vitro*.

Key words: *Cinnamomum cassia*, anti-inflammation, anti-analgesic, anti-rheumatic activity, carrageenan, complete Freund's adjuvant, NO and PGE_2 production, COX-2 and iNOS expression

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ANTIOXIDANT COMPONENT OF SIAMESE NEEM TREE LEAF EXTRACT

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Siamese neem tree, *Azadirachta indica* A Juss var. *siamensis* Valeton is a large evergreen tree in Meliaceae which is usually found in Southeast Asia especially Thailand. In Thai traditional medicine, its young leaves and flowers are used as tonic, antipyretic, antiinflammatory and antihemorrhoid agents. The young leaves and flowers have been commonly consumed as a vegetable. This experiment reports the antioxidant activity of crude extracts from the leaves, flowers and stem bark of this plant.

The extracts were tested for free radical scavenging activity using DPPH method, total antioxidant activity determination and TBARS method for the activity on lipid peroxidation formation. The major antioxidant compound was also separated from the leaf aqueous extract and identified as rhynchosin-3-*O*-□D-glucoside. To our knowladge, this is the first time to report antioxidant component from Siamese neem tree.

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ETHYL CAFFEATE, A NOVEL ANTIOXIDANT ISOLATED FROM *BIDENS PILOSA*, SUPPRESSES ACTIVATION OF NUCLEAR FACTOR- B BY INHIBITING ITS ABILITY TO BIND DNA IN MACROPHAGE RAW 264.7 CELLS

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Bidens pilosa Linn. var. *radiata* (Compositae) is a plant widely found in tropical and subtropical regions of the world and is popularly used as an ingredient in folk medicines or herbal teas for preventing inflammation. In the present study, we investigated the effects and mechanisms of a novel antioxidant, ethyl caffeate, isolated from *B. pilosa* on anti-inflammatory activities. Our results showed that ethyl caffeate potently inhibited LPS-induced nitric oxide (NO) and prostaglandin E_2 (PGE_2) production in RAW 264.7 cells. In addition, ethyl caffeate also suppressed the gene and protein expressions of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) in a dose-dependent manner. Nuclear transcription factor-□B (NF-□B) is involved in regulation of iNOS and COX-2 expression. Activation of NF-□B involves two important steps: (1) the release of the inhibitory I□B subunit, and (2) the nuclear accumulation of the activated NF-□B. Ethyl caffeate did not inhibit LPS-induced degradation of I□B□or translocation of activated NF-□B into the nucleus. The phosphorylation of Erk1/2, p38 and SAPK/JNK in mitogen-activated protein kinase (MAPK) signal transduction pathway was also not responsive to the ethyl caffeate treatment in macrophages. However, treating of LPS-induced RAW 264.7 cells with ethyl caffeate inhibited NF-□B activation by impairing the binding of NF-□B to specific DNA. *In vitro* experiments showed that ethyl caffeate do directly interfere with DNA binding of NF-□B, as evaluated using EMSA assays. Taken together, our results clearly demonstrate that ethyl caffeate suppresses the NF-□B activation and also down regulate the expression of NF-□B regulated proteins such as iNOS and COX-2 *via* interference of the NF-□B/DNA complex formation. Thus, ethyl caffeate may play an important role in reducing both oxidative and nitrosative cellular stress, and would be important for future development as an anti-inflammatory agent.

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DIFFERENTIAL EFFECTS OF *ECHINACEA PURPUREA* EXTRACTIONS ON TNF PRODUCTION IN HUMAN IMMUNE CELLS

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Introduction: *Echinacea* is in prevalent use for its reported immunostimulatory effects but the most effective preparation is unknown. This study's purpose was to analyze constituent content of distinct *Echinacea purpurea* extracts and their effects on TNF production by immune cells. **Method:** Four extractions of fresh *E. purpurea* roots vs. aerial parts (100%, 75%, 33%, and 10% EtOH) were prepared and analyzed by LC-MS to determine alkylamide and phenolic compound concentrations. Influence of these extracts on TNF production in a human monocytic cell line (U937) and human peripheral blood mononuclear cells (PBMC) was evaluated. High molecular weight fractions from the 10% ethanol extract and an alkylamide from the 100% ethanol extract were also tested for immunomodulatory effects. **Results:** Alkylamide concentration increases with increasing ethanol in the extraction menstruum. The 33% EtOH extract contains the highest concentration of total phenolic acid compounds. TNF production in U937 cells is enhanced to different degrees by all *E. purpurea* extracts compared to vehicle control. TNF production in unstimulated PBMC cultures was induced by the more aqueous extracts, and by isolated fractions from these extracts. Differential effects of root vs. aerial extracts on TNF production in mitogenically-stimulated PBMC were also observed. **Conclusions:** Our data are consistent with the hypothesis that polysaccharides present in aqueous extracts and alkylamides present in higher ethanol extractions both contribute to modulation of TNF production in activated immune cells.

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NEW TOXINS FROM ARTHROPODS OF ISLAND MADAGASCAR

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Many kinds of venom principles modulate physiological responses of mammalian signal trans duction systems. Especially, the so-called neurotoxins get increased interest and become useful tools for physiological research. Since 1993 to present, Malagasy and Japanese researchers undertook common program on "Toxins from harmful land animals in Madagascar". The chemical study of scorpion *Grosphus bistriatus* K. venom gland, which alcoholic extract is used in folk medicine against a wide range of deseases, led on the peptide compounds occurence. The analytical results of spider toxins extracted from a single *Nephilengys borbonica* venom gland with the use of **μ**-column HPLC are reported. They afforded the detection of over 40 new acylamines, location of nitrogen atoms and connectivity of methylene units within the poly amines. The structure determinations of new series of acylpolyamines in the spider *Nephila madagascariensis* venom gland is presented. These are new glutaminergic nerve blocker materials. We also describe the data of IsCT, a novel cytotoxic linear peptide from scorpion *Opisthacanthus madagascariensis*, the shortest natural cytotoxic described. On the biodiversity point of view, a such number of new neurotoxins, published for the first time, is of high interest and in accordance with the impressive level endemicity of the fauna of Madagascar. As an example, the percentage of endemism observed in the Madagascan scorpion community is 100.00, while those in Guayana, Ecuador and Paraguay are 76.5, 66.7, 17.0 respectively.

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QUALITY EVALUATION OF TEN COMMERCIALLY AVAILABLE BLACK COHOSH PRODUCTS

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Actaea racemosa L. (black cohosh) product has become increasingly popular as a dietary supplement in the U.S. for the treatment of symptoms related to menopause, but black cohosh products are not subject to the same regulations as pharmaceuticals, and therefore the phytochemical profile of most products is not known.

We have analyzed ten black cohosh products obtained from local markets for their major phytochemical constituents using HPLC and LC-MS. We found that there was significant product-to-product variability for triterpene glycosides which have been widely used in the botanical supplement industry as marker compounds for black cohosh. The amount of the phenolic constituents in each product also varied significantly. In the botanical industry, black cohosh is often extracted with ethanol or isopropanol. Therefore, we compared the chemical profiles of the ten products with those extracts we prepared using three solvents, methanol, ethanol, and isopropanol. The results from the comparisons indicated that all ten products contained black cohosh, but the amount of the extract was significantly different from product to product. Although the active components of black cohosh are still unknown, this work suggests that bioactivity may also vary from product to product.

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CHEMOPREVENTIVE EFFECT OF OXYPHENBUTAZONE, A NONSTEROIDAL ANTI-INFLAMMATORY DRUG ON EPSTEIN-BARR VIRUS ACTIVATION AND TWO-STAGE MOUSE SKIN CARCINOGENESIS

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Oxyphenobutazone (OPB) (4-Butyl-1-(4-hydroxyphenyl)-2-phenyl-3, 5-pyrazolidinedione) is a potent NSAIDs in use for the treatment of chronic inflammatory conditions like rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. In continuation of our studies of the NSAIDs as a source of potential cancer chemporeventive agent (Cancer Lett. 2000;161(2):221-229), we have examined the effect of OPB in the Epstein-Barr virus early antigen (EBV-EA) activation model which was induced by 12-O-tetradecanoylphorbol-13-acetate (TPA) in Raji cells. We also studied its effect in the Peroxynitrite (PN) induced –TPA promoted skin tumors in the mouse skin. Following tumor initiation with 390 nmol of PN, the skin tumor promotion with 1.7 nmol of TPA was significantly inhibited by the oral administration of 0.0025% OPB for two weeks. The tumor incidence and burden was reduced by 20% and 50% respectively at the termination of the experiment. OPB also inhibited the EBV-EA activation at low doses with low toxicity. These data support NSAIDs as a source of cancer chemopreventive compounds.

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A CASE STUDY OF AN 85-YEAR-OLD BLACK COHOSH (*Actaea racemosa* L.) SAMPLE

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A sample of black cohosh (*Actaea racemosa* L.), collected in 1918 by the physician and plant explorer Henry Hurd Rusby, was recently identified in the collections of The New York Botanical Garden and analyzed for its triterpene glycosidic and phenolic constituents qualitatively and quantitatively by HPLC-PDA and LC-MS. A comparison of the triterpene glycosidic and phenolic constituents of the 85-year-old plant sample with those of a modern collection of *Actaea racemosa* showed the similarity of the two samples, confirming the stability of the older sample, despite its curation over the years under a variety of conditions. Quantitative analyses indicated that both plant samples have similar amounts of four major triterpene glycosides; the total amount of six major phenolic constituents measured in the 85-year-old plant material is lower than the amount measured in the modern plant material. Methanol extracts of the two plant materials were tested for their antioxidant activity, and both extracts showed similar antioxidant activity.
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COMPARATIVE CYTOTOXIC EFFECTS OF BETANIN AND ADRIAMYCIN IN PC-3 AND MCF-7 HUMAN CANCER CELL LINES

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Previous cancer chemoprevention studies from our laboratory and other groups have demonstrated that betanin, the commercial extract from *Beta vulgaris* (beet root) can be effective in suppressing the development of tumors in several organs. To further explore this issue, we have compared the cytotoxic effects of betanin with adriamycin in the androgen-independent human prostate cancer cells (PC-3) as well as in the well-established estrogen receptor-positive human breast cancer cells (MCF-7). Treatment of the cells lines with betanin (0.0005mM to 0.5mM) exhibited a dose-dependent cytotoxic effect in both cell lines, which is comparative to adriamycin. The incubation time was three days and reveals a new mechanism for the anticancer activities of betanin. These results support the development of betanin as a potential anti-tumor agent since it lacks apparent toxicity.

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EFFECTS OF CRAMP BARK (*VIBURNUM PRUNIFOLIUM*) AND BLACK COHOSH (*ACTAEA RACEMOSA L.*) ON MAMMALIAN UTERINE CONTRACTILITY

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Many species of the genus Viburnum relax the uterus and are used as antiabortives (Calle et al. 1999). *Viburnum prunifolium* (cramp bark) is one such species traditionally employed to relieve menstrual cramping. We hypothesized that an extract from this plant would inhibit uterine contractions in vitro as is documented for related plants. Black cohosh (*Actaea racemosa L.*) is used to increase uterine contractions at the time of parturition. We hypothesized that an extract of this plant would stimulate uterine contractions. Extracts were generously provided by Dr. Norman J. Farnsworth. Extracts were dissolved in dimethyl sulfoxide (DMSO). In this study, we measured the individual effects of cramp bark and black cohosh on isolated proestrus uteri from virgin rats. We will report the dose response curves on contractile amplitude and frequency as compared to the effects of DMSO in a crossover design. Results suggest that both cramp bark and black cohosh significantly decreased contractile amplitude. The mechanisms by which these two herbal remedies act are yet to be determined.

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ISOLATION AND IDENTIFICATION OF INGREDIENTS IN CRUDE EXTRACTS OF BOSWELLIA CARTERII BIRDW AND THEIR APOPTOTIC EFFECT IN HUMAN LEUKEMIA CELLS.

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The gummy exudates of *Boswellia Carterri* Birdw has been traditionally used in the Ayurvedic system of medicine as an anti-arthritic and has been used as the main component of several Traditional Chinese Medicine to treat cancer. We report here the isolation of ingredients from chloroform crude extract of *Boswellia Carterri* Birdw as well as their apoptosis induction ability in human leukemia cells.
By using chloroform extraction and silica gel chromatography, several pure compounds have been isolated from the chloroform crude extract. Based on LC-MS and IR structure analyses, acetyl-11-oxo-boswellic acid acetate (1), acetyl-□-boswellic acid (2), 3-ketorirucall-8,24-dien-21-oic acid (3) and 3□-acetoxytirucall-8,24-dien-21-oic acid (4) have been identified.
The apoptotic effects of these compounds as well as the crude extract have been determined by morphology and DNA fragmentation as well as FACS analysis. Our results indicate that compounds 1 and 2 mediate the cell apoptosis induction of the crude extract. Compound 1 has been done structure modification by chemical methods. The structure-activity relationship of apoptosis induction and the novel mechanism inducing apoptosis by these compounds will be discussed.

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HPLC CHROMATOGRAPHIC FINGERPRINT OF ASHMI, A CHINESE HERBAL FORMULA AGAINST ALLERGY ASTHMA

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Asthma is a chronic inflammatory lung disease. It has emerged as a major public health problem worldwide, particularly in westernized societies. We recently generated an anti allergy and asthma herbal formula, **ASHMI,** consisting of 3 herbs. In a well-characterized murine model of chronic allergic asthma, it was demonstrated that **ASHMI** suppressed airway hyperresponsiveness (AHR), which was accompanied with markedly reduced inflammation, goblet cell hyperplasia and collagen production, associated with a reduced pulmonary Th2 response, demonstrating a broad spectrum pharmacological actions on the major pathogenesis of asthma.
To evaluate the authenticity, quality, consistency and stability of raw herbal materials and herbal extracts, chromatographic fingerprinting has been inverstigated by RP-HPLC/DAD analysis. From the 2D-chromatographic fingerprint of **ASHMI** at 254nm, 31 diagnostic peaks were observed. By comparison of the on-line UV spectra and retention time (t_R), all diagnostic peaks in the fingerprinting of **ASHMI** were correlated with its individual herbal medicines. Based on the retention time and the on-line UV spectra of chemical markers, peaks **6, 25** in **ASHMI** were identified as liquiritin and glycyrrhetic acid. Chromatographic fingerprinting with marker compounds is a practical and comprehensive approach to identify and standardize **ASHMI**, a novel herbal product.

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WHO PUT EPHEDRINE IN PINELLIA & WHERE IS THE ARISTOLOCHIC ACID?

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FDA's February 11, 2004 ruling on dietary supplements containing ephedrine alkaloids prohibits the US sale of dietary supplements containing pinellia (*Pinellia ternata* (Thumb.) Makino) by identifying it as a source of ephedrine alkaloids based on a 1978 report of ephedrine isolation from pinellia tuber. The presence of ephedrine in dietary supplement products containing pinellia tuber renders them adulterated but the rule does not apply if no ephedrine alkaloids are present. Likewise, dietary supplements containing aristolochic acids (AAs) are adulterated regardless of the source and FDA has been active regarding AA containing products since issuing information letters in May of 2000. More recently, several commercial products on the web have been identified as AA containing on the basis of listing *Aristolochia* spp. or *Asarum canadense* as ingredients, or other ingredients that may be adulterated by AA.
Over 20 products suspected as AA containing were purchased and tested for the presence AA by HPTLC and HPLC-UV, and the results compared. The results from testing crude and processed pinellia samples by HPLC-UV and GC-MS for ephedrine content are also presented.

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ANALYTICAL METHODS FOR THE ANALYSIS OF HYPERICIN IN PLASMA TO SUPPORT A CLINICAL TRIAL OF ST. JOHN'S WORT (*Hypericum perforatum*) FOR ANXIETY

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In the analysis of the efficacy and safety of botanicals via clinical trials, our research team advocates the partnering of clinical research with pharmacognosy, such that clinical outcomes (positive or negative) can be assessed in relation to measures of marker and/or active constituents in patient plasma. St. John's Wort (SJW) has been studied most exhaustively in the clinic for the treatment of depressive disorders. Like other antidepressants, SJW may also be useful in long-term management of anxiety disorders, although to the best of our knowledge, this has never been tested clinically. Thus, an 8-week, open-label trial of SJW extract (Kira brand of LI160; LichtwerPharma) was initiated in 30 patients meeting the DSM-IV diagnostic criteria for an array of anxiety disorders. Patients were assessed for baseline symptoms using the Hamilton Anxiety index (HAM-A) and then received 900 mg LI160/day (300 mg, t.i.d.). Compliance was monitored by remaining pill counts, and, at 24 hr following the final SJW dose, subjects were reassessed by HAM-A and blood drawn to quantify hypericin plasma concentrations. In this study, all patients exhibited hypericin plasma levels that ranged from 1.7 to 19.5 ng/mL. Although the magnitude of HAM-A reductions did not correlate directly with hypericin plasma concentrations, there was a trend toward 4 ng/mL as the threshold for clinical efficacy. Several analytical challenges of note were overcome in quantifying hypericin in human plasma. Correlation of clinical outcomes with plasma concentrations of marker compounds should be a required component of human botanical efficacy trials.

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COMPARISON OF THE ESTROGENIC PROPERTIES OF *TRIFOLIUM PRATENSE* AND *HUMULUS LUPULUS*

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There is a clear association between hormone replacement therapy and the development of cancer in breast and endometrial tissues. *Trifolium pratense* L. (red clover) is commonly used as an alternative to alleviate menopause-associated hot flashes since it contains isoflavones, but has had mixed results in clinical trials. *Humulus lupulus* L. (hops) has not traditionally been used to alleviate hot flashes, but it has recently been reported to contain an estrogenic prenylflavanone, 8-prenylnaringenin (8-PN) active at the nM level. The two botanicals and isolated compounds, daidzein (D), genistein (G), biochanin A (B), and formononetin (F) from a red clover methanol extract and 6-prenylnaringenin (6-PN), 8-PN, isoxanthohumol (IX), and xanthohumol (XN) from a hop chloroform extract, were compared. The red clover extract tested in the estrogen receptor (ER) α and β binding assays and the alkaline phosphatase (AP) enzyme induction in the Ishikawa cell line had an IC_{50} of 18.0 and 2.0 μg/mL and an EC_{50} of 1.7 μg/mL, respectively, while the hop extract had an ERβ IC_{50} of 300 μg/mL and AP EC_{50} of 2.0 μg/mL. Both red clover and hops as well as G and 8-PN significantly upregulated both pS2 and progesterone receptor (PR) mRNA compared to the solvent control. Based on these data, hops become increasingly attractive for the development of a suitable herbal dietary supplement to alleviate symptoms associated with menopause. (Supported by NIH Grant P50 AT00155 from the Office of Dietary Supplements, NCCAM, and NIGMS).

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PRODUCTION OF PYRROCIDINES BY THE MAIZE ENDOPHYTE *ACREMONIUM ZEAE* AND THEIR OCCURRENCE IN INFECTED KERNELS

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Acremonium zeae is a common corn endophyte that is typically asymptomatic, although it is occasionally implicated in stalk rot. Studies in our laboratories showed that *A. zeae* isolates are antagonistic to the kernel-rotting and mycotoxin-producing fungi *Aspergillus flavus* and *Fusarium verticillioides*, and that they can interfere with *A. flavus* infection and aflatoxin contamination of preharvest maize kernels. Chemical studies of an extract from maize kernel fermentations of *A. zeae* revealed that at least part of this activity was caused by pyrrocidines A and B; two compounds of mixed polyketide-amino acid origin originally reported from a different fungal source in 2002 by researchers at Wyeth-Ayerst. In the present study, pyrrocidines (including two new, minor analogs) were detected in fermentation extracts of 11 out of 13 isolates of *A. zeae* obtained from maize kernels harvested in various U.S. locations. In addition, pyrrocidines were detected by LC- MSMS in whole maize kernels removed at harvest from ears of a commercial hybrid that were wound-inoculated in the milk stage with *A. zeae*. Selected-ion monitoring and MS/MS fragmentation patterns helped to confirm the presence of these metabolites. Highlights of this work will be presented, and its potential significance will be discussed.

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OPTIMIZATION OF *IN VIVO* AND *IN VITRO* MODELS FOR THE EVALUATION OF SEXUAL AROUSAL AND ERECTILE FUNCTION IN MALE RATS

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The improvement and optimization of techniques used to detect sexual activity in experimental animals are among the main challenges facing researchers in this field. A number of methods are in use for this purpose. However, no critical analysis has been made to evaluate the methodological approach for the evaluation of sexual arousal and erectile function in the male rats.
In view of the current trends and improvement in technology to evaluate of sexual activity, practical aspects of various models have been discussed and optimized approach has been suggested considering, (1) the conventional method for testing male sexual behavior to study the copulatory pattern-mountings, intromission, ejaculations, refractory period (2) mounting and non-contact exposure of males to receptive females (3) sexual orientation activity (4) penile reflex test (5) hormonal testing (6) cavernosometry -intracavernous pressure and cavernosum strip; and (8) and telemetric recording using small transmitters. Most experiments are performed under general anesthesia or sedation, while a conscious model is also used to evaluate the sexual activity. Further more, new ways of pharmaco-application are have been added to the existing techniques. Considering all, we analyze here the problems arising from the techniques and the reliability of the data obtained by various methods.

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TOXICITY STUDIES OF *TEUCRIUM STOCKSIANUM* BOISS., USED IN TRADITIONAL MEDICINE IN THE ARABIAN GULF

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In the present study *Teucrium stocksianum* Boiss. (Lamiaceae) was studied for toxicity studies. The study includes the evaluation of acute, sub-acute (15 days) and sub-chronic toxicity (90 days), tests for clastogenic activity, and teratogenicity studies. The animals were observed for toxic signs and symptoms and body weight changes were recorded. Oral LD_{50} values was found > 6400 mg/kg. The blood was analysed for WBC, RBC, Hgb, PCV, MCV, MCHC and platelets and the serum was analysed for total protein, albumin, globulin, SGOT, SGPT, LDH, CPK, BUN, creatinine, iron, chloride, calcium, magnesium, sodium and potassium. The vital were examined and weights were recorded.
Our results for acute study no overt signs and symptoms up to the dose level 1 g/kg, administered orally. Sub-acute treatment produced weight gain in the first week of treatment only. Some animals showed swelling in the testes and penis during the treatment. A significant increase in SGOT and decrease in CPK value were observed in the treated group. The plant was found devoid of clastogenic activity. Teratogenicity data revealed no teratogenic or fetotoxic effects. Data from the present investigation provide some indications on the toxicity profile of the plants which may be helpful in assessing its suitability for clinical use.

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EFFECTS OF 10% ETHANOLIC EXTRACT OF *ALPINIA GALANGA* ON THE SEXUAL ACTIVITY IN EXPERIMENTAL ANIMALS

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Alpinia galanga (Fam. Zingiberaceae), is a small shrub distributed throughout Arabia. The local traditional healers consider this plant to be a good remedy for impotence and nervous debility. However, these claims have not been verified scientifically. The present study was undertaken to investigate the effect of 10% ethanolic extract of *A. galanga* (rhizomes) on intracavernous pressure (ICP) and copulatory behaviour in male rats. Male rats were anaesthetized and the prepuce was de-gloved to expose the proximal shaft of the penis. Administration Alpinia extract into the cavernous tissue of the male SD rats, produced a significant increase in ICP compared to the control and positive control-sodium nitroprusside, values being expressed as a % of basal ICP. The effect of extract of *A. galanga* was tested on copulatory behaviour in albino mice after the acute oral treatment (400 and 800 mg/kg). The parameters studied include mount latency, intermission latency, ejaculation latency, mount frequency, intermission frequency, ejaculation frequency, and mean intermission interval. The results from the copulatory behaviour study show that acute treatment with *A. galanga* produced a significant increase in ejaculation frequency and mean intromission interval at the dose of 800 mg/kg as compared to the control. The results of the present study indicate that 10% ethanol extract of *Alpinia galanga* enhances the sexual activity in male animals supporting, its traditional use as a sexual stimulant.

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SELECTIVE INHIBITION OF COX-2 BY CO_2 EXTRACTS FROM BUTTERBUR ROOTS *(PETASITES HYBRIDUS)*

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Rhizomes of butterbur, *Petasites hybridus L.* (Asteraceae), have a long tradition in the treatment of inflammatory diseases. The effects of several lipophilic extracts prepared from the rhizomes of *Petasites hybridus* by supercritical CO_2 as well as of petasin and isopetasin on cyclooxygenase mediated formation of prostaglandin E_2 were investigated. The extracts were characterized by their gaschromatograms and by thin layer chromatography. They differed in the content of petasin and isopetasin: A: 2.1 % and 0.4 %, B: 0.2 % and 0.1 %, C: 12.1 % and 6.1 % and D: 21.9 % and 9.4 %.
All extracts were found not to inhibit COX-1 (IC_{50} > 400 µg/ml), but they showed a strong inhibitory activity against the inducible isoform COX-2 (A: IC_{50} = 30.4 µg/ml; B: IC_{50} = 60.6 µg/ml; C: IC_{50} = 22.6; D: IC_{50} = 20.0 µg/ml). This activity was not correlated to the content of petasin and isopetasin. Also pure petasin and isopetasin inhibited neither COX-1 nor COX-2 (IC_{50} > 400 µM).
Therefore, these *Petasites hybridus* extracts can be regarded as natural selective inhibitors of COX-2.

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CHEMISTRY OF KAVA RHIZOME AND ITS POTENTIAL ADULTERANTS

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Kava (*Piper methysticum* G. Forst., Piperaceae) is a South Pacific shrub which is widely cultivated for its massive rhizome. Anxiolytic herbal drugs based on the lipophilic kava extracts recently disappeared from the international market due to a suspected link to liver failures. By contrast, the water-based traditional kava drink remains popular in Oceania and liver failure has not been reported with its use. Quite advanced among medicinal plants, in kava the active components (kavalactones) are well known. Kava is regarded as one of the best-researched herbal drugs. Perhaps as a result of this, kava quality has been evaluated solely on the basis of kavalactone content. The most trusted plant part is the peeled rhizome. In practice, however, different 'grades' of kava raw materials have been available, even aerial parts. We discovered that not all chemical differences between these 'grades' are necessarily detectable with HPLC methods used in kava industry, because these were developed for kavalactone determination in rhizome only. In contrast, by employing GC-FID, some critical differences between plant parts can be detected. For instance, aboveground parts are rich in pipermethystine, a potential liver toxin. Related piperidine alkaloids may occur along with it. For underground parts, bornyl cinnamate appears to be typical. It has been previously identified as a potential anti-inflammatory agent. The kava example shows that it is important not only to know the chemistry of the proper plant part for an herbal drug, but potential adulterants can be included in research and chemical analysis in order to minimize doubtful preparations.

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EXTRACTION, IDENTIFICATION, DOSE, AND CLINICAL APPLICATIONS OF MEDICINAL MUSHROOMS

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The use of fungi for medicinal applications goes back several thousand years in Asia and at least 2,000 years in Europe. Numerous preliminary in vitro and invo studies demonstrate extracts of some widely-used species such as *Trametes versicolor*, *Lentinus edodes*, *Ganoderma lucidum*, and *Cordyceps chinensis* have a wide range of immunomodulating effects, besides anticancer, antimutagenic, hypercholesterolemic, hypoglycemic, and a number of other interesting effects. This presentation will concisely review the current literature, human clinical trials, and clinical applications of *Trametes versicolor* and *Lentinus edodes*, after a brief overview of the historical uses of 10 species, and current uses of commercially-available extracts.

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TRAGANTH AS A CONDITIONING AGENT IN SHAMPOO FORMULATION

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Astragalus Gummifer is a small branching thorny shrub, the stem of which exudates a gum, these have a horny appearance, are nearly colorless. The primary source of Gum Tragacanth is the desert highlands of northern and western Iran, particularly Zagros Mountain region. Tragacanth has soluble and insoluble portions in water. The insoluble part "Bassorin" swells in water and gives a thick paste.
In Iranian folkloric medicine it is believed tragacanth in addition to written uses has beneficial effects on hair. It has been used for its conditioning effect and hair styling. So in this research we used tragacanth mucilage 5% in shampoo formulation. First the physical stability of shampoo was investigated, then, since optical and frictional properties of polymer films are of significant relevance to the applications of polymers in hair care products, The effect of tragacanth on polymer film properties was investigated. The comparative optical and frictional results between shampoo with and without tragacanth clearly demonstrate the tragacanth superior film properties. Microscopic Techniques such as scanning electron microscopy (SEM) provides powerful explanation for the differences noted between two shampoos.

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PROFILING SAPONINS AND OTHER PHYTOCHEMICALS IN COW COCKLE (SAPONARIA VACCARIA L.) BY LC-DAD-MS. EXAMINATION OF FRACTIONS FOR CYTOXICITY AGAINST SOME HUMAN CANCER CELL LINES.

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Cow cockle (*Saponaria vaccaria* L.) is a weedy member of the Pink Family (Caryophyllaceae) which is widely distributed throughout North Amera, Europe and Asia. The seed has a history of use in traditional Chinese medicine (Wang bu liu xing), predominantly as a galactogue and treatment for amenorrhea, and is known to be a rich source of triterpene saponins, cyclic peptides (4 – 9 amino acids) and C-gylcosyl flavonoids.
As part of a program for evaluating the potential of various species as new value-added crops with applications to human health, we have examined the phytochemical profiles of several accessions of cow cockle grown under local conditions (northen great plains) using a relatively rapid HPLC method employing a combination of diode array and mass detection.
Large variabiltiy was noted in the amounts and types of cyclic peptides present in the various accessions. Less variability was noted in the saponin profiles. Segetoside I, a bisdesmosidic quillaic acid type saponin was the main saponin observed in the variants examined.
Fractionation of crude seed extracts was carried out using solid phase extraction with C-18 media and water-methanol gradients. Several fractions exhibited cytotoxicity against human lung, breast, and colon cancer cell lines, with IC_{50} values < 10 ug/ml.

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MULTIVARIATE STATISTICAL ANALYSIS OF AGRICULTURAL, MORPHOLOGICAL AND PHYTOCHEMICAL CHARACTERISTICS OF *ECHINACEA PURPUREA* PLANTS

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Echinacea purpurea is an important medicinal plant in modern phytotherapy. To optimize its cultivation, we studied the influence of agricultural parameters (irrigation, age of plantation, location, harvest time) on plant morphology (height, number of flowers, fresh and dry weight of individual organs (flowers, leaves and stems), density and length of leaf stomata). The content of cichoric and caftaric acid in individual organs was also correlated to agricultural and morphological parameters.
A drastic decrease of height and weight of plant with increasing age of plantation was found, but age had no influence on the cichoric and caftaric acid contents. The content of cichoric acid in individual organ is in good correlation with the content of caftaric acid in the same organ. The content of both substances in leaves is in good correlation with their content in stems, but not in flowers. The weight of leaves is also in good correlation with the weight of stems but in much lower correlation with the weight of flowers.
Irrigation increased the yield for 50 %, but surprisingly had no influence on leaf stomata. Leaf stomata were most significantly influenced by harvest time.

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SEQUENCE ANALYSES OF NUCLEAR RIBOSOMAL ITS TO DEVELOP MOLECULAR MARKERS FOR A HERBAL MEDICINE, DANG GUI

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Dang Gui is a herbal medicine used to nourish the blood, to promote blood circulation, to relieve pain and to moisten the intestine in Korea, China and Japan. However, the roots of different *Angelica* species have been used in these countries. In Korea, the dried roots of *Angelica gigas* are defined as Dang Gui. However, in China, ones of *Angelica sinensis* are used. The dried roots of both *Angelica acutiloba* and *A. sinensis* are used as Dang Gui in Japan. In Korean markets, the dried roots of these three species are prescribed as Dang Gui without the discretion regarding the species of original plants. In this study, we analyzed the sequences of nrDNA ITS to develop molecular markers, with which the species of original plant could be identified. From the determined sequences of ITS, recognition sites of selected restriction enzymes were mapped. Among them, Hae III, Hinf I, Msp I and Sma I provided useful molecular markers to distinguish the species of original plants. The molecular markers developed from PCR-mediated RFLP can be adopted as an identification tool to control the quality of Dang Gui in markets.

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THE VASODILATIATION EFFECT OF DECURSIN AND DECURSINOL ANGELATE FROM ANGELICA GIGAS

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The roots of *Angelica gigas* Nakai (Umbelliferae) have been used as herbal medicine known as 'Dang Gui' in Korea, in contrast to Japan and China where ones of *A. sinensis* or *A. acutiloba* have been used. In the Oriental Medicine, Dang Gui is considered to nourish the blood and promote blood circulation. The water and methanol extracts of *Angelica gigas* roots showed the vasodilatation effect on the thoracic aorta strips of rat, of which contraction was induced by 5-HT. Methanol extract was more potent than water extract, and methanol fraction was most potent for vasodilatation. Decursin and decursinol angelate from the roots of *A. gigas* were active compounds effective for vasodilatation. Their structure was verified by Mass, ^{1}H NMR, and ^{13}C NMR spectral analyses.

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THE EFFECT OF ACANTHOPANACIS SENTICOSI RADIX ON ALLERGIC IMMUNE REACTION

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The anti-allergy effect of water extract of Acanthopanacis senticosi Radix was examined on the B cells from healthy BALB/c mice. The various cytokines related with allergy were measured by flow-cytometry and RT-PCR. The anti-allergy effects of the extract were also identified by examining the production of various cytokines. The extract extract showed inhibitory effect on CD23, CD69, and IgE expression in murine splenic B cells stimulated with anti-CD40 mAb and rIL-4. The extract also inhibited the transcript expression, and the production of cytokines i.e., IL-1β, IL-4, IL-6, IL-10, TNF-α, TGF-β1, and INF-γ, as well as the histamine release from mast cells. The extract showed no significant cytotoxicity when measured with murine normal lung fibroblasts by modified SRB assay.

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VASODILATION EFFECTS OF DECURSIN MIXTURES ON 5-HT-INDUCED CONSTRICTION IN RAT THORACIC AORTA

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In order to elucidate the herbal active compounds on vasodilation of isolated rat thoracic aorta, we have examined the bioactive guided fractionation from *Angelica gigas* Nakai (*A. gigas*). The vasodilation of isolated rat thoracic aorta was investigated in vessel segments suspended for isometric tension recording by polygraph. The 85% methanol extract of the roots of *A. gigas* showed vasorelaxation activity of 88.6% at 0.3mg/ml. The extract was partitioned chloroform, ethylacetate, n-butanol and water fractions. The more active chloroform layer showed a dose-dependent and significant activity. Further fractionation of the chlorofrom fraction on silica gel gave six fractions. Faction-2 at 1 mg/ml showed vasorelaxation activity of 63.6% in isolated rat thoracic aorta. We obtained the two compounds from fraction-2. However, it was showed a weak vasorelaxation compare with fraction-2. Two compounds were identified decursin and decursinol angelate by ^{1}H-NMR, ^{13}C-NMR. We found out this result, it is possible that the inhibition effect of *A. gigas* on 5-HT-induced vasoconstriction is due to the mixture of decursin and decursinol angelate.

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AN HPLC METHOD WITH PRE-COLUMN DERIVATIZATION FOR QUANTIFICATION OF HEXACOSANOL AND OCTACOSANOL-CONTAINING PRODUCTS

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Hexacosanol (**1**) and octacosanol (**2**) are high molecular weight aliphatic alcohols. In combination with other minor alcohols are known as policosanol, which is obtained from sugar cane wax. They also are widely occurred in edible and non edible plants as free and in esterified form. Recently, a number of literature described these alcohols as cholesterol lowering agents.
An HPLC method with pre-column derivatization was attempted. In this method, **1**, **2,** and all analyzed samples were derivatized with benzoyl chloride, butyl benzoate (**3**) was used as an internal standard, and employing a reversed phase column, with UV detection at 228 nm, and MeOH/H_2O (70:30). Method precision was evident in the consistency of retention times (9.85, 5.66, 14.17 for **1**, **2** and **3**, respectively). The limit of quantification for **1** and **2** was about 0.31 μg/mL and 0.25 μg/mL, respectively. This method was utilized to determine the content of **1** and **2** in products of sugar-cane mud such as the foam and sediment of different regions, and a finished product (policosanol capsules) and two commercial policosanol samples, in addition to some edible and non edible plants.

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ALKALOIDS ISOLATED FROM RHIZOMA CORYDALIS DECUMBENTIS HAVE STRONG ANTI-ARRHYTHMIA EFFECT

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Rhizoma Corydalis Decumbentis is a plant used as a Traditional Chinese Medicine for the treatment of arrhythmia. A feasible method to extract and purification of total alkaloids from *Rhizoma Corydalis Decumbentis*, and their pharmacological activities of these total alkaloids were reported here. The dry tuber of *Rhizoma Corydalis Decumbentis* was first extracted with ethanol solution. The components in this ethanol fraction were concentrated under the condition of decreasing pressure, and were dissolved into a 2% concentration HCl solution, and were filtered with filter board. The filtrate solution was added on cation exchange resin column (D001), and was eluted with 5% ammonia ethanol. The elution was concentrated under the condition of decreasing pressure (60 ^{o}C, below 0.1 Pa), and the residue was dried under vaccum condition and has been found to contain >70% of alkaloids including protopine, tetrahydropalmatine, *et al*, by HPLC analysis. The anti- arrhythmia effect of this total alkaloid in a rat model caused by aconitine was tested in which Lidocaine used as a positive control drug. This total alkaloid at dose of 7.5mg/kg significantly postponed the occurring time of ventricular premature (VP) and ventricular tachycardic with a better therapeutic effect than that of Lidocaine treatment ($P<0.05$). The isolation method of this total alkaloids from *Rhizoma Corydalis Decumbentis* meets a large scale of preparation. The evident anti-arrhythmia effect of this total alkaloid suggests it could be developed into a new treatment for arrhythmia.

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EXTRACTION OF TOTAL FLAVONOID FROM FLOS ABELMOSCHI AND ITS ANTI-ULCER EFFECT

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The flower of Flos Abelmoschi has been used as a Traditional Chinese Medicine to treat ulcer. To study its effective components, ethanol extracted fraction was analyzed and its anti-ulcer effect was tested.
The dry flower of Flos Abelmoschi was extracted with ethanol and the ingredients were recovered under the condition of decreasing pressure. The concentrated product was dissolved into water and pass through filter board. The filtrate was applied to macroporous absorption resin column and washed with gradient elution of water-ethanol (from 10% to 50%) and the 40% ethanol fraction was collected, and further concentrated under the condition of decreasing pressure (70 ^{o}C, below 0.08 Pa). The dried fraction was tested to contain >50% total flavonoid including quercetin, quercetin-3'-glucoside, *et. al*., by HPLC analysis.
The pharmacological effect of this total flavonoid on oral mucosal ulcer-induced by acetic acid or mechanical damage in rabbits was compared with a positive control of Watermelon Frost Spray (a Traditional Chinese Medicine). The total flavonoid at dose of 40 mg/kg markedly reduced the area of oral ulcer caused by either acetic acid or mechanical damage comparing with the control group at a relevant time (4.5 days, 7.5 days). In addition, the total flavonoid also inhibited growth G^{+} and G^{-} Bacteria in a bacteriostatic assay.

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ANTI DIABETIC ACTIVITY OF STEMS OF *TINOSPORA CORDIFOLIA*

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Tinospora cordifolia (Guduchi) is a widely used shrub in folk and Ayurvedic system of medicine for various properties. The root extract of the plant have shown to posses' anti diabetic activity. Present study was aimed at evaluating the anti diabetic activity of stems of *Tinsopora cordifolia.* The drug was powdered and subjected to extraction procedures, water soluble extractives were removed and the extract was dried so as to obtain a dry powder. The aqueous extract was then evaluated for in-vivo antidiabetic activity against alloxan induced diabetes and in glucose loaded rats.

Alloxan causes selective destruction of beta cells which are involved in the production of insulin. Deficiency of insulin after alloxan treatment leads to an elevation in the blood glucose levels. After the treatment with aqueous extract of *Tinospora cordifolia* there was a significant reduction in the blood glucose levels. Glucose tolerance was also found to be enhanced. Both these properties of *Tinsopora cordifolia* extract indicate that the extract has good hypoglycemic activity.

Our present study supports the traditional usage of the entire plant of *Tinospora cordifolia* by the Ayurvedic physicians for the control of diabetes.

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ANTIMICROBIAL ACTIVITIES OF ESSENTIAL OILS FROM *Oenanthe javanica* DC

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Essential oils from plants are a promising source for novel natural anti-microbial agents especially against drug-resistant pathogens, though their activities are generally milder than commercial synthetic antifungal drugs. *Oenanthe javanica* is one of the favorite wild vegetables, which has a unique fragrance. This has been cultivated in the spring on the field in Korea. It has hemostatic, hematinic, and diuretic activities. It has been sometimes indicated also for the treatment of pneumonia in folks-medicine.

In this study we analyzed the essential oils from two cultivars of *O. javanica* and evaluated their anti-microbial activities by the broth dilution method and disk diffusion test against the selected pathogenic microorganism. On the basis of these results, checkerboard micro titer tests were performed and isobolograms were constructed to determine the combined effect of the essential oils and ketoconazole.

As the results, both of the essential from *O. javanica* oils as well as the main component of these oils, α –terpinolene (28.0%), dl-limonene (16.0%), γ-terpinene (10.3%), β-pinene (9.7%), and β-caryophyllene (3.6%), showed different patterns of susceptibility against the tested organism. The activities were dose dependent.

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ANTIANGIOGENIC ACTIVITY OF OLEIC ACID FROM SAW PALMETTO (*SERENOA REPENS*) BERRIES AND A STRUCTURE-ACTIVITY RELATIONSHIP (SAR) STUDY ON RELATED FATTY ACIDS

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Aqueous ethanolic extract of the berries of Saw Palmetto [*Serenoa repens* [(Bartram) small] is one of the eight constituents of PC SPES (PC for prostate cancer and SPES in Latin for "hope"). This complex herbal preparation has gained popularity as an alternative therapy for advanced prostate cancer (PC) due to its demonstrated clinical efficacy and improvement of quality of life for hormone-refractory prostate cancer patients. Investigation of all eight constituents of PC SPES using a novel in vitro human endothelial cell-based assay for angiogenesis demonstrated antiangiogenic activity of only two constituent plants, one of which was Saw Palmetto. Bioactivity-guided fractionation afforded an inseparable mixture of two fatty acids identified as oleic and hexadecanoic acids in the ratio of 3:1. Further studies indicated that only oleic acid was responsible for the observed biological activity. The isolation and identification of oleic acid as the constituent responsible for antiangiogenic activity of Saw Palmetto, and an SAR study on eleven commercially available linear C_{18} fatty acids related to oleic acid will be presented.

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ANTI-INFLAMMATORY AND ANALGESIC PROPERTIES OF *POTHOMORPHE UMBELLATA* AERIAL PARTS ETHANOLIC EXTRACT.

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Potomorphe umbellata (L.) Miq. (Piperaceae) known in Brazil as "caapeba" or "pariparoba", has been used as analgesic, diuretic and spasmodic agent and for the treatment of variety of ailments including inflammatory disorders and malaria, asthma and gastro-intestinal diseases. Anti-inflammatory and analgesic activities as well as the median lethal dose (LD_{50}) of aqueous-ethanolic extract of the aerial parts of *P. umbellata* (PHE) were evaluated for in animal models. The ED_{50} for the inhibition of carrageenan induced rat paw edema was determined to be 550 mg/kg, and the LD_{50} higher than 2.0 g/kg. Three fractions, hexane, methylene chloride, and ethyl acetate, obtained by partition of PHE with respective solvents also showed inhibition of the edema induced by carrageenan over a period of 4 hours. The number of writhings induced by acetic acid solution (0.6%, i.p.) was decreased by 22% in the group treated orally with PHE. The above results suggest that *P. umbellata* crude extract has analgesic and anti-inflammatory activities supporting its folkloric use for the treatment of these conditions.

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ANTI-INFLAMMATORY ACTIVITY OF *POTHOMORPHE UMBELLATA* AERIAL PARTS ETHANOLIC EXTRACT AGAINST HISTAMINE INDUCED *IN VIVO* MODELS.

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b. Laboratório de Fitofármacos, Universidade de Alfenas, MG, Brazil.
c. National Center for Natural Products Research, School of Pharmacy, The University of Mississippi, University, MS 38677, USA.

Potomorphe umbellata (L.) Miq. (Piperaceae) known in Brazil as "caapeba" or "pariparoba", has been used as analgesic, diuretic and spasmodic agent and for the treatment of variety of ailments including inflammatory disorders, malaria and gastro-intestinal diseases. Anti-inflammatory activity of aqueous-ethanolic extract (PHE) of the aerial parts of *P. umbellata* was evaluated for in animal models. PHE had marginal effect on the inhibition of the inflammation process in the rat paw edema or increase of vascular permeability induced by histamine. However, when dextran was used as phlogistic agent, PHE (550 mg/kg, p.o.) inhibited inflammation process significantly (34.1%). PHE also inhibited granulomatous tissue formation in rats substantially. The above results suggest that PHE has a potential anti-inflammatory activity on histamine induced animal models, supporting its folkloric use for the treatment of inflammatory ailments.

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INCREASING THE RATE OF THROUGHPUT IN NATURAL PRODUCT CHARACTERISATION USING EXACT MASS MEASUREMENT WITH POLARITY SWITCHING AND PARALLEL ANALYIS.

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As a result of the nature of natural product extracts containing non-polar and polar compounds long HPLC gradients analysis times result, in order to achieve better analyte separation. In the data presented the analysis time was one hour. For the analysis of four flavonoid standards and four *Passiflora* extracts a total analysis time of four hours was required for LC-MS data to be acquired. In order to increase productivity, a 5-Way MUX™ source was interfaced to the oa-TOF allowing the independently pumped eluents from 4 LC columns to be analysed in parallel on the same mass spectrometer. This reduced the analysis time to one hour for four samples, just 25% of the previous analysis time. Historically performing polarity switching was more challenging, due to the technology used. The previous power supply stabilisation time required one second, when the polarity was switched. New technological advances enable the power supplies to rapidly reach a stable equilibrium, hence the LCT Premier polarity switching rate has been improved by 70%, and can now switch at 0.2 seconds. The fast switching time makes more polarity switching more amenable to the chromatographic time frames, with very good mass accuracy being obtained in both positive and negatives modes. The combination of polarity switching with full spectra acquisition and high sensitivity provides an efficient route to detecting unknowns in one analysis. A selection of flavonoids previously determined to be present in the extracts of *Passiflora edulis* were targeted to illustrate the exact mass measurement performance using polarity switching. The analytes of interest were detected in both positive and negative electrospray mode, generated, hence further increasing beyond doubt, the confidence in the elemental compositions generated for the flavonoids detected. Using real time exact mass centroid data acquisition, mass measurement errors of < than 3ppm has been achieved routinely for the target species using polarity switching. Both polarity switching and parallel analysis combined with oa-TOF provide a route to faster natural product characterisation.

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QUANTIFICATION AND CHARACTERISATION OF C-GLYCOSIDIC FLAVONOIDS FROM NATURAL PRODUCTS USING Oa-TOF-MS.

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Previously LC-TOF instruments have been restricted by limited dynamic range; which leads to errors in quantification at high concentrations. Here we present data using an oa-TOF (orthogonal acceleration time of flight) system with extended dynamic range capability that widens the utility of this technology for natural product profiling and quantification studies. A newly developed bench top oa-TOF mass spectrometer was used, which incorporates new hardware and software control technology to meet the increased analytical demands of the natural products arena. The highly specific data generated provides an extra degree of information that aids interpretation of the data. Exact mass measurement has been achieved routinely at < 3ppm RMS. Real-time exact mass centroid data acquisition using positive ion electrospray has been performed for the study undertaken. The dynamic range enhancement (DRE) with this instrument operates routinely with the enhanced an integral dual reference sprayer (Lockspray). Both DRE and Lockspray operation are automated and are transparent, the transformation in flexibility, allows the easy 24-7 operation of quadrupoles to be extended to oa-TOF. Dynamic range enhancement is simply "sensitivity switching" this novel approach allows the dynamic range to be increased. Three *Passiflora* species were profiled. They are utilised as phytomedicines in Brazil due to the sedative properties that are related to the presence of flavonoids in leaves. As a result of the importance of flavonoids and their glycosides to these species, the identification and/or structural determination of such compounds occurring in leaves play an important role. Hydroethanolic extracts of *P.incarnata*, *P.edulis* and *P.caerulea* were all analysed using oa-TOF LC-MS DRE . Using the LCT Premier (Waters) equipped with a integral dual ESI source, the presence of 6-C and 8-C flavonoid glycoside isomers (vitexin/isovitexin and orientin/isoorientin) have been possible using exact measurement and elemental composition calculation. This further allows for the specific identification of the species from which the flavonoids have been extracted. Utilising the functionality of Oa-TOF low level analyte detection can be achieved when acquiring data over a wide mass range, exact mass measurement has been used as a tool for unequivocal identification of flavonoid isomers. Using isoorientin as the target flavonoid of interest, it has been possible to illustrate four orders of dynamic range and quantify the level of isoorientin in the plant extracts profiled.

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BOTANICAL DRUG DEVELOPMENT IN THE US-AN UPDATE ON BOTANICAL DRUG SUBMISSION AND REVIEW FROM CENTER FOR DRUG EVALUATION AND RESEARCH, FDA

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This presentation covers the collaborative review experience of botanical drug submissions between the Botanical Review Team (BRT) and new therapeutic divisions at CDER, FDA. Statistics of botanical drug applications as well as other scientific and regulatory issues related to botanical drug review will also be included. Over 200 botanical submissions as Investigational New Drug applications (INDs) or pre-INDs have been filed. Most the INDs/pre-INDs were filed post the passage of the Dietary Supplement Health and Education Act (DSHEA), with 116 applications (21 pre-INDs and 95 INDs) submitted to CDER between 1999 to 2003.
There are continuing and steady interest in further development and early phase clinical studies (e.g. Phase I/II) of botanical new drugs, however, very few late stage studies (e.g., Phase III studies) have been initiated.

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ORGANIC ACIDS ISOLATED FROM OLIBANUM ARE POTENT ANTI-ARTHRITIS AGENTS.

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Olibanum, a secrete resin from *Boswellia carterii* Birdw. has been used as Traditional Medicine for treatment of arthritis. Total organic acid, the active components, was extracted and its anti-arthritis effect was determined in rate models.
The dry gum resin of *Olibanum* was extracted with ethanol first. Ethanol soluble fraction was recovered under the condition of decreasing pressure. The concentrated product was dissolved to 4% sodium hydroxide solution and was extracted with ethyl acetate again. Then, the basic solution was diluted with water to a pH value 5~6 and obtained a precipitation that was filtered, washed with neutral water, and dried under vaccum condition. More than 70% organic acids including □-boswellic acid, Acetyl-□-boswellic acid and other organic acid was determined by HPLC.
This total organic acid significantly inhibited cotton granulation tissue proliferation and foot swelling induced by adjuvant relative arthritis in rats at dose of 50mg/kg. In addition, this total organic acid increased the permeability of blood capillary ($P<0.05$). The anti- inflammation effect of this total organic acid is more active over Zhengqingfengtongning tablet (a Traditional Chinese Medicine) with a significant difference ($P<0.05$). These data suggest the total organic acid could be developed into a novel treatment for arthritis.

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QUANTITATIVE DETERMINATION OF APORPHINES IN *CASSYTHA FILIFORMIS* L.: METHODOLOGY AND VALIDATION.

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Aporphines from *C. filiformis* have been shown to possess several biological activities among which vasorelaxant and cytotoxic properties (1-2).
A sensitive and accurate procedure based on an alkaloid extraction coupled to a LC-UV-MS determination has been developed for the separation and quantification of the major aporphines in *C. filiformis*. The extraction step and the liquid chromatography (LC) conditions were optimized in order to improve the selectivity of the method. The procedure uses a mobile phase consisting of water containing 10 mM ammonium acetate adjusted to pH 3 with acetic acid-acetonitrile (90:10, v/v) (A) and acetonitrile (B) in a gradient mode on a 5 µm RP-select B column material. The method was completely validated using cassythine as reference standard, and successfully applied to the determination of these pharmacologically interesting aporphines in 7 different batches of *C. filiformis.* The detection and quantitation limits of cassythine were found to be 13 and 20 µg/ml, respectively. The results showed variations in the total alkaloid content in samples from 0.11 to 0.43 %.
(1) Wu YC, et al. Phytoterapy Research 1998; 12: S39-41
(2) C. Stévigny, et al. Planta Medica 2002; 68: 1042-1044

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STANDARDS OF EVIDENCE FOR SAFETY, EFFICACY, AND QUALITY TO OBTAIN A CANADIAN NATURAL HEALTH PRODUCT LICENCE FOR SALE

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As of January 1, 2004, all natural health products (NHPs) for sale in Canada must undergo pre-market assessment for safety, efficacy, and quality, and be granted a Product Licence prior to being sold. All importers, manufacturers, packagers, and labellers of NHPs require a Site Licence granted upon demonstrated compliance to specific NHP Good Manufacturing Practices.
NHPs include traditional, homeopathic, and modern medicines made from plants, algae, bacteria, fungi, non-human animal materials, their extracts and isolates, vitamins, amino acids, fatty acids, synthetic duplicates of the above, minerals, and probiotics. Generally excluded are drugs requiring a prescription, radiopharmaceuticals, certain biologics (e.g. vaccines, blood products), antibiotics, tobacco, controlled drugs, injectable drugs, and combinations of conventional drugs with NHPs. Allowable claims include treatment or prevention, risk reduction, structure-function, health maintenance and paradigm-specific, e.g. Traditional Chinese Medicine or Ayurveda.
Applications for product licences must provide supporting evidence that meets specific standards with respect to the publication type, strength, credibility, quality, and sufficiency of information.

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CHARACTERIZATION OF MEDICINAL ZINGIBERACEAE USING ISSR

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Several Zingiberaceae, including ginger (*Zingiber officinale*) and turmeric (*Curcuma longa*), have gained popularity in the USA because of their use as botanical dietary supplements against inflammatory conditions. However, correct identification of these plants is not always a simple matter because morphological evidence is lacking. An accurate identification method is essential for botanical authentication. DNA fingerprinting technology is useful to identify and validate plant samples even if not enough morphological data are available. We used ISSR (Inter-simple Sequence Repeats) DNA fingerprinting analysis to determine the relationships between 21 species of medicinal Zingiberaceae including *Curcuma* and *Zingiber* and six of their closely related genera. Six informative ISSR primers were identified and the conditions for ISSR band production and visualization were optimized. Using non-denaturing polyacrylamide gels with silver staining, numerous ISSR polymorphisms were observed. We will discuss the significance of the dendrograms obtained as a result of our studies. Most importantly, this approach appears to be able to distinguish the closely related Zingiberaceae species.

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ISOLATION OF ANTIPLASMODIAL COMPOUNDS FROM *CASSIA SIAMEA* STEMBARK EXTRACT

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Malaria, one of the diseases caused by protozoa is responsible for the high rate of morbidity and mortality in the developing world, especially in the tropical countries. It is estimated that malaria is the cause of the death of between 1.5 and 2.7 million people each year with renewed increase in parasite resistance. The search for new antimalarial drug is essential and requires identification of new biochemical targets for drug development and new chemical entities.
In the course of the identification and evaluation of potential antimalarial components from the Nigerian ethnobotany, *Cassia siamea* L. was selected for evaluation. The *in vitro* bioassay-guided fractionation and isolation using the multi resistant strain of *Plasmodium falciparum* (K1) in the parasite lactate dehydrogenase assay led to the identification Emodin and Lupeol as the antiplasmodial compounds by spectroscopic techniques. Both compounds were isolated by a combination of chromatographic techniques from the dichloromethane fraction of the crude methanol extract of the stem bark of *C. siamea*, with $IC_{50} > 5$ for both compounds.

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ARGEMONE PLATYCERAS ETHYLACETATE FRACTION ANTAGONIZES LTD_4-INDUCED CONTRACTIONS IN GUINEA PIG AIRWAYS.

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Argemone platyceras Link & Otto (papaveraceae) is traditionally used to treat asthma, cough and bronchitis in Mexican traditional medicine. The methanol extract of the flowers was assayed for bronchoconstriction induced by antigen and by several agonists in guinea pig trachea. The methanol extract significantly inhibited (10 □g/mL, $p < 0.01$) the contractile response to ovalbumin in trachea from sensitized guinea pigs and the bronchoconstriction response to carbachol (100 □g/mL, $p< 0.01$) and histamine (100 □g/mL, $p < 0.05$). A bioassay-guided fractionation of the extract was performed by partitioning with dichloromethane/ethylacetate/metanol-water. Only the ethylacetate fraction produced a significant inhibition of the contractile response to ovalbumin in trachea from sensitized guinea pigs and of the bronchoconstriction induced by leukotriene D_4 (LTD_4). The results of this study suggest a competitive antagonistic effect of the ethylacetate fraction. A phytochemical screening has showed the presence of glycosylated flavonoids in the ethylacetate fraction.

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PHYTOCHEMICAL VARIATION IN STINGING NETTLE (URTICA DIOICA) EXTRACTS PROCESSED WITH DIFFERENT SOLVENT EXTRACTION RATIOS.

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Stinging nettle (*Urtica dioica*) root extract is currently and historically used in the treatment of benign prostatic hyperplasia (BPH). A variety of theories exist as to the mode of action and therefore the phytochemicals responsible for the therapeutic effect. Past research has indicated that plant sterols as well as polysaccharide fractions are the active compounds.
This research was conducted to evaluate processing conditions and their effect on the chemical composition of the resulting extracts. Extractions were conducted using various ethanol concentrations in an aqueous-ethanol solvent medium. In addition, extractions with water alone were performed. Variations in the yield of extracted soluble solids have been detected across the different solvent ratios. Results of phytochemical analyses indicate that, as alcohol concentration increases, plant sterols (β-sitosterol and total sterols) increase in the extract. However, the same increase in alcohol concentration also results in an increased extraction ratio, indicating that the extraction becomes less efficient with higher alcohol levels in the solvent. As ethanol concentrations decreased, more of the water-soluble fraction was extracted (measured as dextrose).
Results of phytochemical analyses of plant sterols and water-soluble fractions will be discussed, along with phytochemical fingerprints yielded by each extraction condition. Implications for specialized extraction methods will also be discussed.

P:188 ANALYSIS AND ENHANCEMENT OF TYROSINASE INHIBITORY ACTIVITY OF STILBENES FROM *VERATRUM PATULUM* BY ENZYMATIC BIOCONVERSION

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P:189 AN OPTIMIZED *Streptomyces* PLATFORM FOR THE PRODUCTION OF NATURAL PRODUCTS BY HETEROLOGOUS EXPRESSION OF DIVERSE BIOSYNTHETIC PATHWAYS.

Mervyn Bibb; Maureen Bibb; Rekha Chakraburtty; Theresa Fo; JianGen Gong; Brian Green; David Gustafson; Martin Keller; Biyu Li; Dylan Mason; Eric Mathur; Theresa Nibert; Rogelio Oseguera; Ashish Paradkar; John Podtetenief; Asfia Qureshi*; Lisa Rahbaek; Melvin Simon; Alex Simon; Jay Short; Axel Trefzer; Mustafa Varoglu; Gary Woodnutt; Ken Wong
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P:190 *IN VITRO* CULTURES FROM FLOWER ORGANS OF *LEUCOJUM AESTIVUM*

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P:191 CANTHARIDIN FROM *LYTTA VESICATORIA:* MOLECULAR MODES OF CYTOTOXIC ACTION

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P:192 CEPHALOTAXINE AND HOMOHARRINGTONINE FROM *CEPHALOTAXUS HAINANENSIS*: CYTOTOXICITY AS ANALYZED BY MICROARRAY AND HIERARCHICAL CLUSTER ANALYSIS

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P:193 MOLECULAR DIFFERENTIATION OF *ASTRAGALUS* RADIX BY SEQUENCE CHARACTERIZED AMPLIFIED REGION ANALYSIS

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P:194 GENOME-WIDE OVEREXPRESSION SCREENS IN YEAST AND MAMMALIAN CELLS FOR SMALL MOLECULE TARGET IDENTIFICATION AND BIOLOGICAL MECHANISM STUDIES

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P:195 BIOCATALYTIC REDUCTION OF KETONES IN THE PROCESS DEVELOPMENT OF PHARMACEUTICAL INTERMEDIATES

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P:196 SECONDARY METABOLITES FROM ENDOPHYTIC FUNGI ISOLATED FROM THE CHILEAN GYMNOSPERM *PRUMNOPITYS ANDINA*

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P:197 PRODUCTION AND QUANTITATIVE ESTIMATION OF CRYPTOTANSHINONE FORMED IN CALLUS CULTURES OF *SALVIA MILTIORRHIZA* BUNGE

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P:198 EFFECTS OF PHYSICAL AND CHEMICAL MODIFICATIONS ON THE DISINTEGRANT AND DISSOLUTION PROPERTIES OF *TACCA INVOLUCRATA* STARCH

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P:199 A FUNCTIONAL GENOMICS APPROACH TOWARD THE UNDERSTANDING OF PLANT SECONDARY METABOLISM: II. FUNCTIONAL ANALYSIS AND COMBINATORIAL BIOCHEMISTRY IN DIFFERENT EXPRESSION SYSTEMS

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P:200 USE OF BIODEGRADABLE PHOSPHOLIPID VESICLES AS CARRIERS FOR CHLORANPHENICOL AND ITS APPLICATION TO BONE MARROW PROTECTION IN THE RABBITS

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P:201 FIELD SELECTION AND MICROPROPAGATION OF *CURCUMA LONGA* L.

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P:202 ISOLATION OF PODOPHYLLOTOXIN FROM ENDOPHYTE FUNGI OF *PODOPHYLLUM PELTATUM.*

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P:203 THE USE OF POLYMERASE CHAIN REACTION (PCR) FOR THE IDENTIFICATION OF *EPHEDRA* IN DIETARY SUPPLEMENTS

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P:204 PHYLOGENETIC RELATIONSHIPS IN *PIMPINELLA* (UMBELLIFERAE) BASED ON ESSENTIAL OIL ANALYSIS AND NUCLEAR AND CHLOROPLAST SEQUENCES

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P:205 MODELING ANTIFUNGAL SAPONINS AND BIOMASS PRODUCTION IN FLASK SYSTEMS FROM HAIRY ROOT CULTURES OF *Solanum chrysotrichum*

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P:206 LARGE-SCALE CULTIVATION OF *SOLANUM CHRYSOTRICHUM* HAIRY ROOTS : PRODUCTION OF FIVE ANTIFUNGAL SAPONINS IN 2 AND 10L AIRLIFT BIOREACTORS

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P:207 KINETIC PRODUCTION OF TRITERPENOIDS IN HAIRY ROOTS SUSPENSION CULTURES OF GALPHIMIA GLAUCA

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P:208 INSILICO FUNCTION ASSIGNMENT OF HUMAN CHROMOSOME 6 OPEN READING FRAMES

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P:209 PRODUCTION OF THE MANZAMINE ALKALOIDS BY A SPONGE ASSOCIATED MICROBE OF THE GENUS MICROMONOSPORA.

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P:210 ANTIINFECTIVE AGENTS FROM MARINE ACTINOMYCETES COLLECTED FROM JAMAICA.

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P:211 PRODUCTION OF PLANTS WITH AN OPTIMIZED METABOLITE SPECTRUM BY AN INNOVATIVE BIOTECHNICAL PRODUCTION PROCESS

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P:212 ANTI-APOPTOTIC EFFECTS OF TOLUQUINOL ISOLATED FROM *PENICILLIUM* SP. F020150

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P:213 APOPTOTIC ACTIVITY OF BETULINIC ACID DERIVATIVES ON MURINE MELANOMA B16 CELL LINE

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P:214 BIOSYNTHESIS OF CURCUMINOIDS AND GINGEROLS IN MEDICINAL PLANTS FROM THE ZINGIBERACEAE.

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P:215 GENETIC POTENTIAL FOR SECONDARY METABOLITE PRODUCTION IN MYXOBACTERIA, CYANOBACTRIA AND MARINE PROTEOBACTERIA

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P:216 METABOLIC PROFILING OF FLAVONOIDS AND ISOFLAVONOIDS IN *M. TRUNCATULA* USING HPLC-UV-ESI-MS AND GC-MS

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P:217 NEW EFFICIENT VIRUS-BASED PLANT EXPRESSION SYSTEM FOR PROTEINS AND ENZYMES OF SECONDARY METABOLITE PRODUCTION INSTANCING THE EXPRESSION OF A NOVEL ESTERASE OF *RAUVOLFIA SERPENTINA*

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P:218 THE BIOSYNTHESIS OF PRODIGIOSIN STUDIED BY LC-MS

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P:219 BIOSYNTHESIS OF ACETATE-DERIVED NAPHTHYLISOQUINOLINE ALKALOIDS AND NAPHTHOQUINONES

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P:220 THE FAVORSKII-LIKE CARBON REARRANGEMENT IN THE BIOSYNTHESIS OF ENTEROCIN

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P:221 KETOREDUCTION TIMING IN AROMATIC POLYKETIDE ASSEMBLY -AN ALTERNATIVE MODEL FOR POLYKETIDE BIOSYNTHESIS

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P:222 HETEROLOGOUS EXPRESSION OF TWO *FUSARIUM* TRICHOTHECENE P450 GENES

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P:223 INDUCTION OF APOPTOSIS IN A LEUKEMIA CELL LINE BY TRITERPENE SAPONINS FROM *ALBIZIA ADIANTHIFOLIA*

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P:224 INVESTIGATING LIGNAN AND ALKALOID BIOSYNTHESIS IN PLANTS THROUGH GENOMICS APPROACHES

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P:225 BIOSYNTHESIS OF SAFRAMYCIN MX1 FROM MYXOCOCCUS XANTHUS

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P:226 BIOSYNTHETIC ORIGIN OF THE METABOLITES PRODUCED BY THE CULTURED LICHEN MYCOBIONTS

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P:227 EARLY STEPS IN THE BIOSYNTHESIS OF FUSCOL/FUSCOSIDES

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P:228 FURTHER EVIDENCE FOR A POLYKETIDE ROUTE TO THE PHYTYL SIDECHAIN OF CHLOROPHYLL IN *EUGLENA GRACILIS*

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P:229 PAPUAMIDE A, INHIBITOR OF HUMAN IMMUNODEFICIENCY VIRUS FUSION

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P:230 MOLECULAR GENETICS OF SAPONIN BIOSYNTHESIS IN *SAPONARIA VACCARIA*

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P:231 BIOSYNTHESIS OF THE JAMAICAMIDES, NEW MIXED POLYKETIDE-PEPTIDE NEUROTOXINS FROM THE MARINE CYANOBACTERIUM *LYNGBYA MAJUSCULA*

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P:232 PROTEIN-PROTEIN INTERACTIONS IN THE MEP PATHWAY

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P:233 CHEMICAL AND MICROBIAL TRANSFORMATION STUDIES OF THE BIOACTIVE MARINE NATURAL PRODUCTS SIPHOLANE TRITERPENES

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P:234 OPTIMIZATION OF ANTICANCER MARINE NATURAL PRODUCTS: CHEMICAL AND MICROBIAL TRANSFORMATION STUDIES OF LATRUNCULIN B, SARCOPHINE, AND SIPHOLANE TRITERPENES

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P:235 MICROBIAL METABOLISM OF DIHYDROKAWAIN

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P:236 THE INHIBITION OF PROSTAGLANDIN BIOSYNTHESIS BY THYMOQUINONE: CYCLOOXYGENASE –1 AND -2 IN VITRO ASSAYS

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P:237 THE ELICITATION OF TAXOID PRODUCTION BY METHYL JASMONATE IN SUSPENSION CULTURES OF YEW (TAXUS BACCATA L.)

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P:238 NEW ORSELLINIC ACID ESTERS FROM THE ENDOPHYTIC FUNGUS *CHAETOMIUM GLOBOSUM*

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P:239 LIGNANS, SEROTONIN-PHENYLPROPANOIDS AND ECDYSTEROIDS FROM *LEUZEA CARTHAMOIDES* AND THEIR EFFECT ON INSECT HERBIVORES

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P:240 PIGMENTATION PRODUCING CELLS ASSOCIATED WITH THE APOSEMATIC COLORATION FOUND IN THE ECTEINASCIDIN PRODUCING ASCIDIAN *ECTEINASCIDIA TURBINATA*.

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P:241 INDUCTION OF CYTOTOXIC SESTERTERPENES IN THE MARINE SPONGE, *SPONGIA TUBULIFERA*

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P:242 DEFENSIVE CHEMICALS IN THE VICEROY BUTTERFLY (*LIMENITIS ARCHIPPUS*) AND ITS LARVAL HOST-PLANT, CAROLINA WILLOW (*SALIX CAROLINIANA*)

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P:243 PHENOLIC CONSTITUENTS OF *CELOSIA CRISTATA* L. SUSCEPTIBLE TO SPINACH ROOT ROT PATHOGEN *APHANOMYCES COCHLIOIDES*

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P:244 ANTIFUNGAL ACTIVITY OF MEDICINAL PLANT EXTRACTS TO GINSENG PATHOGENS

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P:245 ALPHA-PINENE AND LIMONENE, TWO NATURALLY OCCURRING MONOTERPENES AS LEADS FOR NEW INSECTICIDES

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P:246 ON THE TRACK OF HUMAN ODORS THAT ATTRACT MOSQUITOES

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P:247 VOLATILES FROM CACTUS HOSTPLANT OF *CACTOBLASTIS CACTORUM* MOTH

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P:248 ESSENTIAL OIL ANALYSIS OF SEVENTEEN EUROPEAN, AFRICAN AND ASIAN *HYPERICUM* L. (CLUSIACEAE) SPECIES

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P:249 PHYTOCHEMICAL AND BIOSYSTEMATIC INVESTIGATIONS OF NEW AND OLD WORLD *HYPERICUM* L. SPECIES (CLUSIACEAE): SUMMARY OF A THREE-YEAR PROJECT

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P:250 ACTIVITIES OF *DALBERGIA SAXATILIS* (HOOK, F.) AGAINST PENTYLENETETRAZOLE AND ELECTRICALLY-INDUCED SEIZURES IN MICE

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P:251 THE CONSTITUENTS OF THE RHIZOMES OF *ZINGIBER OFFICINALE* AND THEIR BIOLOGICAL ACTIVITY

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P:252 SCREENING OF HIV-1 INHIBITION FROM MEXICAN CLUSIACEAE AND ISOLATION OF CALANOLIDES FROM *CALOPHYLLUM BRASILIENSE* LEAVES

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P:253 NEW COUMARINS AND AN ISOEUGENOL DERIVATIVE FROM *PELARGONIUM SIDOIDES*

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P:254 ALKALOIDS WITH CHOLINESTERASE INHIBITORY ACTIVITY

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P:255 MANIPULATING REACTION-INDUCED SHIFTS FOR DIFFERENCE SPECTRO-PHOTOMETRIC ESTIMATION OF VARIOUS NATURAL PRODUCTS CALSSES

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P:256 THE GC-MS ANALYSIS OF THE HEXANE EXTRACT FROM BARK OF *JUNIPERUS BREVIFOLIA*

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P:257 MOLECULAR SYSTEMATICS OF EUODIA AND THE SUBFAMILIES RUTOIDEAE AND TODDALIOIDEAE IN RUTACEAE

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P:258 FASTER PLANT DRUG IDENTIFICATION USING DATA BASE OF CLASSICAL PHARMACOGNOSY AND MODERN ANALYTICAL TOOLS

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P:259 DETECTION OF CYTOTOXIC ACTIVITY OF ACTINOMYCETES ASSOCIATED MARINE INVERTEBRATE FROM PERSIAN GULF

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P:260 PHYTOCHEMICAL INVESTIGATION OF THE VOLATILE CONSTITUENTS OF LEAVES OF *JUGLANS NIGRA* L. CULTIVATED IN EGYPT

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P:261 ANTIMICROBIAL CONSTITUENTS OF THE THOMPSON SEEDLESS RAISINS (*VITIS VINIFERA* L.) AGAINST SELECTED ORAL PATHOGENS

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P:262 ANTIMICROBIAL ACTIVITY OF *JATROPHA CURCAS* L. AND *JATROPHA MULTIFIDA* L. AGAINST BACTERIA S.T.D. ORGANISMS

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P:263 PHYLOGENETIC PLANT PEPTIDE SELECTION

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P:264 A NEW GLYCOPEPTIDE FROM *CHOLCHICUM SPECIOSUM* (L.)

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P:265 PHARMACOLOGY OF *SOPHORA SECUNDIFLORA*

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P:266 THE EFFECT OF ULTRAVIOLET LIGHT ON FLAVONOLS FROM THE CACTI *OPUNTIA WILCOXII* AND *O. VIOLACEA*

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P:267 MOLECULAR AUTHENTICATION OF THE HERB *RADIX STEMONAE*

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P:268 THE COMPOSITION OF ESSENTIAL OILS FROM VARIOUS PARTS OF THREE SUBSPECIES OF *PIMPINELLA TRAGIUM* VILL.

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P:269 PRELIMINARY RESULTS ON THE IDENTIFICATION OF BIOLOGICALLY ACTIVE METABOLITES OF THE TROPICAL MEDICINAL PLANT *ELAEOPHORBIA DRUPIFERA* USING GC-MS AND FTICR-MS TECHNIQUES

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P:270 HIGH YIELD OF ARTEMISININ FROM *ARTEMISIA ANNUA* GROWING IN EGYPT

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P:271 A NEW OLEANANE GLYCOSIDE FROM *ASTRAGALUS CAPRINUS*

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P:272 FERULA GUMOSA: PHYTOCHEMICAL VARIABILITY IN IRAN

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P:273 A TRIP THROUGH THE KUWAITI DESERT – SOME PHYTOCHEMICAL HIGHLIGHTS

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P:274 ANTIOXIDANT ACTIVITY AND EPICATECHIN CONTENT OF EIGHT CULTIVARS OF TARO (*COLOCASIA ESCULENTA*)

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P:275 SAFROLE CONTENT OF A TRADITIONAL MICRONESIAN TEA

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P:276 APOPTOTIC ANTICANCER EFFECT OF ALVARADOIN E ISOLATED FROM *ALVARADOA HAITIENSIS*

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P:277 PHYTOCHEMICAL INVESTIGATION OF *MAGNOLIA BIONDII* PAMP. (FLOS MAGNOLIAE, XINYI), A TRADITIONAL CHINESE MEDICINAL PLANT

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P:278 FARINA AND EXUDATE COMPOSITION IN SOME SPECIES OF *PRIMULA* L. SECT. *AURICOLA* DUBY

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P:279 PARALLEL EXTRACTION OF LICHEN COMPOUNDS

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P:280 APPLICATION OF LC-SPE-NMR IN THE IDENTIFICATION OF LIGNANS IN *PHYLLANTHUS URINARIA* AND *P. MYRTIFOLIUS*

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P:281 TROPANE ALKALOIDS FROM THE SOUTHAFRICAN PERENNIAL HERB *FALKIA REPENS* (CONVOLVULACEAE)

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P:282 PHENETIC ANALYSIS OF FOUR SPECIES OF *CASIMIROA* (RUTACEAE)

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P:283 CHEMOTAXONOMIC SIGNIFICANCE OF FLAVONES IN *CASIMIROA* (RUTACEAE) AND ANTI-INFLAMMATORY ACTIVITY OF 5,6,2',3',4'-PENTAMETHOXYFLAVONE

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P:284 THE SKIMIWALLINOLS, MINOR COMPONENTS OF THE EPICUTICULAR WAX OF COCOS NUCIFERA.

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P:285 THE ANTIPYRETIC ACTIVITY OF AQUOEUS LEAF AND STEM BARK EXTRACT OF DRUM TREE *(CORDIA MILLENII).*

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P:286 LEONTOPODIC ACID – A NOVEL HIGHLY SUBSTITUTED GLUCARIC ACID DERIVATIVE FROM EDELWEISS (*LEONTOPODIUM ALPINUM* CASS.) AND ITS ANTI-OXIDATIVE PROPERTIES

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P:287 *IN VITRO* LEUKOTRIENE BIOSYNTHESIS INHIBITORY ACTIVITY OF *LEONTOPODIUM ALPINUM* CASS. CONSTITUENTS

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P:288 INHIBITORY EFFECT OF KOLAVIRON (A *GARCINA KOLA* HECKEL SEED EXTRACT) ON MITOCHONDRIAL MEMBRANE PERMEABILITY TRANSITION (MMPT) PORE IN NORMAL AND DIABETIC RATS

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P:289 ANALGESIC AND ANTI-INFLAMMATORY ACTIVITY OF THE AQUEOUS LEAF EXTRACT OF *BYRSOCARPUS COCCINEUS*

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P:290 ANTHRANOID COMPOUNDS WITH ANTIPROTOZOAL ACTIVITY FROM *VISMIA ORIENTALIS*

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P:291 EVALUATION OF THE SEDATIVE PROPERTIES OF THE DECOCTION OF THE ROOTS OF *PFAFFIA IRISENOIDES*

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P:292 GASTROPROTECTIVE AND CYTOTOXIC EFFECT OF LABDANE DITERPENES FROM *ARAUCARIA ARAUCANA* AND THEIR SEMISYNTHETIC DERIVATIVES

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P:293 SPASMOLYTIC ACTIVITY OF THE ROOT EXTRACT OF *CISSAMPELOS MUCRONATA*

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P:294 MENTTATION OF URIC ACID SECRATION BY FOUR MEDICINAL HERBS

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P:295 INHIBITION OF LENS ALDOSE REDUCTASE BY MANGIFERIN AND ISOMANGIFERIN

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P:296 MICROBIAL TRANSFORMATION OF CURCUMIN

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P:297 NEW WHO GUIDELINE AND EC DIRECTIVES ON TRACEABILITY: A CHANCE FOR THE AMELIORATION OF QUALITY AND SAFETY OF MEDICINAL PLANT RAW MATERIAL

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P:298 A METHOD FOR SELECTING PLANTS WITH ANTI-INFLAMMATORY PROPERTIES USING A CROSS-CULTURAL COMPARISON OF ETHNOPHARMACOLOGICAL INFORMATION OF AUSTRALIA AND CHINA

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P:299 ANTIBACTERIAL ACTIVITY OF CRUDE EXTRACT OF *EUGENIA JAMBOLANA*

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P:300 MOLECULAR AND CHEMICAL AUTHENTICAION OF *SAUSSUREA LAPPA* CLARK, AN ENDANDERED CHINESE MEDICINAL MATERIAL

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P:301 ANTIBACTERIAL ACTIVITY OF DIFFERENT PARTS OF *VINCA ROSEA*

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P:302 PLANTS IN USE AS HERBAL MEDICINES (I) IN EDO STATE, NIGERIA.

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P:303 ANTIMICROBIAL SCREENING OF EXTRACT AND FRACTIONS OF *CASSIA NIGRICANS* VAHL (CAESALPINACEAE) AND ITS EFFECTS ON *HELICOBACTER PYLORI*.

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P:304 STUDIES ON THE ANTI-INFLAMMATORY AND ANALGESIC ACTIVITIES OF LATEX OF *CALOTROPIS PROCERA*

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P:305 ANTIBACTERIAL ACTIVITY OF ETHANOLIC EXTRACTS OF *NERIUM INDICUM*

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P:306 ANTIBACTERIAL ACTIVITY OF ETHANOLIC EXTRACTS OF *HIBISCUS ROSA-SINENSIS*

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P:307 PHENOLIC ACIDS IN BASIL (*OCIMUM* SPP.)

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P:308 BIOARON C IN THE TREATMENT OF UPPER RESPIRATORY TRACT INFECTIONS IN CHILDREN - RESULTS OF A OPEN LABEL STUDY IN POLAND

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P:309 ANTI-PYRETIC AND ANTI-INFLAMMATORY ACTIVITIES OF THE AQUEOUS LEAF EXTRACT OF *TRIDAX PROCUMBENS* L.

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P:310 ANALGESIC ACTIVITY OF THE AQUEOUS ROOT EXTRACT OF *LECANIODISCUS CUPANIOIDES* IN ANIMAL MODELS

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P:311 ROSMARINIC ACID ISOLATION FROM *LAVANDULA VERA* CELL SUSPENSION USING SUPPORT-FREE LIQUID-LIQUID CENTRIFUGAL PARTITION CHROMATOGRAPHY

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P:312 EFFECTS OF A STANDARDIZED, TRADITIONALLY PREPARED EXTRACT OF *CETRARIA ISLANDICA* ON CYTOKINE SECRETION OF DENDRITIC CELLS *IN VITRO* AND RHEUMATOID ARTHRITIS IN RATS *IN VIVO*.

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P:313 FUNGAL BIOACTIVITY ASSOCIATED TO SINKHOLES (CENOTES) FROM YUCATAN.

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P:314 DEVELOPMENT OF AN *IN-VITRO* METHOD FOR THE SIMULTANEOUS EVALUATION OF THE INHIBITORY ACTIVITY OF HERBAL EXTRACTS ON SIX DRUG METABOLISING CYTOCHROME P450 ENZYMES

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P:315 *IN-VITRO* CYTOTOXICITY ACTIVITY OF DIOSQUINONE, A NAPTHOQUINONE EPOXIDE.

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P:316 *IN VITRO* ANTI-*HELICOBACTER PYLORI* ACTIVITIES OF METHANOL EXTRACT OF *EUCALYPTUS GRANDIS*

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P:317 *IN VITRO* CYTOTOXIC ACTIVITY OF *KIGELIA PINNATA* FRUITS

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P:318 BIOASSAY GUIDED FRACTIONATION OF MOLLUSCICIDAL SAPONINS FROM THE FRUIT OF *LAGENARIA BREVIFLORA* ROBERT FAMILY CUCURBITACEAE

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P:319 NATURAL PRODUCT DRUG DISCOVERY THAT TARGETS TUMOR HYPOXIA

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P:320 SAPONINS QUANTIFICATION BY HYDROLYSIS FROM *Agave lecheguilla* Torr; A RAPID METHOD.

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P:321 GROWTH INHIBITION and APOPTOSIS OF LYMPHOID & MYELOID LEUKEMIA CELLS BY DUAL *vs.* SPECIFIC 5-AND 12- LOX INHIBITORS

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P:322 SOLUBILIZATION OF ILL-SOLUBLE LICHEN COMPOUNDS IN NON-TOXIC SOLVENTS FOR PHARMACOLOGICAL SCREENING

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P:323 "NEW DRUGS FROM MARINE NATURAL RESOURCES OF JAMAICAN REEFS": DEVELOPMENT OF AN INTERNATIONAL COOPERATIVE BIODIVERSITY GROUP PROGRAM

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P:324 TUBERCULOSIS ANTIMICROBIAL ACQUISITION AND COORDINATING FACILITY (TAACF)

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P:325 SASANG CONSTITUTIONS ANALYSIS BY GENE POLYMORPHISM

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P:326 PRELIMNARY SCREENING OF *Psoralea corylifolia* EXTRACTS FOR PHOTOTOXIC COMPOUNDS USING *Artemia salina* (brine shrimp) BIOASSAY

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P:327 A PANEL OF UBIQUITIN ASSAYS: IDENTIFICATION OF NAUTRAL PRODUCT INHIBITORS OF SPECIFIC E3 UBIQUITIN LIGASES

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P:328 ANTIPROLIFERATIVE ACTIVITY OF *PIPER AMALAGO* LEAVES

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P:329 IN VITRO SCREENING OF TELOMERASE INHIBITOR FROM NATURAL PRODUCTS

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P:330 *IN- VITRO* ANTI-MYCOBACTERIAL ACTIVITIES OF THREE SPECIES OF *COLA* PLANT EXTRACTS (STERCULIACEAE).

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P:331 ISOLATION AND FUNCTIONAL CHARACTERIZATION OF HSP90-ACTIVE SMALL MOLECULE NATURAL PRODUCTS FROM THE RHIZOSHPHERE OF SONORAN DESERT PLANTS

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P:332 DETERMINATION OF PHORBOL AND LECTINS FROM *Ditaxis heterantha*

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P:333 ACUTE TOXICOLOGICAL STUDIES OF *Jungia paniculata* AND *Chuquiraga spinosa* (ASTERACEAE) IN EXPERIMENTAL ANIMALS.

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P:334 CYTOTOXIC, CYTOSTATIC AND GENOTOXIC EFFECTS OF ARGENTATINS A AND B ON PROLIFERATING LYMPHOCYTES

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P:335 *GENTIANELLA AUSTRIACA* AND *GENTIANA DINARICA* SIGNIFICANTLY MODULATE MICRONUCLEI FORMATION IN HUMAN LYMPHOCYTES

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P:336 INHIBITION OF INDUCIBLE NITRIC OXIDE SYNTHASE IN ACTIVATED RAW 264.7 MACROPHAGES BY EXTRACTS OF CHINESE MEDICINAL PLANTS

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P:337 *IN VITRO* AND *IN* VIVO ANTIMALARIAL PROPERTIES OF ISOSTRYCHNOPENTAMINE, AN INDOLOMONOTERPENIC ALKALOID FROM *STRYCHNOS USAMBARENSIS*.

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P:338 FLAVONOIDS OF ST. JOHN'S WORT REDUCE HPA-AXIS FUNCTION IN THE RAT

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P:339 A PHARMACOLOGICAL AND TOXICOLOGICAL EVALUATION OF *HALOXYLON RECURVUM*

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P:340 SOME HORMONAL EFFECTS FOR THE HYPHAENE THEBAICA L. Mart

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P:341 TRANSPORT OF LIGNANS FROM *SCHISANDRA CHINENSIS* ACROSS CACO-2 CELL MONOLAYER

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P:342 THE ENDOCANNABINOID SYSTEM AS A TARGET FOR ALKAMIDES FROM ECHINACEA ROOTS

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P:343 DIFFERENTIAL DISPLACEMENT RATIOS—A PHARMACOLOGICAL SCREENING STRATEGY EMPLOYED TO IDENTIFY NOVEL PHARMACOLOGICAL ACTIVITY PRESENT IN PLANT EXTRACTS

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P:344 STUDIES ON ANTISPASMODIC ACTIVITY OF ESSENTIAL OIL FROM *ARTEMISIA MARITIMA* AND *JUNIPERUS EXCELSA*

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P:345 BIOASSAY GUIDED FRACTIONATION OF MALAYSIAN PLANTS FOR POTENTIAL ANTIDIABETIC AGENT.

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P:346 ANTIOXIDANT AND LFA-1/ICAM-1 DEPENDENT CELL ADHESION INHIBITORYY ACTIVITY OF POLYPHENOLIC COMPOUNDS FROM *VERBASCUM SALVIIFOLIUM*

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P:347 ETHNOMEDICINE IN KOREA : THE PAST AND THE PRESENT

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P:348 ANTISPASMODIC EFFECT OF THE ETHNOL EXTRACT OF *HYOSCYMUS NIGRUM* SEEDS IS MEDIATED THROUGH DUAL BLOCKADE OF MUSCARINIC RECEPTORS AND CALCIUM INFLUX.

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P:349 CHARACTERIZATION OF SYNTHETIC DIHYDROBENZOFURAN LIGNANS WITH ANTILEISHMANIAL ACTIVITY

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P:350 CYTOTOXIC EVALUATION OF A NEW COUMARIN ISOLATED FROM *CASIMIROA PUBESCENS* (RUTACEAE).

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P:351 α-AMYLASE INHIBITORS EXTRACTED FROM TRADTIONALLY USED DIABETIC PLANTS AND THEIR POTENTIAL AS NOVEL ANTI-DIABETIC TREATMENTS.

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P:352 IN-VITRO ANTIPLASMODIAL AND ANTITRYPANOSOMAL ACTIVITY OF MARULA (*SCLEROCARYA BIRREA* (A.RICH.) HOCHST)

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P:353 IN-VITRO SCREENING OF MALAYSIAN PLANTS BY INDUCTION OF INSULIN SECRETION FOR POTENTIAL ANTIDIABETIC EFFECTS.

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P:354 PRELIMINARY STUDIES ON *PURWOACENG* (*PIMPINELLA ALPINA* KDS), AN OLD FAMOUS JAVANESE HERBAL APHRODISIAC

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P:355 SOME MOLLUSCICIDAL COMPOUNDS FROM THE LATEX OF *EUPHORBIA CONSPICUA*

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P:356 CHEMOPREVENTIVE POTENTIALS OF *TABEBUIA AVELLANEDAE* AND ITS ACTIVE COMPOUNDS AGAINST SKIN CARCINOGENESIS

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P:357 CANCER CHEMOPREVENTIVE AGENTS, SERRATANE-TYPE TRITERPENOIDS FROM *PICEA JEZOENSIS*

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P:358 CHEMOPREVENTION OF NITRIC OXIDE DONOR INDUCED CARCINOGENESIS BY NATURAL SOURCE COMPOUNDS AND EVALUATION OF THE ROLE OF MAP KINASE SIGNALING PATHWAY

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P:359 BIOLOGICALLY ACTIVE TETRANORTERPENOID DILACTONES FROM PLANT PATHOGENIC FUNGI

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P:360 FUNGI AS A SOURCE FOR NOVEL MEDICINES

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P:361 STRUCTURALLY DIVERESE NATURAL PRODUCT AGONITS OF LXR FROM *GARCINIA HUMILIS.* (PART 4 OF 4)

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P:362 STRUCTURALLY DIVRESE NATURAL PRODUCT AGONISTS OF LXR FROM PLANT AND MARINE SOURCES (PART 3 OF 4)

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P:363 STRUCTURALLY DIVRESE NATURAL PRODUCT AGONISTS OF LXR FROM MICROBIAL SOURCES (PART 2 OF 4).

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P:364 NEW CLASS OF CANCER CHEMOPREVENTIVE AGENTS DERIVED FROM THE MARINE NATURAL PRODUCT SARCOPHINE

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P:365 SEARCHING FOR NEW COMPOUNDS WITH ANTI-INFLAMMATORY PROPERTIES IN *WITHERINGIA SOLANACEA* L´HER (SOLANACEAE)

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P:366 TROPICAL-INDIGENOUS MARINE SPONGES AS SOURCES OF CYTOTOXIC COMPOUNDS

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P:367 ACTIVITY OF (+)- AND (-)-USNIC ACIDS AGAINST BACTERIA GROWN IN BIOFILM *vs.* PLANKTONIC PHASE

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P:368 EFFECT OF SELECTED BENZYLBENZOATES ON THE CALMODULIN DEPENDENT ACTIVITY OF THE ENZYME cAMP PHOSPHODIESTERASE

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P:369 CONVOLVULACEOUS RESIN GLYCOSIDES INDUCE NON-SELECTIVE PORE FORMATION IN CELL MEMBRANES

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P:370 INHIBITION OF LEUKOTRIENE BIOSYNTHESIS BY QUINOLINONE ALKALOIDS FROM THE FRUITS OF *EVODIA RUTAECARPA*

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P:371 LEUKOTRIENE METABOLISM INHIBITORY ACTIVITY OF NEOLIGNANS ISOLATED FROM THE SEEDS OF *MAGNOLIA GRANDIFLORA* L.

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P:372 CYNATROSIDE B FROM *CYNANCHUM ATRATUM* HAS ANTI-ACETYLCHOLINESTERASE AND ANTI-AMNESIC ACTIVITIES

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P:373 TWO NOVEL HEPATOPROTECTIVE STILBENE GLYCOSIDES OF *ACER MONO* LEAVES AGAINST H_2O_2 –INDUCED TOXICITY IN PRIMARY CULTURES OF RAT HEPATOCYTES

Hyekyung Yang[1], Song Won Lim[1], Seung Hyun Kim[1], Eun Sil Kim[1], Jeong Seon Yoon[1], Ki Yong Lee[1], Mi Kyeong Lee[1], So Young Kang[2] and Young Choong Kim[1,*] [1]College of Pharmacy and Research Institute of Pharmaceutical Science,
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P:374 INVESTIGATION OF RADICAL SCAVENGINGOF CHLOROFORM , METHANOL EXTRACTS AND FLAVONOIDS OF TEUCRIUM POLIUM L.(LAMIACEAE) FROM IRAN, PAPOLATION KERMAN

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P:375 A PRELIMINARY STUDY ON THE ANTIOXIDANT AND ANTI-INFLAMMATORY ACTIVITY OF *SIDERITIS PERFOLIATA* SUBSP. *PERFOLIATA*

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P:376 RESULTS FROM A SAFETY TRIAL WITH A NEW HOLISTIC GINKGO FRESH PLANT EXTRACT

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P:377 ANTIMICROBIAL AND ANTITUMOUR ACTIVITY OF AZOREAN ENDEMIC PLANTS

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P:378 ANTITRYPANASOMAL ACTIVITIES OF SELECTED APORPHINES AND INTERACTION WITH DNA AND TOPOISOMERASES.

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P:379 THE ANTITUMORAL HYDROALCOHOLIC EXTRACT OF *Bursera fagaroides* (*B.f.*) INHIBITS KIDNEY ODC ACTIVITY IN THE MURINE L5178Y LYMPHOMA MODEL

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P:380 IDENTIFICATION OF STRUCTURALLY DIVERSE NATURAL PRODUCTS AS ANTICOCCIDIAL AGENTS BY SCREENING FOR INHIBITORS OF APICOMPEXAN cGMP-DEPENDENT PROTEIN KINASE

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ANALYSIS AND ENHANCEMENT OF TYROSINASE INHIBITORY ACTIVITY OF STILBENES FROM *VERATRUM PATULUM* BY ENZYMATIC BIOCONVERSION

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Tyrosinase, a key enzyme is responsible to biosynthesize the melanin in melanocytes. The three thousand extracts of plants were incubated with hydrolytic enzymes in the tyrosinase inhibitor screening process because of enhancement of inhibitory effect on the mushroom tyrosinase. About 3.5 % of the extracts i.e. 120 extracts were enhanced their inhibitory activities. Among them, *Veratrum patulum* extract was selected for active compounds purification and identified those as stilbenes compounds, resveratrol and its derivatives. Kinetic parameters on mushroom tyrosinase of the constituents were evaluated and all the stilbenes in *Veratrum patulum* inhibited mushroom tyrosinase in a non-competitive manner.
According to the kinetic parameters, resveratrol and oxyresveratrol showed a stronger inhibitory effect on mushroom tyrosinase activity than their glycosylated derivatives. The enhancement of tyrosinase inhibitory effect of the whole extract using cellulase is supposed to increase the concentration of aglycon which has superior inhibitory activity to its glycoside.
Oxyresveratrol in *Veratrum patulum* did not decrease the amount of tyrosinase protein in Melan-a cells nor did the amounts of Tyrp1 and Dct protein in the western blot experiment. These results showed that oxyresveratrol inhibits tyrosinase enzyme only so as to interfere melanin biosynthesis in Melan-a cell.

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AN OPTIMIZED *Streptomyces* PLATFORM FOR THE PRODUCTION OF NATURAL PRODUCTS BY HETEROLOGOUS EXPRESSION OF DIVERSE BIOSYNTHETIC PATHWAYS.

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Diversa has developed an optimized *Streptomyces* host for the production of novel natural products by heterologous biosynthetic pathway expression. Bioactive compounds deriving from non-ribosomal peptide synthases, types I, II and III polyketide synthases, and deoxy sugars, nucleoside, shikimate and fatty acid subunits have been isolated. The pathways, ranging in size from 6 kb to 60 kb, have been expressed from Gram positive and Gram negative bacteria as well as environmental sources. We have successfully adapted this platform to high throughput screening for the discovery of anti-infective compounds. This demonstrates the feasibility of using a single organism for the expression and discovery of biosynthetically diverse compounds from a wide range of sources. An example of both targeted as well as non-targeted pathway screening will be illustrated.

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IN VITRO CULTURES FROM FLOWER ORGANS OF LEUCOJUM AESTIVUM

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Leucojum aestivum, also called snowflakes is currently the main commercial source of galanthamine, which was recognized as an effective medicine for the treatment Alzheimer's disease. Recently the biotechnological approach using *in vitro* cultures has been considered as an alternative for production of this alkaloid. The obtaining of *in vitro* cultures from flower organs (flower sticks, stems, ovaries and anthers' filaments) of *Leucojum aestivum* was investigated. The influence of different concentrations and combinations of growth regulators (2,4-D, BAP and kinetine) was studied. When the explants from stems and flower sticks were cultivated only with cytokines, the organized structure like bulbs and shoot clumps were established. Primary root formation was observed when flower sticks were cultivated with low auxin concentrations (2,4-D: 0.5 mg/L or 1.0 mg/L). The best result, concerning the callogenesis was obtained when anthers' filaments were cultivated in presence of 2,4-D or BAP/2,4-D.
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CANTHARIDIN FROM *LYTTA VESICATORIA:* MOLECULAR MODES OF CYTOTOXIC ACTION

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Cantharidin (CAN) from *Lytta vesicatoria* exhibits profound cytotoxicity against tumor cells. We investigated molecular mechanisms that determine cellular response to CAN. Alkaline and neutral comet assays showed that CAN induced DNA single and double strand breaks that were repaired in a dose- and concentration-dependent manner. Cell lines harboring endogenous wild-type (CHO-9), mutant (43-3B), or wild-type transfected ERCC1 (43-3B/ERCC1) were, however, similar sensitive to CAN, indicating that the nucleotide excision repair pathway is not involved in repair of CAN-induced DNA repair. CAN was less active in WTK1 lymphoblast cells with mutated p53 than in TK1 lymphoblast cells with wild-type p53. Multidrug-resistant MDR1-expressing CEM/ADR5000 cells did not exhibit cross-resistance to CAN as compared to drug-sensitive parental cells, indicating no role of the MDR-phenotype for cellular sensitivity to CAN. Mining the microarray database of the NCI by using COMPARE analyses provided 50 out of 9706 genes whose mRNA expression correlated with IC50 values for CAN. Subjecting the mRNA expression of these 50 genes to hierarchical cluster analysis allowed to predict sensitivity or resistance of the 60 cell lines to CAN. The present investigation represents a starting point to dissect the genes and molecular pathways involved in cellular response to CAN in greater detail.

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CEPHALOTAXINE AND HOMOHARRINGTONINE FROM *CEPHALOTAXUS HAINANENSIS*: CYTOTOXICITY AS ANALYZED BY MICROARRAY AND HIERARCHICAL CLUSTER ANALYSIS

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Homoharringtonine (HHT) is an ester of cephalotaxine (CET), both of which originate from the Chinese coniferous tree *Cephalotaxus hainanensis*. HHT inhibited tumor cell growth at molar ranges comparable to established cytostatic drugs, whereas CET was 3-4 orders of magnitude less active. MDR1-overexpressing, but not MRP1- or BCRP-overexpressing multidrug-resistant cells were cross-resistant to both drugs. CET and HHT were significantly more active in p53 wild-type cell lines than in p53-mutated ones. Mining the N.C.I.'s database (http://dtp.nci.nih.gov) for the mRNA expression of 465 genes in 55 cell lines and correlating the data with the IC_{50} values for CET and HHT showed significant correlations for 61 (13%) and 122 (26%) of these genes, respectively. As an example for drug target validation, we have analyzed U-87MG.ΔEGFR cells transduced with a deletion-mutated, constitutively activated epidermal growth factor receptor. These cells were indeed more resistant to HHT than mock vector-transfected control cells. The present investigation represents a starting point to dissect the genes and multiple molecular pathways involved in the tumor cells' responses to CET and HHT in greater detail.

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MOLECULAR DIFFERENTIATION OF *ASTRAGALUS* RADIX BY SEQUENCE CHARACTERIZED AMPLIFIED REGION ANALYSIS

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Astragalus radix is a traditional Chinese herbal medicine commonly used as an immune modulator. The botanical origins of *Astragalus* radix consist of the roots of *Astragalus membranaceus* (Fisch.) Bge. or *A. membranaceus* (Fisch.) Bge. var. *mongholicus* (Bge.) Hsiao. Since they are closely related, it is difficult to identify them by morphology, microscopic characteristics and chemical compositions. In this study, we identify a sequence characterized amplified region (SCAR) marker of *A. membranaceus* var. *mongholicus* by using random amplified polymorphic DNA (RAPD) technique.
Among forty RAPD primers screened, eight of them were able to generate reproducible polymorphic bands which distinguished the two *Astragalus* medicines. An approximately 1.3 Kb polymerase chain reaction (PCR) fragment from *A. membranaceus* var. *mongholicus* was selected, sequenced and converted to a SCAR marker. The specificity of 20 bp primer pairs derived from this sequence was further examined by different *Astragalus* samples. The results indicated the primers are unique to *A. membranaceus* var. *mongholicus*.

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GENOME-WIDE OVEREXPRESSION SCREENS IN YEAST AND MAMMALIAN CELLS FOR SMALL MOLECULE TARGET IDENTIFICATION AND BIOLOGICAL MECHANISM STUDIES

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Target identification is commonly the bottleneck in drug discovery. We describe a genetic screen in *Saccharomyces cerevisiae* that is based on multicopy gene suppression and facilitates small molecule target identification. An array of yeast transformants harboring a yeast genomic library on multicopy plasmid was examined for resistance to compounds that inhibit yeast growth. A comparison of array growth patterns for various such inhibitors allowed for differentiation between nonspecific and compound-specific suppressors. One compound, a screen hit from a kinase-directed heterocyclic small-molecule library, was characterized in greater detail. The screen revealed affected pathways and enabled the putative determination of the small molecule targets that were then genetically and biochemically validated. To extend the scope of methodology beyond the yeast growth inhibitors, we also employed a phenotypic complementation strategy in mammalian cells. For proof-of-concept, an arrayed collection of full-length expression cDNAs (27,000 clones) was utilized to identify genes which conferred resistance to apratoxin A, a marine natural product with antiproliferative activity against tumor cell lines. Specifically, individual genes in the cDNA matrix were transfected into human cancer cells utilizing high-throughput methodology, and post-screen analysis provided insight into the compound's mechanism of action and revealed putative cellular targets of the molecule. These results demonstrate the utility of the outlined approach in the rapid deconvolution of small molecule targets.

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BIOCATALYTIC REDUCTION OF KETONES IN THE PROCESS DEVELOPMENT OF PHARMACEUTICAL INTERMEDIATES

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The original synthetic scheme for a prospective drug candidate required the synthesis of S-1-(2-bromo-4-fluorophenyl)ethanol (**1**). Microbial reduction of 2-bromo-4-fluoroacetophenone **2** provided the chiral alcohol **1**. Baker's yeast was found to be the best for providing the alcohol **1** in high yield with high enantiomeric excess. The process was scaled up to kg scale during initial drug evaluation. The synthetic scheme was later changed, requiring the use of {5-fluoro-2-[(1S)-1-hydroxyethyl]}benzenebutanoic acid methyl ester **3**. Biocatalytic reduction of (2-acetyl-5-fluoro)benzenebutanoic acid methyl ester **4** to the chiral hydroxy ester **3** was explored. Though some microorganisms reduced the keto ester **4** to the chiral hydroxy ester **3** in high enantiomeric excess, hydrolysis of the ester group complicated the process and reduced the yield. The ketoreductase enzyme responsible for the reduction was purified and cloned. Reduction of the keto ester **4** by the cloned organism provided the S-hydroxy ester **3** in high yield and high enantiomeric excess.

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SECONDARY METABOLITES FROM ENDOPHYTIC FUNGI ISOLATED FROM THE CHILEAN GYMNOSPERM *PRUMNOPITYS ANDINA*

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The gymnosperm tree *Prumnopitys andina* (Poepp. ex Endl.) de Laub. presents association with endophytic fungi, some of them could be taken into culture from wood samples. Two endophytic fungi were cultured in liquid media and several secondary metabolites were isolated and identified by spectroscopic methods. *Penicillium janczewskii* K.M.Zalessky cultured in potato-dextrose (PD) medium afforded the quinolone peniprequinolone and the dioxopiperazine derivative gliovictin. This fungus produced Pseurotin A when cultured in yeast-malt-glucose (YMG) medium. From *Microsphaeropsis olivacea* (Bonord.) Hohn grown in solid medium (rice), the following compounds were obtained: butyrolactone I, enalin, 7-hydroxy-2,4-dimethyl-3(2H)-benzofuranone, botrallin, graphislactone A, ulocladol and 2,5-diacetylphenol. Botrallin and graphislactone A inhibited the enzyme acetyl cholinesterase "in vitro" with IC_{50} of 6.1 and 8.1 μg/ml, respectively. The cytotoxicity of both compounds towards human lung fibroblasts (IC_{50}) was 329.8 and > 1000 μM, respectively.

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PRODUCTION AND QUANTITATIVE ESTIMATION OF CRYPTOTANSHINONE FORMED IN CALLUS CULTURES OF *SALVIA MILTIORRHIZA* BUNGE

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Salvia (Dan-Shen) is one of the important genus consisting of *ca*. 900 species in the family Lamiaceae and some species of *Salvia* have been cultivated worldwide for use in folk medicine and for culinary purposes. Effect of N^6- benzyladenine (BA) on tanshinone formation in callus cultures of *Salvia miltiorrhiza* were examined in an attempt to increase the productivity of a medicinal compound, cryptotanshinone.

Primary callus was induced by culturing leaf explants on Murashige and Skoog's (MS) basal medium supplemented with 1.0 mg l^{-1} 2,4-dichlorophenoxyacetic acid (2,4-D) in darkness. The callus proliferated further on MS basal medium containing 1.0 mg l^{-1} 2,4-D and 0.5 mg l^{-1} BA and was analyzed for cryptotanshinone by high performance liquid chromatography (HPLC). Omission of 2,4-D from the medium resulted in a marked increase in the content of cryptotanshinone in callus. Callus cultured on the MS basal medium supplemented with 0.1, 0.2, 0.5, 1.0, and 2.0 mg l^{-1} of BA contained significant amounts of cryptotanshinone.

Maximum yield of cryptotanshinone (4.59 ± 0.09 mg/g dry wt.) was observed in the callus cultured on MS basal medium supplemented with 0.2 mg l^{-1} BA for sixty days. Cryptotanshinone was isolated from callus through silica gel column chromatography followed by preparative TLC and characterized based on NMR and Mass spectral data.

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EFFECTS OF PHYSICAL AND CHEMICAL MODIFICATIONS ON THE DISINTEGRANT AND DISSOLUTION PROPERTIES OF *TACCA INVOLUCRATA* STARCH

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The effects of physical (pregelatinization) and chemical (acid hydrolysis) modifications on the distintegrant and dissolution properties of *Tacca involucrata* Starch (Tacca starch) were investigated in lactose based tablets containing 0.001% w/w of riboflavin as tracer substance, 10% w/w Tacca starch as disintegrant, 3% w/w acacia as binder, 1% w/w stearic acid as lubricant and enough quantity of lactose as diluent. The starch was incorporated intragranularly, extragranularly and intra/extragranularly. Regardless of the mode of incorporation, Tacca starch was most efficient in effecting the disintegration of the tablets and releasing their riboflavin contents in its unmodified form. In this regard, pregelatinized Tacca starch was more effective as a disintegrant than the acid hydrolysed form of the starch. Generally, fastest disintegration and dissolution were obtained with extragranular incorporation of the three forms of the starch. On the basis of dissolution efficiency values ($D.E^{15}$), the modifications did not result in any retardation in riboflavin release from the tablets.

Keywords: Tacca starch, pregelatinization, acid hydrolysis, extragruanular, intragranular intra/extragranular, dissolution efficiency.

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A FUNCTIONAL GENOMICS APPROACH TOWARD THE UNDERSTANDING OF PLANT SECONDARY METABOLISM: II. FUNCTIONAL ANALYSIS AND COMBINATORIAL BIOCHEMISTRY IN DIFFERENT EXPRESSION SYSTEMS

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A novel technology platform, developed by us, facilitates the discovery of differentially expressed genes in any plant system without pre-existing sequence knowledge and allows therefore the isolation of specific full-length cDNAs which can be further characterized by:
A. Functional analysis by homologous expression
In our tobacco BY-2 model system the overexpression of 22 genes resulted in three lines exhibiting an altered alkaloid accumulation pattern compared to controls. Targeted metabolite analysis is carried out by HPLC-PDA.
B. Combinatorial biochemistry by heterologous expression
The genes derived from the tobacco transcriptional profiling are used for the transformation of other species, too. One of the tested genes for example influences the tropane alkaloid biosynthesis, which is partly the same as for nicotine alkaloids, in *Hyoscyamus muticus* hairy roots. The effects on the completely different terpenoid indole alkaloids in *Catharanthus roseus* hairy roots are also investigated. GC- and LC-systems are used for the analysis of alkaloids.

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USE OF BIODEGRADABLE PHOSPHOLIPID VESICLES AS CARRIERS FOR CHLORANPHENICOL AND ITS APPLICATION TO BONE MARROW PROTECTION IN THE RABBITS

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Biodegradable phospholipids such as phosphatidylcholine are employed as drug carriers and in the delivery of pharmacologically active drugs to certain tissues and organs of the body. They are known to be non-toxic and they reduce toxicity associated with many compounds including anti-tumor and immounosuppresive agents. We report here the synthesis and application of a biodegradable phospholipid as carrier for chloramphemical and the bone marrow protection offered by the chloramphenicol loaded phosphatidylcholine in experimental rabbits.
The chloramphenicol loaded phosphatidylcholine was stabilized with polyethylene-glycol 600 (PEG 6000) evaluated for entrapment efficiency, polydspersibility and drug release testing. The chlorampehniol loaded phoshotidylchone was administered to experimental rabbits. Haematcount count and bone marrow histology were used as indices of bone marrow protection.
The overall results indicated that chloramphecIol loaded phospotidylchotine stabilized with PEG 6000 reduced bone marrow toxicity caused by chloramphenicol in experimental rabbit.

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FIELD SELECTION AND MICROPROPAGATION OF *CURCUMA LONGA* L.

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Curcuma longa L. is clinically proved to be effective for the treatment of dyspepsia and gastric ulcer. For medicinal purpose, the quality of turmeric is based on the amount of curcuminoid and volatile oil, pharmacologically active compounds. We reported high variation in the active compounds among turmeric grown in different parts of Thailand. Therefore, there is a strong need to genetically improve and cultivate turmeric with high and stable contents of curcuminoid and volatile oil. We performed a field experiment for the selection of elite plants for phytomedicine production. The result demonstrated significant differences among rhizome yields and curcuminoid contents from different accessions, but not volatile oil contents. The averages of curcuminoid contents varied from 5.3 to 8.0 % and volatile oil content from 6.2 to 7.7 %. This chemical variation may be caused by differences in their genetic background. Furthermore, we isolated the elite individual plants containing high amounts of curcuminoid (up to 9.7 %) and volatile oil (up to 9.0 %). A number of 5,000 plants were regenerated from one terminal bud using an effective micropropagation protocol, then transferred to 5 provinces of Thailand. We observed significant differences among finger rhizome yields, curcuminoid, and volatile oil contents from the plants grown in different areas. The amounts of curcuminoid and volatile oil of harvested *C. longa* rhizomes reached the standard of WHO monograph.

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ISOLATION OF PODOPHYLLOTOXIN FROM ENDOPHYTE FUNGI OF *PODOPHYLLUM PELTATUM*. A.E. Eyberger, R. Dondapati, and J.R. Porter*. University of the Sciences, Philadelphia, PA 19104 USA.

Podophyllotoxin is essential for the semi-synthesis of a number of cancer chemotherapeutic drugs. This compound has become more difficult to obtain because one source plant, *Podophyllum hexandrum*, has become rare or endangered due to over-collection. Populations of the other major source plant, *P. peltatum*, may not withstand sustained collection. Through examination of endophyte fungi obtained by culture from tissues of *P. peltatum*, we have discovered two strains of *Phialocephala fortinii* that produce measurable amounts of podophyllotoxin. The compound identity has been confirmed through HPLC-DAD and LC-MS data. Although these fungi grow slowly, they have been cultivated on yeast malt broth, malt broth, malt agar, and Sabouraud's dextrose agar. Continued studies directed toward optimization of the podophyllotoxin production by these fungi may yield conditions that will lead to commercially-viable production capabilities.

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THE USE OF POLYMERASE CHAIN REACTION (PCR) FOR THE IDENTIFICATION OF *EPHEDRA* IN DIETARY SUPPLEMENTS

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Ephedra spec. (Ma Huang) has been used for centuries in traditional Chinese medicine. In the 20th century it became very popular in the US as a dietary supplement because of its positive influence upon weight loss and performance enhancement. But recent studies associated *Ephedra* with 155 deaths and dozens more heart attacks and strokes. In regard to public safety, the FDA implemented a policy to ban *Ephedra* from the market beginning by April 12, 2004.
We report here the identification of a molecular marker to distinguish *Ephedra* from other plant species. The identification of this marker was done by the amplification of a chloroplast genetic region by Polymerase Chain reaction (PCR) and sequencing of the amplified product. Sequence comparison to the same region from other plants facilitated the discovery of unique *Ephedra* regions, which were used to design an *Ephedra* specific marker. The use of this marker on dietary supplements and its sensitivity will be discussed.

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PHYLOGENETIC RELATIONSHIPS IN *PIMPINELLA* (UMBELLIFERAE) BASED ON ESSENTIAL OIL ANALYSIS AND NUCLEAR AND CHLOROPLAST SEQUENCES

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The genus *Pimpinella* (Umbelliferae) is represented in the flora of Turkey by 27 species, five of which are endemic. Especially anise (*Pimpinella anisum*) is highly valued since ancient times and it is used as carminative, sedative, antidepressant, antispasmodic, antifungal, diuretic, pectoral, and tonic in traditional medicine. The essential oil from *P. anisum* fruits is also valuable in the pharmaceutical industry. Both the extract and essential oils of *Pimpinella* species are known to have a high content of phenylpropanoid derivatives. The 2-hydroxy-5-methoxy-1-(*E*)-propenylbenzene structural moiety of these compounds is called pseudoisoeugenol and so far it has only been found in the *Pimpinella* genus. Besides these characteristic phenylpropanoids, a number of C_{12} sesquiterpenes such as geijerenes and azulenes occur in considerable amounts in *Pimpinella* oils. In this study, phylogenetic relationships among 26 species were evaluated using ITS 1, ITS 4 nuclear rDNA and psbA-trnH cpDNA sequences. The significance and occurrence of phenylpropanoids, azulenes and geijerenes are discussed from a phylogenetic, chemical and biosynthetic perspective.

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MODELING ANTIFUNGAL SAPONINS AND BIOMASS PRODUCTION IN FLASK SYSTEMS FROM HAIRY ROOT CULTURES OF *Solanum chrysotrichum*

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Hairy root cultures of the Mexican species *Solanum chrysotrichum* were used to produce three potent antifungal saponins. The saponins known as SC2, SC3 and SC4, were obtained at maximum yields of 0.45, 0.15 and 0.87 mg g_{DW}^{-1} respectively. Only SC2 was produced all along the culture period with a biomass relation given by $SC2_{(\mu g)} = 1.16 X_{(gFW)}$ ($R^2 = 0.65$). Some experiments were done in an attempt to optimize saponins and biomass production, observing that complete B5 nutrient medium, supplemented with 30 g l^{-1} sucrose at continuous light, were best suited for roots growth and saponins production. A model for indirect biomass estimation (X_{FW}) on-line was obtained by conductivity (C) and volume (V) measurements as:

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$$X_{FW} = \frac{C_0 V_0 - C V_0 - X_{FW0}\left(\frac{\beta C}{1000} - \alpha\right)}{\alpha - \frac{C}{1000}\beta}$$

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LARGE-SCALE CULTIVATION OF *SOLANUM CHRYSOTRICHUM* HAIRY ROOTS : PRODUCTION OF FIVE ANTIFUNGAL SAPONINS IN 2 AND 10L AIRLIFT BIOREACTORS

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Internal-loop draught-tube airlift reactors of 2 and 10 l with a novel fitness were used to optimize hairy roots growth and production of antimycotic saponins from the Mexican species *Solanum chrysotrichum*. In the 2 l reactor with a mesh draught with extensions and helixes, roots were homogeneously distributed all along the culture area, achieving a better growth than in flasks or in the 10 l reactor. As a consequence, the observed growth rates were 0.115 and 0.077 d^{-1} in 2 and 10 l reactors, and 0.08 d^{-1} in flasks. The production of the saponins SC5 and SC6 (0.028 and 0.056 mg g_{DW}^{-1}), was only observed in cultures growing in 2 l reactors in which the saponins SC2 and SC4 (7.17 and 0.137 mg g_{DW}^{-1}) were also recovered.
The production of SC2, which represent the most active saponin from this species, was 6 times higher in 2 l reactors in comparison with values obtained from leaves of wild plants. Also, this accumulation was 17 and 4 times higher than yields obtained in flask cultures and in the 10 l reactor respectively. The gas holdup behavior in the 2 l reactor changed with roots production, conditioning the 10 l scale-up to non typical parameters.

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KINETIC PRODUCTION OF TRITERPENOIDS IN HAIRY ROOTS SUSPENSION CULTURES OF GALPHIMIA GLAUCA

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The production of the triterpenoids 6-acetoxy galphimine B (a sedative principle), maslinic acid, and the novel compound glaucacetalin A, was quantified by HPLC in biomasses and nutrient media of *Galphimia glauca* hairy root cultures. Batch cultures of the hairy root suspension line VYT obtained through infection of cotyledons with *Agrobacterium rhizogenes* ATCC15834, were grown for 40 days in shake flasks containing B5 medium without phytohormones. A maximum biomass of 11 g/l DW was obtained at 33 days in culture and the doubling time was of 6 days Throughout the growth cycle, fresh and dry weight, triterpene production and uptake of sucrose, glucose and fructuose were registered. Glaucacetalin A was secreted into the nutrient media reaching a maximun concentration of 2.14 mg/l after 25 days, while 6-acetoxy galphimine B and maslinic acid were recovered from root biomasses at maximum concentrations of 0.12 and 0.427 mg/g, respectively.

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INSILICO FUNCTION ASSIGNMENT OF HUMAN CHROMOSOME 6 OPEN READING FRAMES

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Human chromosome 6, the largest and latest metacentric chromosome sequenced till date constitutes 6% of the human genome. It occupies unique position in biomedical research due to its association with several diseases like cancer, schizophrenia, epilepsy, parkinson's etc. The worth of a genome is associated with annotation, thus several efforts were made to ensure that chromosome 6 annotation is of high quality. It was made available for analysis via vertebrate genome annotation (VEGA) database. Initial analysis of chromosome revealed that it encodes 1557 genes of which 1059 have defined ORF. Of these 1059, we observed that 104 and 96 genes are still unannotated, in known and novel categories respectively. This provided us an opportunity to assign function to these unannotated ORF's.
These 200 unaanotated transcripts were downloaded from VEGA database (Release date: 17 September 2003) and compared against peptide library generated from 62 organisms (10 Archaea, 45 Bacteria and 7 Eukaryotes) using Peptide Library based Homology Search Tool (PLHOST). Putative function to these transcripts are assigned based on the presence of invariant peptide, only if, peptide of 8 amino acid or longer are present identically in at least 3 different organisms. Subsequently, the functions were reconfirmed using various tools available in public domain, if possible.
This resulted in identification of 41 genes harboring 83 invariant peptides, whose putative function has been inferred. In case of 8 genes we value add on the existing information while in 17 cases completely new information is gathered and in the rest 16 cases concurrent information is obtained as already available through InterPro. The updated VEGA database (Release date: 13 April 2004) also confirms our results, with only 13 genes awaiting confirmation. The details of the analysis will be presented.

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PRODUCTION OF THE MANZAMINE ALKALOIDS BY A SPONGE ASSOCIATED MICROBE OF THE GENUS MICROMONOSPORA.

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The manzamines are a group of β-carboline derived alkaloids from a diverse range of sponges. The activity of manzamine A against malaria is remarkable and represents an important lead for the treatment of this global health care concern. The diversity of manzamine structures, taxonomy of producing sponges and geographic locations where the sponges were collected has contributed to speculation that the consortium of microorganisms living in association with these sponges is responsible for the biosynthesis of this group of alkaloids.
Our investigation has focused on the cultivation of microbes from manzamine sponges, screening for manzamine production, and the identification of conditions to induce and enhance manzamine yields from the manzamine producing *Micromonospora* M42.
The results of our investigations associated with the culture of the microbe M42 which produces a metabolite first identified from a sponge in high yields as well as the impact on sustainable production and supply of manzamine and other marine natural products will be discussed.

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ANTIINFECTIVE AGENTS FROM MARINE ACTINOMYCETES COLLECTED FROM JAMAICA.

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Marine microorganisms have been shown to be a rich source for bioactive compounds and still remain largely unexplored. The track record of Actinomycetes as an important source of secondary metabolites in the history of drug discovery has been firmly established. In order to find new sources and new bioactive compounds as antiinfective agents from marine Actinomycetes, we explored a number of Jamaica's sponges and marine sediments for new actinomycetes to evaluate for the production of new antibiotics.
The results of preliminary screening and characteristics of some of our recently isolated Actinomycetes will be reported.

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PRODUCTION OF PLANTS WITH AN OPTIMIZED METABOLITE SPECTRUM BY AN INNOVATIVE BIOTECHNICAL PRODUCTION PROCESS

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Active substances obtained from plants are known for their complex and well-tolerated biological effects. Often the biological activity of the whole spectrum of active substances is much higher than of each compound. The quality of active substances from plants harvested in nature or cultivated in fields varies depending on the environmental conditions. Infestation, diseases and the application of pesticides additionally decreases the quality of the raw materials. Here we report a new biotechnical production process to standardize the concentration and spectrum of active compounds. A low cost bioreactor system based on the temporary immersion principle has been developed. It allows automated large scale *in vitro* production of differentiated plant organs. It will be shown, that the productivity of secondary metabolites in these systems is higher compared to field grown plants. Moreover, the control of environmental parameters *in vitro* can be used to modify the content as well as the spectrum of the produced metabolites. Detailed results for phenolic compound, alkaloid and Camptothecin producing plants will be discussed during the presentation.
This is a promising technology to produce extracts with an optimized biological activity without any contamination at all. For further optimization this technology will be supplemented with *in vitro* screening systems for a fast optimization process.

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ANTI-APOPTOTIC EFFECTS OF TOLUQUINOL ISOLATED FROM *PENICILLIUM* SP. F020150

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In the course of screening for the substances inhibiting apoptosis of U937 human leukemia cells induced by etoposide (10 μg/ml), *Penicillium* sp. F020150 producing a high level of inhibitor was selected. The regulating compounds were purified from the ethyl acetate extract by sephadex LH-20 column chromatography and HPLC. The inhibitory substance was purified and identified as toluquinol by spectroscophic methods.
To clarify the mechanism of apoptosis inhibition by toluquinol, we examined the effects of toluquinol on the activities of caspase cascade in U937 human leukemia cells induced by etoposide (10 μg/ml). Toluquinol showed inhibitory activity of caspase-3 induction, a major protease of apoptosis cascade, with and IC_{50} value of 0.8 μg/ml after 8 h of etoposide treatment. The expression level of, caspase-3, -8, -9 and PARP was also inhibited by toluquinol in a dose-dependent manner. But there was no change in the levels of Bax, and cytochrome c. However, toluquinol inhibited cytochrome c/dATP-mediated apoptosome complex formation, release of the active caspase-9. These results suggest that toluquinol inhibits drug-induced apoptosis via apoptosome complex and caspase cascade down regulation.

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APOPTOTIC ACTIVITY OF BETULINIC ACID DERIVATIVES ON MURINE MELANOMA B16 CELL LINE

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Mitochondrion plays an important role in the process of apoptosis, and has thus become one of the targets for the search of potential chemotherapeutic agents. Betulinic acid, a naturally occurring triterpene, has been shown to exert a direct effect on the mitochondria resulting in apoptosis, particularly in cells of neuroectodermal origin such as melanoma and neuroblastoma cells. We have isolated several natural derivatives of betulinic acid from the root of a Chinese medicinal herb *Pulsatilla chinensis* and evaluated their cytotoxicity. Of the compounds tested, 3-oxo-23-hydroxybetulinic acid has the strongest cytotoxic effect on murine melanoma B16 cells, followed by 23-hydroxybetulinic acid, betulinic acid, lupeol and betulin. Exposure of B16 cells to 3-oxo-23-hydroxybetulinic acid caused a rapid increase of reactive oxidative species production and a concomitant dissipation of mitochondrial membrane potential in a dose- and time-dependent manner, leading to apoptosis as demonstrated by fluorescence microscopy, gel electrophoresis, and flow cytometric analysis. Cell cycle analysis further demonstrated that 3-oxo-23-hydroxybetulinic acid dramatically increased DNA fragmentation at the expense of G1 cells, manifesting potent apoptotic property. The structure-cytotoxicity relationship of betulinic acid derivatives will be discussed.

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BIOSYNTHESIS OF CURCUMINOIDS AND GINGEROLS IN MEDICINAL PLANTS FROM THE ZINGIBERACEAE.

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The curcuminoids and gingerols are natural products found in turmeric (*Curcuma longa L.*) and ginger (*Zingiber officinale* Rosc.) rhizome tissues. These natural products possess anti inflammatory properties and thus are of medicinal value and importance. However, despite their relevance, no studies have been reported in the scientific literature that have even sought to identify the enzymes involved in the synthesis of these compounds. The present investigation describes the identification of enzymes in the potential biosynthetic pathway leading to the production of the curcuminoids and gingerols. Assays for enzymes in the biosynthetic pathway identified the corresponding enzyme activities in protein crude extracts from leaf, shoots and rhizome from ginger and turmeric. These enzymes included phenylalanine ammonia lyase (PAL), polyketide synthase (PKS), *p*-coumaroyl shikimate transferase (CST), *p*-coumaroyl quinate transferase (CQT), caffeic acid *O*-methyltransferase (COMT), and caffeoyl-CoA *O*-methyltransferase (CCOMT). All crude extracts possessed activity for all of these enzymes, with the exception of PKS. The results of PKS assays showed detectable curcuminoid synthase activity in the turmeric extracts with the highest activity found in the leaves. Acknowledgments, this work was supported by NIH/NCCAM/ODS grants 5P50 AT 00474-04 and 3P50 AT00474-04 S1, to BNT.

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GENETIC POTENTIAL FOR SECONDARY METABOLITE PRODUCTION IN MYXOBACTERIA, CYANOBACTRIA AND MARINE PROTEOBACTERIA

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Specific phylogenetic groups like myxobacteria and cyanobacteria produce a wide range of natural products with potent biological activities. Among these secondary metabolites especially polyketides and non-ribosomal peptides, which are produced by polyketide synthases (PKS) and non-ribosomal peptide synthetases (NRPS) are of interest due to their important pharmaceutical properties. The distribution of PKS and NRPS genes in myxobacterial, cyanobacterial and marine, mostly proteobacterial, strains isolated from boreal sponges of the Norwegian Lophelia reef was investigated by PCR studies with degenerate primers deduced from conserved sequence motifs of ketosynthase domains of PKS type I and of aminoacyl-adenylation and thiolation domains of NRPS. A phylogenetic analysis was conducted with deduced amino acid sequences of these PKS gene fragments. The phylogenetic tree revealed that the corresponding ketosynthase domains encoded by the PKS gene fragments are not conserved within these different phylogenetic groups. Similar ketosynthase domains can be found in distantly related cyanobacterial and proteobacterial strains while closely related strains can contain rather diverse domains. These results strongly suggest that PKS genes are transferred horizontally between different phylogenetic groups. Furthermore, this screening study can be used to gain information about the genetic potential of marine bacteria for secondary metabolite production.

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METABOLIC PROFILING OF FLAVONOIDS AND ISOFLAVONOIDS IN M. TRUNCATULA USING HPLC-UV-ESI-MS AND GC-MS

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An integrated functional genomic approach is being used to study legumes. This approach involves correlated measurements of the transcriptome, proteome and metabolome to better understand legume biology and its interaction with the environment. As part of the metabolic approach, profiling of natural products such as saponins and flavonoids is underway. Previously, we have reported on the metabolic profiling of saponins using HPLC coupled with electrospray mass spectrometry (Huhman and Sumner; 2002). Here, we present an integrated approach utilizing HPLC-UV-ESI-MS and GC-MS based methods for profiling of isoflavonoid and flavonoid glucosides in the model legume *Medicago trancatula* plant and cell culture. Under optimized conditions, we were able to simultaneously identify 29 flavonoids including 16 isoflavone glucosides, 9 flavone glucosides and 4 isoflavone aglycones in *M. trancatula;* ion structures were confirmed using tandem mass spectrometry MS/MS. This study also found that the roots contained isoflavones as the major flavonoids, whereas the aerial portions had flavones as the major flavonoids. In addition, alterations in the levels of these flavonoids and isoflavonoids in response to yeast/fungal elicitation will be described.

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NEW EFFICIENT VIRUS-BASED PLANT EXPRESSION SYSTEM FOR PROTEINS AND ENZYMES OF SECONDARY METABOLITE PRODUCTION INSTANCING THE EXPRESSION OF A NOVEL ESTERASE OF *RAUVOLFIA SERPENTINA*

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The research is focused on the exploration of different enzymes of the Indian medicinal plant *Rauvolfia serpentina*. These enzymes are involved in the biosynthesis of *ajmaline*, an antiarrhythmic alkaloid. After the testing of several gene expression systems including the ones based on insect cells, yeast and bacteria, we have chosen a transient plant virus-based expression system in *Nicotiana benthamiana* leaves. The main advantages of the system are that it provides an opportunity for fast and efficient optimisation of an expression level, thus allowing to avoid complicated and time-consuming stable transformation and to reach the yield impossible in other systems. As an example we will present the expression of a novel specific soluble esterase of *ajmaline* biosynthesis. After isolation we started the common enzyme testing like activity test by means of specific incubation with the original substrate. We detected an extraordinary high enzyme activity which was not attainable with other expression systems and which is much higher than in *Rauvolfia serpentina* cell suspension cultures. The future target is the expression of Cytochrom-P450 enzymes to use the advantages of the described expression system for these membrane-bound enzymes whose activity is normally hard to detect.

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THE BIOSYNTHESIS OF PRODIGIOSIN STUDIED BY LC-MS

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Prodigiosin is a linear tripyrrole produced by some *Serratia* sp. It is a typical secondary metabolite, appearing only in the later stages of bacterial growth.
We have identified a cluster of 21634 bp in *Serratia* 39006 responsible for the biosynthesis of prodigiosin. Based on sequence alignments and previous studies, we propose a bifurcated pathway for the biosynthesis, culminating in the enzymatic condensation of the end products of the two pathways, 4-methoxy-2,2'-bipyrrole-5-carbaldehyde (MBC) and the monopyrrole, 2-methyl-3-n-amyl-pyrrole (MAP).
To verify the pathway several mutants were created by transposon mutagenesis and in-frame deletions by PCR and crude extracts of the mutants were studied by LC-MS. The mutants were unable to make prodigiosin and were shown to accumulate either MAP or MBC, identified by comparison to synthetic MAP and literature data for MBC. Pigmentation could be reestablished by either cross-feeding experiments or by adding MAP/MBC.
We also report a new synthesis of MAP.

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BIOSYNTHESIS OF ACETATE-DERIVED NAPHTHYLISOQUINOLINE ALKALOIDS AND NAPHTHOQUINONES

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Lianas of the Ancistrocladaceae and Dioncophyllaceae plant families are indigenous to the tropical rain forests of Africa and Southeast Asia. They produce the structurally unique naphthylisoquinoline alkaloids, which are pharmacologically promising secondary metabolites. Some of the naphthylisoquinoline alkaloids possess significant antiprotozoal acitivities and may therefore constitute novel agents against tropical diseases like malaria and leishmaniasis.

In addition to their potent bioactivities, naphthylisoquinoline alkaloids have an intriguing biogenesis. Whereas all other isoquinoline alkaloids in plants derive from aromatic amino acids, naphthylisoquinolines originate from acetate. It has been postulated that a polyketide synthase synthesizes the carbon skeleton of the naphthyl and isoquinoline moieties. An aminotransferase should catalyze the incorporation of nitrogen into the isoquinoline precursor, which is then joined with the naphthalene part by a *C-C* phenol coupling reaction.
This project is aiming to characterize and isolate the three enzymes postulated to be involved in naphthylisoquinoline biosynthesis by biochemical and molecular genetic methods. In addition, the related biosynthetic pathway leading to acetate-derived naphthoquinones will be studied.

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THE FAVORSKII-LIKE CARBON REARRANGEMENT IN THE BIOSYNTHESIS OF ENTEROCIN

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The marine actinomycete "*Streptomyces maritimus*" produces a structurally diverse series of polyketides known as the enterocins and wailupemycins, which are derived from an uncommon benzoate starter unit and seven malonates. The polyketide undergoes a rare favorskii-like carbon rearrangement during biosynthesis to form a highly relative enterocin precursor. This reaction is catalyzed by the FAD-dependent oxygenase EncM. When this encoding gene *encM* was disrupted through single crossover homologous recombination, the resultant mutant was unable to produce the rearranged polyketides. Heterologous expression of *enc*M and the enterocin "minimal polyketide synthase (PKS)" *enc*ABCDLN in *Streptomyces lividians* K4-114 resulted not only in the production of the expected unrearranged wailupemycins D-G but also in the rearranged desmethyl-5-deoxyenterocin. Heterologous expression of *enc*M and the actinorhodin "minimal PKS" genes *act*I-ORF1-3, however, did not result in the production of the similar rearranged compounds, suggesting that the acetate-primed poly-β-ketides are not suitable substrates for the favorskiiase EncM.

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KETOREDUCTION TIMING IN AROMATIC POLYKETIDE ASSEMBLY - AN ALTERNATIVE MODEL FOR POLYKETIDE BIOSYNTHESIS

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In the accepted model for aromatic polyketide biosynthesis, the timing of ketoreduction in aromatic type II polyketide assembly occurs after the complete synthesis of the linear poly-β-ketide. Like enterocin and the wailupemycins, all ketoreduced aromatic polyketide synthase (PKS) products, including those derived from the actinorhodin (*act*) PKS, are similarly reduced at the ninth carbon from the carboxy terminus of the assembled polyketide irrespective of polyketide chain length.
Results of heterologous expression and mutagenesis of the enterocin (*enc*) PKS ketoreductase EncD suggest that unlike other type II PKSs, ketoreduction is essential for polyketide production. Our data also suggest that ketoreduction occurs during polyketide chain elongation rather than after completion, thus representing an alternate model for type II polyketide assembly. Our model is supported by the identification of a series of truncated hexaketides derived from the heterologous expression of the *act* PKS.

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HETEROLOGOUS EXPRESSION OF TWO *FUSARIUM* TRICHOTHECENE P450 GENES

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Fusarium graminearum and *F. sporotrichioides* produce the trichothecene mycotoxins 15-acetyldeoxynivalenol and T-2 toxin, respectively. In both species, disruption of the P450 monooxygenase-encoding gene *Tri4* blocks production of the mycotoxins and leads to the accumulation of the trichothecene precursor trichodiene. To further characterize its function, the *F. graminearum Tri4* (*FgTri4*) was heterologously expressed in the trichothecene-nonproducing species *F. verticillioides*. Transgenic *F. verticillioides* carrying the *FgTri4* converted exogenous trichodiene to the trichothecene biosynthetic intermediate isotrichodermin. Conversion of trichodiene to isotrichodermin requires seven steps, two of which can occur non-enzymatically. Precursor feeding studies done in the current study indicate that wild-type *F. verticillioides* has the enzymatic activity necessary to carry out the seventh step, the C-3-acetylation of isotrichodermol to form isotrichodermin. Together, the results of this study suggest that the *Tri4* protein catalyzes the remaining four steps and is therefore a multifunctional monooxygenase. We also used this approach to look at oxygenation steps near the end of the biosynthetic pathway controlled by *Tri1*.

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INDUCTION OF APOPTOSIS IN A LEUKEMIA CELL LINE BY TRITERPENE SAPONINS FROM *ALBIZIA ADIANTHIFOLIA*

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The present study examines the effects of three acacic acid-type triterpene saponins (**1**, **2**, and **3**) which are 21-acyl-3,28-di-O-glycosides acylated with salicylic acid or with monoterpenic acids, together with two prosapogenins obtained from the roots of *Albizia adianthifolia* (Mimosaceae) on Jurkat cells. Compounds **1**, **2**, and **3** were found to be cytotoxic, whereas the prosapogenins were found to be lymphoproliferative on this cell type. We demonstrated that at 5 μM for **1** and at 1 μM for **3**, these compounds induced apoptosis in these cells by disruption of the mitochondrial membrane potential and a DNA ladder was observed when Jurkat cells were incubated with 1 μM of **3** for 24 hrs.
By comparison between the biological activities of the native compounds with those of the prosapogenins, we showed in this work the important role of the acylation and esterification by different moieties at C-21 and C-28 of the aglycone in the apoptosis-inducing capacity, particularly the monoterpene-quinovosyl moieties linked at C-21.

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INVESTIGATING LIGNAN AND ALKALOID BIOSYNTHESIS IN PLANTS THROUGH GENOMICS APPROACHES

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Podophyllotoxin has antiviral and antineoplastic activity, and is used to produce anti-cancer drugs. However, the best source of podophyllotoxin is an endangered Indian species, *Podophyllum hexandrum*, which is susceptible to over-harvesting. Henbane (*Hyoscyamus* spp.) produces tropane alkaloids that are used in anesthesia, ophthalmology, prevention of motion sickness and treatment of Parkinson's disease. Our ongoing research is aimed at identifying genes involved in making podophyllotoxin and tropane alkaloids with a view to enhance their production. For our study of podophyllotoxin biosynthesis, a full-length cDNA library was made from the rhizomes of a North American species, *Podophyllum peltatum*. From the tropane alkaloid producing plant, *Hyoscyamus niger*, a subtracted cDNA library was constructed. The cDNA clones were randomly picked from the libraries and sequenced. To date, 4315 ESTs were obtained from a *Podophyllum* library, and 2286 ESTs from a *Hyoscyamus* library. Similarity and related searches were used to make tentative functional assignments corresponding to particular cDNAs. The results of silencing two known genes encoding enzymes of tropane alkaloid biosynthesis, putrescine N-methyltransferase and hyoscyamine 6β-hydroxylase, will be reported. Progress in the identification of candidate cDNAs through heterologous expression and gene silencing technology will be discussed.

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BIOSYNTHESIS OF SAFRAMYCIN MX1 FROM MYXOCOCCUS XANTHUS

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Saframycin MX1, from *Myxococcus xanthus*, is an isoquinoline antibiotic that is formed through a unique modification of the nonribosomal peptide synthetase (NRPS) mechanism. The saframycin family of compounds constitutes a promising group of natural products in cancer chemotherapy. Within the family, the marine ascidian metabolite ecteinascidin-743 (Et-743) shows the greatest potential. Therefore, the engineering of Et-743 analogs could yield promising new chemotherapeutic agents. In order to facilitate genetic engineering to create new saframycin and Et-743 analogs, we are investigating the substrate specificities of saframycin biosynthetic enzymes.
Entire *safA*, *safB*, and *safC* genes from the known saframycin MX1 biosynthetic gene cluster were cloned and sequenced. The adenylation and methyltransferase domains were expressed as soluble constructs in *Streptomyces lividans* TK24 under control of the *ermE2* promoter. The His-tagged proteins were purified, and assays to determine their substrate specificities were performed. Based upon these studies, a revised biosynthetic pathway is proposed.

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BIOSYNTHETIC ORIGIN OF THE METABOLITES PRODUCED BY THE CULTURED LICHEN MYCOBIONTS

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Lichens are symbiotic organisms comprised of a fungus, mycobiont, and a photosynthetic partner, photobiont. They produce diverse characteristic secondary metabolites. On the other hand, cultures of lichen mycobionts have an ability to produce substances which have never been detected in the lichenized state. From our interest in the relationship between symbiosis and metabolism of lichen, the biogenetic origin of the carbon skeleton in graphislactones and graphenone was investigated.
Feeding of ^{13}C-labelled acetate to the mycobionts of *Graphis prunicola* resulted in moderate incorporation into new metabolites graphislactones E and F to demonstrate that graphislactones might be biosynthesized *via* alternariol. Feeding experiments to the mycobionts of *G. handelii* have established that the C_{10}, C_3 and C_1 units in graphenone are originated from acatate, succinate and methionine, respectively.
The present studies demonstrated that the metabolic pathways of mycobionts are closely similar to those of free-living fungi and the dormant fungal metabolism might be normally suppressed in symbiotic state with photobionts, but expressed in the isolated mycobiont.

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EARLY STEPS IN THE BIOSYNTHESIS OF FUSCOL/FUSCOSIDES

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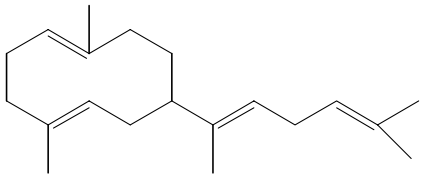
Fuscosides are diterpene arabinose glycosides isolated from the Caribbean soft coral *Eunicea fusca.* They and the aglycone fuscol are potent anti-inflammatory compounds with long-lasting effect and have a selective inhibitory action against leukotriene production in murine models of inflammation. Their anti-inflammatory effect is comparable to the commercially available indomethacin.
Early steps in the fuscoside biosynthetic pathway have been investigated using a radioactivity-guided isolation. The diterpene cyclase product (**1**) was identified from a cell-free extract of the marine soft coral *E. fusca*, which was incubated with ^{3}H-geranyl geranyl diphosphate. The intermediacy of the isolated new compounds in fuscol/fuscoside biosynthesis using a cell-free extract of *E. fusca* will be presented.



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FURTHER EVIDENCE FOR A POLYKETIDE ROUTE TO THE PHYTYL SIDECHAIN OF CHLOROPHYLL IN *EUGLENA GRACILIS*

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Previous studies on isoprenoid biosynthesis in *Euglena gracilis* have established that this organism utilizes the mevalonate pathway to produce sterols and the mevalonate and methylerythritol phosphate pathways to produce carotenoids. The labeling patterns for the phytyl side chain of chlorophyll from experiments with either 1-^{13}C-acetate or 1-^{13}C-glucose are consistent with a mevalonate route to phytol, but incubation with U-$^{13}C_6$-glucose revealed an alternate route. After numerous experiments aimed at supporting an isoprenoid origin for phytol failed, a polyketide route was considered. Biosynthetic experiments with 2-^{13}C-malonic acid, $^{13}CD_3$-CO_2Na, and $CD_3{}^{13}CO_2Na$ have now strongly supported a polyketide route to phytol. Apparently an unusual polyketide synthase is involved in the construction of this "isoprenoid" compound in *E. gracilis*. An additional observation was that the side chain of *a*-tocopherol is also formed by this unique route.

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PAPUAMIDE A, INHIBITOR OF HUMAN IMMUNODEFICIENCY VIRUS FUSION

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Papuamide A is a cyclic depsipeptide, isolated from the sponges *Theonella mirabilis* and *Theonella swinhoei*, which has been shown to have potent anti-human immunodeficiency virus (HIV) activity in a T cell cytoprotection assay. Rapid identification of a site of action for papuamide A was accomplished after successful biotinylation of papuamide A, without a significant loss of anti-HIV activity. Surface plasmon resonance was utilized to study binding interactions between papuamide A and HIV proteins and protein peptide libraries. These initial HIV protein/peptide interactions indicated papuamide A binds strongly to a region of HIV glycoprotein 41 (gp41) cytoplasmic tail. HIV gp41 is a transmembrane protein found in the envelope of HIV and is responsible for mediating viral and cell membrane fusion. Therefore, we tested papuamide A in a vaccina-virus based fusion assay in which papuamide A was shown to be almost 100% inhibitory at concentrations as low as 10 μg/mL with an estimated IC_{50} of approximately of 4 μg/mL (2.8 μM).

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MOLECULAR GENETICS OF SAPONIN BIOSYNTHESIS IN *SAPONARIA VACCARIA*

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Cowcockle or *Saponaria vaccaria* produces a variety of saponins of the quillaja type, as well as sterol glycosides, especially spinasterol glucoside. These saponins have a variety of commercial uses including a role as adjuvants in vaccines. As part of a larger program to investigate and identify the genes involved in plant natural product biosynthesis using expressed sequence-tag-based approaches, we have initiated a study of saponin biosynthesis in *S. vaccaria*. A cDNA library and corresponding expressed sequence tag collection from *S. vaccaria* has been generated. Two cDNA clones have been isolated which show sequence similarity to sterol glucosyltransferases. Full length clones have been isolated and expressed in *E. coli*. Characterization of the enzyme activities, especially substrate specificities of these putative glucosyltransferase will be reported.

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BIOSYNTHESIS OF THE JAMAICAMIDES, NEW MIXED POLYKETIDE-PEPTIDE NEUROTOXINS FROM THE MARINE CYANOBACTERIUM *LYNGBYA MAJUSCULA*

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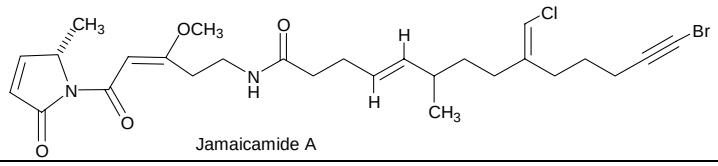
A screening program for bioactive compounds from marine cyanobacteria led to the isolation of jamaicamides A-C. Jamaicamide A is novel and highly functionalized lipopeptide containing an alkynyl bromide, vinyl chloride, β-methoxy eneone system, and pyrrolinone ring. The jamaicamides show sodium channel blocking activity and fish toxicity. Precursor feeding to jamaicamide-producing cultures mapped out the series of acetate and amino acid residues, and helped develop an effective cloning strategy for the biosynthetic gene cluster. The 58 kbp gene cluster is composed of 17 open reading frames that show an exact co-linearity with their expected utilization. A novel cassette of genes appears to form a pendent carbon atom possessing the vinyl chloride functionality; at its core this contains an HMG-CoA synthase-like motif, giving insight into the mechanism by which this functional group is created.



Jamaicamide A

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PROTEIN-PROTEIN INTERACTIONS IN THE MEP PATHWAY

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Isoprenoids (= terpenoids) are the most structurally diverse family of compound found in nature. More than 23 000 isoprenoid molecules are known to date. Many isoprenoids have biotechnological applications as drugs, flavours, pigments, perfumes or agrochemicals.

IPP and the isomeric compound, DMAPP are the fundamental building blocks of isoprenoids in all organisms. Until recently it was generally assumed that IPP was derived solely from mevalonate synthesized from the condensation of three molecules of acetyl-CoA. However, in the early 1990s two research groups independently demonstrated the existence of a novel, mevalonate-independent pathway for IPP synthesis known as the 1-deoxy-D-xylulose 5-phosphate / -C-methyl-D-erythritol 4-phosphate (MEP) pathway. This latter mevalonate-independent pathway utilizes pyruvate and glyceraldehyde 3-phosphate as starting materials for production of IPP.

In the past few years efforts have focused on the discovery of the enzymes involved in this MEP pathway. However, possible protein-protein interactions between proteins of the pathway have not been investigated. In order to address this question, we are using yeast two-hybrid and tap-tagging approaches, to map interactions between all the members of the pathway.

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CHEMICAL AND MICROBIAL TRANSFORMATION STUDIES OF THE BIOACTIVE MARINE NATURAL PRODUCTS SIPHOLANE TRITERPENES

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Nineteen sipholane triterpene have been reported so far from the Red Sea sponge *Siphonochalina siphonella* by Kashman and coworkers without any significant biological activity. Our study of a recent collection of this sponge afforded the new sipholane triterpene named sipholenone I, along with the known sipholenols A, and F in a relatively high yield. Since both sipholenone I and sipholenol A show effective anticancer activities in our assays, both compounds were subjected to chemical and microbial transformation studies in an attempted to generate new diverse derivatives with enhanced bioactivity range. Several new semisynthetic analogs of sipholenone I were generated using chemical reactions. Reaction of sipholenone I with Lawesson's reagent afforded 4-thio-$\Delta^{19,20}$-dehydrosipholenone I. Two sipholenone I semicarbazone derivatives were obtained by its reaction with semicarbazide. Results of bioconversion studies of sipholenol A using three fungal species belonging to the genera *Cunninghamella* and *Mucor* will also be presented. Some of the new analogs show enhanced cytotoxicity. Their activity was comparable with the toxicity of the standard anthracycline antitumor antibiotic doxorubicin.

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OPTIMIZATION OF ANTICANCER MARINE NATURAL PRODUCTS: CHEMICAL AND MICROBIAL TRANSFORMATION STUDIES OF LATRUNCULIN B, SARCOPHINE, AND SIPHOLANE TRITERPENES

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The marine macrolide latrunculin B isolated from the Red Sea sponge *Negombata magnifica* is a potent disruptor of the cytoskeleton protein actin. Our study of a recent collection of the Red Sea sponge *Siphonochalina siphonella* afforded a new cytotoxic sipholane triterpene named sipholenone I, along with the known sipholenols A, and F in a high yield. Sarcophine is an anticancer cembranoid diterpene isolated from the Red Sea soft coral *Sarcophyton glaucum*. Several new cytotoxic semisynthetic analogs of latrunculin B, sipholenone I, sipholenol A, and sarcophine were generated. Results of biocatalysis studies of latrunculin B (using several bacterial isolates cultured from the sponge *N. magnifica*), sipholenol A, and sarcophine will also be presented.

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MICROBIAL METABOLISM OF DIHYDROKAWAIN

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Styryl α-pyrones are considered to be the main pharmacologically active constituents of the South Pacific plant plant, *Piper methysticum* Forst (Piperaceae), commonly referred to as kawa-kawa or kava. It has been used as an intoxicating beverage by the natives. Investigations on kava preparations have indicated the possibility of having analgesic, spasmolytic, neuroprotective and antimitotic activities. Preparations of kava are used in Europe and North America to manage mild anxiety disorders. Chemical investigations have lead to the isolation and characterization of nineteen kavalactones, the most abundant being desmethoxyyangonin, yangonin, dihydrokawain, kawain, dihydromethysticin and methysticin.
As part of our program on microbial transformation studies, the kavalactone, dihydrokawain, was screened using thirty organisms. Several organisms showed the ability to transform but *Rhizopus arrhizus* (ATCC 11145) was selected for the preparative stage as it showed higher transformation efficiency. The metabolites formed were (8*S*)-hydroxydihydrokawain and 3′-hydroxydihydrokawain. They were more polar than dihydrokawain and may hence contribute to the elimination of the parent compound. The absolute configuration of 8-hydroxydihydrokawain was established via a Mosher's ester protocol.

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THE INHIBITION OF PROSTAGLANDIN BIOSYNTHESIS BY THYMOQUINONE: CYCLOOXYGENASE –1 AND -2 IN VITRO ASSAYS

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The seeds of *Nigella sativa* Linn. (*Ranunculaceae*), commonly known as black cumin, are used in traditional medicine all over the world for the treatment and prevention of a number of diseases and conditions that include asthma, inflammation, arthritis, bronchitis and eczema. Recent studies have demonstrated their anticancer, anti-inflammatory, antihistaminic, antibacterial and analgesic activities. Many of these effects are attributed to thymoquinone, which is the main compound of *N. sativa* seed essential oil. In this study, we aimed to determine the *in vitro* inhibition of cyclooxygenase-1 (COX-1) and –2 (COX-2) activities by thymoquinone.
The radiochemical assay was based on the inhibition of COX-1 and –2 catalyzing the biosynthesis of prostaglandin E_2 and D_2, respectively, from [^{14}C] radioactive arachidonic acid. The identity and quantity of the COX reaction metabolites was determined by HPLC performed on C_{18} reversed phase column with an on-line radioactivity flow detector.
IC_{50} values and percentage inhibition of different thymoquinone concentrations were compared with aspirin and indomethacin as positive control samples.
Acknowledgement: This work was financially supported by grant GA CR 525/02/0257, COST 843.10 and Research project Z4 055 905.

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THE ELICITATION OF TAXOID PRODUCTION BY METHYL JASMONATE IN SUSPENSION CULTURES OF YEW (TAXUS BACCATA L.)

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The European yew (*Taxus baccata* L.) is an important source of taxane diterpenoids also known as taxoids, especially of 10-deacetylbaccatin III, which is the precursor of the anticancer drug Taxol® (Paclitaxel) and its derivative Taxotere®. One of the promising methods of the investigation of taxoid production is use of plant cell cultures. The elicitation of the yew cell cultures by methyl jasmonate results in an enhancement of taxoid production. In this work we report a comparison of changes in the production of the main taxoids in elicited and not elicited *T. baccata* cell suspension cultures during the cultivation period.
Concentrations of taxoids were measured in the cultivation medium as well as in cells. Taxoids were identified by HPLC analysis based on LC/MS and UV/PDA. The changes of concentration of the most important taxoids (10-deacetylbaccatin III, baccatin, taxininne M and paclitaxel) were found to differ considerably during cultivation.

Acknowledgment: This work was financially supported by grant AS CR IBS4055301 and Research project Z4 055 905.

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NEW ORSELLINIC ACID ESTERS FROM THE ENDOPHYTIC FUNGUS *CHAETOMIUM GLOBOSUM*

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In our continuing search for anticancer agents from plant-associated microorganisms of the Sonoran desert we have investigated a cytotoxic EtOAc extract derived from the endophytic fungus, *Chaetomium globosum* occurring in the stem tissue of *Ephedra fasiculata*. Bioassay-guided fractionation of this extract afforded three novel orsellinic acid esters, 2-oxo-pent-3-enyl orsellinate (**1),** 2-oxo-3,4-dihydroxypentyl orsellinate **(2)**, and 2-oxo-4-hydroxypentyl orsellinate **(3)** along with orsellinic acid, orcenol, trichodion, aureonitol. Isolation and structure elucidation of **1** – **3** and cytotoxic activities of all compounds in a panel of four sentinel cancer cell lines, NCI-H460 (non-small cell lung), MCF-7 (breast), MIA Ca Pa-2 (pancreatic), and SF-268 (CNS glioma), will be presented.

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LIGNANS, SEROTONIN-PHENYLPROPANOIDS AND ECDYSTEROIDS FROM *LEUZEA CARTHAMOIDES* AND THEIR EFFECT ON INSECT HERBIVORES

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Root extracts from *Leuzea carthamoides* (Willd.) DC., [syn. *Rhaponticum carthamoides* (Willd.) Iljin] have been used in the folk medicine of Siberia, especially for regeneration and stimulation of human physical and mental potency. The plant, endemic to southern Siberia, is now cultivated as a medicinal plant also in Europe. Extracts contain large scale of isoprenoids (sesquiterpene lactones) and polyphenolics (flavonoids). However, the recent reports turned attention mainly towards ecdysteroids, analogues of the insect moulting hormone ecdysone. Roots and seeds became a rich source of ecdysteroids, e.g. 20-hydroxyecdysone, ajugasterone C, makisterone A and a series of their structure analogues (http://ecdybase.org). We used these ecdysteroids, as well as their chemically transformed derivatives, for assessing their insect moulting hormone activity in a bioassay, in which the activity reflects their binding affinity to the ecdysteroid receptor. Large-scale separations afforded discovery of new minor ecdysteroid side chain lactones: leuzeasterone, carthamosterone and their analogues. From the same crude fractions were isolated also dibenzylbutyrolactone lignans: tracheloside, carthamoside and their aglycones, together with new phenylpropanoid conjugates: *cis* and *trans* N-feruloyl- and N-isoferuloyl- serotonins. The chemoecological and/or pharmacological potency and utilisation of *Leuzea carthamoides* attributed to the described compounds will be discussed.

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PIGMENTATION PRODUCING CELLS ASSOCIATED WITH THE APOSEMATIC COLORATION FOUND IN THE ECTEINASCIDIN PRODUCING ASCIDIAN *ECTEINASCIDIA TURBINATA*.

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Bright orange pattern in *Ecteinascidia turbinata* that ascidian predators have learned to avoid is produced by a unique cell type found concentrated in areas vital for the survival and fitness of this colonial ascidian. Concentrated distally, these cells are located in sub ectodermal regions below the animal's tunic occurring densely in the animal's siphons. Surface view of *E. turbinata* shows the orange cells have a central body with cytoplasmic projections that radiate in all directions in the plane of the ectodermal surface. Microscopy of cross cut regions of the oral siphons shows these cells in the areas that lead to muscle layer. TEM of cells show tubular membrane bundles which extend into cellular projections whose origins are associated with the Golgi apparatus. Rough endoplasmic reticulum is actively manufacturing a secretory product modified and packaged in these Golgi regions. These cells are in optimal positions to provide defense against predators.

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INDUCTION OF CYTOTOXIC SESTERTERPENES IN THE MARINE SPONGE, SPONGIA TUBULIFERA

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Spongia tubulifera, a marine sponge found among the fouling community in the Florida Keys, responds to environmental manipulation by up- or down-regulation of secondary biosynthetic pathways leading to a diversity of sesterterpenes. Certain sesterterpenes have been shown to exhibit potent anti-inflammatory and anti-tumor properties. Field experiments were designed to induce this chemical defense system, thereby increasing secondary metabolic diversity. Metabolites were then extracted and analyzed for ecological and pharmaceutical activity.

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DEFENSIVE CHEMICALS IN THE VICEROY BUTTERFLY (*LIMENITIS ARCHIPPUS*) AND ITS LARVAL HOST-PLANT, CAROLINA WILLOW (*SALIX CAROLINIANA*)

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Insects employ an extraordinary array of defenses against predators, including chemical toxicity and protective coloration. A well-known warningly colored butterfly species is the viceroy butterfly (Nymphalidae: *Limenitis archippus*). The viceroy was originally described as a palatable, Batesian mimic of the unpalatable monarch and queen butterfly species. More recent predator bioassay experiments indicated that the viceroy is unpalatable itself, and in some instances, more unpalatable than the monarch or queen. This mimicry system was reclassified as Mullerian where all participants are unpalatable to predators even though the mechanism of viceroy unpalatability was unknown. Many unpalatable butterfly species sequester defensive compounds from their larval host-plants. Viceroy larvae feed on willows, which contain defensive compounds known as phenolic glycosides. No willow-feeding butterfly species is known to sequester these compounds; however, other willow-feeding insects, such as leaf beetles, are known to sequester phenolic glycosides from host-plants to deter predator attack. Using HPLC-MS, we investigated if the adult viceroy butterfly sequesters phenolic glycosides from its larval host-plant, the Carolina willow (Salicaceae: *Salix caroliniana*). We found both the host-plant and the adult viceroy contains four phenolic glycosides: salicin, salicortin, tremulacin, and temuloidin, which are known to have varying degrees of anti-herbivore and/or anti-predator properties.

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PHENOLIC CONSTITUENTS OF *CELOSIA CRISTATA* L. SUSCEPTIBLE TO SPINACH ROOT ROT PATHOGEN *APHANOMYCES COCHLIOIDES*

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The pathogenic and motile zoospores of *Aphanomyces cochlioides* known as a cause of spinach root rot and sugar beet damping-off diseases are attracted to the roots of host plants and establish the infection. The host-specific attractant cochliophilin A (**1**, 5-hydroxy-6,7-methylenedioxy-flavone) has been isolated so far only from host plants, spinach (*Spinacia oleracea*), sugar beet (*Beta vulgaris*) and pigweed (*Chenopodium album*) all belonging to Chenopodiaceae. In the present study, **1** was isolated for the first time from cockscomb (*Celosia cristata*: Amaranthaceae) susceptible to *A. cochlioides*. Together with **1**, the presence of a new isoflavone, 5-hydroxy-6-hydroxymethyl-7,2'-dimethoxy-isoflavone (**2**), and four flavones with an unsubstituted B-ring, 5-*O*-methylcochliophilin A (**3**), 5-hydroxy-7-methoxy-flavone (**4**), 5,7-dimethoxy-flavone (**5**) and 5-hydroxy-6,7-dimethoxy-flavone (**6**) was confirmed in *C. cristata* L. Compound **6** as with **1** showed remarkable attractant activity toward the zoospores.
The structures of the isolates were identified by spectroscopic methods.
The content of cochliophilin A wasdetermined to e *ca*. 7μg/g of the fresh seedlings by ^{1}H-NMR method.

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ANTIFUNGAL ACTIVITY OF MEDICINAL PLANT EXTRACTS TO GINSENG PATHOGENS

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One hundred fifty extracts of medicinal plants were assessed for antifungal activity to several plant pathogens isolated from the lesion of Korean ginseng (*Panax ginseng)* by paper disc method *in vitro.*
Two out of 150 medicinal plant extracts tested had strong antifungal activity against *Cylindrocarpon destructans, Alternaria panax, Botrytis cinerea,* and *Fusarium* sp. They also showed heat (40□ to 100□) and pH(pH 4 to pH 10) stability, respectively.
This result provides an insight that medicinal plant extracts may be used as an effective biochemical fungicide to ginseng diseases. Further results will be discussed.

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ALPHA-PINENE AND LIMONENE, TWO NATURALLY OCCURRING MONOTERPENES AS LEADS FOR NEW INSECTICIDES

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Infectious and parasitic diseases represent a serious health problem in the developing countries. Chagas disease, transmitted mainly by *Triatoma infestans*, is the most important parasitic disease in Latin America and is the cause of nearly 50,000 deaths a year. An estimated 100 million people are at risk in 21 countries and, according to the World Health Organization, 16 to 18 million people are infected.
Former experience has shown that eradication of the insect vectors is one of the best methods to reduce pathogen transmission and prevent the parasitic diseases from spreading.
In a previous work, essential oils from some Bolivian plants have been evaluated as natural insecticides against *Triatoma infestans* and the main terpenes present in the essential oils were also evaluated in order to search for the active components.
Alpha-pinene and limonene, two naturally occurring monoterpenes present in most of the essential oils, showed a low insecticidal activity against these insects. However, when hydroxylation and epoxidation reactions were carried out with these monoterpenes, several products were obtained with an improved insecticidal activity. In this work we report the experimental conditions for the preparation of these compounds, the isolation and structural elucidation and their ovicidal properties against *Triatoma infestans*.

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ON THE TRACK OF HUMAN ODORS THAT ATTRACT MOSQUITOES

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Malaria is spread by mosquitoes, which transmit the parasite *Plasmodium* to humans by biting them. Human odor is an important clue used by mosquitoes in host-seeking. Knowing what attracts mosquitoes would help to take measures against the spread of malaria.
Some techniques of headspace analysis such as the use of adsorbents or solid phase micro-extraction are tools to sample human body odor. Some possible attractants were found by comparing persons with differential attractiveness to *Anopheles gambiae*. The technique of electro-antennography coupled to gas-chromatography is also a good complementary tool for testing the possible biological activity of the odor compounds. Tools and clues are presented in the poster accompanied by a discussion on the challenges that emerged from this research.

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VOLATILES FROM CACTUS HOSTPLANT OF CACTOBLASTIS CACTORUM MOTH

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South American *Cactoblastis cactorum* moth has been established for 70 years in Australia as a successful, introduced biological control of the exotic pest cactus *Opuntia stricta*. *C. cactorum* larvae can quickly destroy certain *Opuntia* cacti species. CO_2 detection at close range by *C. cactorum* was shown by Stange (1997) to influence ovipositioning on a cactus hostplant, *O. stricta*. Biogenic volatile organic compounds (BVOCs) influence long-range hostplant selection and ovipositioning by other moth species, but BVOC influence over *C. cactorum* is unknown. Moreover, little information about cacti BVOCs exists at all.

Solid phase microextraction – gas chromatography mass spectrometry (SPME-GCMS) analysis of *O. stricta* cacti headspace BVOCs revealed candidate chemical cues for *C. cactorum* ovipositioning behavior. Electrophysiological properties of *C. cactorum* olfactory receptor neurons were also determined. Some olfactory receptor cells of female moths are specialized and respond strongly to nerolidol and other terpenes.

A better understanding of *C. cactorum* ovipositioning behavior can support sensible management of this westward-bound pest in North America.

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ESSENTIAL OIL ANALYSIS OF SEVENTEEN EUROPEAN, AFRICAN AND ASIAN *HYPERICUM* L. (CLUSIACEAE) SPECIES

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The essential oil analysis of seventeen (17) species of the economically valuable genus *Hypericum* L. (St. John's Wort; Clusiaceae) native to parts of Europe, Africa and Asia has been conducted. These areas of the world represent particularly rich regions of diversity for the genus. Dried and ground aerial material from flowering plants was subjected to microdistillation to isolate volatile compounds, which were subsequently analyzed by GC/MS. This study represents, to our knowledge, the first report of essential oil constituents for thirteen (13) of these species. For those species where the oils have already been analyzed, our results are compared to those of previous researchers. Several of these species have ornamental, medicinal, or conservation value and are of particular interest from the perspective of phytochemical research. Information gathered from essential oil studies has proved to be of value in chemotaxonomic research. Phytochemical profiles based on qualitative aspects of volatile constituent occurrence vary considerably, and may be useful for distinguishing among species.

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PHYTOCHEMICAL AND BIOSYSTEMATIC INVESTIGATIONS OF NEW AND OLD WORLD *HYPERICUM* L. SPECIES (CLUSIACEAE): SUMMARY OF A THREE-YEAR PROJECT

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Hypericum L. (St. John's Wort; Clusiaceae), a medicinally and ornamentally important genus of nearly 420 species, is distributed in temperate and tropical mountain regions worldwide. The most widely recognized and economically important species is common St. John's Wort (*H. perforatum* L.), which is sold for use in nutritional supplements and botanical preparations in the United States and in medications in Europe. The genus is currently divided into thirty-six (36) taxonomic sections, defined on the basis of morphological features. Phytochemically, *Hypericum* species are of considerable interest and those thus far investigated have been shown to produce a broad range of bioactive secondary metabolites, including terpenoids, fatty acids, steroids, flavonoids, biflavones, xanthones, and anthraquinone and phloroglucinol derivatives. A summary of the results from a three-year dissertation research project involving phytochemical and biosystematic investigations conducted on seventy-four (74) taxa of *Hypericum* is presented. The implications of this research, in terms of systematic relationships among the species and future directions for phytochemical research in the genus, are discussed.

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ACTIVITIES OF *DALBERGIA SAXATILIS* (HOOK, F.) AGAINST PENTYLENETETRAZOLE AND ELECTRICALLY-INDUCED SEIZURES IN MICE

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The aqueous root decoction of *Dalbergia saxatilis* (DS) is used to manage convulsive disorders in African folklore medicine. We have previously reported the anticonvulsant effects against strychnine and picrotoxin seizures, as well as depressant, anxiolytic and muscle-relaxant activities of DS.
In this study, DS was tested against pentylenetetrazole (PTZ) seizures, and electrically- induced threshold tonic extension (TTE) and kindling seizures in mice. In the PTZ model, DS (50, 100, 200 mg/kg) was administered orally to groups of mice, 30 min. before 75mg/kg PTZ and onset to seizures noted. In the TTE test, foot shock was delivered through an electrode before treatment and 1h post- treatment. Electrical kindling was produced twice daily at 48h interval by electrodes, which delivered 2mA, 60HZ (alternating current for 0.2s) in groups of mice divided into three groups in which 200mg/kg of the extract was administered orally, before strychnine thus: - Group I: throughout the 1st-7th kindling; group II: During the 1st-4th; and Group III: during the 5th-7th foot shock. Groups IV and V received 10ml/kg, distilled water and 2mg/kg, diazepam, respectively, instead of DS. Onset to tonic hind-limb extension (THE) was determined, in the kindling experiment.
DS produced a dose-dependent protection against PTZ and elevated the TTE. In the electrical kindling, DS retarded the development and progression of THE, but produced an insignificant delay to THE in kindled mice.
These results indicate that DS might provide protection against generalized absence and partial seizures, which further justifies its use in the management of epilepsies and convulsions in traditional African medicine.

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THE CONSTITUENTS OF THE RHIZOMES OF *ZINGIBER OFFICINALE* AND THEIR BIOLOGICAL ACTIVITY

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The rhizomes of *Zingiber officinale* Roscoe is one of well known spices in the traditional Chinese medicine as stomachic, antiemetic, antidiarrheal, expectorant, antiasthmatic, hemostatic and cardiotonic for the treatment of several gastrointestinal and respiratory diseases. In the course of our continuing research for novel biologically active compounds from natural sources, screening work for thrombolytic and vasorelaxing activity was carried out. The ether extract of the rhizome of *Z. officinale* was found to show antiplatelet aggregation activity and produce a vasorelaxing effect. Bioassay-directed fractionation led to the isolation and characterization of four new compounds, [6]-dehydrogingerol (**1**), *O*-methyldehydrogingerol (**2**), gingernal (**3**), and methyl dihydroferulate (**4**), as well as twenty-five known compounds **5**-**29**. Compounds **7**, **8**, **13**-**15**, **17** and **18** at 0.2-1 μg/mL exhibited the most potent inhibition (61−100 %) of the rabbit platelet aggregation induced by arachidonic acid (100 μM). All of the test compounds showed 50 % inhibition of rat aorta tonic construction induced by high K^+ (80 mM) at 30−100 mg/mL.

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SCREENING OF HIV-1 INHIBITION FROM MEXICAN CLUSIACEAE AND ISOLATION OF CALANOLIDES FROM *CALOPHYLLUM BRASILIENSE* LEAVES

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The organic plant extracts from the leaves of the 21 species of Clusiaceae that thrive in Mexico were screened for anti HIV-1 reverse transcriptase activity in a non-radiactive immuno colorimetric assay. The extracts of 5 species (23.8%) exhibited significant inhibition (≥70%) of HIV-1 RT activity, but only 4 extracts showed reduced toxicity to human lymphocytic MT2 cells and were further tested as inhibitors of HIV-1 IIIb/LAV replication in a cellular system. The best extract was *Calophyllum brasiliense* (hexane) which inhibited HIV-1 RT (IC_{50}= 29.6 μg/ml), and showed an EC_{50}= 92.5 μg/ml, on MT2 cells. This extract also showed significant inhibition on viral replication (ED_{50}= 37.1 μg/ml). Further bioguided fractionation of this extract, lead to the isolation of three anti HIV-1 dipyranocoumarins: calanolide A, B, and soulttrolide. Other isolated compounds from *C. brasiliense* such as apetalic acid, isoapetalic acid, a structural isomer of isoapetalic acid, friedelin, canophyllol and amentoflavone were devoid of HIV-1 RT inhibitory activity. Calanolide C was also obtained as a natural product and showed moderate inhibitory properties. This is the first time that calanolides are obtained from the leaves from a Neotropical *Calophyllum* species.

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NEW COUMARINS AND AN ISOEUGENOL DERIVATIVE FROM *PELARGONIUM SIDOIDES*

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Pelargonium sidoides DC (Geraniaceae) is a popular medicinal plant in areas of southern Africa and highly valued by traditional healers and the native population for its curative properties (1, 2). For example, the roots are employed to cure infections of the respiratory tract and gastrointestinal disorders, while the aerial parts of this species are used for the healing of wounds. In contrast to the roots, little information is available of the constituents of the aerial parts.

An acetone-water extract (4:1) of the aerial parts of *P. sidoides* was subjected to a polarity fractionation using dichlormethane, ethylacetat and *n*-butanol successively. Subsequent separation of the ethylacetat soluble extractives by a combination of chromatographic techniques led to the isolation of 4-allyl-2,5-dimethoxyphenol-1-O-β-glucopyranoside, a new natural product, accompanied by taxifolin-3-β-glucopyranoside and dihydrokaempferol-3-β-glucopyranoside, the latter being reported from this source for the first time. The structures of these compounds were established from spectroscopic (EI-, FAB-MS, 1H-, 13C-NMR, HETCOR, 1H,1H-COSY, optical rotation) studies.

From the *n*-butanol fraction, three coumarin derivatives were obtained. Although magnolioside (7-methoxycumarin-6-β-glucopyranoside) and fraxetin-7-β-glucopyranoside represent known compounds, their occurrence in plants is rare and the reported spectroscopic data for fraxetin-7-β-glucopyranoside appear critical (3). Most notably among the identified coumarins is 6,7-dihydroxycumarin-8-sulfate, extending the series of the small group of naturally occurring sulfated analogues. That the wealth of coumarins so far found in this plant source is expanded by the characterization of additional coumarins is highly remarkable.

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ALKALOIDS WITH CHOLINESTERASE INHIBITORY ACTIVITY

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The Ellman method, using spectrophotometry and also applied to TLC detection, was used to monitor acetylcholinesterase inhibitor activity in extracts of traditional Korean and Nigerian plant medicines reputed to be useful for memory enhancement in old age. Activity was found in the alkaloidal portion of the methanolic extracts of *Epimedium koreanum* from Korea and *Crinum jagus* and *C. glaucum* from Nigeria. Bioassay-guided fractionation led to the isolation of a novel aporphine alkaloid related to magnoflorine, with IC_{50} of 3.1μM (physostigmine = 0.25 μM). Similar work on *C. glaucum* yielded four alkaloids of which the most active was hamayne (IC_{50} 250 μM) whilst *C. jagus* gave only haemanthamine which was not very active . This is the first report of alkaloids from *C. jagus* and the first report of cholinesterase properties for the four alkaloids isolated from these two *Crinum* species.

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MANIPULATING REACTION-INDUCED SHIFTS FOR DIFFERENCE SPECTRO-PHOTOMETRIC ESTIMATION OF VARIOUS NATURAL PRODUCTS CALSSES

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Difference spectrophotometry (**DS**) detects very small changes in a chromophore environment. Proper manipulation of experimental DS techniques ensures interference cancellation and minimizes prior fractionation-purification steps. The Author *et la* elaborate on alternative DS technique and develop simple specific assay procedures for various natural products classes.
Studied Classes: **I**). Alkaloids (morphine, codeine, narceine, colchicine, reserpine, yohimbine). **II**). Flavonoids (rutin, hesperidin, quercitin). **III**). Sesquiterpines (santonin, judaicine). **IV**). Coumarins (xanthotoxin, imperatorin). **V**). Resins and balsamic acids (benzoic, cinnamic). **VI**). Chromones and hemilignans (khellin, and arctiin).
DS Alternatives; **(1)**. Shift reagent DS ($AlCl_3$, CH_3COONa, CH_3ONa, etc.). **(2)**. $_PH$-induced DS; (acid or neutral vs alkaline or neutral). **(3)**. Reactions-induced DS (compound vs reaction products; saponification of esters, cleavage of lactones, coupling ...etc).
Figures of DS are given, manipulation of maxima, minima, isosbestic points and amplitudes to cancel irrelevant absorption and determine optimum measurement wave lengths are all discussed.

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THE GC-MS ANALYSIS OF THE HEXANE EXTRACT FROM BARK OF *JUNIPERUS BREVIFOLIA*

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Because of its geographic position, Azores becomes very interesting as a potential source of new compounds with biological activity. One of these sources can be the *Juniperus brevifolia* (Cedro do mato). This species is the only conifer endemic from Azores and it has been traditionally used in shipbuilding. The dichloromethane extract from leaves and core of *J. brevifolia* exhibited a significant citotoxic activity against some human tumour cell lines HeLa and Hep-2.
Pursuing our work on the study of this plant, we decided to study the hexane extract of the bark of *J. brevifolia*. This extract was submitted to a GC-MS analysis, before and after alkaline hydrolysis, in order to analyze free and esterified components. The results showed that their constituents were essentially diterpenoids mainly abietane- and pimarane-type compounds, fatty acids and sterols. The quantitative analysis was carried out and showed that 6,7-dehydroferruginol (16.5 %) and totarol (24.7%) are the major components of the extract followed by sitosterol (5.6%). Fatty acids occurred mainly as esters of long chain alcohol (eicosanol) and diterpenes.Detailed results will be presented and discussed.

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MOLECULAR SYSTEMATICS OF EUODIA AND THE SUBFAMILIES RUTOIDEAE AND TODDALIOIDEAE IN RUTACEAE

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Classifications properly portraying the phylogenetic relationship of plants would help guide the search for leads for bioactive components from related taxa. The genus *Euodia* (Rutaceae) is a good example. DNA sequences of chloroplast *trnL* intergenic spacer region of 37 species belonging to 14 genera were analysed. The results, in good agreement with conclusions from morphological and chemical studies, demonstrated that *Euodia* is not monophyletic and its members should be placed in three genera: *Euodia*, *Melicope* and *Tetradium*. The phylogenetic trees so constructed also suggested that subfamilies Rutoideae and Toddalioideae established by Engler should be merged into one. Further analyses of other DNA regions indicated that the sequence differences would help in the authentication of herbal products derived from *Tetradium ruticarpum* and distinguishing them from those derived from adulterants and substitutes.

Partial support was received from Hong Kong Jockey Club Institute of Chinese Medicine.

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FASTER PLANT DRUG IDENTIFICATION USING DATA BASE OF CLASSICAL PHARMACOGNOSY AND MODERN ANALYTICAL TOOLS

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Drug identification is the main stay in quality control of herbal drugs more so with closely related species. Data of classical pharmacognosy combined with modern analytical techniques gives a faster identification and also give new leads.

From a data of classical pharmacognosy of 15 authenticated spices of genus *Cassia* containing anthraquinones used in ethenobotany- photo documentation,morphological and microscopical and chemical characters of leaves, fruits and seeds in combination with HPTLC finger prints, protein analysis by PAGE presented with reference to *C.obtusifolia* and C.*tora* are presented

Few differences from the data give a faster identification and when combined with modern analytical tools give a surer identification. Results presented.

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DETECTION OF CYTOTOXIC ACTIVITY OF ACTINOMYCETES ASSOCIATED MARINE INVERTEBRATE FROM PERSIAN GULF

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The purpose of this study has been screened the actinomycetes with cytotoxic activity which has been isolated of marine invertebrate such as corals , sponges and tunicates in the Persian Gulf.The results of this study show that the actinomycetes counts have been only 2.1% of total isolated bacteria .The majority of the isolated geneus were belong to type I actinomycetes.Cytotoxic activity has been studied with MTT assay .The 14.75% of marine actinomycetes cultures displayed cytotoxic activity on human epidermis carcinoma cells(KB) and breast carcinoma (MCF-7).The 3.8% of isolated marine actinomycetes cultures display cytotoxic activity IC50 below 5 $\mu g\ ml^{-1}$ .These results indicate that marine symbiotic actinomycetes associated tunicates ,corals and sponges from warm waters is the small group of isolated bacteria but these small group have a good therapeutic potential and they could be use as a source for cytotoxic agents in order to applied in the experimental discovery antitumor activity.

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PHYTOCHEMICAL INVESTIGATION OF THE VOLATILE CONSTITUENTS OF LEAVES OF *JUGLANS NIGRA* L. CULTIVATED IN EGYPT

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Juglans nigra L. is a large tree grown mainly in Eastern United States, North Africa, East Asia and cultivated in Egypt. The plant is used in folk medicine as antihypertensive, antidiabetic, for eczema, syphilis, astringent and anthelmintic.

The volatile constituents of the fresh leaves were prepared by hydrodistillation, analysed by GC/MS. The detected peaks were identified by their mass spectral data on the basis of computer-feed system and comparison of their fragmentation patterns with those reported in literature. Further confirmation was done by comparison reported retention indices. From the fourty three components, thirty components were identified representing about 73% of the total volatile content. The most abundant constituents were found to be 3-Hexen-ol (Z), Octanol and Dibutyl phthalate (8.5, 21, 8.8% respectively).

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ANTIMICROBIAL CONSTITUENTS OF THE THOMPSON SEEDLESS RAISINS (*VITIS VINIFERA* L.) AGAINST SELECTED ORAL PATHOGENS

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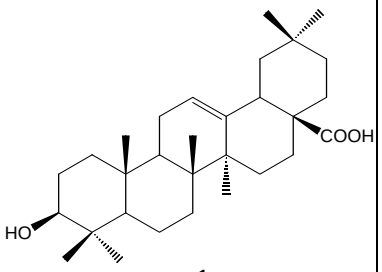
In a continuing effort to identify plant-derived antimicrobial compounds against oral pathogens, bioassay directed fractionation of the hexane-soluble fraction of the methanol extract of the Thompson seedless raisins (*Vitis vinifera* L.) yielded eight known compounds: oleanolic acid (**1**), oleanolic aldehyde, linoleic acid, linolenic acid, betulin, betulinic acid, 5-(hydroxymethyl)-2-furfural, and β-sitosterol. From the EtOAc-soluble fraction rutin and β-sitosterol glycoside were isolated. The structures were established by spectroscopic methods. In an attempt to increase the resultant antimicrobial activity of **1**, a series of acylation and etherification reactions were performed on compound **1**. The antimicrobial activity of all the isolates except β-sitosterol and β-sitosterol glycoside and the chemical transformation products were evaluated for their potential antimicrobial activity utilizing *Streptococcus mutans* and *Phorphyromonas gingivalis*. Compound and its derivatives showed moderate antibacterial activity against *S. mutans* and *P. gingivalis* with minimum inhibitory concentration (MIC) values ranging froμ 7.8 to 1000 μg/ml and 3.9 to 1000 mg/ml, respectively. (Supported by the California Raisin Marketing Board)



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ANTIMICROBIAL ACTIVITY OF *JATROPHA CURCAS* L. AND *JATROPHA MULTIFIDA* L. AGAINST BACTERIA S.T.D. ORGANISMS

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Jatropha curcas and *Jatropha multifida* are ornamental, multipurpose shrubs belonging to the Family Euphorbiaceae. They are grown in home gardens in West Africa. Many Jatropha plants have toxic and irritant properties and are used in folklore medicines in Africa, Asia and Latin America. Phytochemical and bioactivity studies of these plants have yielded many bioactive compounds including diterpenoids and alkaloids. As part of the continuing investigation of the biological activity of Jatropha species, the extracts of the title plants were screened against microorganisms responsible for bacteria sexually transmitted diseases. The methanolic extracts of the stem and root of both plants displayed potent activity against Gardinella sp., *Klebsiella* sp., *Candida albicans* and *Neissera gonorrhea*.

Phytochemical screening of the extracts revealed the presence of terpenoids, alkaloids and saponins. Fractionation to isolate the active constituents of the extracts is in progress. Details of the bioassay and isolation of the active constituents will be reported.

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PHYLOGENETIC PLANT PEPTIDE SELECTION

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Selection of plant material in medicinal investigations usually relies on information from traditional use or chemosystematics. Both strategies have their disadvantages. Traditionally used plants often contain known compounds and thus require dereplication to produce new and interesting compounds, and extensive nuctleotide sequencing followed by sophisticated analysis has proven most chemosystematic systems to be corrupt.

In our work with biologically active, small peptides we propose ways to carry out a fast preselection that minimize time spent on dereplication as well as confirming or rejecting supposed relationship between plant species and genera.
By using PCR to screen for the gene correlating to the peptide three advantages are reached:
1) the probability of presence of peptide is asserted,
2) the primary structure of the peptide becomes apparent, and
3) the strategies of isolation can be directed to minimize the need for dereplication.

Further advantages with using this screening based on genetic features are the minimal amount of plant material needed for screening, and that molecular engineering can be used to provide large amounts of peptides for biological testing.

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A NEW GLYCOPEPTIDE FROM *CHOLCHICUM SPECIOSUM* (L.)

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Out of 50% EtOH extract of the corms of *C. speciosum* population Asalem – Khalkhal, a glycopeptide isolated and hydrolyzed in 6 N HCl. The hydrolyzed was subjected to JEOL amino acid analyzer for physiological fluid system. Three peaks were recorded which were not corresponded to any protein amino acids: γ-amino-n-butyric acid, pipecolic acid, glucose amine. In our research no glycopeptide was found containing these compounds in addition to protein amino acids.
In elementary pharmacological studies, we found, in spite of the reported toxicity of the corms being due to its alkaloids content, injection of 1 mg of the glycopeptide causes sleepiness on rats, and death after 24 hrs. Injection of 10 mg of the glycopeptide causes death in 2-3 hrs.

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PHARMACOLOGY OF *SOPHORA SECUNDIFLORA*

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S. secundiflora or mountain laurel, mescal beans has been used by Indians as a hallucinogen. The alkaloid extract of the seeds was not toxic to rats. The free amino acid extract also had no visible effects. However, the mixture of the two caused death by tonic and colonic.
The free pipecolic and 4OH-pipocolic acids found in the seeds can cause the reaction.
We discuss how the mechanism of the mixture may work.
It has been shown the above-mentioned compounds, decarboxylate at the present of brain and kidney homogenates, producing Strongly basic compounds : Piperidin, 4-OH-Piperidin.

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THE EFFECT OF ULTRAVIOLET LIGHT ON FLAVONOLS FROM THE CACTI *OPUNTIA WILCOXII* AND *O. VIOLACEA*

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Prickly pear cacti are common succulents indigenous to the southwestern United States, where they are commonly employed in desert-style landscaping and consumed as foodstuffs. The outer stem tissues contain flavonoids, which are thought to protect plants from detrimental effects of UV light. Mature samples of *O. violacae* exposed to natural solar light were found to contain statistically equivalent amounts of flavonols as those examples grown in UV-depleted solar light. Mature and young samples of *O. wilcoxii* grown in solar light were found to contain more flavonols than those grown in UV depleted light. Ground (inner) tissue cells for both species were found to possess little to no flavonols. A new flavonol glycoside, isorhamnetin 3-O-[2"-α-L-rhamnopyranosyl-3"-β-D-glucopyranosyl]-β-D-glucopyranoside, was isolated from the outer tissues of *O. violacae*.

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MOLECULAR AUTHENTICATION OF THE HERB *RADIX STEMONAE*

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The Chinese herb Radix Stemonae (Baibu), according to the Pharmacopoeia of the People's Republic of China, comes from the dried root tuber of Stemona japonica, S. sessilifolia and S. tuberosa. It is an antitussive for "moistening the lung" and "relieving cough." Roots of Asparagus species are frequently found as adulterants of Radix Stemonae in Yunnan Province. DNA sequences of the 5S ribosomal DNA spacer and of chloroplast matK and trnL regions of four Stemona species (Stemona japonica, S. parviflora, S. sessilifolia, and S. tuberosa) and of Asparagus filicinus were analyzed and found useful for differentiating the five taxa from one another. These molecular markers could be used for her authentication for Radix Stemonae.

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THE COMPOSITION OF ESSENTIAL OILS FROM VARIOUS PARTS OF THREE SUBSPECIES OF *PIMPINELLA TRAGIUM* VILL.

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Essential oils from fruits, aerial parts (without fruits) and roots of three subspecies of *Pimpinella tragium* Vill.; subsp. *lithophila* (Schischkin) Tutin, subsp. *polyclada* (Boiss. & Heldr.) Tutin, subsp. *pseudotragium* (DC.) Matthews growing in Turkey were examined by GC/MS. The composition of the essential oils showed differences. Geijerene (23%-32%) was the main compound in the essential oils from three different parts of *P. tragium* ssp. *lithophylla*. (*Z*)-β-Farnesene and epoxy pseudoisoeugenol-2-methyl butyrate were the major components in the essential oil of fruit and aerial part of *P. tragium* ssp. *polyclada* (57%, 23 and 20%, 22%, respectively), whereas 4-methoxy-2-(3-methyloxiranyl)-phenyl angelate (40%) was found as major component in the root oil. The fruit oil of *P. tragium* ssp. *pseudotragium* contained α-pinene (16%) and β-bisabolene (19%) as major components. β-Pinene (31%) was the major compound in the essential oil of aerial parts. In the root oil 4-methoxy-2-(3-methyloxiranyl)-phenyl angelate (31%) and epoxy pseudoisoeugenol-2-methyl butyrate (19%) were the major components.

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PRELIMINARY RESULTS ON THE IDENTIFICATION OF BIOLOGICALLY ACTIVE METABOLITES OF THE TROPICAL MEDICINAL PLANT *ELAEOPHORBIA DRUPIFERA* USING GC-MS AND FTICR-MS TECHNIQUES

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Elaeophorbia drupifera (Thonn) stapf. is a common tree found in tropical regions of the world, and grows in the coastal plains and occasionally in closed forests. The plant grows to a height of above 15.3 metres with still branches and slightly spiny branchlets. It has a grey bark and produces copious amounts of white latex when cut. Previous workers report that the crude extracts of *E. drupifera* showed significant *in vitro* anti-tumour activities involving a panel of solid tumours of human origin (lung and colon) and the P-388 lymophocytic leukemia system. Lethality studies with crude extract prepared from the roots of *E. drupifera* in mice by other workers showed a dose-mortality relationship with an LD_{50} of 145 mg/kg mice. The extract (2-260 µg/kg) was tested in graded doses on the blood pressure and heart rate of urethane anaesthetized rats. The results showed that the extract decreased both the blood pressure and heart rate in a dose-dependent manner. They conclude that the crude extract from the roots of *E. drupifera* probably contains acetylcholine-like agent(s), which interferes with the cholinergic mechanism, as well as catecholamine-like agent(s) exhibiting mainly alpha-adrenoceptor activity.

The goal of this project was to isolate and characterize the metabolites of *E. drupifera* with putative biological activity. Preliminary phytochemical screening of the dried leaves of *E. drupifera* revealed the presence of alkaloids, saponins (steroids and triterpenoids), glycosides, phenolic compounds other than tannins, but the absence of flavonoids, anthraquinones, tannins and cardiac glycosides. The use of FTICR-MS complimented by GC-MS methods enabled us to detect over 400 unique metabolites of which a substantial number were known. The technology involved in the mining of the data would be explained and the implications of the findings will be discussed.

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HIGH YIELD OF ARTEMISININ FROM *ARTEMISIA ANNUA* GROWING IN EGYPT

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From seeds provided by the Institute of Materia Medica, Shanghai, China, the herb *Artemisia annua* was cultivated in Kaha province, Egypt, where the climatic conditions are belonging to the temperate zone. The content of artemisinin during the vegetative period was monitored. The influence of different fertilizer treatments, including farm yard manure (organic), biofertilizers, and NPK fertilizer, was also studied. The highest level of artemisinin (0.80 % dry wt) was found in the leaves during the pre-flowering stage (5-month old plants). This value comes next to the Vietnamese cultivar (0.86 % dry wt), which is the highest in the world. In the following stage (predominantly inflorescences, 6-month old plants), the content decreased to 0.70 % dry weight, and a minimum content of 0.1 % dry wt was found during the following months. In contrast to a previous report, the artemisinin crystals isolated from plants collected in the pre- and during the flowering stages, in addition to the crude extracts showed no detectable amounts of the clinically undesirable artemisitene(HPLC). The highest yield of artemisinin was obtained from plants treated with the organic fertilizer. The content of the other bioprecursors, such as artemisinic acid and arteannuin B, was also determined. All the analyses were conducted by a published HPLC method with pre-column derivatization.

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A NEW OLEANANE GLYCOSIDE FROM *ASTRAGALUS CAPRINUS*

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Astragalus caprinus Maire (Fabaceae), is an endemic plant of North Africa, used in Tunisian traditional medicine to treat hemorrhoids. One saponin was previously isolated from the roots and characterized as a cycloartane-type triterpene glycoside.
We describe in this work the isolation of a novel oleanane-type triterpene saponin with two know molecules, soyasapogenol B and astragaloside VIII. Their structural elucidation was performed mainly by 2D NMR techniques (COSY, TOCSY, NOESY, HSQC, HMBC) and mass spectrometry. The new saponin was determined as 3-*O*-[α-L-rhamnopyranosyl-(1 2)-ß-D-glucuronopyranosyl]-22-*O*-ß-D-apiofuranosyl-soyasapogenol B.
These results corroborated those which described soyasapogenol B as a taxonomic marker of the Fabaceae family.

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FERULA GUMOSA: PHYTOCHEMICAL VARIABILITY IN IRAN

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Ferula gummosa is an endemic species of Iran. Its resin, referred to in the book of Exodus as galbanum, has antispasmodic, carminative, expectorant and stimulant properties. It is primarily used in the treatment of spasmodic conditions of the respiratory and digestive systems. The essential oil is used extensively in perfumery. Galbanum is frequently adulterated. Currently, five times more resin is offered for sale on the European market than is actually collected in Iran. Our project was aimed at extending our understanding of the phytochemical variability to facilitate identification of typical adulterants.
Georges Betti took numerous samples of strictly identified specimens of wild populations of *Ferula gumosa* in three Iranian geographic zones with distinct differences in geology and climate: Khorassan, Elburz and Zagros. The samples were analysed by the Centre National de Recherche Scientifique. The analytical data was correlated with origin and chemotype, as well as the analytical profiles of typical adulterants such as *Ferula asa-foetida* or *Dorema amoniacum*. More than 160 phytochemical components, including some not previously described, were identified in galbanum. The results of our work underline the importance of traceability.

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A TRIP THROUGH THE KUWAITI DESERT – SOME PHYTOCHEMICAL HIGHLIGHTS

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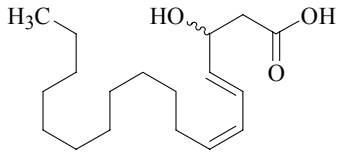
The flora of Kuwait consists of approximately 400 naturalized vascular plants, many of which occur in wadis, notably the Wadi-Al-Batin, which is a series of interconnecting dry river beds that run in a north easterly direction along the Kuwait-Iraq border. Some species are salt and heat tolerant and survive the July and August months when temperatures regularly exceed 50°C. We have been characterizing natural products of certain taxa and new sesquiterpenes from *Pulicaria crispa* (Asteraceae), and a new antibacterial hydroxy fatty acid (**1**) from *Scrophularia deserti* (Scrophulariaceae) have been isolated. Compound **1** had minimum inhibitory concentrations of 32 μg/mL against four species of mycobacteria, and 32 μg/mL against a strain of multidrug-resistant (MDR) *Staphylococcus aureus*. This paper discusses the phytochemistry and antibacterial activity of these Kuwaiti desert plants.



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ANTIOXIDANT ACTIVITY AND EPICATECHIN CONTENT OF EIGHT CULTIVARS OF TARO (*COLOCASIA ESCULENTA*)

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The edible corms of eight taro (*Colocasia esculenta*) cultivars were extracted in methanol and analyzed by high performance liquid chromatography coupled with a photodiode array and selected ion mode mass spectrometry (SIM LC-MS). Epicatechin was detected in all cultivars and quantified by SIM LC-MS. Extracts were also screened for antioxidant activity using the 1,1-diphenyl-2-picrylhydrazyl (DPPH) assay. There was wide variation in both antioxidant activity (IC_{50} = 26.64 µg/ml to 131 µg/ml) and (-)-epicatechin content (6.9 mg/100g to 36.6 mg/100g). Anthocyanins and other flavonoids were also detected. The antioxidant activity is believed to be the result of a complex mixture of antioxidant polyphenolic compounds present in the extracts.

This work was supported by the American Society of Pharmacognosy undergraduate research award and the Minority Access to Research Careers program, NIH-SCORE award S06GM008225.

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SAFROLE CONTENT OF A TRADITIONAL MICRONESIAN TEA

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Cinnamomum carolinense is endemic to the Caroline Islands in the South Pacific, where it has long been used to make a medicinal tea and refreshing hot drink. The bark is harvested from trees located on the volcanic mountains of the island and brewed to make the drink. Safrole is a known carcinogen found in many species of *Cinnamomum*. No previous phytochemical studies of this plant have been published, and there were fears that habitual consumption of the tea could be dangerous to human health. HPLC-PDA and LC-MS analyses confirmed the presence of the carcinogen in alcoholic extracts of *C. carolinense* bark shavings, but safrole was not detected in the tea. The preparation method may degrade the safrole.

This work was supported in part by NIH-SCORE grant S06GM008225. K.A. Reynertson is supported by NIH-NCCAM NRSA F31AT000801.

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APOPTOTIC ANTICANCER EFFECT OF ALVARADOIN E ISOLATED FROM *ALVARADOA HAITIENSIS*

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Anthracenone *C*-glycoside alvaradoins E isolated from the leaves of *Alvaradoa haitiensis* Urb. (Simaroubaceae) was found to have potent inhibitory activities with cultured cancer cells and with *in vivo* hollow fiber model. With a DAPI assay, treatment of LNCaP cells with alvaradoin E showed chromatin condensation, a morphological characteristic of apoptosis. Mitochondrial membrane potential, analyzed with a $DiOC_6$ uptake assay, showed dose-dependent membrane depolarization caused by alvaradoin E treatment. Also, with an annexin V-FITC assay system, treatment of HL-60 cells with 0.07 μM alvaradoin E for 24 h increased annexin V-FITC binding from 3 to 25.9%. Finally, with the TUNEL assay system, treatment of HL-60 cells with 1.12 μM alvaradoin E for 32 h increased FITC-dUTP binding for 10-fold. These data suggest alvaradoin E to be an effective anticancer agent that induces apoptosis. Support of this work was provided by grant U19 CA52956, funded by the National Cancer Institute.

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PHYTOCHEMICAL INVESTIGATION OF *MAGNOLIA BIONDII* PAMP. (FLOS MAGNOLIAE, XINYI), A TRADITIONAL CHINESE MEDICINAL PLANT

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Flower buds of *Magnolia biondii* Pamp., *M. sprengeri* Pamp. and *M. denudata* Desr. (Flos Magnoliae, Xinyi; Magnoliaceae) are listed in the Chinese pharmacopoeia for their use as remedies against headache and nasal obstruction in colds, sinusitis and catarrh. Flos Magnoliae is usually administered in combination with e.g. the roots of *Angelica dahurica* (Radix Angelicae) or with *Mentha piperita* (Herba Menthae). Many more biological activities have been reported from Flos Magnoliae such as hypotensive activity, antimicrobial activity and TNFα-inhibitory activity.

The flower buds contain mainly essential oils and tetrahydrofurofuran lignans. In our investigation, a thorough analysis of the dichloromethane extract of the flower buds of *M. biondii* was carried out as well as an analysis of the essential oil. The lignans epimagnolin and epieudesmin are described for the first time to occur in this plant as well as the sesquiterpenes parthenolide and oplodiol.

The results of a TLC fingerprint analysis for differentiation between *M. denudata*, *M. liliflora* and *M. biondii* are presented as well.

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FARINA AND EXUDATE COMPOSITION IN SOME SPECIES OF *PRIMULA* L. SECT. *AURICOLA* DUBY

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The aim of this work is to give a phytochemical and a morphological contribution to the taxonomy of the genus *Primula*, sect. *Auricula*.
For the first time it has been investigated the composition of farinose and fluid exudates on leaf and flower surfaces.
The morphological analysis has been made by OM and SEM. Exudates and farinas are connected to trichomes, glandular secreting type, consisting of an unicellular head supported by a long stalk and a rectangular shaped neck. As a result there is a great intraspecific variability in morphology, size and dimensional ratio of the 3 elements of the trichomes. At SEM, farinas appear disposed around the gland of each trichome and made of needle shaped material, randomly extruded
The phytochemical analysis has been realized plunging the leaves into the n-hexane. The extract obtained has been dried and chromatographed with HPLC. The compared analysis of farinose exudates, showed the presence of 4'-idrossiflavone both in *P. auricula* and in *P. albenensis*. A different composition of the exudates of *P. daonensis* and *P. hirsuta* was found.

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PARALLEL EXTRACTION OF LICHEN COMPOUNDS

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Lichens contain specific and original compounds which have been poorly investigated for their biological activities.

As extraction is a crucial step in this investigation, various conditions (solvent, temperature, time…) were compared using a semiautomated reactor (Syncore® Reactor) [a] originally designed for combinatorial chemistry. The main advantages of such an approach are simplicity, efficacy, and reproducibility in a very short time for multiple experiments.
Indeed, this apparatus allows extraction, filtration and evaporation of 24 samples run simultaneously in a few hours, and therefore a fast selection of the most appropriate conditions of extraction for a given lichen, a class of compounds or even a lichen compound.
To perfect these High Throughput experiments, a well known lichen, the Iceland moss, *Cetraria islandica* (L.) Ach. was extracted. Sixty conditions were carried out and results were analyzed with TLC and/or HPLC.
This process will be an interesting tool for parallel extraction and biological screening and would be suitable for crustose lichens which are available in very small amounts.

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APPLICATION OF LC-SPE-NMR IN THE IDENTIFICATION OF LIGNANS IN *PHYLLANTHUS URINARIA* AND *P. MYRTIFOLIUS*

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Several novel lignans from *Phyllanthus urinaria* L. and *P. myrtifolius* M. (Euphorbiaceae)[1-3]. Of these, phyllamyricin B and retrojusticidin B have been demonstrated to have a strong and selective inhibitory effect on HIV-1 reverse transcriptase[4].

To accelerate the research speed in identifying bioactive lignans, an efficient and practical methodology should be developed. Application of LC-SPE-NMR hyphenated technique in analyzing lignans present in these plants were undertaken. An LC system with good resolution for lignans in *P. urinaria* and *P. myrtifolius* were developed. In the process of these experiments, several problems of using this technique, such as solvent suppression, peak trapping, and cartridge drying, were solved. This technique is demonstrated to be an efficient and powerful method in structural determination of each compound using minute amount of plant material.

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TROPANE ALKALOIDS FROM THE SOUTHAFRICAN PERENNIAL HERB *FALKIA REPENS* (CONVOLVULACEAE)

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Tropane alkaloids are characteristic secondary metabolites in species of many convolvulaceous genera (e.g. *Convolvulus*, *Merremia*). This applies to classical more or less lipophilic tropanes as well as to calystegines, hydrophilic nortropane derivatives. In the present study *Falkia repens* L.f., a member of the tribe Dichondreae s.l., already known as calystegine-positive, has turned out to contain a broad profile of lipophilic alkaloids as well, mainly tropan-3-ol esters. From the roots and rhizoma 3α-acetoxy-, 3α- and 3β-(2-methylbutyryl)oxy-, 3α- and 3β-*trans*-feruloyloxytropane, and furthermore tropan-3-one and 3β-tropanol were isolated. Their structures were elucidated by means of ^{1}H-NMR, H-H-COSY, ^{13}C-NMR, EI-MS, and HR-MS measurements. Moreover, several minor alkaloids could be characterized by GC-MS data. This is the first report on the occurrence of lipophilic tropane alkaloids in the tribe Dichondreae s.l..

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PHENETIC ANALYSIS OF FOUR SPECIES OF *CASIMIROA* (RUTACEAE)

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The small genus *Casimiroa* Llave et Lex. (Rutaceae) comprises only 10 species and grows on the tropical and subtropical areas of Central America and Mexico
Due to its commercial value and its putative medicinal properties *C. edulis* is the most extensively studied species. However, there is a great deal of confusion on the taxonomic situation among *C. edulis* and *C. sapota*.
In order to clarified this situation we determine the interspecific variation of the coumarins presented in 34 individuals of *C. edulis*, 12 of *C. pubescens*, 8 of *C. calderoniae* and 8 of *C. sapota* by HPLC. These data, along with the morphologic data, were used to assemble a qualitative and quantitative database for these species and used for ordination analyses using NTSYS.
The results showed that the four species analyzed could be delimited in four different groups, although *C. edulis* and *C. sapota* are very close taxa.

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CHEMOTAXONOMIC SIGNIFICANCE OF FLAVONES IN *CASIMIROA* (RUTACEAE) AND ANTI-INFLAMMATORY ACTIVITY OF 5,6,2',3',4'-PENTAMETHOXYFLAVONE

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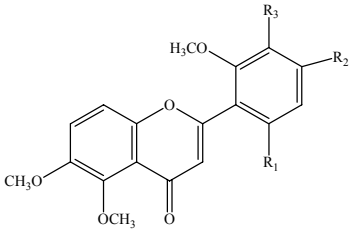
As part of our ongoing investigation on biologically active compounds from Mexican plants and specially from *Casimiroa* genus, now we wish to report the isolation of zapotine (**1**) and 5,6,2',3',4'-pentamethoxyflavone (**2**) from seeds of *Casimiroa pubescens* Ram. (Rutaceae).
The presence of these two compounds is in total agreement with previous studies from species of this genus. Furthermore, it seems that the 5,6-disubstituted flavone-type is a chemical characteristic of the genus.
On the other hand, **2** showed a doses-dependant anti-inflammatory activity in the ear edema-induced by TPA test.



1: R_1= OCH_3, R_2= R_3H

2: R_1= H R_2= R_3OCH_3

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THE SKIMIWALLINOLS, MINOR COMPONENTS OF THE EPICUTICULAR WAX OF COCOS NUCIFERA. Gloria Arvizu-Méndez, Fabiola Escalante-Erosa, Luis M. Peña-Rodríguez*. Grupo de Química Orgánica, Unidad de Biotecnología, Centro de Investigación Científica de Yucatán. Calle 43 No. 130, Col. Chuburná, Mérida, Yucatán, 97200, México. E-mail: lmanuel@cicy.mx

All aerial organs of higher plants are covered by a continuous wax layer on the surface of the cuticle. This layer protects plant cells from various environmental factors such as drought and UV damage, and acts as a first line of defense against insects, bacteria and fungal pathogens. In some higher plants, morphological and chemical studies carried out on epicuticular waxes have been used to correlate the nature and the chemical composition of the wax, with the susceptibility of the plant to insect attack or to chemical agents.
We have recently reported the identification of the major components of the epicuticular wax of *Cocos nucifera* and showed that they are both useful as chemotaxonomical markers and play a significant role in the resistance or susceptibility of coconut palms to the lethal yellowing disease. As part of an ongoing project on the study of the chemical composition of epicuticular waxes of different plant species, we have been successful in isolating and identifying a number of minor cycloartane derivatives, all related to skimiwallin and isoskimiwallin, from the epicuticular wax of *C. nucifera*. Details of the isolation and identification will be presented.

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THE ANTIPYRETIC ACTIVITY OF AQUOEUS LEAF AND STEM BARK EXTRACT OF DRUM TREE *(CORDIA MILLENII)*.

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Cordia millenii, K.O & S (Boraginaceae) is a perennial tree widely dispersed in the Tropics of Africa where the combined aqueous extract of the leaf and stem bark are popularly used for various ailments including fever, pain and cough. This study is aimed at investigating its antipyretic activity. Temperature was induced in matured rabbits by intravenous injection of klebsiella organism into their mid auricular vein. Aqueous leaf and stem bark extract were administered orally in doses of 250 and 500mg/kg to two different groups, aspirin 250mg/kg was given orally to a third group while the control group received 10ml/kg distilled water orally. The result showed that the extract caused a significant ($p< 0.05$) dose dependent reduction of pyrogen –induced temperature. Preliminary phytochemical analysis revealed the presence saponins, cardiac glycosides, anthraquinones and reducing sugars. The study therefore supports its use in folk medicine as an antipyretic agent, the mechanisms of action however calls for further investigation.

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LEONTOPODIC ACID – A NOVEL HIGHLY SUBSTITUTED GLUCARIC ACID DERIVATIVE FROM EDELWEISS (*LEONTOPODIUM ALPINUM* CASS.) AND ITS ANTI-OXIDATIVE PROPERTIES

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Leontopodic acid - a novel full substituted hexaric acid derivative, was isolated from the aerial parts of Edelweiss as one of the major compounds. The complex structure of leontopodic acid - 2-[(3*R*)-3-hydroxybutanoate]-3,4,5-tris-[(2*E*)-3-(3,4-dihydroxy-phenyl)-2-propenoate]-D-glucaric acid - was elucidated by mass spectrometry, 1D- and 2D-NMR spectroscopy and HPLC monitored transesterfication. The antioxidative properties were investigated by the *Briggs-Rauscher* (*BR*) reaction method, an oscillating redox-reaction system operating at pH 1.6 (near that of stomach fluids) and by the TEAC method operating at pH 7.4. *BR* experiments identified leontopodic acid as potent natural antioxidant (rac_m of leontopodic acid 3.4 ± 0.5; rac_m of caffeic acid 1.68) whereas TEAC method placed leontopodic acid (TEAC value of 1.53 ± 0.11) at an antioxidative level comparable to the literature value of caffeic acid (TEAC value of 1.66).

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IN VITRO LEUKOTRIENE BIOSYNTHESIS INHIBITORY ACTIVITY OF *LEONTOPODIUM ALPINUM* CASS. CONSTITUENTS

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Phytochemical investigations of the roots of *Leontopodium alpinum* Cass. resulted, as recently reported, in the isolation and structure elucidation of more than 30 constituents of different substance classes like bisabolan-derivatives, ligans, polyacetylenes, diterpenic acids, sesquiterpenes, and others. Twenty-three of the obtained compounds were tested in an *ex vivo* leukotriene biosynthesis inhibition assay using intact human leucocytes, as well as in two *in vitro* enzyme inhibition assays (COX-1 and COX-2). The bisabolane derivates (IC_{50}: 7.7 to 10.2 µM), one of the lignans (IC_{50}: 10.7 µM) and an *ent*-kaurenic acid derivative (IC_{50}: 10.4 µM) showed remarkable inhibitory effects on the LTB_4 synthesis comparable to the positive control zileuton (IC_{50}: 10.4 µM). None of the tested compounds showed *in vitro* inhibitory activity against COX-1 or COX-2 isoenzymes when tested at a concentration of 25 µM.

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INHIBITORY EFFECT OF KOLAVIRON (A GARCINA KOLA HECKEL SEED EXTRACT) ON MITOCHONDRIAL MEMBRANE PERMEABILITY TRANSITION (MMPT) PORE IN NORMAL AND DIABETIC RATS

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Mitochondrial Ca^{2+} level regulates the activation of the mitochondrial membrane permeability transition (MMPT) pore opening, In this study, the inhibitory effects of kolaviron (KV) – a biflavonoid fraction of Garcina kola (Heckel) seed extracts on MMPT was evaluated in mitochondria isolated from the livers of normal and alloxan-induced diabetic rats.
Ca^{2+}- induced mitochondrial swelling or MPT was more pronounced in normal rats than in alloxan-induced diabetic rats. Varying concentrations of kolaviron significantly inhibited the extent of swelling ($P< 0.05$) in a concentration-dependent manner in mitochondria from diabetic rats but to a lesser extent in normal rats. Although spermine, significantly reduced ($P< 0.05$) mitochondrial swelling, the degree of reduction by KV was higher than that of the standard inhibitor. These findings suggest that KV may be useful in the control of the extent of opening of MMPT pore and consequently regulating programmed cell death.

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ANALGESIC AND ANTI-INFLAMMATORY ACTIVITY OF THE AQUEOUS LEAF EXTRACT OF *BYRSOCARPUS COCCINEUS*

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Byrsocarpus coccineus (Connaraceae) is used as a herbal remedy for ear-ache, muscular and rheumatic pain in West Africa. The analgesic and anti-inflammatory effects of the aqueous leaf extract of *Byrsocarpus coccineus* (ABC) were studied in mice and rats using the acetic acid-induced writhing, formalin-induced, tail immersion and cold water tail flick pain tests; and the carrageenan-induced paw oedema and formaldehyde-induced arthritis inflammation models. ABC (50-400mg/kg; p.o) showed a dose-dependent and significant ($p<0.05$) inhibition of pain in all the analgesic models used. ABC (400mg/kg) gave a significantly higher inhibition (55.6%) than acetylsalicylic acid (ASA; 44.8%). Its effect on the 1st and 2nd phases of the formalin test (14.3%, 34.8%) was comparable to that of ASA (12.3%, 36.1%) respectively. In the tail immersion and tail flick tests, ABC induced a dose-dependent increase in latency of tail withdrawal. The highest dose produced a significant inhibition of 15.7% against 24.4% for morphine in the tail immersion test. In the tail flick test, the value was 65.5% compared to 86.3% for morphine. ABC produced significant inhibition of carrageenan-induced oedema, while in the formaldehyde arthritis model, ABC elicited a percentage inhibition of 23.2%, against 34.7% for indomethacin. Results obtained suggest that ABC acts via peripheral and central mechanisms. These findings justify the traditional use of ABC in the treatment of pain and inflammation.

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ANTHRANOID COMPOUNDS WITH ANTIPROTOZOAL ACTIVITY FROM *VISMIA ORIENTALIS*

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Phytochemical investigation of the 80% ethanolic extract of stem bark of *Vismia orientalis* Engl. (Guttiferae or Clusiaceae), a plant used in traditional medicine in Tanzania, resulted in the isolation of 3-geranyloxy-6-methyl-1,8-dihydroxy-anthraquinone, emodin, vismione D and bianthrone A_1. Vismione D exhibited a broad range of antiprotozoal activities against *Trypanosoma brucei rhodesiense* and *T. cruzi* (IC_{50} < 10 μg/ml), *Leishmania donovani* (IC_{50} 0.37 μg/ml) and *Plasmodium falciparum* strain K1 (IC_{50} 1.0 μg/ml). However, it was also slightly cytotoxic against human L6 cells (IC_{50} 4.1 μg/ml). Emodin showed antileishmanial activity (IC_{50} 2.0 μg/ml), while its IC_{50} against L6 cells was 20.3 μg/ml. Other activities observed for emodin against both *Trypanosoma* species and *P. falciparum*, for bianthrone A_1 against *T. b. rhodesiense* and *P. falciparum*, and for 3-geranyloxy-6-methyl-1,8-dihydroxy-anthraquinone against *T. b. rhodesiense*, *L. donovani* and *P. falciparum* were in the range of 10 to 50 μg/ml. None of the compounds showed antibacterial or antiviral (including HIV) activity.

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EVALUATION OF THE SEDATIVE PROPERTIES OF THE DECOCTION OF THE ROOTS OF *PFAFFIA IRISENOIDES*

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Pfaffia irisenoides Kunth (Amaranthaceae) a plant known as the "brasilian ginseng" is used in several countries for the treatment of a wide variety of human diseases. In Venezuela this plant is called "valeriana" and "cachimbillo". The plant is sold by herb vendors as a tranquilizer, promoting sleep. In the present study we have evaluated the sedative activity of a lyophilised aqueous extract of *P. irisenoides* roots in rats. The results revealed that the extract, administered intraperitoneally, reduce the spontaneous motor activity, even in a higher magnitude when was compared with bromazepam. The sedative actions probably explain at least part of the therapeutic efficiency claimed for this plant in traditional medicine.

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GASTROPROTECTIVE AND CYTOTOXIC EFFECT OF LABDANE DITERPENES FROM *ARAUCARIA ARAUCANA* AND THEIR SEMISYNTHETIC DERIVATIVES

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The resin from *Araucaria araucana* (Mol) K. Koch was used by the Mapuche indians to treat ulcers and help cicatrization. Some 30 natural and semisynthetic *Araucaria* diterpenes were isolated or prepared to assess their gastroprotective activity on experimentally induced gastric lesions in mice and cytotoxicity in human lung fibroblasts (MRC-5) and human epithelial gastric (AGS) cells. At 100 mg/kg, highest gastroprotective effect was provided by compounds **1**-**2**, **4**-**5**, **7**, **9**, **21** and **25** being as active as lansoprazole at 20 mg/kg. Highest cytotoxicity towards AGS cells was observed for compounds **1**, **4**, **19** and **23** (IC_{50} in the range 27-41 μM) while **4**, **15** and **19** (IC_{50} 26-32 μM) were most active against fibroblasts. The best activity/cytotoxicity ratio was found for the derivative **25** with a lesion index comparable to lansoprazole at 20 mg/kg and a cytotoxicity in the range 889 to >1000 μM in MRC-5 and AGS cells, respectively.
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SPASMOLYTIC ACTIVITY OF THE ROOT EXTRACT OF *CISSAMPELOS MUCRONATA*

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Ethanolic root extract of *Cissampelos mucronata* was investigated for spasmolytic activity. The intraperitioneal LD_{50} in mice was 283 ± 36 mg/kg. Phytochemical analysis indicated the presence of flavonoids, sterols/triterpenes, tannins, alkaloids, glycosides and carbohydrates. The extract (50-200 mg/kg) inhibited intestinal motility in mice and reduced enhancement of intestinal motility induced by carbachol. It also potently relaxed the rabbit jejunum and reversibly inhibited the contraction evoked by acetylcholine, serotonin and histamine in various smooth muscle preparations. The concentration of the extract that produced 50% inhibition (IC_{50}) of the maximal contractions induced in the guinea pig ileum by calcium chloride, acetylcholine, histamine, serotonin and nicotine were 35.67, 37.43, 42.35, 48.24, and 63.76 μg/ml respectively. The extract also inhibited the contractions induced by Ca^{2+} in the presence of a high K^+, Ca^{2+} - free depolarizing solution. The spasmolytic effect of the extract is likely mediated partly through a decrease in Ca^{2+} availability. The results indicate that the ethanolic root extract of *C. mucronata* contains pharmacologically active principle(s) with spasmolytic properties, thus justifying its use in traditional medicine for the treatment of intestinal spasm.

Keywords: Spasmolytic activity, *Cissampelos mucronata* root.

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MENTTATION OF URIC ACID SECRATION BY FOUR MEDICINAL HERBS

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Gout represents a group of diseases with excessive amounts of monosodium uratea.
The metabolic disease affects mainly men in their fifth decade. About 90% of the patients with hyperuricemia have a diminished renal clearance of uric acid. Allopurinol is the most common drug used today to treat Gout disease, but is known to have multiple side effects and is not well tolerated by part of the patients. The 4 Medicinal herbs, ONONIS SPINOZA, ORTHOSIPHON, URTICA DIOICA, ZEA MAIS, are used for "cleaning the kidney from the gravel".
In the double blind controlled study, patients with uncomplicated gout disease where randomly assigned to an experiment and a placebo group. Patient in the experiment group were treated with a water-based extract of the above-mentioned medicinal herbs. The extract was given daily for a period of four weeks. A baseline 24 hours urine collection of uric acid was perform on the day of enrolment, and after four weeks of treatment with ether placebo or herbal extract.
Results: at the forth week of experiment in the treated 14 patients, 24 h uric acid secretion increased by average of 30%-from average of 483 mg a day to 628 mg (Statistical significance p-0.0272). In the control group, treated only with placebo, there was no significant change in the uric acid excretion rate before and after four weeks of treatment.
Conclusion: In our study, the four medicinal herbs significantly increased the excretion of uric acid. Moreover Patient treated according to our Protocol in the study where free from side effects

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INHIBITION OF LENS ALDOSE REDUCTASE BY MANGIFERIN AND ISOMANGIFERIN

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It has been suggested that aldose reductase or polyol pathway appears to be a crucial link between the systemic metabolic disturbances associated with diabetes and the specific tissue dysfunction and damage responsible for diabetic neuropathy. It has been expected, therefore, that inhibition of this enzyme activities my provide a therapeutic approach to treat of these complications.

Studies of flavonoids and protopine alkaloids possessed inhibitory activity of aldose reductase. The xanthones mangiferin and isomangiferin have been isolated from different Iris sppl. (I. Nigrican, I. Atrofusca, I. Atropurpurea, and I. Petrana). .
Aldose reductase activity of freshly prepared supernatant was assayed spectrophotometrically by determining the decrease in NADPH absorbance at 340 nm. The effects of inhibitors on the enzyme activity were determined by including in the reaction mixture 0.2 ml of each compound being tested at different concentration. The results showed that both compounds were found to display significant inhibitory activity, being isomangiferin is more potent that mangiferin, comparing with the reference standard quercitrin.

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MICROBIAL TRANSFORMATION OF CURCUMIN

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In Asian traditional folk medicines, turmeric (*Curcuma longa*) is used internally for conditions such as fever, allergies, jaundice and other liver ailments. Externally it is used to reduce inflammation and swelling caused by sprains, cuts and bruises. It is a powerful anti-inflammatory agent, useful for such conditions as arthritis. Curcumin, the yellow pigment in turmeric, has been demonstrated to prevent malignancies in various tissues in rodents, mainly in the intestinal track. It has been shown to inhibit angiogenesis *in vitro* and *in vivo*. Angiogenesis has emerged as a popular target for the development of effective anti-cancer agents.
Microorganisms, especially fungi, have been shown to be predictors of mammalian drug metabolites. They have the ability to produce metabolites in sufficient quantities for complete structure elucidations and further biological studies. Screening-scale microbial metabolism studies of curcumin were conducted with forty fungal cultures. Scale-up fermentation with *Pichia anomala* resulted in the production of several metabolites. The major metabolites isolated were characterized as, 5-hydroxy-1,7-bis(4-hydroxy-3-methoxyphenyl)heptan-3-one and 3,5-dihydroxy-1,7-bis(4-hydroxy-3-methoxyphenyl)heptane.

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NEW WHO GUIDELINE AND EC DIRECTIVES ON TRACEABILITY: A CHANCE FOR THE AMELIORATION OF QUALITY AND SAFETY OF MEDICINAL PLANT RAW MATERIAL

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A new EU directive on the traceability of heral raw material and a new WHO guideline on Good Agricultural and Collection Practise will ultimately improve quality, safety, efficacy and reproducibility of herbal medicines. As shall be explained with examples from currently running traceability projects for more than 20 different medicinal plants, major consequences of the new guidelines will be:

- Unambiguous botanical identification of medicinal plants
- Selection of cultivars tailored to the use of the final product
- Protection of the environment
- Decreasing danger of adulterations, and thus of accidental toxicity
- Better reproducibility of clinical effects of medicinal plant preparations

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A METHOD FOR SELECTING PLANTS WITH ANTI-INFLAMMATORY PROPERTIES USING A CROSS-CULTURAL COMPARISON OF ETHNOPHARMACOLOGICAL INFORMATION OF AUSTRALIA AND CHINA

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As a part of research program in the search of anti-inflammatory agents from Australian medicinal plants, a method for selecting suitable plants for laboratory studies has been developed. The method is based on a cross-cultural comparison of ethnopharmacological information of Australia and China. It firstly documents the ethnopharmacological information described in the Australian aboriginal medicine and the traditional Chinese medicine and then used the Chinese information as "standard" references to analyze and select Australian plants. The documented information includes the traditional use in the treatment of inflammation conditions, botanical identification, modes of preparation and administration, and chemical constituents. This information was compiled to form an ethnopharmacological dataset using the Microsoft Excess. From all available Australian and Chinese ethnopharmacological information, fifty-seven plants with potential anti-inflammatory action from Australia and forty from China were identified and recorded. By analyzing and comparing the ethnobotany, ethnopharmacology and phytochemistry of these plants in the two datasets, eleven Australian plants was selected for laboratory studies on inhibiting prostaglandin synthases and lipoxygenases, on cytotoxicity and on chemistry (Li et al 2003). It is anticipated that this ethnopharmacological method of plant selection will increase the possibility of obtaining right plant candidates from the vast plant kingdom for the development of useful therapeutic agents (Li et al 2004).

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ANTIBACTERIAL ACTIVITY OF CRUDE EXTRACT OF *EUGENIA JAMBOLANA*

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Eugenia jambolana belongs to family *typhaceae*, is traditionally used in various preparations for chronic diarrhea and dysentery and as gargle in sore throat beside its antidiabetic activity has also been established. Thus, we have tried to prove its antibacterial activity in an assay. The antibacterial assay has performed to check the antibacterial activity of crude extract of different parts against both gram-positive and gram-negative. The different parts of *Eugenia jambolana* (leaves, stem, root, seed) exhibited broad spectrum activity against both gram-positive and gram-negative organisms along with the maximum zone of about 10mm.

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MOLECULAR AND CHEMICAL AUTHENTICAION OF *SAUSSUREA LAPPA* CLARK, AN ENDANDERED CHINESE MEDICINAL MATERIAL

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Saussurea lappa Clark. (*Aucklandia lappa* Decne.), a medicinal herb of the family Compositae, is grown in the Himalayas and Middle Eastern countries. The species in wild is endangered and listed in Appendix I of CITES. Radix Saussurea, the dry root of *Saussurea lappa*, has long been used as a traditional Chinese medicinal material for promoting the flow of qi and improving digestion. In China, there are substitutes and adulterants in the market, such as *Vladimiria*, *Inula* and some poisonous *Aristolochia* species.
As a means to generate reliable markers for authentication, we have generated DNA sequences and GC-MS fingerprints of *Saussurea lappa* and seven related species. Our data indicate that the interspecific variation of the ITS sequences and the 5S rRNA spacer domain are high. GC-MS fingerprints provide species specific peaks and hierarchical clustering analysis of the fingerprints also gives consistent profile similarity scores for species differentiation.

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ANTIBACTERIAL ACTIVITY OF DIFFERENT PARTS OF *VINCA ROSEA*

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Abstract:
Vinca rosea belongs to family *Apocynaceae*, an erector procumbent herb or under shrub containing latex. It possesses known antibacterial, antimicrobial, antimalarial, antifungal, anticancer and antiviral activities. We have screened out this plant for its antibacterial potential using antibacterial assay. The different parts of *Vinca rosea* (leaves, stem, flower and root) have been used and their ethanolic extracts were subjected to antibacterial assay. The crude ethanolic extracts (leaves, stem, flower and root) of *Vinca rosea*, did not exhibited antibacterial activity against *Stapylococcus aureus*. Moreover, leaves, stem and flower extracts were also ineffective against *Pseudomonas aureogenosa*, beside this the leave extract did not exhibited activity against C*ornybacterium difhtheriae*, similarly, crude extract of stem did not shown activity against *Shigella boydii.* The most effective was the ethanolic extract of the root which exhibited broad spectrum antibacterial activity against *Salmonella typhi* having zone of inhibition measuring 24mm.

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PLANTS IN USE AS HERBAL MEDICINES (I) IN EDO STATE, NIGERIA.

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ETHNO-BOTANICAL INFORMATION ON SOME NIGERIAN MEDICINAL PLANTS, (PART1).
Data for plants used as phytomedicines in Edo State of Nigeria were collected both for the herbal medicines supplied by the practicing herbalists as the results of consultations and the plants freely available in the markets for self-medication.The information was collected using a questionnaire as the instrument. The following informations were to be given pertaining to any plant used. The plant name (in the language of the herbalist (since most of them have not received any formal education), the plant part(s) used, method of parathion, mode of administration, medical indication(s), dosage, place and time of collection and any reported side effects. Also required was use of incanations/spiritualism. Where there was a language problem in understanding the questionnaire a local interpreter was available to help, while the authors filled the questionnaire as the answers were being given. Patients who were met at the time of visit to the Clinics (mostly family house of the practionner) were interviewed as to the efficacy and side effects of their prescriptions. They were positive on the benefits.
50 herbalists were visited 2001-2003. 23 gave the information voluntarily, 5 refused to have anything written down and 2 refused to participate. Questionnaire was collated and reference (Vernacular books) were used to get the Scientific names of the plants. From the number collected, this report submits information on five plants only for each of the families collected. Of all the information collected, only 40 plants are here- reported. This data are used for the Development of Nigerian Natural Medicines Projects and Nigerian Pharmacopoes of Medicinal Plants and will serve any race of humas involved in medicinal agents of plant origin.

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ANTIMICROBIAL SCREENING OF EXTRACT AND FRACTIONS OF *CASSIA NIGRICANS* VAHL (CAESALPINACEAE) AND ITS EFFECTS ON *HELICOBACTER PYLORI.*

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Cassia nigricans Vahl (Caesalpinaceae) is a shrub that grows widely in Savannah grassland of West Africa. The plant is widely used in ethno medicine in Northern Nigeria for treatment of various gastrointestinal disorders. We set out to evaluate the effect of the methanolic extract (and its various fractions) of *Cassia nigricans* on *Helicobacter pylori*, a pathogenic organism implicated in peptic ulcer. The investigations were carried out using modified cup plate agar diffusion method for *Helicobacter pylori.* The antimicrobial effect of the various fractions of this plant extract was also determined against *Candida albicans, Pseudomonas aeruginosa, Bacillus subtilis, Staphylococcus aureus, Escherichia coli, Salmonella typhimurium, Shigella spp (Salmonella shigella)* and *Klebsiella pneumoniae* using the broth dilution method. The methanolic extract and fractions of *Cassia nigricans* exhibited varying degrees of antimicrobial activity on some pathogenic organisms. The minimium inhibitory concentration ranges from 190 to 2000μg/ml for the methanolic extract and those of its fractions (A, B, C, D. E and C^1) whereas the minimium inhibitory concentration against *Helicobacter pylori* ranges from 12.5-200μg/ml but fractions C^1, D and E had little or no activity against *Helicobacter pylori.* The results indicate that *Cassia nigricans* may be a source of compounds with therapeutic potential against gastric and peptic ulcers associated with *Helicobacter pylori* infections.

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STUDIES ON THE ANTI-INFLAMMATORY AND ANALGESIC ACTIVITIES OF LATEX OF *CALOTROPIS PROCERA*

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Calotropis procera (Ait). R.Br. (Asclepiadaceae), a wild growing tropical plant possesses multifarious medicinal properties and has been advocated for a variety of disease conditions. In the present study the dry latex (DL) of *C. procera* was evaluated for its *in-vivo* anti-inflammatory and analgesic activities. The anti-inflammatory potential of DL was studied in various acute and chronic animal models of inflammation. Oral administration of DL significantly inhibited the rat paw oedema induced by carrageenin and Freund's adjuvant in a dose dependent manner. Such an effect of DL was associated with a decrease in vascular permeability. It also significantly decreased the formation of granulation tissue in response to carrageenin and UV induced erythema. In all the models, the anti-inflammatory activity of DL was comparable to standard anti-inflammatory drugs. The analgesic activity of DL was evaluated in the acetic acid induced writhing and tail-flick models. A significant dose dependent analgesic effect was obtained in the writhings model and the effect was more pronounced than standard analgesic, aspirin. In the tail-flick model, the analgesic effect of DL was comparable to aspirin. Further, the analgesic doses of DL were also tested for its effect on spontaneous motility and motor coordination by the holeboard and rotarod tests. Thus, our study indicates that DL exhibits potent anti-inflammatory and analgesic activities. (AS is a SRF of CSIR)

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ANTIBACTERIAL ACTIVITY OF ETHANOLIC EXTRACTS OF *NERIUM INDICUM*

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Nerium indicum belongs to family *Apocynaceae*, is traditionally used in the treatment of ulcer, piles, ring worm, skin diseases such as eczema, impetigo and leprosy. Thus, the extracts of *Nerium indicum* have been screened for antibacterial activity in an assay. The different parts of *Nerium indicum* (leaves, flower and root) exhibited broad spectrum activity against *Shigella boydii*, but leave extract found to be ineffective against *Pseudomonas aureogenosa* and *Salmonella typhi*. The most effective was the ethanolic leaves shown antibacterial activity against *Streptococcus pyogens* having zone of inhibiton measuring 30mm.

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ANTIBACTERIAL ACTIVITY OF ETHANOLIC EXTRACTS OF *HIBISCUS ROSA-SINENSIS*

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Hibiscus rosa-sinensis, (rosa-sinensis = Chinese Rose) is a tropical plant belongs to family Malvaceae. Different parts of *Hibiscus rosa-sinensis* including leaves, stem and flowers contains antibacterial components as they exhibited antibacterial activity both against gram-positive and gram-negative organisms. The ethanolic extracts of leaves, stem and flowers of *Hibiscus rosa-sinensis* were evaluated for its antibacterial activity using an assay. The antibacterial assay has performed to check the antibacterial activity of ethanolic extract of different parts against both gram-positive and gram-negative. All the three extracts of *Hibiscus rosa-sinensis* (leaves stem and root) exhibited broad spectrum activity against both gram-positive and gram-negative organisms. The broader zone is obtained with ethanolic extract of s stem which gave zone of inhibition measuring 18 mm. All the three extracts didn't show any zone of inhibition

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PHENOLIC ACIDS IN BASIL (*OCIMUM* SPP.)

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Lamiaceae plants commonly contain caffeic acid derivative phenolics. As well as antioxidant activity, these compounds are expected to have new medicinal bioactivity used for treatments of renal disease, anti-HIV, etc. Gradual changes in production of phenolic acids in five different *Ocimum* species: *O. sanctum, O. minimum, O. citriodorum, O. gratissimum, O. basilicum* "Broad leaf" and *O. basilicum* "Narrow leaf" was studied during 50 days *in vitro* culture. The content of phenolic acids in roots, stems, leaves and liquid media were analyzed using HPLC. Sweet basil (*O. basilicum* L.) plantlets produced the highest amount of phenolic acids in compare to other examined species. The total concentration of phenolic acids in plant tissues during the growth exhibited a decrease in content with development but increase in content of root exudates into the liquid media.

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INVESTIGATION OF RADICAL SCAVENGING OF TEUCRIUM POLIUM L. (LAMIACEAE) ESSENTIAL OIL FROM IRAN, PAPOLATION KERMAN

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Teucrium polium(kalpureh) has been used in traditional medicine for many purp-oses such as antibacterial, antiinflammatory, analgesic, anti diabetes mellitus and
etc. The plant was collected from Kerman province in May 2002 and essential oil of dried and powdered of top flowered plant was prepared by hydro distillation [0.4 ml %(V/W)].It was analyzed by GC and GC/MS on DB1 and DB5 columns.
From 86 components 76 ones were identified .The antioxidant activity of ess.oil was investigated by lipid per oxidation (FTC) and free radical scavenging (DPPH) methods. AA% of 30 µl ess.oil in FTC method after 72 hrs (26.74 µg/ml) was more than 10 mg Vite.E and 0.1 mg(100 µg)BHA. IC50 of Ess.oil in DPPH method after 15 min. (5.8µg) was as potent as 5 µg of BHA. The component and antioxidant activity of ess.oil will be discussed.

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ANTI-PYRETIC AND ANTI-INFLAMMATORY ACTIVITIES OF THE AQUEOUS LEAF EXTRACT OF *TRIDAX PROCUMBENS* L.

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Tridax procumbens Linn (Compositae) is common in tropical southern part of Nigeria, where various ethnomedicinal uses have been claimed for the aqueous leaf extract of the plant. Ethno-medical uses of the plant include treatment of cough, hypertension, inflammatory conditions and fever. Despite these claims, very limited medicinal uses have been documented, which includes antibacterial, wound healing, and blood pressure- and heart-rate lowering effects. To elucidate the ethno-medical claims, this study investigated the antipyretic and anti-inflammatory actions of the orally administered aqueous leaf extract of *Tridax procumbens* (TP). Four agents were used to induce pyrexia, namely, *Klebsiella aeruginosa(KA)* and turpentine in rabbits, as well as 2,4–Dinitrophenol (2,4-DNP) and *d*-amphetamine sulphate in rats. For anti-inflammatory effects, TP was tested; in rats against carrageenan and dextran-induced rat paw oedema, as well as formaldehyde-induced arthritis-like inflammation. The results showed that TP produced a dose-dependent and significant (P<0.01-0.001, student *t*-test) reduction in hyperthermia induced by *KA,* 2,4-DNP, *d*-amphetamine and turpentine; and significant reduction in paw volume in the carrageenan induced oedema and formaldehyde-induced arthritis-like inflammation, but did not produce any significant (P< 0.05*)* effects in the dextran-induced oedema. These results indicate that TP possesses antipyretic and anti-inflammatory activities, supporting the use of the aqueous root decoction of this plant in folk medicine, for the treatment of fever and inflammation.

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ANALGESIC ACTIVITY OF THE AQUEOUS ROOT EXTRACT OF *LECANIODISCUS CUPANIOIDES* IN ANIMAL MODELS

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Lecaniodiscus cupanioides is a medicinal plant that is widely used in folk medicine of West Africa, for various ailments. In Nigeria, the aqueous root extract of *Lecaniodiscus cupanioides* (LC) is reported to be effective against inflammatory conditions and hepatomegaly, among other uses. Moreover, there are claims by herbal medical practitioners in Nigeria that LC is useful against acute and chronic pain, and is safe. We have reported the safety potential of LC. This present study, reports the analgesic action of LC. The effect of LC (100 – 400mg/kg) was investigated against various pain models in rodents, such as hot plate, formalin- induced, tail immersion, tail clip and writhing tests in mice, as well as tail flick test in rats.

The results showed that LC produced a significant (P<0.05- 0.001) prolongation of the reaction times in the hot- plate, tail immersion, tail flick and tail clip tests; and significantly and dose-dependently produced an increased pain threshold in both the first and second phases of the formalin pain test. In the writhing test, LC significantly inhibited writhing frequency. In all these models, with exception of tail clip and the first phase of formalin-induced pain tests, LC (400mg/kg) produced effects comparable (P< 0.05, t-test) to the standard reference drugs, aspirin or morphine. The results indicate that LC has potent analgesic action, mediated centrally and peripherally, justifying its use in the management of pain, in traditional African medicine.

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ROSMARINIC ACID ISOLATION FROM *LAVANDULA VERA* CELL SUSPENSION USING SUPPORT-FREE LIQUID-LIQUID CENTRIFUGAL PARTITION CHROMATOGRAPHY

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Rosmarinic acid is a recurrent secondary metabolite in Lamiaceae and Borraginaceae species. The interest for rosmarinic acid has grown as it has been recognised as a good health promoting substance in medicinal plants, herbs and spices. Interesting biological properties have been confirmed (antimicrobial, antiviral, antiinflammatory, antioxydizing activity). Industrial perspectives trigger the research on large-scale production and purification of rosmarinic acid. Cell suspension production is currently under evaluation, but purification is not straightforward. We used an original development mode applied to Centrifugal Partition Chromatography (CPC) to isolate in one batch 160 mg of pure rosmarinic acid from 5 g of crude ethanolic extract of *Lavandula vera* cell suspension. The development mode is ion-exchange centrifugal partition chromatography (IXCPC) using a ionic liquid as exchanger and iodide as displacer. Previously fundamental work characterized the displacement process through model samples and *in-silico* numerical modelisation. A software is available for further optimization. This application of the IX displacement mode on support-free liquid-liquid chromatography opens new perspectives in the field of preparative chromatography of ionized compounds. Both the advantages of the liquid nature of stationary phase and of the displacement mode motivate further development of this new separation mode, especially application to preparative separation of challenging bioactive natural products.

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EFFECTS OF A STANDARDIZED, TRADITIONALLY PREPARED EXTRACT OF *CETRARIA ISLANDICA* ON CYTOKINE SECRETION OF DENDRITIC CELLS *IN VITRO* AND RHEUMATOID ARTHRITIS IN RATS *IN VIVO*.

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Iceland moss, *Cetraria islandica* (L.) Ach. (Parmeliaceae), is one of a few lichen species currently used for medicinal purpose in Europe. The extract and some isolated constituents have shown interesting biological activity including immunological effects.
The aim of the study was to standardize a traditionally prepared aqueous extract with respect to both low- and high-molecular compounds; protolichesteric acid, fumarprotocetraric acid, lichenan and isolichenan using RP- HPLC and NMR-spectroscopy, and to examine the effect of the extract and its pure constituents in a dendritic cell model *in vitro* to determine cytokine secretion of the cells. The effect of the extract on rheumatoid arthritis rat-models *in vivo* was also investigated. Cultured human monocyte-derived dendritic cells treated with high concentration of the water extract (200 and 100 µg/ml) secreted increased levels of IL-10 of 2.6 and 2.1 ng/ml and decreased levels of IL-12 of 14.0-13.0 ng/ml, above background levels. This was reflected in reduced inflammation of antigen-induced arthritis in rats that were s.c. treated with 2.5 mg/kg of the extract 3 times per week. This suggests an anti-inflammatory role of the water extract through stimulation of an anti-inflammatory phenotype of the dendritic cells.

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FUNGAL BIOACTIVITY ASSOCIATED TO SINKHOLES (CENOTES) FROM YUCATAN.

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Fungi are recognized as an important potential source of natural products with high structural diversity and significant biological activity. Many of the products currently used for human or animal therapy, as well as for controlling pests in agriculture, are produced by microbial fermentation or are derived from chemical modification of a microbial product. Researchers are studying now the production of bioactive metabolites from novel fungal species isolated from unexplored regions of the world. One of these sources are freshwater sinkholes known as "cenotes" in the Yucatan Peninsula. To date, approximately 70 fungal strains have been isolated from two undisturbed cenotes. A number of fungal isolates have been cultured and their corresponding organic crude extracts obtained. These extracts have been evaluated by the antioxidant (bleaching of beta-carotene and DPPH reduction) and antimicrobial assays. The latter has been carried out using three bacteria (*Staphyloccocus aureus, Pseudomonas aeuroginosa*, and *Bacillus subtilis*), one yeast (*Candida albicans*), and four phytopathogenic fungi (*Phytophtora infestans*, *Colletotrichum gloesporioides*, *Fusarium oxysporum*, and *Alternaria tagetica*).Our preliminary results have allowed the detection of several fungal strains with potential for production of bioactive metabolites; these include *Acremonium pseudozeylanicum*, *Cladosporium cladosporioides*, *Emericella variecolor*, *Gliomastix musicola*, *Gliocadium roseum*, *Papullaspora pallidula*, and a strain of *Volutella sp*.

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DEVELOPMENT OF AN *IN-VITRO* METHOD FOR THE SIMULTANEOUS EVALUATION OF THE INHIBITORY ACTIVITY OF HERBAL EXTRACTS ON SIX DRUG METABOLISING CYTOCHROME P450 ENZYMES

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In recent years only microtitre plate-based fluorescence assays were used for the high throughput screening of herbal extracts with inhibitory activity on drug metabolising Cytochrome P450 (CYP) enzymes. Major drawbacks of these methods include quenching and intrinsic fluorescence of plant extracts and the lack of validated methods. Here we present a newly developed and validated *in-vitro* method for the simultaneous evaluation of the inhibitory potency of plant extracts on six drug metabolising CYP enzymes. The substrate/enzyme cocktail consisted of tacrine (CYP1A2), paclitaxel (CYP2C8), tolbutamide (CYP2C9), imipramine (CYP2C19), dextromethorphan (CYP2D6) and midazolam (CYP3A4). Determination of inhibitory activity was performed using LC/MS with automated sample extraction which allowed the selective quantification of product ions in the Single Ion Monitoring mode without interferences. Selectivity was proven by comparing the IC_{50} values of known synthetic inhibitors and crude plant extracts from feverfew and devil's claw using the individual (single) substrates/isozymes and the substrate/enzyme cocktail, respectively. Inhibitory activities of crude extracts from kava-kava, devil's claw, fo-ti, feverfew, eucalyptus and peppermint were obtained for all applied CYP enzymes with IC_{50} values between 20 and 500 µg/ml.

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IN-VITRO CYTOTOXICITY ACTIVITY OF DIOSQUINONE, A NAPTHOQUINONE EPOXIDE.

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Diosquinone, a naphthoquinone epoxide previously isolated from the root bark of *Diospyros mespiliformis* (Hostch) and *D. tricolor* [Ebenaceae] is been assessed for cytotoxicity activity against ten cancer cell lines by standard NIH method. The ethno-pharmacological claim of this plant and the previously observed good antibacterial activity of this compound among the others isolated from this plant suggest its probable cytotoxicity activity.
Diosquinone was observed to be very active against most of the cancer cell lines. It shows very good activity against all the cell lines tested with ED_{50} value ranging between 0.18µg/ml. against Human Glioblastoma (U373) to 4.5µg/ml. against Hormone dependent human prostrate cancer (LNCaP).

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IN VITRO ANTI-_HELICOBACTER PYLORI_ ACTIVITIES OF METHANOL EXTRACT OF _EUCALYPTUS GRANDIS_

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The etiologic agent of peptic ulcer, duodenal ulcer, chronic gastritis, gastric adenocarcinoma and related gastro duodenal disorders has been traced to *Helicobacter pylori.* Current therapy have not yielded much success due to cases of bacterial resistance, side effects, non-patients compliance and consequent relapse of *H.pylori* infection(1). The aim of this work is to establish the anti-*H. pylori* activity of *Eucalyptus grandis*, a medicinal plant used in the treatment of gastrointestinal problems.
Crude hexane and methanol extracts of *E.grandis* stem bark were screened against a standard strain ATCC 43504 and ten clinical strains of *H.pylori* using agar diffusion method on Mueller-Hinton agar supplemented with defibrinated horse blood and grown in a microaerophilic incubator (2). Hexane extract was less active compare to the methanol extract. All the strains except UCH 97002 and UCH 98020, were inhibited by the methanol extract to varying degrees. The minimum inhibitory concentration against the susceptible strains tested ranged between 0.39 and 1.56 mg/ml.
The effect of the methanol extract was tested on the urease activity of strains tested revealed a decreased with increase in the concentration of the extract. The addition of the methanol extracts enhanced cell aggregation of seven of the *H.pylori* strains leading to a decrease in microbial cell surface hydrophobicity (CSH) . The SAT titer decreased from >3 to <1.5 for five of the strains and to < 3 for two of the strains.
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IN VITRO CYTOTOXIC ACTIVITY OF *KIGELIA PINNATA* FRUITS

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The fruits of *Kigelia pinnata* DC (Bignoniaceae) are the most commonly used part of this plant, and in southern Africa anecdotal reports describe the use of the fruit to treat skin cancer (Houghton , 2001). Extracts of ripe DF and unripe fruits FF made with dichloromethane DCM and methanol M were tested for cytotoxicity using the SRB assay (Skehan *et al.*,1990) on three different cell lines: C32 melanoma, SVK-14 keratinocytes and HF human fibroblasts. At 48 hours (C32 and HF) and at 72 hours (SVK-14) recovery (Rec) of the cells was tested by washing the extracts off from the cells and replacing by normal media, in order to investigate whether any effect was cytotoxic or cytostatic. Vinblastine sulfate(Vinb) for the C32 and HF cell lines and dithranol (Dithl) for the SVK-14 cells were used as positive controls. Two duplicate tests for each crude extract were performed and the IC_{50} was calculated .
The dichloromethane extract of the ripe fruit was the most cytotoxic against the C32 and the SVK-14 cell lines, although high IC_{50} values were obtained HF, thus demonstrating some selectivity.
Stiefel Laboratories are acknowledged for financial support of this project.
Houghton PJ, (2001) *South African Journal of Botany* **68**:1420-1428.
Skehan P *et al.*. (1990) *J Natl. Cancer Inst*. **82**:1107-1112

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BIOASSAY GUIDED FRACTIONATION OF MOLLUSCICIDAL SAPONINS FROM THE FRUIT OF *LAGENARIA BREVIFLORA* ROBERT FAMILY CUCURBITACEAE

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Plant molluscicide is still considered viable, environmental friendly, cheap, and affordable means of controlling the intermediate snail host of schistosomiasis in developing countries like Nigeria where the prevalence is still very high. The high cost of synthetic molluscicides and /or chemotherapy prohibits their use.
Many plants have been screened for their intrinsic molluscicidal properties in Nigeria, with a few showing as promising plant molluscicides. However, only *Tetrapleura tetraptera* qualifies as a candidate plant molluscicide that can be used for control programme.
In the continued search for suitable plant molluscicide, the molluscicidal bioassay of *Lagenaria breviflora* fruit extracts were made with intermediate host snail *Biomphalaria pfeifferi;* the seed extract presented with LD_{100} of 30ppm and the pulp extract LD_{100} of 80ppm and can be considered a viable plant molluscicide for field test. Bioassay guided fractionation of the methanolic seed extract resulted in the isolation of three bidesmosidic saponins; KJCF 9, 11 & 13 with LD_{50} 23, 13 and 8.5 ppm respectively.
The structures were established by using spectroscopic method including 2D NMR.
Key words: *Lagenaria breviflora* Robert, Molluscicidal activity

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NATURAL PRODUCT DRUG DISCOVERY THAT TARGETS TUMOR HYPOXIA

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The existence of hypoxic regions is a common feature of solid tumors. The extent of tumor hypoxia correlates with advanced disease stages and poor prognosis. Hypoxic tumor cells are more resistant than normoxic tumor cells to radiation treatment and chemotherapy. These hypoxic tumor cells are considered an important contributor to disease relapse. Tumor hypoxia represents an important unmet therapeutic need for cancer treatment.
A molecular targeted approach was designed to discover natural product-derived drug leads that target tumor hypoxia. A cell-based HTS assay was developed in the hypoxia responsive human breast carcinoma T47D cells. Natural product-rich extracts from plants, marine organisms, and microbes were examined for HIF-1 inhibitory activities. The transcription factor HIF-1 is a key regulator of oxygen homeostasis. HIF-1 inhibition has been shown to retard tumor growth in animal models. Active extracts were subsequently subjected to a panel of secondary bioassays for dereplication and prioritization. Bioassay-guided fractionation of the medicinal plant *Saururus cernuus* extract yielded a series of dineolignans that are potent HIF-1 inhibitors. These compounds were further characterized in a panel of *in vitro* bioassays.

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SAPONINS QUANTIFICATION BY HYDROLYSIS FROM *Agave lecheguilla* Torr; A RAPID METHOD.

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Agave lecheguilla Torr. (lechuguilla) is a plant which belongs to the *Agavaceae* family. It usually grows in semiarid zones in Mexico. Lechuguilla is mainly used to obtain "Ixtle" fiber by craving its leaf, which is composed of 15% of fiber and 85% of pulp. This pulp contains different compounds, where saponins are highlighted because of their diverse pharmacological uses. We have found different methods, through several tests, such as hemolytic effect detection, foam formation and some method based in colorimetric reactions, which gave qualitative information about the type of saponin. However, quantification of these compounds is complicated because the reported method is based of reaction with H_2SO_4, which has resulted too oxidizing and hardly repetitive. Therefore, is necessary a method which allows a rapid quantification of saponins.
The essay proposed for reaching this objective is based on in the molecule hydrolysis in order to liberate saccharides joined to saponins. These saccharides were quantified by Miller method (1959). The application of this method permits the saponins quantification by the determination of the saccharides generated by hydrolysis of the molecule. As a result, we obtained a high correlation index. The content of saponins established by bibliography is found between 1 –2%; however, this method reports values from 0.5-1.7% for the same plant. Correlation between hemolytic effect and hydrolytic method will be show.

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GROWTH INHIBITION and APOPTOSIS OF LYMPHOID & MYELOID LEUKEMIA CELLS BY DUAL *vs.* SPECIFIC 5-AND 12- LOX INHIBITORS

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The arachidonic acid enzymes 5- and 12-lipoxygenases (LOXs) have been implicated as mediators of growth and survival of malignant cells and have been shown to be upregulated in several types of cancer. Their involvement in leukemia, however, is controversial. Dual inhibitors of 5- and 12-LOXs, the lichen metabolites protolichesterinic acid (PA) and lobaric acid (LA), as well as selective 5-LOX inhibitors, the lichen compound baeomycesic acid (BA) and the anti-asthmatic drug zileuton, were tested for growth inhibitory- and death-inducing effects on six leukemic cell lines using the thymidine uptake- and TUNEL assays. PA proved most effective and caused significant growth inhibition (EC_{50} 4.2 - 11.3 μg/ml) and apoptosis of all cell lines tested. LA was a less effective growth inhibitor but showed similar potency for inducing apoptosis. Cells of lymphoid origin (JURKAT, CCRF-CEM, CCRF-SB) appeared to be somewhat more sensitive to the effects of PA and LA than those of myeloid origin (HL-60, K-562). In contrast, the specific 5-LOX inhibitors BA and zileuton showed minimal effects in both assays. The significant growth inhibitory- and apoptotic effects expressed by the dual LOX inhibitors has prompted further studies to see whether the activity is correlated to lipoxygenase inhibition and to what extent other mechanisms of action are involved.

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SOLUBILIZATION OF ILL-SOLUBLE LICHEN COMPOUNDS IN NON-TOXIC SOLVENTS FOR PHARMACOLOGICAL SCREENING

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Bioactivity screening of natural compounds is often impeded by the poor solubility shown by these metabolites in non-toxic solvents. Lichen compounds representing different chemical classes were chosen as prototypes for poorly soluble natural compounds and an effort made at finding solubilizing agents that fulfilled two set criteria; capacity to solubilize the compounds whilst being free of direct activity against 4 cultured cell lines. Thus, atranorin (ATN), fumar-protocetraric acid (FPCA) and usnic acid (UA) were chosen as representatives of ill-soluble depsides, depsidones and dibenzofurans respectively. A number of solvents, co-solvents, surfactants and complex forming agents were screened for activity against the cancerous cell lines K-562 (leukemia), T-47D (breast), Panc-1 (pancreas) and PC-3 (prostate) in a standard proliferation assay. Most of the solvents proved toxic with the exception of propylene glycol, polyethylene glycol 400 (PEG 400), 2-hydroxypropyl-β-cyclodextrin (HP-β-CD) and 2-hydroxy-propyl-γ-cyclodextrin (HP-γ-CD). The cyclodextrins proved to be the most suitable agents for solubilizing the lichen compounds for the proliferation assay. The greatest rise in solubility was obtained for FPCA, for which solubility increased 300-fold, from 0.03 mg/ml in water to 8.98 mg/ml in 10% HP-β-CD as determined by HPLC. The non-toxic solubilizing agents identified in this study could prove useful for pharmacological testing of other poorly soluble natural products.

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"NEW DRUGS FROM MARINE NATURAL RESOURCES OF JAMAICAN REEFS": DEVELOPMENT OF AN INTERNATIONAL COOPERATIVE BIODIVERSITY GROUP PROGRAM

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The ICBG program has successfully coupled natural products sourcing with biodiversity conservation and benefit sharing to the host country. However, concerns persist that local stakeholders have been excluded from the process, thus in 2003 a planning grant period was instituted to provide adequate time for informed consent of stakeholders. The aims of this ICBG program are to: (1) discover marine natural products from Jamaican reefs as prototypes for developing new therapies for cancer and infectious diseases, (2) develop biological and chemical data relative to ecological factors in support of marine conservation and restoration efforts, and (3) contribute to sustainable economic development and scientific/technological enrichment in Jamaica. This planning portion of the project is aimed at developing scientific partnerships within Jamaica, appropriate agreements with relevant permitting agencies, and a plan for short- and long-term benefit sharing among relevant constituents. To this end a series of informational meetings were held for potential stakeholders within Jamaica, and a social survey was developed to assess their concerns. The results of these surveys, and a review of prior research efforts, are being used to target study sites for preliminary data in the final year of this planning grant.

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TUBERCULOSIS ANTIMICROBIAL ACQUISITION AND COORDINATING FACILITY (TAACF)

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The evolution of drug resistant strains of TB has renewed the search for more active and selective anti-TB agents. The TAACF program was established in 1994 by the National Institutes of Health's National Institute of Allergy and Infectious Diseases (NIAID) to facilitate the search for new anti-TB compounds by integrating the components of the drug discovery and development process. We offer at no cost to our suppliers *in vitro* screening by NHDC; *in vivo* screening in a murine aerosol model by CSU; and repository and program coordination by SRI, all under the direction of NIAID. In our 10 years, we have contacted 8,024 researchers from all over the world. As of 4/30/04, 72,273 compounds have been accepted for screening. 65,752 compounds have been screened in our primary assay, and 6,767 compounds have progressed to our secondary confirmation and toxicity assays. 5,788 compounds have been tested or are being considered for our more advanced screens, and 118 compounds have been evaluated in our in vivo screens. While our efforts have not resulted in a new anti-TB drug, we have identified many new lead compounds. We continue to seek new compound suppliers.

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SASANG CONSTITUTIONS ANALYSIS BY GENE POLYMORPHISM

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Sasang Medicine(Dong-ui-su-se-bo-won) is Korean indigenous medicine with 4 constitutions among oriental medicine ranges, and includes 4 physical characteristics such as Taeum, Taeyang, Soum and Soyang. Nowadays, several study groups has been interested in genetic factors of Sasang constitutions, and investigated the relationship between Sasang constitutions and many candidate genes including ABO blood group, HLA system or ACE gene as a component of renin-angiotensin system, but no precise relation between these candidate genes and Sasang constitution has yet been established. To estimate the relationship between genetic components (angiotensinogen, ACE and angiotensin II type1 receptor genes) of renin-angiotensin system and Sasang constitutions, we performed the association studies using gene polymorphisms as genetic markers for total 99 Korean subjects (Taeyang, 3 cases; Taeum, 25 cases; Soyang 41 cases; Soeum 30 cases). Genotype distributions of each candidate gene were determined by PCR-RFLP and agarose gel electrophoresis methods.The genotype frequencies of three candidate genes were not significantly different from the data from Korean general population ($P > 0.05$). However, there were less significant differences in genotype and allele frequencies of three candidate genes among each groups ($P > 0.05$). Further studies using large sample size and other candidate genes will be required.

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PRELIMNARY SCREENING OF *Psoralea corylifolia* EXTRACTS FOR PHOTOTOXIC COMPOUNDS USING *Artemia salina* (brine shrimp) BIOASSAY

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Psoralea corylifolia is an annual medicinal plant found in India and Pakistan and the seeds from this plant are widely used as an ayurvedic medicine for vitilago- a skin condition wherein white patches appear on the skin due to the absence of melanin (skin pigment). Furanocoumarins present in this plant are believed to induce melanin production but have limited use due to their phototoxicity. Thus identification of compounds that stimulate melanin production but are not phototoxic would be useful.
Seeds of *Psoralea corylifolia* were sequentially extracted with solvents of increasing polarity using soxhlet extraction. Solvents used for the extraction were hexane, benzene, ether, ethyl acetate, methanol, butanol and water. These extracts are being screened for phototoxicity using a brine shrimp mortality assay as the larvae of brine shrimp (*Artemia salina*) are extremely sensitive to phototoxic compounds.
Development of the bioassay methods and the preliminary screening results of the aqueous and alcoholic extracts will be presented.

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A PANEL OF UBIQUITIN ASSAYS: IDENTIFICATION OF NAUTRAL PRODUCT INHIBITORS OF SPECIFIC E3 UBIQUITIN LIGASES

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The process of ubiquitinylation plays a role in a wide range of cellular functions including protein degradation and molecular signaling and suggests many potential targets for therapeutic intervention in cancer and other diseases. Broad-based proteasome inhibitors can induce apoptosis in cancer cells, for example, and inhibitors of ubiquitin protein ligases (E3s) provide the promise of greater specificity in certain pathologies. We developed a suite of assays for screening potential inhibitors of E3s that target either their self-ubiquitinylation or their interaction with other enzymes or proteins. We report the use of these assays to search for natural product inhibitors of the self-ubiquitinylation of MDM2, an E3 ligase known to be important in the regulation of p53 and cancer. We carried out a high-throughput primary screen for inhibitors of this activity using the NCI natural products extract repository containing over 144,000 extracts, an NCI natural products library of about 3500 pure compounds, and an MSD library of 100,000 small molecules. The variability of the assay over the entire screen was good, with an overall CV below 10% and a Z' score of 0.74. The natural product extract library had a hit rate of about 2% while the purified natural product libraries had hit rates between 0.1% and 0.5%. Evaluation of the hits (>3 standard deviations from the mean activity) against each of the other assays in our suite (MDM2, XIAP, NEDD4, RNF28, and UbcH5b) determined the specificity and revealed patterns of inhibition that relate to general structural motifs and other characteristics of the ligases. Final hit rates of the natural product extract library after selectivity screening was below 0.1% In the natural product extract library the inhibition profiles were distinct for different sample sources, with plant extracts showing a much larger number of inhibitors than fungal extracts, and marine extracts containing more inhibitors when extracted in aqueous solvent than in organic solvent. These data allowed for the segregation of interesting samples including those containing MDM2 and RING-finger specific inhibitors. We continue to study the identified extracts to isolate the active components and assess their value as therapeutics.

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ANTIPROLIFERATIVE ACTIVITY OF *PIPER AMALAGO* LEAVES

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Piper amalago (Piperaceae) is commonly used by Central America folk medicine to treat rheumatism, aches, swelling, pains and skin affections. The few phytochemical studies led to isolation and characterization of amides, sesquiterpenes and lignans. Recently, a topical anti-inflammatory activity has been described for the chloroform and methanol extracts of its leaves. In the search for new antiproliferative drugs, the methanol extract of *P. amalago* leaves was studied *in vitro* on KB cells. A colorimetric assay based on quantification of cell protein content with sulforhodamine B showed a concentration-dependent antiproliferative activity for the extract (IC_{50} = 11.5 μg/ml). Its separation on Sephadex LH-20 yielded three macro-fractions, one of which showed a significant activity (IC_{50} = 2.7 μg/ml). RP-HPLC analysis led to the isolation of some known compounds (e.g. sesartemin, kaempferol) and a new lignan (5-5'-diirdoxymatairesinol) from this fraction. The structural elucidation of all compounds was based on their NMR spectral data, including those derived from ^{1}D-TOCSY, ^{2}D-COSY, HSQC and HMBC experiments. The molecular formulas were confirmed by MS analysis. The new lignan showed an interesting cytostatic activity (IC_{50} = 2.03 μM), in comparison to cisplatin, the reference antitumoral drug (IC_{50} = 0.37 μM).

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IN VITRO SCREENING OF TELOMERASE INHIBITOR FROM NATURAL PRODUCTS

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Telomerase is a reverse transcriptase that synthesizes telomeric DNA repeats onto chromosome ends. Telomerase activation and telomere shortening in human somatic cells have been implicated in cell tumorigenesis and immortalization. Previous studies led to the proposal of telomerase as a cancer marker and a promising therapeutic target for novel anticancer drugs. In order to find the potential inhibitors against telomerse activity, different strategies have been developed to inhibit telomerase activity and interfere with tumor development. We screened about 1500 fractions from 500 kinds of natural products including traditional Chinese medicines, India herbs, Vietnamese herbs, spices, vegetables, fruits, cereals, and edible mushrooms. The inhibitory effects of these materials against telomerse activity were tested in HL-60 cell line using PCR based telomeric repeat amplification protocol (TRAP) assay. PCR products were determined by using non-denaturing polyacrylamide gel electrophoresis. Telomerse inhibiting activity was evaluated by comparing detected DNA ladders. Screening results indicate that hexane, ethyl acetate, and water extract of *Rhodiola crenulata*, hexane and ethyl acetate extract of *Hedyotis diffusa* Willd, water extract of *Dolichos lablab* and *Angelica dahurica*, showed strong telomerase inhibiting activity at the concentration of 10 μg/ml. Activity-guided isolation was further performed to obtain active compounds. So far, 15 crystal compounds have been obtained from *Hedyotis diffusa*, and *Rhodiola crenulata,* their chemical structure and anticancer activity are undergoing.

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IN- VITRO ANTI-MYCOBACTERIAL ACTIVITIES OF THREE SPECIES OF _COLA_ PLANT EXTRACTS (STERCULIACEAE).

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Extracts obtained from three Nigerian Sterculiaceae plants: *Cola accuminata, C. nitida* and *C. milleni* were screened for anti-mycobacterium properties using a slow growing *Mycobacterium bovis* ATCC 35738 [designated BCG Mexican and known to have some virulence in mouse and guinea pig) at 1000µg/ml using the radiometric (BACTEC) method. The extracts were also tested against six fast growing ATCC strains of *M. vaccae* using the broth microdilution method.

The methanol extracts from both leaves, stem bark and root bark of *Cola accuminata* and from the leaves and stem bark of *C. nitida* and *C. milleni* were not active at the highest concentration of 1000 µg/ml. Only the methanol extract of root bark for both *C. nitida* and *C . milleni* were found to be potent against both *M. bovis* and strains of *M. vaccae*. The minimum inhibitory concentration (MIC) of *C. nitida* against *M. bovis* is 125µg/ml while the MIC of *C. milleni* against *M. bovis* is 62.5µg/ml after at least 6 days of inhibition with growth index (GI) units lesser than or equal to the change in GI units inoculated with a 1/100 of the BACTEC inoculum for a control vial.

The minimum inhibitory concentration of *C. milleni* against the six ATCC strain of *M. vaccae* ranged from 62.5µg/ml to 250µg/ml while for *C. nitida* ranged from 500µg/ml to above1000µg/ml. Evidently, *C. milleni* has the highest inhibitory activity against both *M. bovis* and strains of *M. vaccae* used. Rifampicin, the positive control used has strong activity against *M. bovis* at the tested concentration of 5µg and 10µg/ml and 4 to 8µg/ml against the 6 strains of *M. vaccae*.

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ISOLATION AND FUNCTIONAL CHARACTERIZATION OF HSP90-ACTIVE SMALL MOLECULE NATURAL PRODUCTS FROM THE RHIZOSHPHERE OF SONORAN DESERT PLANTS

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In a multidisciplinary effort to isolate and characterize novel small molecule secondary metabolites targeting heat shock protein-90 (Hsp90) function, we have investigated microorganisms living in association with plants in North American Southwest deserts. Based on the reasoning that 1) the Southwest deserts are highly diverse in plants and associated microflora but to date relatively unexplored; 2) desert plants and microorganisms are adapted to heat stress; and 3) inhibitors of Hsp90 and many other anticancer agents are derived from microbial sources, we hypothesized that the desert Southwest could be a source of microorganisms that produce Hsp90-active small molecules. To test this hypothesis we developed a moderate throughput, two stage screening strategy designed to identify inhibitors of Hsp function. Utilizing this strategy we isolated the Hsp90-active resorcylic macrolide, monocillin I. This compound competes with geldanamycin, the prototypic Hsp90 inhibitor for binding to the protein, and impedes the chaperone activity of Hsp90 as demonstrated by the inhibition of the refolding of heat denatured luciferase. It also depletes cellular levels of two Hsp90 client proteins—the estrogen receptor (ER) and the insulin-like growth factor receptor 1 (IGF-1R). Isolation of monocillin I provides proof of principle that our screening strategy can be used effectively for discovering natural product small molecule modulators of Hsp90 function.

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DETERMINATION OF PHORBOL AND LECTINS FROM *Ditaxis heterantha*

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Ditaxis heterantha Zucc., (azafrán de bolita) is a plant of the *Euphorbiaceae* family, which grows in the semiarid regions of Mexico. Its seeds are used by the inhabitants of the regions where it grows as a natural color for foods. Several seeds as leguminous have compounds that hinder the correct absorption of nutrients in some foods. These compounds are called antinutritionals. The presence of some antinutritional factors in *Ditaxis*, such as tannins, cyanogens, saponins and trypsin inhibitor, has been previously studied but low concentrations or absence of them were found. On the other hand, some members of this family have diterpene esters of phorbol which are tumor promoting compounds. Moreover; phytohemaglutinins are present, although they are not characteristic of this family as they are normally found in leguminous. The aim of this work was to determine the concentrations of both phorbol and lectins in *Ditaxis heterantha.*
Quantification of phorbol was carried out by HPLC while lectins were quantified by human erythrocytes hemagglutination and latex agglutination methods.

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ACUTE TOXICOLOGICAL STUDIES OF *Jungia paniculata* AND *Chuquiraga spinosa* (ASTERACEAE) IN EXPERIMENTAL ANIMALS.

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Jungia paniculata and *Chuquiraga spinosa* (Asteraceae) are widespread in the Peruvian Andes between 2500 - 3500 m of altitude. *J. paniculata* (matico) is an herbaceous plant employed in folk medicines as an anti-inflammatory and genitourinary antiseptic. *C. spinosa* (huamanpinta) is a bush used against prostate pathologies and as diuretic and vermifuge. No toxicological investigations have been carried out on these plants. We have previously observed that single oral doses (500 mg/Kg) of 50% EtOH extracts in rat did not resulted any adverse effects. We have now investigated the oral toxicity of 50% ethanolic extract of both plants in rats though determination of LD_{50} values. LD50 values have been determinate by the AOT425StatPgm: Acute Oral Toxicity Statistical Program (175, 550 and 2000 mg/Kg).
Oral doses of 2000 mg/Kg of 50% EtOH extracts have not produced mortality or significant changes in the behavior and gross appearance of internal organs of rats (heart, liver, kidneys, ovaries and pancreas). Nevertheless, an increase of the size of the spleens has been observed but no alterations have detected in further histological analysis.
The low toxicity of *Jungia paniculata* and *Chuquiraga spinosa*, evidenced by high LD_{50} values, and organ integrity, suggest a wide margin of safety for therapeutic doses of these plants.

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CYTOTOXIC, CYTOSTATIC AND GENOTOXIC EFFECTS OF ARGENTATINS A AND B ON PROLIFERATING LYMPHOCYTES

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The cytotoxic, cytostatic and genotoxic effects of argentatins A and B on proliferating human lymphocytes were determined using the in vitro cytokinesis-block micronucleus assay.[&]
Experiments were performed using blood from six healthy, non-smoker donors who had not taken any drug at least 15 days prior to sampling. The test compounds were evaluated at three different concentrations (5, 15 and 25 μM). Argentatin A showed to be cytotoxic at 25 μM and had not cytostatic or genotoxic effects (5-25μM) on proliferating lymphocytes. On the other hand, argentatin B did not decrease lymphocyte viability at concentrations tested. The cytostatic effects in terms of the Nuclear Division Index shown by this compound (at 25 μM) and mitomycin C (1 μM) were not significantly different ($p>0.05$). The results show that argentatin B is a cytostatic and non-genotoxic compound that could be a lead compound in further synthetic research. The differences in the kind of activity found in both argentatins tested will be useful for the determination of structure-activity relationships.
[&] Fenech M., 2000. *Mutation Research 455,* 81.
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GENTIANELLA AUSTRIACA AND _GENTIANA DINARICA_ SIGNIFICANTLY MODULATE MICRONUCLEI FORMATION IN HUMAN LYMPHOCYTES

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Radioprotective effects *in vitro* of *Gentianella austriaca* (A. et J. Kerner) Dostal and *Gentiana dinarica* Beck., extracts was assessed. Micronuclei formation and cell proliferation potential were quantified in cultured peripheral blood lymphocytes; unirradiated controls and irradiated samples (^{60}Co γ rays, dose of 2 Gy) employing cytochalasin block micronucleus test (CBMN). Irradiated blood lymphocytes were treated with extracts as well as flavonoid and xanthone compounds isolated from both species. For each sample parallel culture was set up for measurement of malondialdehide (MDA). Radioprotective properties of 16 samples were evaluated by counting micronuclei in treated cells according to method of Fenech et al (1993). Harvested lymphocytes from parallel cultures were isolated on Lymphoprep, washed in physiological saline, lysed in refrigerator on –37^{o}C and prepared for MDA measurement. Some samples displaied weak clastogenic properties: increase the yield of micronuclei in irradiated sample, which was followed with lowering the proliferation of treated cells and enhancement of MDA level. On the other hand, some displaied radioprotective effects: significantly reduce the incidence of radiation-induced micronuclei, do not affect proliferation of treated cells and significantly reduce MDA level.

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INHIBITION OF INDUCIBLE NITRIC OXIDE SYNTHASE IN ACTIVATED RAW 264.7 MACROPHAGES BY EXTRACTS OF CHINESE MEDICINAL PLANTS

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NO acts as a key signal in the cardiovascular and nervous system, plays a role in host defence and has homeostatic activities.Therefore NO is an interesting target for drug research.
135 hexane, methanol and water extracts of chinese herbal drugs were screened for their effects on inducible nitric oxide synthase in the macrophage cell line RAW 264.7 induced by interferon-γ and bacterial lipopolysaccharide. The effect was determined by measuring nitrite release into culture supernatants.
The water extracts of *Coptis chinensis*, *Lonicera japonica*, *Polygala tenuifolia* and *Sanguisorba officinalis* were highly active, whereas the extracts of *Angelica dahurica*, *Forsythia suspensa*, *Prunella vulgaris*, *Scutellaria baicalensis* and *Senecio scandens* had a moderate inhibitory activity.The identification of the active principles is in process.

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IN VITRO AND *IN* VIVO ANTIMALARIAL PROPERTIES OF ISOSTRYCHNOPENTAMINE, AN INDOLOMONOTERPENIC ALKALOID FROM *STRYCHNOS USAMBARENSIS*.

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Isostrychnopentamine (ISP) is an asymmetric indolomonoterpenic alkaloid isolated from the leaves of *Strychnos usambarensis.* The *in vitro* antiplasmodial activities against five *Plasmodium falciparum* cell lines were evaluated: ISP possessed an *in vitro* IC_{50} near 0.1 µM against all *P. falciparum* cell lines tested (chloroquine-resistant and chloroquine-sensitive lines) and showed antiplasmodial selectivity compared to cytotoxicity on human cell lines. The stage-dependant susceptibility to a short exposure of ISP was then investigated. The ring stage was shown to be the most sensitive one, but all stages were affected by ISP treatment. By means of fluorescence microscopy, it was shown that ISP was not accumulated inside the food vacuole of the parasite. Finally, the *in vivo* antimalarial activities against the *P. berghei* NK173 and *P. vinckei petteri* murine strains were determined. The ED_{50} *in vivo* was about 30 mg/kg/day by intraperitoneal route (after 4 days treatment).

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FLAVONOIDS OF ST. JOHN'S WORT REDUCE HPA-AXIS FUNCTION IN THE RAT

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A common biological alteration in patients with major depression is the activation of the hypothalamic-pituitary-adrenal (HPA) axis, manifested as hypersecretion of adrenocorticotropic hormone (ACTH) and cortisol. The hyperactivity of the HPA axis in depressed patients can be corrected during clinically effective therapy with standard antidepressant drugs such as imipramine, indicating that the HPA axis may be an important target for antidepressant action. We previously showed that a methanolic extract of St. John's wort (SJW) and hypericin, one of its active constituents, both have delayed effects on the expression of genes that are involved in the regulation of the hypothalamic-pituitary-adrenal (HPA) axis [1], whereas the phloroglucinol derivative hyperforin was inactive in the same model [2]. Since flavonoids of SJW are also discussed as active constituents it was of interest to determine whether these compounds can modulate HPA-axis function. Imipramine (15mg/kg), hypericin (0.2 mg/kg), hyperoside (0.6 mg/kg), isoquercitrin (0.6 mg/kg) and miquelianin (0.6 mg/kg) given daily by gavage for two weeks significantly downregulated circulating plasma levels of ACTH and corticosterone by 40-70%. However, none of the compounds tested had an effect on plasma ACTH and corticosterone levels after chronic treatment (daily gavage for 8 weeks).
[1]Butterweck V, Winterhoff H, Herkenham M. Mol Psychiatry 2001: 6: 547-564
[2] Butterweck V, Winterhoff H, Herkenham M. Neuropsychopharmacology 2003: 28: 2160 - 2168.

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A PHARMACOLOGICAL AND TOXICOLOGICAL EVALUATION OF *HALOXYLON RECURVUM*

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Haloxylon recurvum Bunge ex Boiss (Chenopodiaceae) is perennial shrub with glabrous leaves, distributed chiefly from the Mediterranean region to Central and South Asia. It is traditionally reported for its toxic potential and applied externally to treat insect stings.
We investigated *in vivo* toxic potential of crude methanolic extract of whole plant and its n-hexane, chloroform, butanol, ethylacetate, and aqueous soluble fractions by determining their acute toxicity and acute neurotoxicity in mice using Lorke's method and inverted screen test. Effects of crude methanolic extract and its fractions on behavior were also observed. *In vitro* studies were also conducted in order to investigate their antilipoxygenase, antibacterial and antifungal activities.
All the fractions showed narrow margin of safety in mice, except aqueous fraction, which did not produce any mortality even at the highest dose tested (5000 mg/kg). At non-lethal doses, only aqueous fraction (1264.9 mg/kg) was found to produce neurotoxicity in mice. In *in vitro* lipoxygenase inhibition assay, all the testing materials showed significant inhibitory activity. Crude methanolic extract showed the potent antifungal and antibacterial activity against common human pathogens of all the materials tested, indicating synergistic interaction between fractions.
We conclude that the traditionally reported toxicity of this plant is verified by narrow margin of safety of its components. Various extracts and fractions of *H. recurvum* are found to be active in *in vitro* studies. Further studies are required in order to isolate and differentiate the most active and toxic compounds from *H. recurvum*.

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SOME HORMONAL EFFECTS FOR THE HYPHAENE THEBAICA L. Mart

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Hyphaene thebaica L. Mart (Doum) , Arecaceae, is an edible, wild plant, native to Upper Egypt, Sudan, Kenya and Tanzania. It was considered sacred to ancient Egyptians. Seeds of Doum have been found in the pharoh's tombs. It has an antihypertensive activity, and it stimulated the contractions of frog's heart and rat intestine but inhibited uterine contractions. It was the symbol of male strength.
In this report , a new effect was tested on two different extracts of the Doum, they are the testosterone level and the sperm count in adult male rats.
The sterols and the hydrocarbons components of the chloroformic extracts with the promising effects were tested again on the adult male rats to find the components responsible of the biological activity.

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TRANSPORT OF LIGNANS FROM *SCHISANDRA CHINENSIS* ACROSS CACO-2 CELL MONOLAYER

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Fruits and seeds of *Schisandra chinensis* (Schizandraceae) are used in traditional Chinese medicine. The pharmacological activities, including hepatoprotective, antioxidant, anticancer and anti-HIV have been attributed to the presence of lignans. This study examined the bioavailability of three major lignans (Schisandrin C, Gomisin A and Gomisin N) isolated from *S. chinensis.* The intestinal epithelial membrane transport across caco-2 cell monolayers was determined. Quantitation of lignans was performed by an HPLC method using a Phenomenex Luna C18(2) (150x4.6 mm, 5 µm) reversed phase column with sodium dihydrogen phosphate-acetonitrile gradient at a flow rate of 1.0 mL per minute. Apical to basolateral permeability coefficient and percent transport were determined and compared under identical conditions with atenolol. Permeability coefficients were also compared with the reported values for mannitol, propranolol and glucose. Sodium fluorescein was used as the marker for paracellular leakage. These compounds, in the concentration range of 50-200 µM, demonstrated substantial linear transport across the monolayer in the apical to basolateral direction, with moderate to high efflux rates and permeability coefficients.

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THE ENDOCANNABINOID SYSTEM AS A TARGET FOR ALKAMIDES FROM ECHINACEA ROOTS

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Alkamides are the major lipophilic constituents of *Echinacea angustifolia* and *Echinacea purpurea* roots as well as of the aerial parts of *E. purpurea, E. angustifolia* and *E. pallida*. Due to the similarity with anandamide, an endocannabinoid, we have evaluated their ability to bind to cannabinoid receptors CB1 and CB2. Each of the alkamides was recognized by both the CB1 and CB2 receptors and can therefore be considered CB ligands. Most of the alkamides showed good metabolic stability as indicated by the similarity between affinity at CB1 determined in the presence/absence of the protease inhibitor PMSF. Certain alkamides exhibited selectivity for CB2 receptors. The results are discussed in terms of receptor affinities affecting IL-8 elaboration in response to challenge with Rhinovirus, and it is suggested that CB2 binding may be the molecular mode of action of Echinacea alkamides as immunomodulators.

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DIFFERENTIAL DISPLACEMENT RATIOS—A PHARMACOLOGICAL SCREENING STRATEGY EMPLOYED TO IDENTIFY NOVEL PHARMACOLOGICAL ACTIVITY PRESENT IN PLANT EXTRACTS

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The incredible advances in genomics, coupled with major technological restructurings in high-throughput pharmacological screening technologies (HTS) promise to revive lagging interest in natural products drug discovery. Traditional pharmacognosy, with exhaustive extraction and chemical isolation prior to pharmacological testing are counter-intuitive, prohibitively laborious, and expensive for most applications of HTS to large extract libraries or populations of mutant plants. In addition, traditional techniques generally require some foreknowledge of the types of chemical entities that may be discovered. These limitations seriously undermine the discovery of truly novel compounds. Alternatively, pharmacological screening of crude extracts can be plagued by problems related to concentration, overlapping or competing activities, and assay interference. Interpretation of data derived from crude extracts may be difficult and limited to simple inferences of activity. Most importantly, screening of crude extracts may fail to identify highly active extract components that may possess novel structure or chemistry, or may be present at very low concentration. This poster describes our ongoing development of a differential screening strategy, used to detect the presence of novel pharmacological activity prior to exhaustive chemical isolation of individual components. For these studies, we have used radioligand binding displacement assays designed to detect subtype selectivity in crude plant extracts t specific nicAChRs. From radioligand binding data, we assign a concentration-based rank of inhibitory activity, and then measure the ratio of activity in related, increasingly specific assays. This ratio of differential activity (DDR) allows for comparison of selective activity in a crude extract to those of standard compounds or extracts. From the DDR we may infer the presence of novel pharmacological activity in a crude extract. Extracts identified as containing novel pharmacological activity using DDR may then be further characterized using bio-assay fractionation, coupled with more traditional pharmacognosy techniques.

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STUDIES ON ANTISPASMODIC ACTIVITY OF ESSENTIAL OIL FROM *ARTEMISIA MARITIMA* AND *JUNIPERUS EXCELSA*

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Artemisia maritima and *Juniperus excelsa* are known to possess antispasmodic use in traditional medicine and we describe here antispasmodic activity the essential oils from these plants.
Volatile oil was extracted by steam distillation using standard procedure given in British Pharmacopoeia 2001. For pharmacological activity, isolated rabbit jejunum was suspended in 10 ml tissue bath containing Tyrode's solution to assess the antisapasmodic activity.
The essential oil extracted from these plants showed dose-dependent (0.03-0.3 mg/ml) relaxation of spontaneous and K^+ (80 mM)-induced contractions of jejunum, suggestive of antispasmodic mediated though calcium channel blockade, which rationalizes the traditional use of the plant.

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BIOASSAY GUIDED FRACTIONATION OF MALAYSIAN PLANTS FOR POTENTIAL ANTIDIABETIC AGENT.

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Although many drugs are available to manage diabetes, in most instances these are expensive and have adverse effects. Many plants are used in traditional medicine for control of diabetes and could provide useful aids in therapy if their activity could be validated. In this study, an α-amylase inhibition *in vitro* model for rate of formation of maltose was used to screen eighteen plant extracts from Malaysia. The most active extract was the hexane extract of *Phyllanthus amarus* which gave significant inhibitory effect with 21% inhibition at 1 mg/ml and 72.4% inhibition when 0.05 mg/ml preincubated with the enzyme first. The study showed that the preincubation method had more inhibition effect than non preincubation method.
The hexane extract of *Phyllanthus amarus* was fractionated by vacuum liquid chromatography using hexane, chloroform and methanol. Fractions with same TLC profile were pooled to give 6 fractions. Each fraction was tested for bioassay and PA4, PA5 and PA6 were the most active with 83%, 70% and 65% inhibition respectively. Work is currently in progress to isolate novel α-amylase inhibitors from these fractions using column chromatography.

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ANTIOXIDANT AND LFA-1/ICAM-1 DEPENDENT CELL ADHESION INHIBITORY ACTIVITY OF POLYPHENOLIC COMPOUNDS FROM *VERBASCUM SALVIIFOLIUM*

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The role of antioxidants in preventing radical induced cytotoxicity and tissue damage in various human diseases is increasingly recognized. In this respect, special interest was focused on *Verbascum salviifolium*, which is reported to have medicinal importance in Turkey. Investigation on *Verbascum salviifolium* had led to the isolation of phenylethanoids, flavone and neolignan glucosides. Our previous screening on 11 phenolic compounds from this plant demonstrated a strong activity towards DPPH radical in TLC aoutographic assay. In our continuing studies, the inhibition on DPPH radical of the phenolic compounds was also measured as spectrophotometrically (Positive controls were (±)-α-tocopherol and 3-BHA). All compounds displayed significant, dose-dependent activity. On the other hand, the antioxidant potentials of the isolated compounds were tested based on their *in vitro* inhibitory effects on reactive oxygen species within cancer cell lines as flow-cytometrically. According to this method, verbascoside (IC_{50} 4.0 μg/ml) was found to be the most potent DPPH radical scavenger, and it was followed by forsytoside B (IC_{50} 16.4 μg/ml), luteolin 7-*O*-glucoside (IC_{50} 17.0 μg/ml) and angoroside A (IC_{50} 17.3 μg/ml) (Positive control was vitamin C: IC_{50} 4.4 μg/ml). To determine their effects on immune response and inflammation, the isolated compounds were also evaluated for their inhibition of aggregation and adhesion of cancer cell lines. The moderate inhibition was achieved by verbascoside (IC_{50} >62.5 μg/ml) (Positive control was cytochalasin B: IC_{50} 43.0 μg/ml).

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ETHNOMEDICINE IN KOREA : THE PAST AND THE PRESENT

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From the beginning of human existence, every culture and people on earth used natural crude resources such as the herbs, leaves, barks, roots, flowers and minerals as medicines. The Korean peninsula, located between the vast Chinese mainland and Japan, has a unique cultural background that goes back five thousand years. In ancient times, the region was deeply influenced by Chinese culture, and traditional medicine in Korea was no exception.
At the start of the 20th century, missionaries from western countries introduced new concepts and techniques of medicine. And during the last century, there was enormous development in modern medical sciences. Even today, however, natural medicine - including folk medicine - plays an important role in Korean health care.
In Korea, a total of 514 crude natural drugs are officially recognized as having medicinal value by the government. That is 131 kinds in Korean Pharmacopoeia (K.P. VIII, 2002) and 383 kinds in Korean Herbal Pharmacopoeia (K.H.P., 2002).
In this presentation, we will review and discuss traditional Korean medicines as it has evolved over the past three thousand years.

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ANTISPASMODIC EFFECT OF THE ETHNOL EXTRACT OF *HYOSCYMUS NIGRUM* SEEDS IS MEDIATED THROUGH DUAL BLOCKADE OF MUSCARINIC RECEPTORS AND CALCIUM INFLUX.

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The seeds of *Hyoscymus nigrum* L. (Hn) have been used in traditional medicine for the treatment of a variety of diseases particularly in spasmodic conditions, such as colic and asthma. We studied the ethanol extract of *H. nigrum* seeds (Hn.Cr) for its possible spasmolytic and bronchodilator activities to rationalize these medicinal uses.
Plant material was soaked in ethanol for 3 days thrice and the combined filtrate evaporated to dryness by Rotary evaporator. Segments of rabbit jejunum and guinea-pig tracheal rings were suspended separately in a 10 ml tissue bath containing Krebs solution at 37 ˚C. Responses were recorded on a grass polygraph.
In jejunum Hn.Cr caused a dose-dependent (1–300 µg/ml) relaxation of spontaneous and K^+-induced contractions, suggestive of calcium channel blockade (CCB). In trachea, it inhibited both carbachol and K^+-induced contractions at the dose ranges of 0.3-3 and 1-100 µg/ml respectively, suggestive of a dual mechanism in its bronchodilator effect. This study provide sound mechanistic base for the traditional use of the plant in colic and asthma.

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CHARACTERIZATION OF SYNTHETIC DIHYDROBENZOFURAN LIGNANS WITH ANTILEISHMANIAL ACTIVITY

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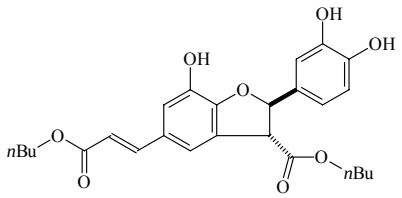
In a series of synthetic dihydrobenzofuran lignans and related benzofurans, the dimerisation product of some lipophylic esters of caffeic acid, such as compound **2g**, showed a high activity against *Leishmania donovani* (axenic amastigotes) (IC_{50} 0.12 µg/ml). The antileishmanial activity was confirmed in an infected macrophage assay (IC_{50} 0.19 µg/ml). On human L6 cells compound **2g** showed an IC_{50} of 6.6 µg/ml. QSAR models for the cytotoxic and antileishmanial activity were generated using *Quasar* receptor surface modelling.



2g

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CYTOTOXIC EVALUATION OF A NEW COUMARIN ISOLATED FROM *CASIMIROA PUBESCENS* (RUTACEAE).

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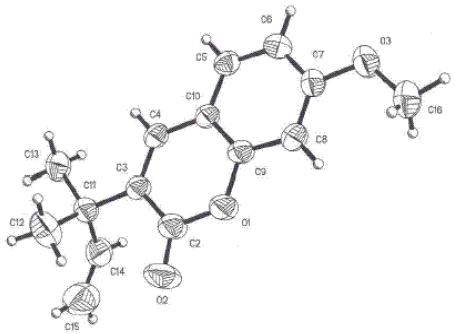
Recently we published the isolation of the cytotoxic pubesamides A and C from *Casimiroa pubescens* seeds[a]. Now we wish to report the isolation and cytotoxic evaluation of pubemarine (**1**), a new coumarin isolated from *C. pubescens* root bark. The structure of (**1**) was determined by chemical, spectroscopic and crystallographic methods. The cytotoxic activity of (**1**) was evaluated in five human cancer cell lines using the SRB assay[b]. The presence of the double bond in (**1**) is essential to the cytotoxic activity, since its dihydro derivative was inactive.



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α-AMYLASE INHIBITORS EXTRACTED FROM TRADTIONALLY USED DIABETIC PLANTS AND THEIR POTENTIAL AS NOVEL ANTI-DIABETIC TREATMENTS.

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A recent review[1] showed that 81% of traditional antidiabetic plants screened for diabetes lowered blood-glucose levels, accounting for 1123 species, 725 genera and 183 families. This inspired research into the development of an assay to test for anti-diabetic activity based upon the inhibition of the digestive enzyme pancreatic α-amylase.
The development and testing of 30 traditional Indian plants[2] resulted in hexane extracts of *Murraya koenigii* Spreng. (Rutaceae) and *Cyperus rotundus* L. (Cyperaceae) showing significant α-amylase inhibitory activity. A sequential soxhlet extraction using hexane, chloroform, methanol and water confirmed that the hexane extract of *Murraya koenigii* (1 mg/mL) and the methanolic extract of *Cyperus rotundus* (1 mg/mL) contained the highest levels of the active inhibitory compounds (44.79, 61.95% inhibition respectively).
Assay-guided fractionation of *Murraya koenigii* using techniques including flash chromatography have yielded fractions with significant activity (54.37. 88.15 and 45.78% inhibition) and isolation of α-amylase inhibitory compounds continues.

This work is supported by a grant from Merck Research Laboratories, Rahway NJ, USA

1)Marles, R. *et al.* (1995) *Phytomed.* 2, 137-189. 2)Bawden, K. *et al* (2002) *J. Pharmacy and Pharmacol* 54 (Sept Suppl) 580.

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IN-VITRO ANTIPLASMODIAL AND ANTITRYPANOSOMAL ACTIVITY OF MARULA (SCLEROCARYA BIRREA (A.RICH.) HOCHST)

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Malaria and Trypanosomiasis are infectious diseases which pose serious health threats to the tropical and sub-tropical regions of the world, and majority of the countries in these regions are developing and cannot afford Western drugs, so alternative treatments have to be sought.
The bark of Marula (*Sclerocarya birrea*) is used in Southern Africa for the treatment of fevers and malaria. Previous screening of the hexane, DCM and methanolic extracts, along with those of 6 other traditional plants, showed that it had significant and selective in-vitro antiplasmodial activity (using *Plasmodium falciparum* K1 and 3D7 and the ^{3}H-hypoxanthine assay) and antitrypanosomal activity (using *Trypanosoma brucei rhodesiense* STIB900 and the Alamar Blue assay). Cytotoxicity was also tested against a mammalian KB cell line.
The DCM extract of the bark which was the most active, has been subjected to further investigation and activity guided fractionation, using different chromatographic methods. This is in progress to isolate the active compounds.

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IN-VITRO SCREENING OF MALAYSIAN PLANTS BY INDUCTION OF INSULIN SECRETION FOR POTENTIAL ANTIDIABETIC EFFECTS.

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Diabetes mellitus has been treated orally with herbal remedies based on folk medicine since ancient times. Traditional herbal remedies are still in use by diabetic patients especially in Third World countries. The present work was carried out to investigate the potential antidiabetic effects of aqueous extracts of 9 Malaysian plant species. These were investigated for stimulatory effect on insulin secretion.
The effect of the aqueous extracts on insulin secretion was examined using a mouse insulinoma cell line (min6 cells). Min6 cells were selected due to their ability to respond to some known secretagogues such as PMA, Forskolin, IBMX and Tolbutamide. The extracts were tested at a concentration of 1 mg/ml. The cells were incubated with the extracts at 37°C for 1 hour and the amount of insulin secreted was quantified using radioimmunoassay. 3 extracts including *Parkia speciosa* seed, *Phithecellobium jiringa* seed and pericarp were found to have a stimulatory effect on insulin secretion. The viability of the cells after being exposed to the extracts was examined using Tryphan Blue Exclusion Test. All extracts were found to be not toxic to the cells.

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PRELIMINARY STUDIES ON *PURWOACENG* (*PIMPINELLA ALPINA* KDS), AN OLD FAMOUS JAVANESE HERBAL APHRODISIAC

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Roots of *Purwoaceng* (*Pimpinella alpina* KDS) is an old famous aphrodisiac which has been used by the Javanese people since the old times especially in Mid Java. This plant grows very high in the mountains between 2000 to 3000 m above the sea level and can be found in Mid, West and East Java,
These preliminary studies included studies on the chemical content profile with HPLC method of the extract and extract fractions, its secondary androgenic effect on the grows of cock's crown comb of one day old male chickens and the rising of libidos in male rats.

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SOME MOLLUSCICIDAL COMPOUNDS FROM THE LATEX OF *EUPHORBIA CONSPICUA*

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Schistosomiasis is a major source of morbidity and mortality for developing countries in Africa, South America, the Caribbean, the Middle East, and Asia. Most of human schistosomiasis is caused by one of five *Schistosoma* trematodes. A combined application of molluscicides, for snail control, and chemotherapy of the affected population is one of the most effective strategies to reduce the prevalence of schistosomiasis in endemic areas. The use of plants with molluscicidal properties is a simple, inexpensive and technologically suitable for focal control of the snail vector.
Traditionally the *Euphorbia conspicua* N. E. Br latex is used in the treatment of leprosies wounds and dermatitis in general, despite its irritant properties. The latex was fractionated in a triterpenic fraction and two irritant fractions. The fractions show very high molluscicidal activity, with values of the lethal concentrations (LC_{90}) of 10.960, 1.645 and 0.121ppm. The irritant fraction II afforded a diterpenoid of the ingenane class very similar to the milliamines, that are very good molluscicidal agents. Other molluscicidal compounds are presented to.

This work was partially funded by the project POCTI/QUI/39380/2001 of Fundação para a Ciência e Tecnologia with FEDER funding and Textile and Paper Materials Center.

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CHEMOPREVENTIVE POTENTIALS OF *TABEBUIA AVELLANEDAE* AND ITS ACTIVE COMPOUNDS AGAINST SKIN CARCINOGENESIS

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Bignoniaceous plants of the genus Tabebuia grow throughout southern North America to South America and has many colloquial names: Ipe, Ipeuva, Aipe, Peuva, Lapacho and Taheebo in ancient Inca.The bark of the plant has been used as diuretic and astringent, and now grows well in the semitropical regions of Brazil. The recent rediscovery of *Tabebuia* plants effective drugs for cancer has made *T. avellanedae*, an important medicinal resource.
In continuation of our chemopreventive studies, crude extracts and including compounds were screened as potential chemopreventive agents by using *in vitro* short-term TPA induced Epstein-Barr virus early antigen(EBV-EA) activation assay. In additional studies, crude powder(obtained from Taheebo Japan, co) ethanol ext. and isolated naphthoquinones were examined for chemopreventive test (DMBA/TPA)and (UVB/TPA) of anti-tumor promoting and initiating effects on mouse carcinogenesis model.
In our evaluation, crude ext. and one naphthoquinone treated Group cause 60-70 % reduction in tumor production. These findingsare important for the interpretation of intervention studies of naturally occurring compounds in rodent and for clinical design.

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CANCER CHEMOPREVENTIVE AGENTS, SERRATANE-TYPE TRITERPENOIDS FROM *PICEA JEZOENSIS*

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Seven serratane-type triterpenoids isolated from the cuticle of *Picea jezoensis* (Pinaceae) were studied their possible inhibitory effects on
Epstein-Barr virus early antigen(EBV-EA) activation induced TPA. All compounds showed strong inhibitory effects on the EBV-EA activation, being stronger than that of Oleanolic acid, which exerts on cancer preventive activity in animal carcinogenesis models. Among these compounds, 13 α , 14 α −epoxy-3 β -methoxyserratan-21 β -ol and 3 β −methoxy-21 α −hydroxyserrat-14-en-29-al were investigated for inhibitory effects in two-stage mouse skin carcinogenesis test on using DMBA as initiator and TPA as promoter.
13α, 14 α −Epoxy-3β−methoxyserratan-21β−ol was found to exhibit the excellent anti-tumor promoting activity in in vivo carcinogenesis. This presentation will summarize the evidence of detail on going research investigating compounds as chemoprevention for human.

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CHEMOPREVENTION OF NITRIC OXIDE DONOR INDUCED CARCINOGENESIS BY NATURAL SOURCE COMPOUNDS AND EVALUATION OF THE ROLE OF MAP KINASE SIGNALING PATHWAY

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The present study was carried out to examine the chemopreventive activity of natural source compounds, colorants and curcumin etc. on nitric oxide(NO) induced carcinogenesis. These experiments also were to demonstrate that exposing the skin of SENCAR mice to natural source compounds prior and during peroxynitrite(PN) treatment inhibits selected intermediate pathway signaling in PN induced carcinogenesis model, using Western blotting assay. In our observation, natural source comounds treated group cause about 60-70 % reduction in tumor after 20 weeks of experiment. Western blotting analysis of qualified epidermal particle protein showed that H-Ras, MEK and p38 expression in mouse skin were abnormal responsible for PN treatment in a time- and dose- dependent manner. The results suggested that the anti-initiating effect of several compounds, may play a role in the inhibition of NO bioaction.

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BIOLOGICALLY ACTIVE TETRANORTERPENOID DILACTONES FROM PLANT PATHOGENIC FUNGI

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The ethyl acetate extract of the plant pathogenic fungus *Oidiodendrum sp*. showed potent activity against *Plasmodium falciparum in vitro* cell cultures. Bioassay-guided fractionation of this extract yielded eight new together with four previously reported tetranorditerpenoid dilactones. Some of these compounds showed potent antimalarial activity with varying degrees of selectivity. Their activity and structure activity relationships will be presented.

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FUNGI AS A SOURCE FOR NOVEL MEDICINES

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Fungi has been used in diet and traditional medicine for thousands years. The discovery of penicillin in 1928 and subsequently other anti-microbial and anti-tumor antibiotics has scientifically proved the medicinal importance of fungi. However, although fungal secondary metabolites represent a large portion of the known anti-infective and anti-tumor biologically-active compounds, of the conservatively-estimated 1.5 million fungal species, only approximately 5% have been described, while only 0.3% have been screened for biological activity. Exploration of ecologically "unusual" habitats, has led to the discovery of a considerable number of novel and even more diverse microbial species. These untapped microbial "factories" possess immense potential for discovery of novel compounds and biotransformation as source of valuable drugs.

A series of novel or untapped fungal species has been explored in this study for their *in-vitro* cytotoxic activity. Fungal extracts were tested by an *in-vitro* assay based on the NCI (National Cancer Institute) method for screening for natural products with anticancer activities, against cancerous and normal cell lines {COR-L23 (Human Caucasian lung large cell carcinoma), C32 (Human Amelanotic melanoma), ACHN (Human renal Adenocarcinoma), HK-2 (Human normal kidney cells line), MRC-5 (Human foetal lung, fibroblast-like)}.

Crude extract ($CHCl_3$:MeOH) of the filamentous fungus coded "P" for confidentiality purposes showed the most potent cytotoxic activity against COR-L23 cell line with IC_{50} 5.23µg/ml. Vacuum Liquid Chromatography was used as the first step in the bioactivity guided fractionation during which 15 (P1-P15) fractions were obtained. Cytotoxicity was located in the fractions P7-P11, and the most active being P9 IC_{50} 1.51µg/ml. Further work is currently in progress to elucidate and identify the active compound(s).

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STRUCTURALLY DIVERESE NATURAL PRODUCT AGONITS OF LXR FROM GARCINIA HUMILIS. (PART 4 OF 4)

Kithsiri Herath,* Hiranthi Jayasuriya, John G. Ondeyka, Robert Borris, Jianhua Wang, Neelam Sharma, Karen MacNaul, John Menke, Anne W. Dombrowski, Marvin J. Schulman, Christine MacCallum, Suzy S. Kwon, Sheo B. Singh.
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Liver X Receptors (LXR) are members of a superfamily of nuclear hormone receptors represented by two subtypes, LXRα and LXRβ. The α-subtype is predominantly present in liver whereas the β-subtype is ubiquitously expressed. Oxysterols have been identified as endogenous ligands for both subtypes. These receptors have been shown to play a role in cholesterol homeostasis. LXRs form heterodimers with the retinoid X receptor, RXR, to regulate the expression, either directly or indirectly, a number of genes involved in cholesterol and fatty acid metabolism. It has been shown that a non-steroidal LXR agonist causes increased expression of ABCA1 and raises the HDL levels in mice. ABCA1 mediates the efflux of cholesterol out of the cells and onto the ApoA1 protein of a HDL particle. Therefore, LXR agonists are expected to provide an opportunity for the development of drugs to increase reverse cholesterol transport and thus decrease peripheral cholesterol levels. Evaluation of our natural product library of microbial, plant and marine extracts in the LXR (liver X receptor) using HTRF binding assay led to the isolation of diverse classes of natural products. Bioassay-guided fractionation of hexane extract of bark and stem of *Garcinia humilis* (Vahl) produced a new polyisoprenylated benzophenone named Guttiferone H. Guttiferone H showed EC_{50} value of 3.4 μM in the LXR assay. Structure elucidation and biological activity will be presented.

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STRUCTURALLY DIVRESE NATURAL PRODUCT AGONISTS OF LXR FROM PLANT AND MARINE SOURCES (PART 3 OF 4)

Hiranthi Jayasuriya*, Kithsiri Herath , John Ondeyka, Jianhua Wang, Neelam Sharma, Karen MacNaul, John Menke, Anne W. Dombrowski, Marvin J. Schulman, Christine MacCallum, Suzy S. Kwon, Robert P. Borris , Sheo B. Singh. Merck Research Laboratories, P. O. box 2000, Rahway, New Jersey, USA
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The efficient regulation of cholesterol biosynthesis, metabolism, acquisition, and transport is an essential function of mammalian cells. A high level of cholesterol is a major risk factor correlated with the occurrence of coronary heart disease and stroke. The nuclear receptor LXR (liver X receptor) is a specialized sensor for cholesterol. Activation of LXR by oxysterols leads to the up-regulation of ABC transport proteins. ABC G5 and G8 have been associated with cholesterol absorption and excretion and ABC A1 with cholesterol clearance via HDL particles. Accordingly, the development of potent selective small molecule agonists, partial agonists and antagonists of LXR can lead to potential therapeutic agents for the treatment of diseases linked to cholesterol and bile acid metabolism and homeostasis. Bioassay-guided fractionation of plant and marine extracts by a HTRF binding assay led to identification of a variety of oxidized lanostanes, two new cycloartanes, triterpenoids, diterpenoids including isopimaranes and miscellaneous marine steroidal compounds as LXR agonists. Plant extracts of *Unonopsis glaucopetalata* and *Minquartia guianensis* yielded Lanosta-7, 9(11), 24-triene-3, 5-diol as the most active and selective LXR agonist with an EC50 of 30nM (full agonist) for Lxr α and >50μM for Lxr β.Isolation,

structure elucidation and biological activities of these compounds will be presented.

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STRUCTURALLY DIVRESE NATURAL PRODUCT AGONISTS OF LXR FROM MICROBIAL SOURCES (PART 2 OF 4).

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Evaluation of our natural product library of microbial, plant and marine extracts in a liver X receptor (LXR) binding assay led to the identification of diverse classes of natural product ligands. LXR-α and –β are members of the nuclear hormone receptor superfamily, and have been shown to be involved in the the regulation of HDL (high density lipoprotein) cholesterol metabolism and transport. Oxysterols are natural ligands of LXR and therefore it is not surprising that more than half of the compounds identified as LXR ligands from all sources were steroidal or triterpenoids. Bioassay-guided fractionation of microbial extracts, mainly fungi and actinomycetes, led to identification of steroids, cyclic depsipeptides, hydroxyl phenyl alkanes and new pentacyclic *bis*-spiro-pyran aromatic ketones. Six steroidal compounds, including cycloeucalenone a cycloartane, and viperidone, were isolated from fungi with IC_{50}'s ranging from 0.1-28 μM. Fungal extracts also yielded two cyclic depsipeptides, enniatin and beauvericin, with IC_{50}'s between 2-4 μM. The dihydroxy phenyl alkanes isolated from an actinomycetes were less potent, with IC_{50}'s between 12 and 40 μM. The new chlorinated pentacyclic *bis*-spiro-pyran aromatic ketone was isolated from a *Streptomyces* sp. with an IC_{50} of 18 μM. Isolation, structure elucidation and biological activities of these compounds will be presented.

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NEW CLASS OF CANCER CHEMOPREVENTIVE AGENTS DERIVED FROM THE MARINE NATURAL PRODUCT SARCOPHINE

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Five new semi-synthetic derivatives of the marine natural product sarcophine were found to significantly inhibit a skin tumor promotion. They showed *in-vitro* activity in the inhibition of Epstein-Barr Virus Early Antigen Activation superior to Sarcophytol-A, a known cancer chemopreventive agent. In the *in-vivo* mouse skin test, they reduced the percentage of mice bearing papilloma and the number of papilloma per mouse. The great reduction in both of these two criteria indicates the potential of these compounds for further development.
The results of these assays in comparison to known cancer chemopreventive agents as well as the anti-proliferation activity and toxicity will be presented.

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SEARCHING FOR NEW COMPOUNDS WITH ANTI-INFLAMMATORY PROPERTIES IN *WITHERINGIA SOLANACEA* L´HER (SOLANACEAE)

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Witheringia solanacea L'Her (Solanaceae) was selected from a EU-funded program (AINP) that utilized various targets of the NF-κB activation cascade to identify new natural products inhibitors of this factor.

Witheringia solanacea is traditional used in Panama as an anti-hypertensive remedy and for general pain. In Mexico it is employed in the treatment of anemia and for skin problems such as fungal infections and acne, and the fruit is used to prepare "salsa".

The leaves of the plant were extracted by soxhlet using solvents of increasing polarity. A luciferase assay was performed to test the biological activity of the extracts. HeLa cells were stably transfected with a luciferase reporter gene controlled by the IL-6 promoter. PMA was used as stimulant of NF-κB at 50 ng/ml for 7h. Two compounds were isolated from the chloroform extract, and were characterized as physalins B and F on the basis of spectroscopic data. This poster will discuss the chemical and biological activity of the extracts and compounds.

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TROPICAL-INDIGENOUS MARINE SPONGES AS SOURCES OF CYTOTOXIC COMPOUNDS

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Marine organisms have shown highly functional enzymatic capabilities to produce secondary metabolites with highly complex chemical structures able to display biological properties as anti-tumoral, anti-bacterial, anti-parasite, etc. The main groups investigated comprise: ascidians, algae, bryozoans, soft-corals and sponges, whilst the most usual compounds are: sterols, phenols, peptides, lactones and terpenes. The discovery of citarabine, a synthetic derivative of a nucleotide-analogues family identified in the Caribbean sponge *Cryptothethya sp.* is a good example of the therapeutic potential of the marine ecosystem. The aim of this research was to evaluate the potential of some tropical-indigenous marine sponges as new sources of cytotoxic compounds. Thirty-five fractions from seven marine sponges were evaluated. The biological activity was analysed by the SRB assay for cell growth, using the human cancer cell lines as *in-vitro* models of cytotoxicity. A range of increasing dilutions (12 replicas) was prepared from a stock solution of 20mg/ml. Cells were culture in 96-well plates at 37°C, and 5% CO_2 atmosphere, exposed to extracts for 72h and then left recovery for three days. Appreciable growth inhibition was observed (IC_{50} = 4.63μg/ml). The findings suggest that the marine organisms studied have an excellent potential as new sources of cytotoxic compounds.

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ACTIVITY OF (+)- AND (-)-USNIC ACIDS AGAINST BACTERIA GROWN IN BIOFILM *vs.* PLANKTONIC PHASE

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As many micro-organisms grow in biofilms in the body, a better correlation between *in vitro* and *in vivo* antimicrobial activity can often be obtained by screening the relevant test substances against organisms grown in a biofilm rather than the conventional planktonic phase. One of the most accessible biofilms is dental plaque formed by oral commensal organisms, predominantly streptococci. Usnic acid occurs in lichens as the (+)- or (-)- enantiomeric form depending on species and has been used commercially in dental products such as toothpaste and mouthwash apart from use in deodorants, antiseptic creams and weight-reducing products. The (+)- and (-)-forms of usnic acid were isolated from *Cladonia arbuscula* and *Alectoria ochroleuca* respectively and tested for activity against several bacteria, including oral commensal bacteria and oral strains of *Candida albicans.* A comparison of the susceptibility of the organisms was made that related to their growth in a planktonic-phase culture compared with growth in a simple mono-culture biofilm. Both enantiomers showed activity against all Gram positive bacteria tested and there was no difference in their degree of activity. *Streptococcus sanguis* was the most sensitive of the strains tested, with minimum inhibitory (MIC)- and minimum bactericidal (MBC)- concentrations in the planktonic culture being identical, 3.9 μg/ml. As expected, bacterial strains were considerably more resistant to usnic acid when they were grown in a biofilm compared with growth of the same strains in the planktonic phase.

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EFFECT OF SELECTED BENZYLBENZOATES ON THE CALMODULIN DEPENDENT ACTIVITY OF THE ENZYME cAMP PHOSPHODIESTERASE

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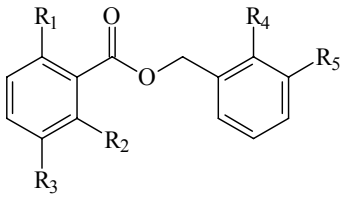
The effect of several natural benzylbenzoates (**1**-**10**) with spasmolytic properties on CaM dependent cAMP phosphodiesterase (PDE) activity was investigated. The results indicated that the metabolites inhibited the activation of the target enzyme in the presence of CaM with potencies similar or higher than chlorpromazine, a well known CaM inhibitor. The IC_{50} values of the active compounds ranged from 12.3 to 23.7 μM. Thus, these natural products are Cam inhibitors and may exert their biological action by inhibiting CaM-dependent processes.

	R_1	R_2	R_3	R_4	R_5
1	OMe	OMe	H	H	*β*-D-glucose
2	OMe	OMe	H	H	OH
3	OMe	OMe	H	H	H
4	OH	H	H	OMe	H
5	OMe	OMe	H	H	OMe
6	OH	OMe	H	H	H
7	OH	OMe	H	H	H
8	OMe	OMe	OMe	H	H
9	OH	OMe	OMe	H	H
10	OMe	OMe	H	H	OMe



Supported by a grant of CONACyT

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CONVOLVULACEOUS RESIN GLYCOSIDES INDUCE NON-SELECTIVE PORE FORMATION IN CELL MEMBRANES

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The purgative convolvulaceous resin glycosides are a family of amphiphilic lipopolisaccharides exhibiting potent, broad-spectrum bactericidal and cytotoxic activities. In an attempt to unravel the mechanism of action of this class of biodynamic compounds, we have studied the interaction of selected members of oligosaccharides from the tricolorin series, major constituents of *Ipomoea tricolor,* with model membranes. In *Sf9* cell membranes of the insect *Spodoptera frugiperda*, the tested oligosaccharides induced current fluctuations suggesting the formation of non-selective pores. Based on these studies, we propose that the resin glycosides kill target cells, at least in part, by interacting with their plasma membrane to induce possible ion flux perturbation. The biological effects confine to the whole molecule suggest that the activity for this type of amphipatic oligosaccharides could be a result of a membrane-permeabilizing function as hypothesized by a membrane insertion model for tricolorin A.

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INHIBITION OF LEUKOTRIENE BIOSYNTHESIS BY QUINOLINONE ALKALOIDS FROM THE FRUITS OF *EVODIA RUTAECARPA*

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The *n*-hexane extract of the fruits of *Evodia rutaecarpa* (Juss.) Benth. (Rutaceae)showed considerable inhibiting effect on leukotriene biosynthesis in human neutophile granulocytes. Bioassay guided fractionation of the extract led to the isolation of the 5 quinolinone alkaloids 1-methyl-2-nonyl-4(1H)-quinolinone, 1-methyl-2-(6*Z*)-6-undecenyl-4(1H)-quinolinone, 1-methyl-2-(4*Z*,7*Z*)-4,7-tridecadienyl-4(1H)-quinolinone, evocarpine and 1-methyl-2-(6*Z*,9*Z*)-6,9-pentadecadienyl-4(1H)-quinolinone. The compounds exhibited inhibitory activity on leukotriene biosynthesis in our newly developed bioassay using human polymorphonuclear granulocytes, with IC_{50} values of 12.1, 10.0, 10.1, 14,6 and 12.3 µM respectively. Structure elucidation of the compounds was achieved by 1 D and 2 D NMR experiments.

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LEUKOTRIENE METABOLISM INHIBITORY ACTIVITY OF NEOLIGNANS ISOLATED FROM THE SEEDS OF *MAGNOLIA GRANDIFLORA* L.

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Magnolia grandiflora L. (Magnoliaceae) was among other *Magnolia* species a widely used medicinal plant of the Native Americans. Its use comprised illnesses such as fevers, arthritis and rheuma which are usually associated with inflammatory processes. Moreover, the seeds of the plant have been used e.g. in Mexican folk medicine to treat epilepsy in children.

It is known that the plant contains large amounts of the germacranolide parthenolide in the leaves and in the bark. The fruits do not contain sesquiterpenoid compounds but contain neolignans such as magnolol and honokiol besides fatty oils. The various activities of the neolignans are well-documented since they constitute the major active compounds of several Asian *Magnolia* species (e.g. the Chinese houpo medicine = cortex of *M. officinalis*).

In this investigation, we report on the activity of several neolignans isolated from the seeds of *Magnolia grandiflora* on leukotriene metabolism in an *ex vivo* bioassay using activated human leukocytes. It could be shown that honokiol has by far the highest activity, followed by magnolol and methylated neolignans.

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CYNATROSIDE B FROM *CYNANCHUM ATRATUM* HAS ANTI-ACETYLCHOLINESTERASE AND ANTI-AMNESIC ACTIVITIES

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We previously reported that seven pregnane glycosides including cynatroside B isolated from the roots of *Cynanchum atratum* significantly inhibited acetylcholinesterase (AChE) activity. In the present study, we characterized the mode of AChE inhibition of cynatroside B, the most potent of these isolated pregnane glycoside inhibitors. We also examined the anti-amnesic activity of cynatroside B. Cynatroside B inhibited AChE activity in a dose-dependent manner and its IC_{50} value was 3.6 μM. The mode of AChE inhibition of cynatroside B was reversible and noncompetitive in manner. Moreover, cynatroside B (1.0 mg/kg body weight i.p.) significantly ameliorated memory impairments induced in mice by scopolamine (1.0 mg/kg body weight s.c.) as measured in the passive avoidance and the Morris water maze tests. We suggest, therefore, that cynatroside B has both anti-AChE and anti-amnesic activities that may ultimately hold significant therapeutic value in alleviating certain memory impairments observed in Alzheimer's disease.

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TWO NOVEL HEPATOPROTECTIVE STILBENE GLYCOSIDES OF *ACER MONO* LEAVES AGAINST H_2O_2 –INDUCED TOXICITY IN PRIMARY CULTURES OF RAT HEPATOCYTES

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The methanolic extract of *Acer mono* MAXIMOWICZ (Aceraceae) leaves showed significant protective activity against H_2O_2-induced toxicity in primary cultures of rat hepatocytes. Using hepatoprotective activity-guided isolation, two novel stilbene glycosides (**1**, **2**) and seven known compounds were isolated from the EtOAc fraction of the methanolic extract: 5-methoxy-(*E*)-resveratrol 3-*O*-β-D-glucopyranoside (**1**), 5-methoxy-(*E*)-resveratrol 3-*O*-β-D-apiofuranosyl-(1→6)-β-D-glucopyranoside (**2**), quercetin, quercitrin, eriodictyol, naringenin, eriodictyol 7-*O*-β-D-glucopyranoside, 5,7-dihydroxychromone 7-*O*-β-D-glucopyranoside and naringenin 7-*O*-β-D-glucopyranoside. Among these compounds, **1** and **2** significantly reduced the release of glutamic pyruvic transaminase into the culture medium from the H_2O_2-injured rat hepatocytes. Furthermore, **1** and **2** significantly preserved the glutathione level and activities of antioxidant enzymes such as superoxide dismutase, glutathione reductase, glutathione peroxidase reduced by the H_2O_2 insult in primary cultures of rat hepatocytes. These results suggest that **1** and **2** exert hepatoprotective activities by maintaining the antioxidant redox

system.

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INVESTIGATION OF RADICAL SCAVENGINGOF CHLOROFORM , METHANOL EXTRACTS AND FLAVONOIDS OF TEUCRIUM POLIUM L.(LAMIACEAE) FROM IRAN, PAPOLATION KERMAN

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Teucrium polium(kalpureh) has been used in traditional medicine for many purpo-ses such as antibacterial, antiinflammatory, analgesic and antidiabetes mellitus, therefore we decided to examine the antioxidant activity of its $CHCl_3$ and MeOH extract by using free radical scavenging (DPPH) method.The plant was collected from Kerman province in May 2002. $CHCl_3$ and MeOH extract were prepared by perculation and concentrated at reduced pressure.The antioxidant activity of MeOH extr. (IC_{50}=262µg/ml) after 30 min. was more than $CHCl_3$ extr. (IC_{50}=683µg/ml) and Vite.E (IC_{50}=5390µg/ml) but less than BHA (IC_{50}=57.5µg/ml).The MeOH extr.was chromatographed on a silicagel column and Watman No.3 PC, 6 compounds were isolated and identified by spectroscopic methods(MS,UV,NMR) as: Apigenin 7-rhamnoglycoside, Kaempferol 3,7,O-diglycoside,Apigenin 6,8,C-diglycoside, Scutellarin, Isoscutellarin and Teucroside.

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A PRELIMINARY STUDY ON THE ANTIOXIDANT AND ANTI-INFLAMMATORY ACTIVITY OF *SIDERITIS PERFOLIATA* SUBSP. *PERFOLIATA*

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Sideritis species (common Greek name "mountain tea") are occurring mainly in the Mediterranean area and are often used as herbal teas in Greece as well as in Turkey, because of their anti-inflammatory, antirheumatic, digestive, anti-ulcer and antimicrobial activities. However, there are no intensive chemical and biological works on the constituents of *Sideritis perfoliata* subsp. *perfoliata*. This research was conducted to isolate the major components from the aerial parts of *S. perfoliata* subsp. *perfoliata* and to evaluate their antioxidant and anti-inflammatory activities *in vitro*. Three flavonoid derivatives and one phenylethanoid were isolated so far, by repeated chromatographic isolation of butanol soluble fraction. Their structures were elucidated as isoscutellarein-7-O-[6′′′-O-acetyl-*β*-D-allopyranosyl-(1→2)]-6′′-O-acetyl-*β*-D-glucopyranoside (**1**), isoscutellarein-7-O-[6′′′-O-acetyl-*β*-D-allopyranosyl-(1→2)]-*β*-D-glucopyranoside (**2**),4′-O-methylisoscutellarein-7-O-[6′′′-O-acetyl-*β*-D-allopyranosyl-(1→2)]-*β*-D-glucopyranoside (**3**) and acteoside (**4**) by the analysis of

spectroscopic evidences.
The extracts, as well as the isolated compounds were tested for their scavenging activity (87-96%) using the free stable radical 1,1-diphenyl-2-picrylhydrazyl radical (DPPH) and for their inhibitory activity toward soybean lipoxygenase, using linoleic acid as substrate.

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RESULTS FROM A SAFETY TRIAL WITH A NEW HOLISTIC GINKGO FRESH PLANT EXTRACT

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We developed a new holistic Ginkgo fresh plant extract which is free of ginkgolic acids (<5 ppm). In an open multicentric clinical trial we assessed the safety and efficacy of 2x1 tablet daily in 59 elderly patients with mild to moderate memory disorders of the none-Alzheimer-type.
Regarding the safety, the vast majority of the patients and the investigators assessed the tablets to be very well or well tolerated. Only a small number of adverse events occurred during the treatment period; laboratory values and vital signs were within the normal range.
From the evaluated efficacy parameters, the DemTect Score values remained the same whereas around 30-40% of all patients reported a beneficial effect on subjective symptoms like concentration, memorization and forgetfulness.
Additionnaly, the mental component of the SF-12 questionnaire improved significantly ($p<0.05$). The results of this safety study show that the new Ginkgo fresh plant extract is safe and efficacious in elderly patients with mild to moderate memory disorders of the none-Alzheimer-type.

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ANTIMICROBIAL AND ANTITUMOUR ACTIVITY OF AZOREAN ENDEMIC PLANTS

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Oceanic islands like the Azorean archipelago are well known as a biodiversity reserve. Due to their distance from the mainland they contain a huge variety of endemic plant species, which can be a potential source of new and interesting pharmaceutical compounds.
In the present work extacts from *Ilex perado* ssp. *azorica* and *Picconia azorica* were assayed for biological activity against microorganisms and human tumour cell lines. Dichloromethane extracts were inactive in the concentrations tested against *Escherichia coli*, *Listeria monocytogenes*, *Candida albicans* and *Candida glabrata*. Methanol extracts, however, were active when tested against the same pathogenic microorganisms: *Picconia azorica* strongly inhibited the growth of *E. coli*, and to a lesser extent of *L. monocytogenes* and both *Candida* species. *Ilex perado* ssp. *azorica* were also active against these microorganisms, although the inthibition was not as strong as that detected for *Picconia azorica.* Methanolic extract of *Ilex perado* ssp. *azorica* was active against H.Ep2, when added in the exponential growth phase of these tumor cell lines. In the same type of assay, no activity was recorded for *Picconia azorica.* Both methanolic extracts inhibited the growth of H.Ep2 and HeLa tumor cell lines, when allowed to act for 72h.

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ANTITRYPANASOMAL ACTIVITIES OF SELECTED APORPHINES AND INTERACTION WITH DNA AND TOPOISOMERASES.

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We evaluated the *in vitro* activity of an alkaloid extract of *Cassytha filiformis* L., a plant used in African traditional medicine to treat, among others, parasitosis, and its 3 major aporphine alkaloids (actinodaphnine, cassythine, and dicentrine) on *Trypanosoma brucei brucei* as well as 4 related commercially available aporphines (bulbocapnine, glaucine, isocorydine, boldine). Only the 3 alkaloids from *C. filiformis* were active on the trypanosomes *in vitro* (IC_{50}= 3-15 μM). Additionally, to analyse their selectivity, we compared the cytotoxicity of these 7 compounds on HeLa cells. In order to elucidate their mechanism of action, the binding mode of these molecules to DNA was studied by UV absorption, circular and linear dichroism spectroscopies. The results of the optical measurements indicated that all 7 aporphines effectively bind to DNA and behave as typical intercalating agents. Biochemical experiments showed that actinodaphnine, cassythine and dicentrine also interfere with the catalytic activity of topoisomerases in contrast to the four other aporphines. These interactions with DNA may explain, at least in part, the effects observed on trypanosomes but does not seem to be directly related to their cytotoxicity [1].
[1] S. Hoet, C. Stévigny *et al*. Planta Medica 2004; 70,5:407-413.

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THE ANTITUMORAL HYDROALCOHOLIC EXTRACT OF *Bursera fagaroides* (*B.f.*) INHIBITS KIDNEY ODC ACTIVITY IN THE MURINE L5178Y LYMPHOMA MODEL

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In the BALB/c mice model with murine L5178Y lymphoma, the hydroalcoholic extract of the medicinal plant *B.f.* presents immunomodulator and antitumoral activities. The extract is active intra peritonally (i.p.) at 100 mg/kg body weight/15 days. In the present work to follow the antitumoral activity of *B.f.*, we measured the levels of the polyamines putrescina (Pu), Spermidina (Spd) and Spermina (Spm) and the ODC activity in different organs (small intestine, mesothelium, kidney) and urine. Experimental data show that, the ODC activity in the kidney increases 35% by day 17 of tumor growth and that the hydroalcoholic extract of *B.f,* when administered i.p. to mice bearing the L5178Y tumor, controls the activity of the ODC in the kidney, which decreased 87% as compared to untreated L5178Y mice. Putrescine urinary levels also decrease in mice treated i.p. with *B.f.* as compared to the same mice that did not receive the plant extract. It is also important to notice that i.p., the plant extract doesn't present collateral effect on the kidney´s physiology. The *B.f.* bark, from which the extract is obtained is rich in flavonoids and saponins. As several authors have demonstrated that flavonoids inhibit the ODC activity, the present experimental data point out that the antitumoral effect of the *B.f.* extract administered i.p. could be due to the action of its flavonoids on ODC activity in the kidney.

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IDENTIFICATION OF STRUCTURALLY DIVERSE NATURAL PRODUCTS AS ANTICOCCIDIAL AGENTS BY SCREENING FOR INHIBITORS OF APICOMPEXAN cGMP-DEPENDENT PROTEIN KINASE

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Protozoan parasites belonging to genus *Eimeria* cause an intestinal disease known as coccidiosis. While coccidiosis occurs in several domesticated and wild animal species, it has major economic impact in the poultry industry. There are several anticoccidial agents that are currently used in prophylactic treatment regimens by the poultry industry. Polyether ionophores have been particularly useful against this disease, but the emergence of resistance to this class of compounds has been observed. In fact widespread resistance to nearly all classes of anticoccidials has led to an urgent need for novel chemotherapeutic agents . Parasite cGMP-dependent protein kinase (PKG) has been validated as a biochemical target for the treatment of coccidiosis (JBC 277:15913, 2002, Euk Cell 1:317, 2002). To discover new anditcoccidial leads, we have screened our library of natural products for inhibitors of parasite PKG. Bioassay-guided fractionation of the microbial and plant derived extracts has led to the discovery of a diverse classes of natural product inhibitors that include alkyl hydroxybenzoic acid, anthraquinones, diketopiperazines, bis-alkyl-dihydroxy-benzaldehydes, aromatic-δ-lactones, polycyclic aromatic ketones, highly susbstituted benzophenones, bi and terphenyls, preussomerins, sesqui- and triterpenoids, and many others. The isolation, structure and activity of these compounds will be presented.

P:381 SYNTHESIS OF ANTI-FILARIAL ANTHRAQUINONES

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P:382 ANNONACEOUS ACETOGENINS: HEMISYNTHESIS & PRO-APOPTOTIC STUDIES OF A BENZOQUINONIC ANALOG OF SQUAMOCIN

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P:383 "TOTALLY" BIOMIMETIC SYNTHESIS OF EPINITRARAMINE

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P:384 ANTICANCER SEMISYNTHETIC DERIVATIVES OF CEMBRANOID DITERPENE SARCOPHINE

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P:385 SYNTHESIS OF MICROFOLICOUMARIN (1) AND PHELLODENOL-C (2), NATURALLY OCCURRING PRENYLATED COUMARINS

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P:386 PROTEIN MEDIATED HYDROGEN PEROXIDE OXYDATION OF HYPERFORIN, THE MAJOR PHLOROGLUCINOL FROM ST. JOHN'S WORT

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P:387 SYNTHESIS AND *IN VITRO* BIOLOGICAL STUDIES OF NOVEL ESTOLIDES OF ANTICANCER ACTIVE 4-*O*-PODOPHYLLOTOXINYL 12-HYDROXYL-OCTADEC-*Z*-9-ENOATE

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P:388 SYNTHESIS, SPECTRAL AND ANTITUMOR ACTIVITY OF OMEGA 6-LINOLEATES OF NATURAL POLY PHENOLS

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P:389 TAXOL PHARMACOPHORE: EXPERIMENTAL EVIDENCE FROM A HIGHLY ACTIVE CONSTRAINED ANALOG NMR

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P:390 NEW SELECTIVE ACETYLCHOLINESTERASE INHIBITORS DESIGNED FROM NATURAL PIPERIDINE ALKALOIDS FROM SENNA SPECTABILIS

Claudio Viegas Junior[1], Dulce Helena Siqueira Silva[1], Maria Claudia Marx Young[2], Eliezer Jesus Barreiro[3], Carlos Alberto Mansour Fraga[3], Newton Gonçalves Castro[4], Mônica Santos Rocha[4], Vanderlan da S. Bolzani[1]* [1]NUBBE, Instituto de Química, UNESP, Araraquara-SP, Brazil; [2]Seção de Bioquímica e Fisiologia de Plantas, Instituto de Botânica, SMA, SP, Brazil; [3]LASSBIO, Faculdade de Farmácia, UFRJ, Rio de Janeiro, Brazil; [4]Departamento de Farmacologia, Instituto de Ciências Biológicas, UFRJ, Rio de Janeiro, Brazil;

P:391 PARALLEL SYNTHESIS OF METAL (II) COMPLEXES OF (+)-USNIC ACID DERIVATIVES

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P:392 CAFFEOYLATION OF ANTHOCYANINS AND THE ENHANCEMENT OF ANTI-A2E PHOTOOXIDATION

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P:393 NATURAL PRODUCTS---THE PRIMARY SOURCE OF BROAD CHEMICAL DIVERSITY IN PESTCIDE DISCOVERY

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P:394 ECHINOSPORAMICIN, A NEW ANTIBIOTIC PRODUCED BY *MICROMONOSPORA ECHINOSPORA, LL*-P175

Haiyin He,[†] Hui Y. Yang,[†] Scott W. Luckman,[†] Valerie S. Bernan,[†] Gordon Tsai,[‡],
Deborah M. Roll,[†] and Guy T. Carter[††]Chemical and Screening Sciences, and [‡]Bioprocess Development Wyeth, 401 N. Middletown Road, Pearl River, NY 10965, USA

P:395 BIOLOGICALLY ACTIVE DITERPENOIDS FROM *JATROPHA PODAGRICA* HOOK

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P:396 MARINE CYANOBACTERIAL METABOLITES WITH CYTOTOXIC, ANTIMALARIAL AND ANTITRYPANOSOMAL ACTIVITY: THE PANAMA INTERNATIONAL COOPERATIVE BIODIVERSITY GROUP.

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P:397 ISOLATION AND IDENTIFICATION OF ANTIMICROBIAL COMPOUNDS FROM A MEMBER OF THE CELASTRACEAE.

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P:398 ANTIFUNGAL METABOLITES FROM LAB AND PAB

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P:399 RUBRUMINE, A NOVEL FUNGICIDAL AND INSECTICIDAL COMPOUND FROM PENICILLIUM RUBRUM

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P:400 IMMUNOMODULATING POLYSACCHARIDES FROM THE LICHEN *THAMNOLIA VERMICULARIS* VAR. *SUBULIFORMIS.*
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P:401 07H239-A, A NEW CYTOTOXIC EREMOPHILANE SESQUITERPENE FROM THE MARINE-DERIVED XYLARIACEUS FUNGUS LL-07H239
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P:402 CHEMICAL MODIFICATION-AIDED SEPARATION OF 4,6-DIHYDROXYBENZOIC ACID DERIVATIVES FROM THE WOOD-ROTTING FUNGUS, *MERULIUS INCARNATUS*, CORTICIACEAE
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P:403 NEW ALTENUENE DERIVATIVES FROM THE FRESHWATER AQUATIC FUNGUS *JAHNULA* SP.
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P:404 PHIALOPINS A-E: NEW SESQUITERPENOIDS FROM A FUNGICOLOUS *PHIALOPHORA* SPECIES
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P:405 CYTOTOXIC AND OTHER CONSTITUENTS OF A STRAIN OF *PENICILLIUM* FROM THE RHIZOSPHERE OF APACHE PLUME OF THE SONORAN DESERT
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P:406 NOVEL ISOCOUMARINS AND A CHROMAN-4-ONE FROM THE RHIZOSPHERE FUNGUS, *PARAPHEOSPHAERIA QUADRISEPTATA*

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P:407 DIVERSE ALKALOIDS FROM MADAGASCAN MANTELLID FROGS.

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P:408 NEW TOXINS FROM ARTHROPODS OF ISLAND MADAGASCAR

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P:409 PHYTOCHEMICAL INVESTIGATION OF *USNEA ARTICULATA* (L.)

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P:410 LICHEN COMPOUNDS FROM TWO *ROCCELLA* SPECIES

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P:411 PRODUCTION OF PHENOLIC COMPOUNDS BY THE CULTURED MYCOBIONTS OF *LECANORA* SP.

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P:412 STEREOCHEMICAL ASSIGNMENT ACROSS LONG DISTANCES BY CD. ABSOLUTE STEREOCHEMISTRY OF THE AGLYCONE OF CAMINOSIDE A

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P:413 EXPLORATION OF THE AQUEOUS EXTRACTS OF *STYLOTELLA AURANTIUM* FROM GUAM
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P:414 NEW MONOMERIC AND DIMERIC XANTHONE DERIVATIVES FROM THE MARINE ALGICOLOUS FUNGUS *ALTERNARIA* SP.
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P:415 NOVEL MERODITERPENOID-RELATED METABOLITES FROM A FORMOSAN SOFT CORAL *NEPHTHEA CHABROLII*
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P:416 A NEW CAROTENOID GLYCOSIDE ISOLATED FROM A MARINE MICROORGANISM, STRAIN T-1: STRUCTURAL DERMINATION AND CULTURAL CHARACTERISTIC
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P:417 PROPOSED BIOSYNTHESIS OF THE MARINE NATURAL PRODUCT SALINOSPORAMIDE A:A NOVEL 20S PROTEASOME INHIBITOR
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P:418 THE ISOLATION OF AINIGMAPTILONE DERIVATIVES FROM THE ANTARCTIC GORGONIAN CORAL *AINIGMAPTILON ANTARCTICUS*
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P:419 ADDITIONAL BROMOTERPENES FROM THE RED ALGA *LAURENCIA LUZONENSIS*
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P:420 MARINE SESQUITERPENOIDS THAT INHIBIT THE LYASE ACTIVITY OF DNA POLYMERASE β

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P:421 1-*O*-SULFATOHEMIBASTADINS 1 AND 3 FROM *IANTHELLA BASTA* (PALLAS). ANTAGONISTS OF THE RYR_1-FKBP12 Ca^{2+} CHANNEL

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P:422 AURANTOSIDES G, H AND I: THREE NEW TETRAMIC ACID GLYCOSIDES FROM A PAPUA NEW GUINEA THEONELLA SP.

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P:423 HYRTIOSENOLIDES A AND B, TWO NEW SESQUITERPENE - METHOXY-BUTENOLIDES AND A NEW STEROL FROM A RED SEA SPONGE *HYRTIOS* SPECIES

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P:424 HYBRIDIZATION IN SOFT CORALS: GENETIC RECOMBINATIONS RESULT IN NOVEL BIOGENIC METABOLITES

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P:425 A NEW ANTIBIOTIC FROM A *STREPTOMYCES* SP. ISOLATED FROM MARINE SEDIMENT COLLECTED IN LA JOLLA, CA

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P:426 DISCOVERY OF (-)-SPIROLEUCETTADINE: THE FIRST NATURAL PRODUCT CONTAINING A FUSED 2-AMINOIMIDAZOLE OXALANE

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P:427 TRUNGAPEPTINS A-C, NEW CYCLODEPSIPEPTIDES FROM THE MARINE CYANOBACTERIUM *LYNGBYA MAJUSCULA*

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P:428 THREE NEW HALOGENATED FURANONES FROM THE ANTARCTIC RED ALGA *DELISEA PULCHRA*

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P:429 MANADOMANZAMINES A AND B, A NOVEL ALKALOID RING SYSTEM WITH POTENT ACTIVITY AGAINST MYCOBACTERIA AND HIV-1

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P:430 TWENTY-SEVEN NEW DITERPENES AND SESQUITERPENES FROM THE JAMAICAN SPONGE *MYRMEKIODERMA STYX*

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P:431 MARINE SPONGES WITH ANTI-INFLAMMATORY ACTIVITY

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P:432 LONG-CHAIN AMINOPOLYKETIDES FROM A MICRONESIAN TUNICATE

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P:433 MANZAMINE-TYPE ALKALOIDS AND THEIR ACTIVITY AGAINST INFECTIOUS DISEASES

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P:434 A NEW PHLOROGLUCINOL DERIVATIVE ISOLATED FROM A *HYPERICUM* SPECIES NATIVE TO THE SOUTHEASTERN UNITED STATES (*H. DOLABRIFORME* VENT., SECTION *MYRIANDRA*)

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P:435 A SPIROLACTONE ISOLATED FROM A *HYPERICUM* SPECIES NATIVE TO THE SOUTHEASTERN UNITED STATES (*H. LLOYDII* (SVENSON) P. ADAMS, SECTION *MYRIANDRA*)

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P:436 NOVEL SECONDARY METABOLITES OF THREE BARBADIAN HERBS OF THE MINT FAMILY (LAMIACEAE): *HYPTIS, LEONOTIS* AND *LEONURUS*

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P:437 ANTI-TUBERCULOSIS COMPOUNDS FROM *MICROMELUM HIRSUTUM*

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P:438 A NEW NON-TOXIC CHROMAN DERIVATIVE FROM *PHYLLANTHUS AMARUS*

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P:439 ANTITUBERCULAR CONSTITUENTS OF *VALERIANA LAXIFLORA* DC.

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P:440 POTENTIAL ANTITUBERCULAR CONSTITUENTS OF *SENECIO CHIONOPHILUS*

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P:441 G.U.E.S.S.WORK HELPS SEPARATE BIOACTIVE NATURAL PRODUCTS

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P:442 A NOVEL ANTIMICROBIAL INDOLIZINIUM ALKALOID FROM *ANIBA PANURENSIS*

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P:443 NOVEL BIOGENETICALLY SIGNIFICANT UNUSUAL CYCLOPROPANOID REARRRANGEMENT REACTION PRODUCT OF GEDUNIN.

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P:444 NOVEL PREGNANE AND 14,15-SECOPREGNANE GLYCOSIDES WITH ANTIPROLIFERATIVE ACTIVITY FROM SOLENOSTEMMA ARGEL .

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P:445 CYTOTOXIC PRINCIPLES FROM THE LEAVES OF *PIPER BARBATUM*

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P:446 SEARCH FOR ANTICANCER, ANTIPARASITIC AND ANTIFUNGAL BIOACTIVE MOLECULES FROM LATINAMERICAN BIODIVERSITY IN A MULTINATIONAL PROJECT

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P:447 CLERODANES DITERPENOIDS FROM *MICROGLOSSA ANGOLENSIS*

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P:448 CYTOTOXIC TRITERPENES FROM THE AERIAL ROOT OF *FICUS MICROCARPA*

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P:449 GROWTH INHIBITION OF *MYCOBACTERIUM TUBERCULOSIS* BY THE CONSTITUENTS OF *MYRCIANTHES COQUIMBENSIS*.

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P:450 (4*R*,5*R*,7*S*,8*S*,9*S*)-7-HYDROXY-8-HYDROXYMETHYL-4-METHYL PERHYDROCYCLOPENTA[*c*]PYRAN-1-ONE FROM *VALERIANA LAXIFLORA*

Smriti Khera[1*], Michael Carducci[2], Barbara N. Timmermann[3]. [1]Department of Pharmaceutical Sciences, [2] Department of Chemistry, [3] Department of Pharmacology and Toxicology, University of Arizona, Tucson AZ 85721.

P:451 HIGH-THROUGHPUT NATURAL PRODUCTS CHEMISTRY METHODS LEAD TO THE DISCOVERY OF A NOVEL ANTIBACTERIAL INDOLOSESQUITERPENE FROM *GREENWAYODENDRON SUAVEOLENS*

Jin-Feng Hu,* Hye-Dong Yoo, Caroline T. Williams, Peadar A. Cremin, Lu Zeng, Eliane Garo, Helene C. Vervoort, Chris M. Lee, Shane M. Hart, Matt G. Goering, Mark O'Neil-Johnson and Gary R. Eldridge Lead Discovery and Rapid Structure Elucidation Group, Sequoia Sciences, Inc., 11199 Sorrento Valley Road, Suite H, San Diego, CA 92121, USA

P:452 ANTIBACTERIAL ALKYLATED SUGARS FROM *ARCTOSTAPHYLOS PUMILA* VIA THE HIGH-THROUGHPUT NATURAL PRODUCTS CHEMISTRY METHODS

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P:453 NEW CYTOTOXIC ISOFLAVONE FROM THE ROOT BARK OF *BROSIMUM UTILE*

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P:454 QSAR STUDIES ON ACETYLCHOLINESTERASE ENZYME INHIBITORY EFFECTS OF AMARYLLIDACEAE ALKALOIDS

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P:455 TRITERPENOIDS AND LIGNANS FROM *PICRORHIZA KURROA* SEEDS

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P:456 BIOACTIVE DITERPENES FROM *COMMIPHORA MUKUL* RESIN

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P:457 BIOACTIVE TERPENOIDS FROM STINKING TOE (*HYMANAEA COURBARIL*) FRUITS

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P:458 BIOACTIVE CONSTITUENTS FROM *CORNUS KOUSA*

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P:459 NEW CYANOPYRIDONES FROM *ACALYPHA INDICA* L.

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P:460 DETERMINATION OF THE MINIMUM ENERGY CONFORMATION OF GLABRESCOL BY MOLECULAR MODELLING.

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P:461 SCREENING OF YUCATECAN PLANTS AND ISOLATION OF A NEW FUNGISTATIC COMPOUND FROM *ACACIA PENNATULA* TO CONTROL *COLLETOTRICHUM GLOEOSPORIOIDES*

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P:462 STRUCTURE AND BIOLOGICAL ACTIVITY OF NEW DIMERIC CARBAZOLE ALKALOIDS FROM *MURRAYA KOENIGII*

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P:463 PHYTOCHEMICAL AND BIOLOGICAL STUDIES ON *ZANTHOXYLUM FLAVUM*

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P:464 THE ISOLATION AND OPTICAL ROTATION MEASUREMENTS OF (+) AND (-) AMMODENDRINE

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P:465 PHENYLPROPANOID AND IRIDOID GLYCOSIDES FROM *SCROPHULARIA NINGPOENSIS*

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P:466 LAEVISANONE, A NEW AND RARE FLAVANONE GLYCOSIDE FROM *NEWBOULDIA LAEVIS* (BEAUV.) SEEM.EX BUREAU

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P:467 A NEW VHR DUAL-SPECIFICITY PROTEIN TYROSINE PHOSPHATASE INHIBITOR FROM *DENDROBIUM MONILIFORME*

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P:468 X-RAY STRUCTURE OF (-) ISTANBOLIN A FROM SENECIO AEGYPTIUS

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P:469 8,15-EPOXYLABDANES. NEW LABDANES FROM ERAGROSTIS VISCOSA

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P:470 NEW KAURANE FROM *PARINARI PUMILA*

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P:471 NEW COMPOUNDS FROM *EUPHORBIA CONSPICUA*

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P:472 INDOLOQUINAZOLINE ALKALOIDS FROM ARALIOPSIS TABOUENSIS AUBREV. ET PELLEGR (RUTACEAE)

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P:473 PRENYLATED ACETOPHENONES FROM *MELICOPE* SPECIES FROM RÉUNION ISLAND

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P:474 NEW FATTY ACID ESTERS ORIGINATE DURING STORAGE BY THE INTERACTION OF COMPONENTS IN PRASAPLAI, A THAI TRADITIONAL MEDICINE

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P:475 ANTI-INFLAMMATORY EVALUATION OF CRUDE EXTRACTS AND ISOLATED CONSTITUENTS OF *SPHENOCENTRUM JOLLYANUM* Pierre

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P:476 NEW ACYLATED IRIDOID GLUCOSIDES FROM *VITEX ALTISSIMA*

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P:477 HOMOISOFLAVONES FROM MUSCARI COMOSUM GROWING IN EGYPT

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P:478 *IN VITRO* EFFECTS OF THE ETHYL ACETATE EXTRACT AND ISOLATED COMPOUNDS FROM *MOMORDICA FOETIDA* BASED ON A GSH-HAEMIN INTERACTION ASSAY

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P:479 ALKALOIDS OF *CORYDALIS* SPECIES AND THEIR ANTIFUNGAL ACTIVITY

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P:480 INVESTIGATIONS OF ALKALOIDS FROM PLANTS OF THE FAMILY *ELAEOCARPACEAE*

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P:481 ISOLATION AND STRUCTURE ELUCIDATION OF SEVEN NEW NATURAL PRODUCTS FROM THE ROOTS OF *PENTAS BUSSEI*

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P:482 BIOLOGICAL AND PHYTOCHEMICAL INVESTIGATIONS ON PAVETTA OWARIENSIS

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P:483 NOVEL XANTHONES FROM THE SOUTH AFRICAN HYACINTHACEAE

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P:484 A NOVEL SESQUITERPENE DILACTONE FROM *MIKANIA NATALENSIS* DC.

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P:485 THE STRUCTURAL ELUCIDATION OF LIMONOIDS AND LIMONOID DERIVATIVES FROM THE MELIACEAE

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P:486 NOVEL ALKALOIDS FROM *CRINUM STUHLMANNII* (AMARYLLIDACEAE)

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P:487 ALKALOIDS FROM *TECLEA NATALENSIS* (RUTACEAE)

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P:488 EXTRACTIVES FROM *SAMADERA MADAGASCARIENSIS* (SIMAROUBACEAE)

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P:489 FLAVONOIDS FROM *Diplotropis ferruginea* BENTH (FABACEAE)
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P:490 PHYTOCHEMICAL INVESTIGATION OF *Nymphaea caerulea* Savigny.
Michael Yoshpa and Ara DerMarderosian*.
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P:491 STUDY ON THE ACTIVE CONSTITUENTS OF *OPUNTIA DILLENII*
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P:492 STUDYING *COLCHICUM* SPECIES IN JORDAN
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P:493 NEW TETRANORDITERPENOID DILACTONE OF FUNGAL ORIGIN
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P:494 A NEW FLAVONOIDAL TRIGLYCOSIDE AND STRUCTURAL CHARACTERIZATION OF FLAVONOIDS FROM FARSETIA AEGYPTIA BY LIQUID CHROMATOGRAPHY – ELECTROSPRAY IONIZATION MASS SPECTROMETRY AND COLLISION-INDUCED DISSOCIATION
Abdelaaty A. Shahat[+]*, Filip Cuyckens[+], Khaled A. Abdel-Shafeek*,[++] Husseiny A. Husseiny[*] , Sandra Apers[+], Sabine Miert[+], Magda Claeys[+], Luc Pieters[+], and Arnold J.Vlietinck[+] *Pharmacognosy and phytochemistry of Medicinal Plants Department, National Research Centre 12311 Dokki, Cairo, Egypt, [++]Al Tahady university, faculty of science chemistry dept., Sirte , Libya, [+]Department of pharmaceutical Sciences, University of Antwerp, B-2610, Antwerp, Belgium .

P:495 NATURAL ALGICIDES FROM TWO RUTACEAE SPECIES

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P:496 ISOLATION AND CHARACTERISATION OF 1,2,3,4,6-PENTAGALLOYL GLUCOSE AN ANTIMYCOBACTERIAL AGENT FROM THE LEAVES OF *ENTANDROPHRAGMA ANGOLENSE*.

Orisadipe, Abayomi T.[a]; D'Ambrosio Michele[b]; Joseph I. Okogun*[a]; Peters Oladosu[a]; Uford S. Inyang [a]; Akinbobola A. Adesomoju[c]; Helena Boschoff[d]; Cynthia Dowd[d]; Clifton Barry III[d]. National Institute for Pharmaceutical Research and Development, P.M.B. 21, Abuja, FCT, Nigeria. Laboratorio di Chimica Bioorganica,Universita degli studi di Trento, Via Sommarive 14, I-38050 Povo-Trento, Italy. Chemistry department, University of Ibadan, Ibadan, Nigeria.Tuberculosis Research section, National Institute for Allergy and Infectious Diseases, NIH, Parklawn drive, Rockville, MD, USA.

P:497 ESTROGENIC ACTIVITY OF ISOLATED COMPOUNDS AND ESSENTIAL OILS OF *PIMPINELLA* SPECIES FROM TURKEY, EVALUATED USING A RECOMBINANT YEAST SCREEN

Shabana I. Khan[1], Nurhayat Tabanca[1,4], Erdal Bedir[1,5], Srinivas Annavarapu[2], Kristine Willett[2], Ikhlas A. Khan[1,3], Nese Kirimer[4] and K. Husnu Can Baser[4]
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P:498 NOVEL ANTIMICROBIAL DITERPENOIDS FROM *TURRAEANTHUS AFRICANUS* (MELIACEAE)

Simplice Tatsimo Ndendoung Joel[1], Jacob Melissa[2], Pierre Tane[3], Beiba L. Sondengam[1], Christopher O. Okunji[4,5], Brian G. Schuster[5], Maurice M. Iwu[4,5], Ikhlas A. Khan [2]
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P:498 ANTIMICROBIAL ACTIVITY GUIDED FRACTIONATION OF *AFRAMOMUM LONGIFOLIUS* (ZINGIBERACEAE)

Simplice Tatsimo Ndendoung Joel[1], Jacob Melissa[2], Pierre Tane[3], Beiba L. Sondengam[1], Christopher O. Okunji[4,5], Brian G. Schuster[5], Maurice M. Iwu[4,5], Ikhlas A. Khan [2,]
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P:500 CHEMICAL AND BIOLOGICAL INVESTIGATION OF *EPHEDRA VIRIDIS*

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P:501 ISOLATION AND STRUCTURE ELUCIDATION OF MODULATORS OF CNS FUNCTION FROM *DRACAENA MANNII*, A CAMEROONIAN MEDICINAL PLANT.

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P:502 NEW CYTOTOXICITY OBSERVED IN CERBINAL, A KNOWN PRODUCT OF *CERBERA MANGHAS*

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P:503 NEW CYTOTOXIC SESQUITERPENE LACTONES FROM *APODOCEPHALA SP.* FROM THE MADAGASCAR RAINFOREST

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P:504 NEW CYTOTOXIC DITERPENOIDS FROM *HUMIRIANTHERA AMPLA* FROM THE SURINAME RAINFOREST

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P:505 IPOMOEASSINS A-E, FIVE NEW CYTOTOXIC MACROCYCLIC GLYCORESINS, FROM THE LEAVES OF *IPOMOEA SQUAMOSA*

Shugeng Cao,[a] Rebecca C. Guza,[a] Andrew Norris,[a] James S. Miller,[b] Jan H. Wisse,[c] and David G. I. Kingston*,[a] [a]Department of Chemistry, M/C 0212, Virginia Polytechnic Institute and State University, Blacksburg, VA 24061, [b]Missouri Botanical Garden, P.O. Box 299, St. Louis, MO 63166, [c]Bedrijf Geneesmiddelen Voorziening Suriname, Commissaris Roblesweg 156, Geyersvlijit, Suriname

P:506 NEW CYTOTOXIC DITERPENES FROM *CASSIPOUREA* SPECIES FROM THE MADAGASCAR RAINFOREST

V. S. Prakash Chaturvedula,[a] Andrew Norris,[a] James S. Miller,[b] Rabodo Andriantsiferana,[c] Vincent E. Rasamison,[c] and David G. I. Kingston*,[a] [a]Department of Chemistry, M/C 0212, Virginia Polytechnic Institute and State University, Blacksburg, VA 24061, [b]Missouri Botanical Garden, P.O. Box 299, St. Louis, MO 63166, and [c]Centre National d'Application et Recherches Pharmaceutiques, B.P. 702, Antananarivo 101, Madagascar

P:507 NEW EUDESMANE DERIVATIVES FROM THE LEAVES OF *MELAMPODIUM CAMPHORATUM* FROM THE SURINAME RAINFOREST EXHIBITING ANTIMALARIAL ACTIVITY

V. S. Prakash Chaturvedula,[a] Afgan Farooq,[a] Stan Malone,[b] Jan H. Wisse,[c] and David G. I. Kingston*,[a] [a]Department of Chemistry, Virginia Polytechnic Institute and State University, Blacksburg, Virginia 24061-0212, [b]Conservation International Suriname, Kromme Elleboogstraat No. 20, Paramaribo, Suriname, and [c]Bedrijf Geneesmiddelen Voorziening Suriname, Commissaris Roblesweg, Geyersvlijt, Suriname.

P:508 NEW LUPANE TRITERPENOIDS FROM *SOLIDAGO CANADENSIS* THAT INHIBIT THE LYASE ACTIVITY OF DNA POLYMERASE β

V. S. Prakash Chaturvedula,[a] Bing-Nan Zhou,[a] Zhijie Gao,[b] Shannon J. Thomas,[b] Sidney M. Hecht,[b] David G. I. Kingston[a,]* [a] Department of Chemistry, M/C 0212, Virginia Polytechnic Institute and State University, Blacksburg, VA 24060, USA

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P:509 SAPONINS FROM *SYZYGIUM GUIANEENSE* EXHIBITING CDC25 ACTIVITY

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P:510 PHYSALINS ACTIVATE PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR-γ (PPARγ) IN BREAST TUMOR CELLS

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P:511 NOVEL GLYCOLIPIDS FROM THE LEAVES OF *Solanum lanceolatum* AND THEIR ANTIINFLAMMATORY ACTIVITY

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P:512 HUMULENE DERIVATIVES FROM *ZINGIBER ZERUMBET* WITH INHIBITORY ACTIVITY OF LIPPOPOLYSACCARIDE-INDUCED NITRIC OXIDE PRODUCTION

Dae Sik Jang[†], Hye-Young Min[‡], Ah-Reum Han[‡], Gwang-Ho Jeohn[§], Tri Windono[§], Sang Kook Lee[‡], and Eun-Kyoung Seo*[,‡] [†]Division of Molecular Life Sciences, and [‡]College of Pharmacy, Ewha Womans University, Seoul 120-750, Korea; [§]College of Pharmacy, University of Surabaya, JL. Raya Kalirungkut, Surabaya 60293, Indonesia.

P:513 ANTITUBERCULAR CONSTITUENTS FROM THE ROOT OF FORMOSAN *ENGELHARDIA ROXBURGHIANA*

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P:514 LIMNOPHILASPIROKETONE, A HIGHLY OXYGENATED STRUCTURALLY NOVEL PHENOLIC DERIVATIVE FROM *LIMNOPHILA GEOFFRAYI*

Dae Sik Jang,[1,4] Bao-Ning Su,[1,5] Alison D. Pawlus,[1,5] William P. Jones,[1,5] Robert A. Kleps,[2] Nuntavan Bunyapraphatsara,[3] Harry H. S. Fong,[1] John M. Pezzuto,[1,6] and A. Douglas Kinghorn[1,5,*] [1]Program for Collaborative Research in the Pharmaceutical Sciences, Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, University of Illinois at Chicago, Chicago, IL 60612. [2]Nuclear Magnetic Resonance Laboratory, Research Resources Center, University of Illinois at Chicago, Chicago, IL 60612. [3]Faculty of Pharmacy, Mahidol University, Bangkok 10400, Thailand. [4]Present address: College of Pharmacy, Ewha Womans University, Seoul 120-750, Korea. [5]Present address: College of Pharmacy, The Ohio State University, Columbus, OH 43210. [6]Present address: Heine Pharmacy Building, Purdue University, West Lafayette, Indiana 47907, USA

P:515 BIOACTIVE COMPOUNDS FROM ATLANTIC FOREST SPECIES *ALCHORNEA GLANDULOSA* AND *A. SISIFOLIA*

Flávia Fujii[1], Lidilhone Hamerski[1], Renata Camargo[1], Regina Higa[1], Vanderlan S. Bolzani[1], M. Claudia M. Young[2], Claudia Pessoa[3], Letícia Lotufo[3] Manoel O. Moraes[3] , Dulce H. S. Silva[1, *] -[1]NUBBE, Instituto de Química, UNESP, Araraquara-SP; [2]Seção de Bioquímica e Fisiologia de Plantas, Instituto de Botânica, SMA, SP; LOE – UFC, Fortaleza, Brazil.

P:516 FRACTIONATION OF THE BARK OF *ELMERILLIA OVALIS* USING A HISTONE DEACETYLASE INHIBITION ASSAY

Esperanza J. Carcache-Blanco, Bao-Ning Su,[1] Soedarsono Riswan,[2] Rachman Ismail,[2] Norman R. Farnsworth, Geoffrey A. Cordell, Jimmy Orjala, Steven M. Swanson and A. Douglas Kinghorn [*,1]

P:517 CONSTITUENTS OF *ZANTHOXYLUM PIPERITUM* FRUITS AND THEIR EFFECTS ON METHICILLIN-RESITANT *STAPHYLOCOCCUS AUREUS*

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P:518 PHYTHOTOXIC COMPOUNDS FROM *HOFMEISTERIA SCHAFFNERI* (A. GRAY) KING & ROBINSON (ASTERACEAE)

Rachel Mata[a], Araceli Pérez[a], Paola Lozano[a], Robert Bye[b] and Edelmira Linares[b]. [a]Facultad de Química and [b]Instituto de Biología, Universidad Nacional Autónoma de México, Mexico City 04510, México.

P:519 ANTIMYCOBACTERIAL COUMARINS FROM *ARRACACIA TOLUCENSIS* VAR *MULTIFIDA*

Isabel Rivero-Cruz[a], Blanca Rivero[a], Mario Figueroa[a], Robert Bye[b], Scott Franzblau[c], Barbara N. Timmermann[d], and Rachel Mata[a] [a]Facultad de Química, and [b]Instituto de Biología, Universidad Nacional Autónoma de México, Mexico City 04510, México. [c]College of Pharmacy, University of Illinois at Chicago, Chicago, Illinois 60612-7231, USA. [d]College of Pharmacy, The University of Arizona, Tucson, Arizona, 85721, USA.

P:520 ADDITIONAL COMPOUNDS FROM THE LEAVES OF *PIPER SANCTUM*.

Isabel Rivero-Cruz[a], Isolda Enríquez[a], Laura Acevedo[a], Iliana Morales[a], Robert Bye[b], Scott Franzblau[c], Barbara N. Timmermann[d], and Rachel Mata[a] [a]Facultad de Química, and [b]Instituto de Biología, Universidad Nacional Autónoma de México, Mexico City 04510, México. [c]College of Pharmacy, University of Illinois at Chicago, Chicago, Illinois 60612-7231, USA. [d]College of Pharmacy, The University of Arizona, Tucson, Arizona, 85721, USA.

P:521 ANTIMYCOBACTERIAL COMPOUNDS FROM THE STEM OF *PIPER SANCTUM*.

Isabel Rivero-Cruz[a], Isolda Enríquez[a], Laura Acevedo[a], Iliana Morales[a], Robert Bye[b], Scott Franzblau[c], Barbara N. Timmermann[d], and Rachel Mata[a] [a]Facultad de Química, and [b]Instituto de Biología, Universidad Nacional Autónoma de México, Mexico City 04510, México. [c]College of Pharmacy, University of Illinois at Chicago, Chicago, Illinois 60612-7231, USA. [d]College of Pharmacy, The University of Arizona, Tucson, Arizona, 85721, USA.

P:522 PHYTOCHEMICAL CONSTITUENTS OF *DIOSCOREA OPPOSITA* RHIZOMES

Marc Sautour[a], Anne-Claire Mitaine-Offer, Tomofumi Miyamoto[b], Hildebert Wagner[c], Marie-Aleth Lacaille-Dubois[a,]* [a] Laboratoire de Pharmacognosie, Unité UMIB, EA 3660, Faculté de Pharmacie, Université de Bourgogne, 7, Bd. Jeanne d'Arc, BP 87900, 21079 Dijon Cedex, FRANCE, [b] Graduate School of Pharmaceutical Sciences, Kyushu University, Fukuoka, JAPAN, [c] Center of Pharmaresearch, Pharmaceutical Biology, University of Munich, 81377 Munich, Germany

P:523 FOUR NOVEL GLYCOSIDES FROM THE ROOTS OF *CUCURBITA FOETIDISSIMA*

Ghezala Gaidi[a], Tomofumi Miyamoto[b], Marie-Aleth Lacaille-Dubois [a,*] [a] Laboratoire de Pharmacognosie, Unité de Molécules d'Intérêt Biologique (UMIB EA 3660), Faculté de Pharmacie, Université de Bourgogne, 7 Bd Jeanne d'Arc, BP 87900, F-21079 Dijon Cedex, FRANCE, [b] Graduate School of Pharmaceutical Sciences, Kyushu University, Fukuoka, JAPAN

P:524 CHEMICAL CONSTITUENT STUDY ON *VITEX AGNUS-CASTUS*

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Department of Medicinal Chemistry and Pharmacognosy, University of Illinois at Chicago, Chicago, IL 60612

P:525 3-O-β-D-XYLOSIDE-16-EPI-CIMIGENOL, A NEW STEREOISOMERIC TRITERPENE GLYCOSIDE FROM *CIMICIFUGA RACEMOSA*

Shao-Nong Chen, Daniel S. Fabricant, Zhi-Zhen Lu, Harry H. S. Fong, Guido F. Pauli, Norman R. Farnsworth* UIC/NIH Center for Botanical Dietary Supplements Research and Department of Medicinal Chemistry and Pharmacognosy, University of Illinois at Chicago, Chicago, IL 60612

P:526 QUASSINOIDS FROM THE LEAVES AND TWIGS OF *CASTELA MACROPHYLLA* (SIMAROUBACEAE)

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P:527 TRITERPENE GLYCOSIDES FROM *ASTRAGALUS TOMENTOSUS* .

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P:528 NEW CYCLOARTANE-TYPE TRITERPENES FROM *ASTRAGALUS KAHIRICUS*.

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David G. I. Kingston [1,*]. [1]Department of Chemistry, M/C 0212, Virginia Polytechnic Institute and State University, Blacksburg, Virginia 24061, USA, [2]Department of Pharmacognosy, Faculty of Pharmacy, University of Alexandria, Alexandria, Egypt

P:529 NEW CYTOTOXIC MONOTETRAHYDROFURANIC ANNONACEOUS ACETOGENINS FROM *ANNONA MONTANA*

Chih-Chuang Liaw, Fang-Rong Chang, Chin-Chung Wu, Shu-Li Chen, and Yang-Chang Wu* Graduate Institute of Natural Products, Kaohsiung Medical University, Kaohsiung 807, Taiwan

P:530 ANTI-PLATELET AGGREGATION OF NEW APOTIRUCALL TYPE SAPONINS FROM THE GALLS OF *SAPINDUS MUKOROSSI*

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P:531 THE NEW C_{18} DIBENZOCYCLOOCTADIENE LIGNANS AND ANTI-HEPATITIS C_{19} HOMOLIGNANS FROM *KADSURA JAPONICA*

Yao-Haur Kuo[1,*], Ming-Der Wu[1,2], Chia-Ching Liaw[1,3], Ya-Wen Hsu[1], Ray-Ling Huang[1], Li-Ming Yang Kuo[1], Chia-Cheng Hung[1], Ya-Ching Shen[3], Chi-Wi Ong[2,*] [1] National Research Institute of Chinese Medicine, Shih-Pai, Taipei, 112. [2] Institute of Chemistry, National Sun Yat-Sen University, Kaohsiung, 804. [3] Institiute of Marine Resources, National Sun Yat-Sen University, Kaohsiung, 804, Taiwan, R.O.C.

P:532 CHROMANOES, DIHYDROCOUMARINES AND PYRANOXANTHONES FROM TAIWANESE *CALLOPHYLLUM BLANCOI*

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P:533 ANTIFUNGAL CYCLOPENTENEDIONES FROM *PIPER CORUSCANS*

Xing-Cong Li,[*,†] Daneel Ferreira,[†] Melissa R. Jacob,[†] Qifeng Zhang,[†] Shabana I. Khan,[†] Hala N. ElSohly,[†] Dale G. Nagle,[‡] Troy J. Smillie,[†] Ikhlas A. Khan,[†,‡] Larry A. Walker,[†,§] and Alice M. Clark[*,†,‡] National Center for Natural Products Research, Research Institute of Pharmaceutical Sciences,[†] Department of Pharmacognosy[‡] and Department of Pharmacology,[§] School of Pharmacy, The University of Mississippi, University, Mississippi 38677

P:534 ISOLATION AND CHARACTERISATION OF 1,2,3,4,6-PENTAGALLOYL GLUCOSE AN ANTIMYCOBACTERIAL AGENT FROM THE LEAVES OF *ENTANDROPHRAGMA ANGOLENSE*.

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P:535 ANTI-STAPHYLOCOCCAL AND CYTOTOXIC COMPOUNDS FROM HYPTIS PECTINATA

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P:536 CHEMICAL ANALYSIS OF THE LIPOPHYLIC RESIN GLYCOSIDES FROM IPOMOEA PES-CAPRAE

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P:537 PHENOLIC METABOLITES OF THE 'SMOKE TREE' *DALEA SPINOSA* (FABACEAE) POTENTIATE ACTIVITY AGAINST MULTI-DRUG RESISTANT ORGANISMS

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P:538 PHARMACOGNOSICAL STUDIES ON NATURAL PRODUCT (I) - STUDIES ON EFFICACY COMPONENT ISOLATION AND STRUCTURAL DETERMINATION OF HOVENIAE SEMEN CUM FRUCTUS

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P:539 CHEMICAL CONSTITUENTS FROM THE NEUTRAL FRACTION OF *OCOTEA LEUCOXYLON*

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P:540 A NEW DAMMARANE TRITERPENE FROM *RHUS CHINENSIS* MILL.

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P:541 CYTOTOXIC ISOPRENYLATED COUMARINS FROM *MAMMEA AMERICANA*

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P:542 NOVEL BIOACTIVE BENZOPHENONES FROM GARCINIA XANTHOCHYMUS FRUITS

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P:543 SCREENING AND DEREPLICATING A PLANT EXTRACT LIBRARY FOR SKIN WHITENING AGENTS

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P:544 MOLECULAR-TARGETED ANTITUMOR AGENTS: *SAURURUS CERNUUS* DINEOLIGNANS ARE POTENT INHIBITORS OF HYPOXIA-ACTIVATED HIF-1

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P:545 PHYTOCHEMICAL INVESTIGATION OF ZANTHOXYLUM SYNCARPUM

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P:546 DPPH, NITRIC OXIDE AND PGE2 PRODUCTION INHIBITORY ACTIVITIES OF PHENOLIC COMPOUNDS FROM *SOPHORA JAPONICA* LINNE

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P:547 ANTICANCER CONSTITUENTS WITH CYTOTOXICITY AND TOPOISOMERASE INHIBITORY ACTIVITY FROM THE ROOTS OF RUBIA CORDIFOLIA L.

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P:548 CYTOTOXIC XANTHONES AND BIPHENYLS FROM THE ROOT OF *GARCINIA LINII*

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P:549 CYTOTOXIC DIHYDROCHALCONE AND FLAVONOIDS FROM THE LEAVES OF *MUNTINGIA CALABURA*

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P:550 CYTOTOXIC CONSTITUENTS FROM STEM BARK OF *JUNIPERUS VIRGINIANA* L.

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P:551 NOVEL AND BIOLOGICAL ACTIVE DITERPENOIDS FROM DIFFERENT EUPHORBIA

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P:552 NEW CARDENOLIDE AND PREGNANE GLYCOSIDES FROM *PERIPLOCA GRAECA*

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P:553 NEW PHENOLIC DERIVATIVES FROM *VERNONIA MAPIRENSIS*

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P:554 IRIDOID GLUCOSIDES FROM *STRYCHNOS SPINOSA*

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P:555 PHENOLIC CONSTITUENTS FROM *CEPHALOTAXUS KOREANA*

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P:556 TWO NEW IRIDOIDS FROM THE AERIAL PARTS OF *PAEDERIA SCANDENS*

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P:557 CYTOTOXIC FLAVONOIDS AND NEW CHROMENES FROM *FICUS FORMOSANA* F. *FORMOSANA*

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P:558 MELANOGENESIS INHIBITORS ISOLATED FROM THE RHIZOMES OF *CURCUMA LONGA*.

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P:559 BIOACTIVITY GUIDED ISOLATION OF POTENTIAL ANTIINFECTIVE PEPTIDE ALKALOID FROM SPHAERANTHUS INDICUS AND EVALUATION OF ITS ANTITUMOR ACTIVITY ON MOUSE EHRLICH ASCITES CARCINOMA IN VIVO

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P:560 COMPARISON OF THE VOLATILE OILS OF SATUREJA ATROPATANA BUNGE. AND SATUREJA MUTICA FISCH. ET C. A. MEY. FROM IRAN

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P:561 ISOLATION AND IDENTIFICATION OF FLAVONOIDS FROM ACHILLEA BIEBERSTEINII AFAN. POPULATION GOLESTAN,IRAN

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P:562 CONSTITUENTS OF THE ESSENTIAL OILS OF STACHYS PILIFERA BENTH. FROM IRAN

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P:563 NEW CYTOTOXIC NORDITERPENE DILACTONES FROM LEAVES OF *PODOCARPUS MACROPHYLLUS* VAR. *MAKI*

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P:564 STRUCTURAL ELUCIDATION OF THE NOVEL GLAUCACETALINS A–C, NOR-FRIEDELANES PRODUCED BY HAIRY ROOTS OF THE SEDATIVE PLANT GALPHIMIA GLAUCA

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P:565 CRYSTAL STRUCTURE OF TRICOLORIN A: MOLECULAR RATIONALE FOR THE BIOLOGICAL PROPERTIES OF CONVOLVULACEOUS RESIN GLYCOSIDES

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P:566 NOVEL ISOCOUMARINS AND A CHROMAN-4-ONE FROM THE RHIZOSPHERE FUNGUS, PARAPHEOSPHAERIA QUADRISEPTATA

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P:567 BIOACTIVE AND OTHER CONSTITUENTS OF *MELAMPODIUM LEUCANTHUM*

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P:568 IN VITRO ANTIPROTOZOAL ACTIVITY OF ETHNOMEDICALLY SELECTED MEMBERS OF THE FAMILY FABACEAE.

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P:569 CYTOTOXIC CONSTITUENTS FROM *AVICENNIA GERMINANS*

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P:570 BIOACTIVITY-DIRECTED FRACTIONATION OF *MYRISTICA BECCARIANA* WARB. (MYRISTICACEAE) USING A MECHANISM-BASED PROTEASOME ASSAY TO ISOLATE MALABARICONE C

Sharnelle S. Phifer,[1] Dongho Lee,[1] Rachman Ismail,[2] Soedarsono Riswan,[2] Robert Wild,[3] Naomi Laing,[3] Khalid Benbatoul,[3] Latifa Benmassaoud,[3] Djaja D. Soejarto,[4] Norman R. Farnsworth,[4] A. Douglas Kinghorn,[4,5] David J. Kroll,[1] Nicholas H. Oberlies,[1] and Mansukh C. Wani[1,*] [1]Natural Products Laboratory, Research Triangle Institute, P.O. Box 12194, Research Triangle Park, NC 27709. [2]Herbarium Borgoriense, Research and Development Center for Biology, Indonesian Institute of Science, 16122 Bogor, Indonesia. [3]Bristol-Myers Squibb Pharmaceutical Research Institute, P.O. Box 4000, Princeton, NJ 08543. [4]Program for Collaborative Research in the Pharmaceutical Sciences, Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, University of Illinois at Chicago, Chicago, IL 60612. [5]Present address: College of Pharmacy, The Ohio State University, Columbus, OH 43210.

P:571 ISOLATION OF DICHAPETALIN A FROM A RECOLLECTION OF THE STEM BARK OF *DICHAPETALUM GELONIOIDES* OBTAINED FROM THE PHILIPPINES

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P:572 LACTONES AND FLAVONOIDS FROM THE LEAVES OF *LITSEA JAPONICA* AND THEIR ANTI- COMPLEMENT ACTIVITY

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P:573 ENT-18-HYDROXY-TRACHYLOBANE-3-β-OL AND ENT-18-HYDROXY-ISOPIMARA-7,15-DIENE-3-α-OL, TWO VASORELAXANT DITERPENES FROM *CROTON ZAMBESICUS* MUELL ARG.

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P:574 TWO NEW APOCAROTENOIDS FROM SEEDS OF *Ditaxis heterantha* Zucc. (Azafran de bolita) A FOOD PIGMENT PRODUCING PLANT.

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P:575 MARINE NATURAL PRODUCTS AS A SOURCE OF AGENTS THAT REVERSE FLUCONAZOLE RESISTANCE

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P:576 FRACTIONATION OF THE LEAVES OF *ORMOSIA SUMATRANA* USING A PROTEASOME INHIBITORY ASSAY

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P:577 ISOLATION OF A NOVEL ALKALOID FROM *CIMICIFUGA RACEMOSA (*L.) NUTT.

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P:578 PENTACYCLIC ISOMERS THROUGH REARRANGEMENT OF CARBON SKELETON OF TAXOL

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P:579 TRANSFORMED CULTURES OF *SOLANUM CHRYSOTRICHUM* FOR THE PRODUCTION OF BIOACTIVE SAPONINS

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P:580 NEW TIRUCALLANE TRITERPENE OF *PANDANUS TECTORIUS VAR. LAEVIS ACTIVE AGAINST MYCOBACTERIUM TUBERCULOSIS* $H_{37}Rv$

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P:581 SIMULTANEOUS QUANTIFICATION OF A- AND B-TRICHOTHECENE MYCOTOXINS IN PLANTS USING LIQUID CHROMATOGRAPHY-TANDEM MASS SPECTROMETRY

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P:582 ISOLATION, CHARACERIZATION AND DOCUMENTATION OF HERBAL REFERENCE SUBSTANCES: TEUCRIN A FROM TEUCRIUM CHAMAEDRYS

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P:583 DETERMINATION OF THE TOXIC ANTHRAQUINONES LUCIDIN AND RUBIADIN IN COMMERCIAL NONI JUICE BY HPLC

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P:584 TROPANE ALKALOIDS FROM THE SOUTHAFRICAN PERENNIAL HERB *FALKIA REPENS* (CONVOLVULACEAE)

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P:585 RHIZOME PROPAGATION OF ACTAEA RACEMOSA L. (BLACK COHOSH) AND ANALYSIS OF ASSOCIATED TRITERPENE GLYCOSIDES

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P:586 POTENTIAL THERAPEUTIC LEADS FROM NATURAL PRODUCTS

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P:587 INVESTIGATION OF RADICAL SCAVENGING OF TEUCRIUM POLIUM L. (LAMIACEAE) ESSENTIAL OIL FROM IRAN, PAPOLATION KERMAN

Narguess Yassa * , Hossain Hasani Sadi. Dept.of Pharmacognosy,Faculty of Pharmacy,Tehran Univ.of Medical Sciences

P:588 COMPARATIVE STUDY OF *DIGITALIS* L. SPECIES FROM PORTUGUESE FLORA

Rita Serrano, [1] Olga Silva,[2]* Filomena Nóbrega,[3] Ana Afonso,[4] Catarina Rozeira,[4] Francisco Rodrigues,[4] João Arrais,[4] Marco Filipe,[4] Rui Vidal,[4] Elsa T. Gomes[2]
[1]Centre for Environmental Biology, Pharmacy's Faculty of Lisbon University (FFUL); [2]Pharmaceutical Sciences Research Centre (CECF- FFUL); [3]National Forest Research Station, Oeiras; [4]FFUL, Av. das Forças Armadas, 1649-019 Lisboa, Portugal.

P:381

SYNTHESIS OF ANTI-FILARIAL ANTHRAQUINONES

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Lymphatic filariasis (elephantiasis) is a global public health disease caused by the parasitic nematodes *Wuchereria bancrofti* and *Brugia malayi* spp. Humans are the only host for *W. Bancrofti*. The estimation by World Health Organization shows that it affects 120 million people globally and made disable 40 million people worldwide both physically and psychosocially. This is one of the top ten parasitid disease health problems in Africa, Asia, the Western Pacific and the Americas. We have recently reported that some of the anthraquinones isolated from daylily roots were active against *Schistosoma mansoni,* one of the agents of schistosomiasis, a trematode infection that affects millions of persons worldwide. Preliminary results indicated that these anthraquinones area lethal to *B. malayi*. We have now synthesized a library of anthraquinones (A to S) including the naturally occurring anthraquinones using Friedel-Crafts Acylation reaction. Anti-filarial activity of A-S was tested against adult female *B. malayi*. Anthraquinones, A, B, D, E, F, J, Q and R were tested at 50 ppm and gave 100% mortality except Q. Since these compounds killed *B. malayi* worms at 50 ppm, the assay was repeated at 5 ppm. Anthraquinone K gave 100% mortality in 3 days and B, F, G, J and N in 5 days. Anthraquinones A, C, E, P, H, I, L, M, R and S were less active but killed the worms within 7-14 days. Albendazole is an oral drug used to treat a variety of parasitic infections and used as a positive control in our assay. It killed the worms in 16 days at 5 ppm. The solvent controls (2% DMSO in RPMI media) and anthraquinones D, O and Q did not show mortality during the assay period (20 days). A dose response study of the most active anthraquinone K was carried out and gave 100% mortality in 5 and 11 days at 2.5 and 1.25 ppm, respectively.

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ANNONACEOUS ACETOGENINS: HEMISYNTHESIS & PRO-APOPTOTIC STUDIES OF A BENZOQUINONIC ANALOG OF SQUAMOCIN

Séverine Derbré,[1] Erwan Poupon,[1] Gaël Roué,[2] Santos Susin[2] and Reynald Hocquemiller[1]
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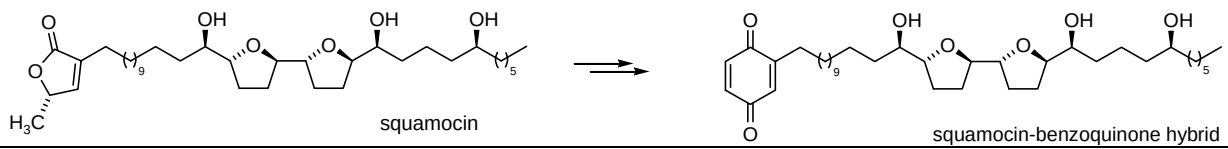
Annonaceous acetogenins are a class of natural products that show potent bioactivities such as antitumor properties. A small library of hemisynthetic analogs of squamocin was prepared with a radical decarboxylation and quinone addition reaction as a key-step. Screening of the analogs according to their pro-apoptotic properties led to the selection of a squamocin/benzoquinone hybrid for further biological studies.



P:383

"TOTALLY" BIOMIMETIC SYNTHESIS OF EPINITRARAMINE

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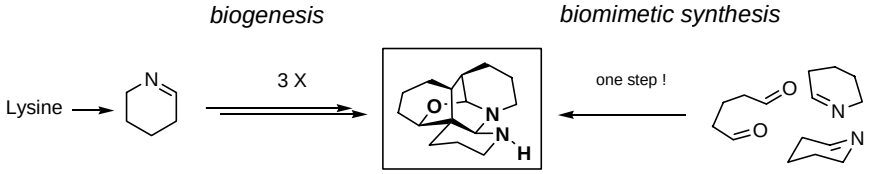
A variety of alkaloids have been isolated from different species of the *Nitraria* genus. For these compounds a common biogenetic origin with a tetrahydropyridine (derived from lysine) as the pivotal intermediate is usually put forward. Remarkable is the racemic form in which several of these alkaloids occur in nature. The purpose of our research is to show that once the correct biosynthetic precursors are prepared, the spontaneous formation, through cascade reactions, of complex polycyclic alkaloids can also be achieved in the laboratory. We will present our first results which have culminated with the "one pot" preparation of natural epinitraramine.



P:384

ANTICANCER SEMISYNTHETIC DERIVATIVES OF CEMBRANOID DITERPENE SARCOPHINE

Swapnali S. Sawant,[†] Paul W. Sylvester,[†] Mitchell A. Avery,[‡] Prashant Desai,[‡] Diaa T. A. Youssef, [§] and Khalid A. El Sayed.*[† †] Department of Basic Pharmaceutical Sciences, School of Pharmacy, The University of Louisiana at Monroe, LA 71209.[‡] Department of Medicinal Chemistry, School of Pharmacy, The University of Mississippi, University, MS 38677.
[§]Department of Pharmacognosy, Faculty of Pharmacy, Suez Canal University, Ismailia 41522, Egypt.

Cembranoids are natural diterpenes possessing 14-membered macrocyclic skeleton. Sarcophine is a furanocembranoid isolated from the Red Sea soft coral *Sarcophyton glaucum*. Sarcophine, its bioconversion products, as well as its semisynthetic derivatives, which are mainly hydroxylated products, are reported to possess cancer chemopreventive activity. In addition, iodination of sarcophine-related cembranoids is known to improve the anticancer activity of the parent cembranoids. These results prompted us to attempt oxymercuration and halogenation of sarcophine. These reactions yielded novel rearranged hydroxylated and halogenated derivatives revealing interesting mechanisms, which were studied with the aid of molecular modeling. Also sulfation of sarcophine resulted in derivatives with improved anticancer activity. Structural mapping of the semisynthetic derivatives was based on high-resolution mass spectral measurements, exhaustive 2D NMR studies, and molecular modeling. The antiproliferative activity of the new products will also be presented.

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SYNTHESIS OF MICROFOLICOUMARIN (1) AND PHELLODENOL-C (2), NATURALLY OCCURRING PRENYLATED COUMARINS

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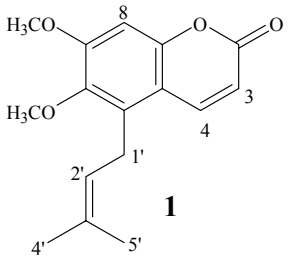
Microfolicoumarin (**1**), isolated from the stem bark of *Cedrelopsis microfoliata*, and Phellodenol-C (**2**), obtained from the leaves of *Phellodendron amurense* var. *wilsonii,* were synthesized for the first time. Details of synthesis and antioxidant activity studies will be presented.



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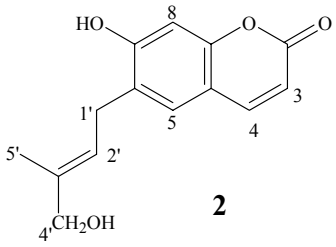

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PROTEIN MEDIATED HYDROGEN PEROXIDE OXYDATION OF HYPERFORIN, THE MAJOR PHLOROGLUCINOL FROM ST. JOHN'S WORT

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Hyperforin is the most abundant lipophilic compounds and an important active component of St. John's wort (*Hypericum perforatum*, L). St. John's wort has been suggested as an alternative herbal treatment for mild to moderate depression and has been referred to as the "Prozac from the plant kingdom". Extracts of *Hypericum perforatum* standardized for hyperforin content, have been correlated in a dose-dependent manner with clinical antidepressive efficacy.
Hyperforin is also an agonist of the human pregnane X receptor system which controls the induction and expression of several proteins involved in drug metabolism and clearance, including the cytochrome P450 isoform (CYP3A4) and the multidrug transporter P-glycoprotein.
Hyperforin is heat-sensitive and susceptible to photodegradation. It decomposes quickly in non polar solvents and is easily attacked by various oxidants. In this communication we present a study on the protein mediated oxidation of hyperforin with hydrogen peroxide. The oxidation targeted the enolized β-dicarbonyl system and was accompanied by a series of unexpected rearrangements that afforded derivatives that might be formed also *in vivo* as part of the metabolism of this compound.

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SYNTHESIS AND *IN VITRO* BIOLOGICAL STUDIES OF NOVEL ESTOLIDES OF ANTICANCER ACTIVE 4-*O*-PODOPHYLLOTOXINYL 12-HYDROXYL-OCTADEC-*Z*-9-ENOATE

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Podophylloxin is a bioactive principle which is isolated from different plant species and particularly abundant in those of genus *Podophyllum*. It is well known natural antitumor agent with severe side effects which lead to the synthesis of its numerous analogs in search of product(s) of improved therapeutic potential. Here, we report an efficient method for the first synthesis of a series of 4-*O*-podophyllotoxin estolides. The hydroxyl group of 4-*O*-podophyllotoxinyl 12-hydroxyl-octadec-*Z*-9-enoate is coupled with the carboxylic groups of a variety of fatty acids to produce quantitative yields of their respective $C_4\alpha$-estolides. These molecules of greater lipophilic character are tested for their *in vitro* cytotoxicity against four human solid tumors, one human leukemia and one non cancerous cells. Estolides are also investigated for their *in vitro* activity against tubulin and topoisomerase II proteins. The results of these studies will be discussed.

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SYNTHESIS, SPECTRAL AND ANTITUMOR ACTIVITY OF OMEGA 6-LINOLEATES OF NATURAL POLY PHENOLS

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[1]National Center for Natural Products Research, Research Institute of Pharmaceutical Sciences, [2]Department of Pharmacognosy, School of Pharmacy, University of Mississippi, University, MS 38677, USA

The protection against several types of cancers by common foods has been observed in multiple epidemiological studies. Flavonoids and fatty acids are generally safe and without adverse side effects and, subsequently, that many of them present in our daily diets. They may be responsible components for such observations. Now greater understanding of health benefits of these natural molecules is developed which may lead to new drug discoveries. Generally chemotherapeutic agents target both cancer as well as normal cells thereby generating undesirable toxic effects. Certain flavonoids and fatty acids are known to treat various cancers. Thus, the synthetic molecules formed by a combination of flavonoids and fatty acids may produce a synergistic anticancer action.
Here, we report for the first time the synthesis and *in vitro* anticancer activity of di-, hexa- and octa- omega 6-lenoleates from a *Z*-dienediphenol (*Ginkgo biloba*) and (-) epigallocatechin, (-) epigallocatechin-3-gallate (jasmine tea/green tea) respectively. Details of the synthetic preparations and their spectral characteristics with the results of their *in vitro* anticancer screening at our center as well as at NCI will be presented.

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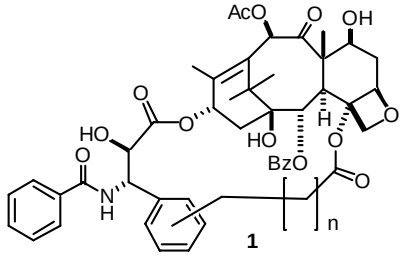
TAXOL PHARMACOPHORE: EXPERIMENTAL EVIDENCE FROM A HIGHLY ACTIVE CONSTRAINED ANALOG NMR

David G. I. Kingston,[a] Thota Ganesh,[a] Jennifer K. Schilling,[a] Susan Bane,[b] Natasha Shanker,[b] Rudravajhala Ravindra,[b] James P. Snyder,[c] and Ami Lakdawala[c]
[a]Department of Chemistry, M/C 0212, Virginia Polytechnic Institute and State University, Blacksburg, Virginia 24061, [b]Department of Chemistry, State University of New York of Binghamton, Binghamton NY 13902-6016, [c]Department of Chemistry, Emory University, Atlanta, GA 30322.

Detailed knowledge of the crucial interaction of taxol and tubulin is of paramount importance in the design and development of highly potent taxol analogs. In an effort to understand the mechanism of action of taxol, we have combined experimental results with molecular modeling and electron crystallographic studies to design and build bridged taxol analogs that are consistent with biophysical data for the taxol pharmacophore. The general structure of these analogs includes a bridge from the C-3' phenyl group to the C-4 position, as exemplified by structure **1**. Two of the resulting constrained analogs have tubulin-assembly and cytotoxic activities equal to or better than those of taxol, indicating that our proposed model for the taxol pharmacophore is essentially accurate. Structures, synthesis, bioactivities, and modeling studies of the constrained analogs will be presented.



1

P:390

NEW SELECTIVE ACETYLCHOLINESTERASE INHIBITORS DESIGNED FROM NATURAL PIPERIDINE ALKALOIDS FROM SENNA SPECTABILIS

Claudio Viegas Junior[1], Dulce Helena Siqueira Silva[1], Maria Claudia Marx Young[2], Eliezer Jesus Barreiro[3], Carlos Alberto Mansour Fraga[3], Newton Gonçalves Castro[4], Mônica Santos Rocha[4], Vanderlan da S. Bolzani[1]*
[1]NUBBE, Instituto de Química, UNESP, Araraquara-SP, Brazil; [2]Seção de Bioquímica e Fisiologia de Plantas, Instituto de Botânica, SMA, SP, Brazil; [3]LASSBIO, Faculdade de Farmácia, UFRJ, Rio de Janeiro, Brazil; [4]Departamento de Farmacologia, Instituto de Ciências Biológicas, UFRJ, Rio de Janeiro, Brazil;

Five new piperidine alkaloids were designed from natural (–)-3-*O*-acetyl-spectaline (**1**) and (–)-spectaline (**2**), that were obtained from the flowers of *Senna spectabilis* (Leguminosae). The semi-synthetic analogues **3-7** were tested in rat brain cholinesterases using Ellman's method. Compounds **3** and **4** were the most potent against acetylcholinesterase (AChE), showing IC_{50} of 4.65 and 15.1 μM, and were less active against butyrylcholinesterase, showing selectivity indexes of 32 and 9.5, respectively. The other three analogues, **5-7**, showed $IC_{50} > 200$ μM and were considered inactive. Compounds **3** and **4** were also tested in scopolamine-induced amnesia and acute cholinergic toxicity protocols. Compound **4** was fully efficacious in reverting the induced amnesia in mice. The two active compounds did not show over-toxic effects at the doses tested *in vivo*. (Granted by Biota-FAPESP Program)

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PARALLEL SYNTHESIS OF METAL (II) COMPLEXES OF (+)-USNIC ACID DERIVATIVES

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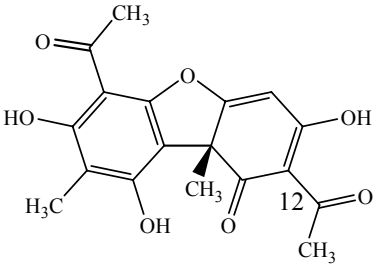
Usnic acid, a widely occurring lichen compound, is well known as antibiotic. Cu(II) complexes with hydrazone usnic acid derivatives were described to enhance activity against *Escherichia coli* and *Staphylococcus aureus*.
So, the preparation of metal complexes with new usnic acid derivatives is an interesting approach for pharmacomodulation.



We report here the synthesis of new ligands, based upon the condensation of the most reactive methyl ketone in 12 with various amines, polyamines, leading to enamine compounds. Some dimeric usnic acid compounds were also prepared from di- or tri-amines. These condensation products were studied for their ability to form complexes with various divalent metals (Cu, Co, Fe, Mn, Ni, Pd, Zn) using a combinatorial method. Preliminary antibacterial results will be presented.

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CAFFEOYLATION OF ANTHOCYANINS AND THE ENHANCEMENT OF ANTI-A2E PHOTOOXIDATION

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[1]Department of Chemistry, Columbia University, New York, NY 10027
[2]Department of Ophthalmology, Columbia University, New York, NY 10028

We have previously shown that anthocyanins from bilberry (*Vaccinium myrtillus*, Ericaceae) have protective activity against the photoxidation of A2E, an aging pigment of retinal pigment epithelium that is implicated in the etiology of age-related macular degeneration (AMD). To potentiate the protective effects of anthocyanins, we have sought an approach to enhancing the stability of anthocyanins as well as its antioxidative activity. Taking lessons from nature, simple caffeic acid was introduced to anthocyanins. The acylated anthocyanins showed two-fold greater protection against A2E photooxidation than did underivatized anthocyanins. In this report, the efficacy of several different esterification methods will be compared.

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NATURAL PRODUCTS---THE PRIMARY SOURCE OF BROAD CHEMICAL DIVERSITY IN PESTCIDE DISCOVERY

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Natural Products Discovery, Syngenta, Jealott's Hill International Research Centre, Bracknell, Berkshire, RG42 6EY, UK

Natural products have one of the most consistently successful sources of new leads for the agrochemical and pharmaceutical industry. The successfully utilisation of natural products as leads has led to the discovery of the blockbuster products such as strobilurins, avermectins and pyrethroids. The drug and pesticides discovery programmers have been impacted significantly by new technologies, and new frontier sciences and cross-disciplinary such as combinatorial chemistry genomic technologies.
Natural products research in leads finding discovery has not been supplanted by any programme and it is still the primary source of broad chemical diversity. Natural products can play vital, mostly non-overlapping, roles in a highly competitive agrochemical and drug discovery programs.
The demand for new leads by the agrochemical and pharmaceutical industries has never been greater. Some examples of our research programmers showed screening of natural products can provide greater structural diversity than standard synthetic chemistry and offers significant opportunities for finding novel lead compounds.

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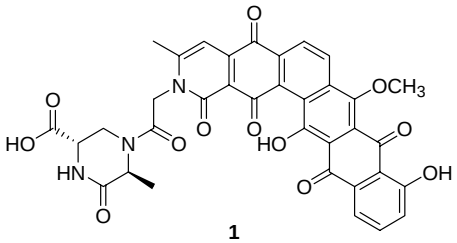
ECHINOSPORAMICIN, A NEW ANTIBIOTIC PRODUCED BY *MICROMONOSPORA ECHINOSPORA, LL*-P175

Haiyin He,[†] Hui Y. Yang,[†] Scott W. Luckman,[†] Valerie S. Bernan,[†] Gordon Tsai,[‡], Deborah M. Roll,[†] and Guy T. Carter[†]
[†]Chemical and Screening Sciences, and [‡]Bioprocess Development
Wyeth, 401 N. Middletown Road, Pearl River, NY 10965, USA

Abstract. In the course of our continuing research to discover novel antibiotics from microbial sources, we isolated a novel antibiotic, designated echinosporamicin (**1**), from the fermentation broth of a new strain of *Micromonospora echinospora*, *LL*-P175. This compound, containing an aromatic polycyclic system and a piperazinone moiety, showed potent and selective activity against G (+) bacteria, including methicillin-resistant staphylococci and vancomycin-resistant enterococci. In this paper, the production, structural determination, and antibacterial activity of **1** are reported.



1

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BIOLOGICALLY ACTIVE DITERPENOIDS FROM *JATROPHA PODAGRICA* HOOK

Olapeju O. Aiyelaagbe[1*], Bolanle A. Adeniyi[2], Olusegun Ekundayo[1], E.Kayode Adesogan[1], James B. Gloer[3]
Department of Chemistry, University of Ibadan, Ibadan, Nigeria[1]; Department of Pharmaceutical Microbiology, University of Ibadan, Ibadan, Nigeria[2]; Department of Chemistry, University of Iowa, Iowa City, IA 52242, USA[3].

Jatropha podagrica Hook is a multipurpose shrub in the family Euphorbiaceae cultivated as an ornamental in different parts of Nigeria. Phytochemical investigations of *Jatropha* species have yielded many bioactive compounds including diterpenoids.
As part of a continuing investigation of the biological activities of the roots of *Jatropha* species, many macrocyclic diterpenoids with antimicrobial activity were isolated from the roots of *Jatropha podagrica* through bioassay-guided fractionation. Some of these diterpenoids are japodagrin, 4E-jatrogrossidentadion, jatrogrossidion, and 2-hydroxyisojatrogrossidion.
These diterpenoids displayed broad-spectrum antibacterial activities against gram-positive and gram-negative bacteria. The results showed that the activity of some of the diterpenoids is comparable to that of some standard antibiotic agents.
Details of the isolation and structure determination of these compounds will be presented.

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MARINE CYANOBACTERIAL METABOLITES WITH CYTOTOXIC, ANTIMALARIAL AND ANTITRYPANOSOMAL ACTIVITY: THE PANAMA INTERNATIONAL COOPERATIVE BIODIVERSITY GROUP.

K.L. McPhail,* P.M. Flatt, T.L. Simmons and W.H. Gerwick
College of Pharmacy, Oregon State University, Corvallis, OR 97331.

Caribbean collections of the marine cyanobacterium *Lyngbya majuscula* have previously yielded an intriguing series of mixed ketide and peptide metabolites, many of which exhibited significant biological activities. We have fractionated extracts from a Panamanian strain of a red *Lyngbya* following results of anticancer, antitrypanosomal and antimalarial bioassays as part of an International Cooperative Biodiversity Groups (ICBG) project based in Panama. Exciting activity results have been obtained for several new and known compounds; the latter were previously isolated from other Caribbean collections as inactive components. Preliminary work on biosynthetic gene sequence alignments comparing the Panama and Curaçao collections will be used to discuss perspectives on the biosynthesis of these and related metabolites from Caribbean strains of *L. majuscula*.

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ISOLATION AND IDENTIFICATION OF ANTIMICROBIAL COMPOUNDS FROM A MEMBER OF THE CELASTRACEAE.

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Members of the Celastraceae are known to produce a number of compounds with biological activity. Of the 50 genera and 800 species of this family, only a few have been thoroughly investigated. Characteristic compounds for this family include the celastroloids, a group of triterpenoid quinonemethides, and the maytansinoids. Both compound classes have been found to have antimicrobial activity. Analysis of a group of extracts from the NCI Open Repository has led to three extracts with possible celastroloids and maytansinoids based on HPLC retention and UV absorbance data. The $MeCl_2$ fractions isolated during SPE were demonstrated to be active against both *Mycobacterium smegmatis* and methicillin-resistant *Staphylococcus aureus* (MRSA) (MIC ≤12.5 μg/mL). Active components were isolated through HPLC PDVB-PS sub-fractionation and LC-MS separations. Chromatographic and spectral analysis has led to the identification of two compounds in the active fractions of one species. The implications of these findings will be discussed.

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ANTIFUNGAL METABOLITES FROM LAB AND PAB

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Departments of Microbiology[2] and of Chemistry[1], Swedish University of Agricultural Sciences SLU, P.O. Box 7015, SE-750 07 Uppsala.

Several antifungal metabolites were isolated and identified from lactic acid bacteria (LAB) and propionic acid bacteria (PAB).The first step is a crude fractionation with solid phase extraction (C_{18}) and followed by two different HPLC step (C_{18} and porous graphitic carbon). Antifungal activity is followed after each fractionation step by a pathogen spore germination bioassay with *Aspergillus fumigatus* (fungus) and *Rhodotorula mucilaginosa* (yeast). The structures of the antifungal metabolites are determined by NMR spectroscopy together with different MS techniques, such as FAB-MS, LC-MS and GC-MS. There are great similarities between the antifungal metabolites from LAB and PAB among the isolated and structure elucidated compounds. The compounds isolated from LAB include several diketopiperazines (DKPs), cyclo(L-Phe–L-Pro), cyclo(L-Phe–*trans*-4-OH-L-Pro), cyclo(L-Phe–*cis*-4-OH-D-Pro), cyclo(L-Leu-*trans*-4-OH-L-Pro) and cyclo(L-Leu-*cis*-4-OH-D-Pro) as well as 3-phenyllactic acid and 3-OH fatty acids (C_{10}, C_{12}, C_{14}). From PAB the DKPs cyclo(L-Phe–L-Pro) and cyclo(Ile-Pro) as well as 3-phenyllactic acid were isolated.
Current work is focused on structure elucidation on antifungal peptides from PAB.

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RUBRUMINE, A NOVEL FUNGICIDAL AND INSECTICIDAL COMPOUND FROM PENICILLIUM RUBRUM

Yucheng Gu,* Rosalia Rodriguez and Paul Stanley
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As part of our discovery research programs on bioactive natural products isolated from different biological sources and the their use as pesticide leads we have investigated *Penicillium rubrum*. The HTS screening of the organic extract of the agar plate showed fungicide activities. HPLC-MS de-replication and bioassay guided fractionation by preparative HPLC-UV-ELSD led to the isolation of Rubrumine. The structures of this novel compound was determined by spectrometric and spectroscopic analyses including LC-MS, HRLC-MS, 1D- and 2D-NMR experiments and by comparison with related compounds. The isolated compound exhibited interesting activities on fungicide and insecticide *in vivo* assay.
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IMMUNOMODULATING POLYSACCHARIDES FROM THE LICHEN *THAMNOLIA VERMICULARIS* VAR. *SUBULIFORMIS.*

Sesselja Omarsdottir[a]*, Jona Freysdottir[b], Berit Smestad Paulsen[c], Elin Soffia Olafsdottir[a].
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Polysaccharides from lichens and fungi have been found to have immunomodulating activity. The aim of this study was to isolate and structure elucidate polysaccharides from *Thamnolia vermicularis* var. *subuliformis* and to investigate the effect of the polysaccharides on *in vitro* immune function in rats. Four polysaccharides were isolated, the heteroglycans; thamnolan, Ths-4 and Ths-5 and the β-glucan Ths-2. The polysaccharides were extracted and purified by conventional methods, and structurally characterized by NMR spectroscopy, metanolysis and methylation analysis. Rat spleen cells (RSC) and peritoneal macrophages (pMø) were cultured in the presence of various concentrations of the polysaccharides and IL-10 and IL-4 secretion of RSC and TNF-α secretion of pMø was measured by ELISA. The proliferation of RSC was determined by ^{3}H-thymidine uptake. All the polysaccharides at 100 μg/ml except Ths-4, stimulated proliferation of rat spleen cells. Ths-4 and Ths-2 at 100 μg/ml and Ths-5 at 100 and 33 μg/ml significantly induced IL-10 production of RSC above background levels but none of the polysaccharides appear to induce IL-4 secretion. Ths-4 (100 μg/ml) significantly induced pMø to secrete TNF-α above background level. These results indicate that these polysaccharides influence cells of the immune system both from the innate and the adaptive system.

P:401

07H239-A, A NEW CYTOTOXIC EREMOPHILANE SESQUITERPENE FROM THE MARINE-DERIVED XYLARIACEUS FUNGUS LL-07H239

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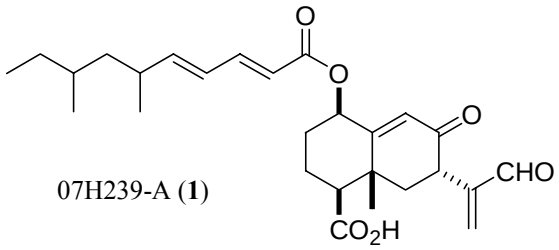
The present research seeks to find new natural products with therapeutic potential as anticancer agents by screening crude extracts against a panel of 25 diverse cancer cell lines. An active fermentation extract from a marine-derived xylariaceous fungus was chosen for follow-up purification with bioassay-guidance. Fractionation led to the decalin derivative 07H239-A (**1**), which was characterized by NMR and mass spectrometry. Although the spectroscopic and spectrometric properties of **1** are remarkably similar to those of Sch 420789, the structure of **1** was firmly established as a unique eremophilane sesquiterpene, with core features common to those of other members of the class. Evaluation of the biological activity of **1** in the 25-cell line assay showed that the compound was cytotoxic towards a variety of cell lines with some selectivity for CCRFCEM leukemia line (IC_{50} = 0.9 μg/ml).



07H239-A (**1**)

P:402

CHEMICAL MODIFICATION-AIDED SEPARATION OF 4,6-DIHYDROXYBENZOIC ACID DERIVATIVES FROM THE WOOD-ROTTING FUNGUS, *MERULIUS INCARNATUS*, CORTICIACEAE

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Natural products isolated from higher fungi have been found to have properties that are beneficial for human health. During the screening process of polypore mushrooms for antimicrobial activity, *Merulius incarnatus*, Corticiaceae exhibited significant activity especially against methacillin resistant *S. aureus* (MRSA). The activity-guided chromatographic separation led to an active fraction, mainly composed of 4,6-dihydroxybenzoic acid derivatives bearing long aliphatic side chains with a different degree of unsaturation. The separation of these compounds proved to be rather difficult due to their close structural similarity. The methylation reaction and further chromatographic separation led to the isolation of several dihydroxybenzoic acid derivatives.
The isolation process and the structure elucidation of these compounds will be presented**.**

P:403

NEW ALTENUENE DERIVATIVES FROM THE FRESHWATER AQUATIC FUNGUS *JAHNULA* SP.

Ping Jiao and James B. Gloer,* Department of Chemistry, University of Iowa, Iowa City, IA, 52242; Jinx Campbell and Carol A. Shearer, Department of Plant Biology, University of Illinois, Urbana, IL, 61801

Fungi are well known as producers of secondary metabolites that display a variety of biological activities. However, several ecological groups of fungi remain underexplored as potential sources of new bioactive natural products. One such group includes fungi that specialize in freshwater aquatic habitats. Our research group has undertaken investigations of freshwater aquatic fungi, and extracts of such isolates have afforded a variety of bioactive metabolites. During these ongoing studies, four new altenuene derivatives were obtained from a *Jahnula* sp. isolated from the Cheoah River in North Carolina. To our knowledge, these compounds are the first secondary metabolites to be reported from any member of the genus *Jahnula*. The structures were determined by analysis of MS, 1D NMR, and 2D NMR data. Relative stereochemistry was assigned using ^{1}H NMR *J*-values and NOE data, while absolute configurations were proposed on the basis of CD spectral analysis of dibenzoate derivatives. Details of the production, isolation, and structure determination of these compounds will be presented.

P:404

PHIALOPINS A-E: NEW SESQUITERPENOIDS FROM A FUNGICOLOUS *PHIALOPHORA* SPECIES

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The chemistry of mycoparasitic and fungicolous fungi is relatively unexplored, despite the fact that many such fungi exert antifungal effects on host species. Our research group has undertaken investigations of these types of fungi as potential sources of new natural products with antifungal activity, as well as other effects. Extracts from cultures of mycoparasitic and fungicolous isolates obtained from field-collected specimens of wood-decay fungi often show antifungal activity against *Aspergillus flavus* and/or *Fusarium verticillioides*. Chemical studies of these extracts have afforded a variety of bioactive metabolites.
During the course of this ongoing project, five new sesquiterpenoids were isolated from cultures of a *Phialophora* species (conidial state of *Ascocoryne sarcoides*). Their structures were elucidated by analysis of 1D and 2D NMR spectra and their absolute configurations were assigned using the exciton chirality CD method. Details of the production, isolation, and structure determination of these compounds will be presented.

P:405

CYTOTOXIC AND OTHER CONSTITUENTS OF A STRAIN OF *PENICILLIUM* FROM THE RHIZOSPHERE OF APACHE PLUME OF THE SONORAN DESERT

Jixun Zhan, E. M. Kithsiri Wijeratne, Christopher J. Seliga, Libia A. Luevano, and A. A. Leslie Gunatilaka*
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In the course of screening rhizosphere microflora of Sonoran desert plants for potential anticancer agents, an EtOAc extract of an unidentified *Penicillum* sp. isolated from the rhizosphere of Apache Plume (*Fallugia paradoxa* D. Don; Rosaceae) was found to be active in both cytotoxicity and Heat Shock Induction Assays (HSIA). Bioassay-guided fractionation of this extract resulted in the isolation and identification of two new natural products, 1,3-dihydroxy-6-hydroxymethyl-7-methoxyanthraquinone and 1,3-dihydroxy-6-methyl-7-methoxyanthraquinone, together with cytotoxic and HSIA active resorcylic macrolides, dehydrocurvularin, 11-methoxycurvularin, and 11-hydroxycurvularin. Structure elucidation of the two new anthraquinones and biological activities of curvularins will be presented.

P:406

NOVEL ISOCOUMARINS AND A CHROMAN-4-ONE FROM THE RHIZOSPHERE FUNGUS, *PARAPHEOSPHAERIA QUADRISEPTATA*

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SW Center for Natural Products Research, Office of Arid Lands Studies, College of Agriculture and Life Sciences, The University of Arizona, Tucson, Arizona 85706-6800, USA

In a study to discover biologically active metabolites from the rhizosphere microflora of Sonoran desert plants, a cytotoxic EtOAc extract of the fungus, *Parapheosphaeria quadriseptata*, occurring in the rhizosphere of the Desert Christmas Cactus (*Opuntia leptocaulis* DC.) was investigated. Bioactivity-guided fractionation of this extract afforded monocillin I as the only cytotoxic constituent. Investigation of the non-cytotoxic fraction afforded three minor but novel isocoumarins, paraphaeosphaerins A – C, biogenetically related to monocillin I, and a new chroman-4-one. Isolation and structure elucidation, including the determination of stereochemistry, of paraphaeosphaerins A – C and the chroman-4-one, and the biosynthetic relationships of monocillin I and paraphaeosphaerins will be presented.

P:407

DIVERSE ALKALOIDS FROM MADAGASCAN MANTELLID FROGS.

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Laboratoire de Chimie Organique "Produit Naturels", Université d'Antananarivo, Antananarivo, 101, Madagascar and Laboratory of Bioorganic Chemistry, NIDDK, NIH, DHHS, Bethesda, MD, 20892-0820, USA.

Madagascan frogs of the genus *Mantella* have afforded in skin extracts a wide range of biologically active alkaloids. The major classes of alkaloids are the pumiliotoxins, allopumiliotoxins, homopumiliotoxins, pyrrolizidines, indolizidines, quinolizidines and decahydroquinolines. All these alkaloids are suspected to come from dietary ants. The evidence that some tricyclic type alkaloids come from dietary coccinnelline species will be given.
Till year 2003, skin extracts from 13 species of *Mantella* frogs from over 30 sites, some in multiple years, have been examined. Over 200 alkaloids have been characterized with some 100 of these being unique to the Madagascan frogs. Currently, two more species and 29 additional sites have been investigated. The profile of alkaloids seems dependent on the site, not the species, with certain alkaloids associated with specific types of habitats. Thus, a tricyclic alkaloid, **261C** ($C_{18}H_{31}N$), major compound from *M betsileo* and *M. expectata*, occurs only in relatively dry habitats, while izidines, such as **217A** and **217B** (both $C_{15}H_{23}N$) are most common in riparian forests, and alkaloids **235C** ($C_{15}H_{25}NO$) and **392** ($C_{22}H_{36}N_2O_4$) only in swamp forests. A revised structure for **235C**, based on ms, ftir and nmr spectral analysis is that of a 7,8-dehydro-8-desmethyl pumiliotoxin. Skin alkaloids of frogs provide a guide to the discovery of the alkaloid-containing arthropods from which the frogs sequester such alkaloids.

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NEW TOXINS FROM ARTHROPODS OF ISLAND MADAGASCAR

Marta Andriantsiferana*, Bodo Noaviarilolona, Li Dai, Yashiro Itagaki, Hideo Naoki, Tsuyoshi Fujita and Terumi Nakajima
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Many kinds of venom principles modulate physiological responses of mammalian signal trans duction systems. Especially, the so-called neurotoxins get increased interest and become useful tools for physiological research. Since 1993 to present, Malagasy and Japanese researchers undertook common program on “Toxins from harmful land animals in Madagascar”. The chemical study of scorpion *Grosphus bistriatus* K. venom gland, which alcoholic extract is used in folk medicine against a wide range of deseases, led on the peptide compounds occurence. The analytical results of spider toxins extracted from a single *Nephilengys borbonica* venom gland with the use of ***μ***-column HPLC are reported. They afforded the detection of over 40 new acylamines, location of nitrogen atoms and connectivity of methylene units within the poly amines. The structure determinations of new series of acylpolyamines in the spider *Nephila madagascariensis* venom gland is presented. These are new glutaminergic nerve blocker materials. We also describe the data of IsCT, a novel cytotoxic linear peptide from scorpion *Opisthacanthus madagascariensis*, the shortest natural cytotoxic described. On the biodiversity point of view, a such number of new neurotoxins, published for the first time, is of high interest and in accordance with the impressive level endemicity of the fauna of Madagascar. As an example, the percentage of endemism observed in the Madagascan scorpion community is 100.00, while those in Guayana, Ecuador and Paraguay are 76.5, 66.7, 17.0 respectively.

P:409

PHYTOCHEMICAL INVESTIGATION OF *USNEA ARTICULATA* (L.)

Françoise Lohézic – Le Dévéhat, Sophie Tomasi, Aurélie Bernard, Amri Bakhtiar* and Joël Boustie .
Lab. Pharmacognosie et Mycologie, Institut de Chimie de Rennes, UPRES 2234, 2, Avenue du Pr Léon Bernard, 35043 Rennes cedex, FRANCE (http://www.upres2234.univ-rennes1.fr), *Lab Pharmacognosy, Jur.Farmasi, FMIPA Univ Andalas, 25221 Padang, INDONESIA

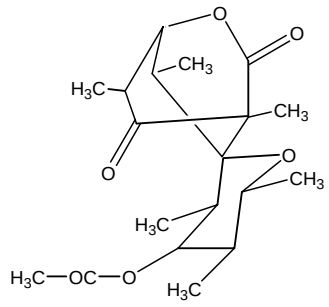
As part of our studies on lichen metabolites, we focused our study on the fruticose lichen *Usnea articulata*, constituent of Benalu The°, a traditional anticancer and anti-infectious medicine used in Asia.
210 g of lichen harvested in Sumatra (Indonesia), was successively and exhaustively extracted using a hot Soxhlet process with 200 ml of *n*-hexane, diethylether, acetone, methanol and water. (+)-Usnic acid (a dibenzofurane derivative), ergosterol peroxide (a steroid) and barbatic acid (a depside) were isolated and identified from the low-polar fractions. A new depsidone along with the four well-known stictic, fumarprotocetraric, norstictic and salazinic acids were isolated from the acetone extract. Further isolation is in progress and biological tests will be run on these lichen compounds.

P:410

LICHEN COMPOUNDS FROM TWO *ROCCELLA* SPECIES

Patricia Romanini, Françoise Lohezic-Le Devehat, Aurélie Bernard, Sophie Tomasi, Joël Boustie*
Lab Pharmacognosie Mycologie, UPRES 2234, Institut de Chimie de Rennes, 2 Av. Prof. Léon Bernard, 35043 Rennes, France **http://www.upres2234.univ-rennes1.fr/**

Roccella fuciformis D.C. and *R. phycopsis* Ach., [*Roccellaceae*] known for centuries to produce the blue dye indigo, are common lichens found on rocks of the Brittany seashore. The present study ran on three extracts (*n*-hexane, diethylether, acetone) was carried out to isolate metabolites in suitable amounts for biological evaluation.



Acetylportentol

Thus, seven compounds were identified to:
6-methoxymethyleugenin (**I**), acetylportentol (**II**), roccellic acid (**III**), methylorsellinate (**IV**), erythritol (**V**), montagnetol (**VI**) and erythrin (**VII**).
(I + II) and **(III)** have been isolated from *R. fuciformis* and *R. phycopsis*, respectively but most of these compounds are found in both species. Moreover, **(I)** is described for the first time from a lichen source and **(IV + VI)** are found for the first time in these species. Further studies are in progress to ascertain the chemotaxonomic value of these findings and the biological interest of these compounds.

P:411

PRODUCTION OF PHENOLIC COMPOUNDS BY THE CULTURED MYCOBIONTS OF *LECANORA* SP.

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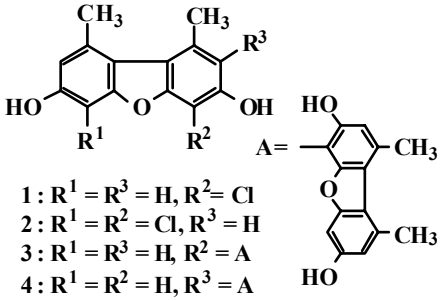
Lichens, a symbiotic association, produce a variety of characteristic secondary metabolites, some of which have been found to exhibit a wide range of potentially useful biological activities. Our recent studies demonstrated that cultures of spore-derived lichen mycobionts have an ability to produce certain lichen substances or novel metabolites under osmotically stressed conditions. It was pointed out that culture of lichen mycobionts could be good sources of new compounds. In the course of our studies on cultured lichen mycobionts, we cultivated mycobionts of the lichen *Lecanora iseana* Räs. and *L. cinereocarnea* (Eschw.) Vain. and isolated from their cultures four new dibenzofurans (**1** – **4**) and one new naphthopyrone (**5**) as well as six known norlichexanthone derivatives and five dibenzofurans.

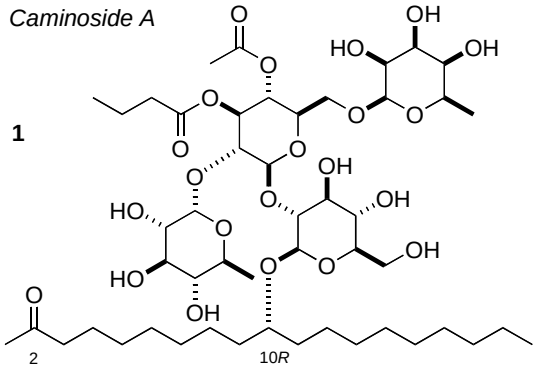


P:412

STEREOCHEMICAL ASSIGNMENT ACROSS LONG DISTANCES BY CD. ABSOLUTE STEREOCHEMISTRY OF THE AGLYCONE OF CAMINOSIDE A

John B. MacMillan[a], Roger G. Linington[b], Raymond J. Andersen[b], Tadeusz F. Molinski[a,*], Department of Chemistry UC Davis, CA 95616 and Department of Chemistry, Earth and Ocean Sciences, University of British Columbia, Vancouver, B.C. Canada, V6T 1Z3

Determination of stereochemistry of substituents in long-chain lipid natural products is hampered by the difficulty of relating configurations of isolated functional groups. We have developed an efficient method for elucidating stereochemistry in remotely substituted 1,*n*-glycols ($n \geq 5$) that exploits exciton coupling circular dichroism (ECCD) in liposomes to transmit stereochemical information between OH groups in long-chain lipids. The method was validated in stereodefined model compounds–synthesized from precursors of known absolute configuration– and used to assign the configuration of the C10 OH group in the aglycone of caminoside A (**1**).[1] Compound **1**, a complex glycolipid isolated from the marine sponge *Caminus sphareoconia*, is an inhibitor of the type III secretory system that is responsible for transmission of virulence factors by several pathogenic bacteria to host cells.[1]



1. Linington, R.G.; Robertson, M.; Gauthier, A.; Finlay, B.B.; van Soest, R.; Andersen, R.J. *Org. Lett.* **2003**, *4*, 4089-4092.

a. UC Davis b. UBC

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EXPLORATION OF THE AQUEOUS EXTRACTS OF *STYLOTELLA AURANTIUM* FROM GUAM

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The marine sponge *Stylotella aurantium* has yielded several biologically active compounds, most notably the palau'amines, hexacyclic bisguanidines which are antibiotic, antifungal, immunosuppressive, and cytotoxic. My research focuses on the reisolation of palau'amines, particularly isopalau'amine, and the search for other new compounds from the aqueous extracts of this sponge. Extraction of the sponge with methanol and water afforded a water-soluble portion that was separated by cation exchange on Cellex CM resin. Sephadex LH-20 chromatography and HPLC were performed to further separate the components of the extract. The resulting fractions were assayed against *S. aureus* and analyzed by NMR and TLC. An 18-mg sample of nearly pure palau'amine was obtained. The water-soluble extract also yielded three nearly pure compounds that do not appear to match anything previously isolated from *Stylotella aurantium*. They are very polar according to their chromatographic behavior, and their NMR spectra suggest that they contain highly conjugated heteroaromatic systems. We shall report on our progress toward identifying these compounds.

P:414

NEW MONOMERIC AND DIMERIC XANTHONE DERIVATIVES FROM THE MARINE ALGICOLOUS FUNGUS *ALTERNARIA* SP.

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Xanthone derivatives are described as so-called "privileged structures" since members of this structural class are able to interact with different types of drug targets. Of special interest are dimeric xanthones such as secalonic acids, for which cytostatic, mutagenic, and teratogenic acitivities are known.
This project focuses on biologically active natural products of the marine fungus *Alternaria* sp., which was isolated from the tissue of an unidentified green alga. The fungus was cultivated on solid biomalt medium for 4 months. LCMS analysis indicated the presence of several interesting compounds in the ethylacetate extract, which also showed antifungal activity in agar diffusion assays. VLC and HPLC separations resulted in the isolation of ten natural products, five of them are new monomeric xanthones, and two are new dimeric structures. Additionally the known compound ascochrome and two furan derivatives were isolated. Ascochrome inhibited the growth of the bacterium *Bacillus megaterium,* the fungi *Microbotryum violaceum*, *Eurotium rubrum* and *Mycotypha microspora*. Currently all compounds are assayed for their cytotoxic activities.

P:415

NOVEL MERODITERPENOID-RELATED METABOLITES FROM A FORMOSAN SOFT CORAL *NEPHTHEA CHABROLII*

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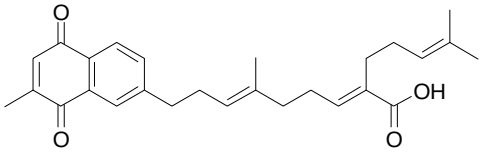
[b] National Museum of Marine Biology and Aquarium, 2 Houwan Road, Checheng, Pingtung 944, Taiwan, R.O.C.

Nine new metabolites, including one novel naphthoquinone derivative, chabrolonaphthoquinone A (**1**), four tetraprenyltoluquinol-related metabolites, chabrolohydroxybenzoquinones A–D (**2**–**5**), and four tetraprenyltoluquinone-related compounds, chabrolobenzoquinones A–D (**6**–**9**) were isolated from the organic extract of a Taiwanese soft coral *Nephthea chabrolii*. The structures of **1**–**9** were elucidated on the basis of spectral data. Also, the biosynthetic pathways of the concerned meroditerpenoids are proposed. To the best of our knowledge, the incorporation of a methyl group of the related meroditerpene to form a naphthoquinone, such as compound **1**, was discovered for the first time.



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P:416

A NEW CAROTENOID GLYCOSIDE ISOLATED FROM A MARINE MICROORGANISM, STRAIN T-1: STRUCTURAL DERMINATION AND CULTURAL CHARACTERISTIC

Hirokazu Kaneno, Yasuji Sumiya, Miyuki Tsushima, Hideyuki Sakaki, Noriaki Kishimoto, Tokio Fujita, Sadayoshi Matsumoto, Wataru Miki, Sadao Komemushi and Akiyoshi Sawabe*
Department of Agricultural Chemistry, Faculty of Agriculture, Kinki University, 3327-204, Nakamachi, Nara city, Nara, 631-8505, Japan

The surface of the sea in tropical and subtropical region is a severe environment for the growth of organisms, because active oxygen and free radicals are generated by intense irradiation with strong sunlight. Recently, it has been reported that the marine microorganisms *Agrobacterium aurantiacum* produced astaxanthin, which has one of the strongest $^1O_2$ quenching activities. Then, focusing on fungal type marine microorganisms, we screened ocean fungus for production of excellent carotenoid with antioxidative activity. Here we report on the structural determination and cultural characteristic of a new carotenoid from marine microorganisms.

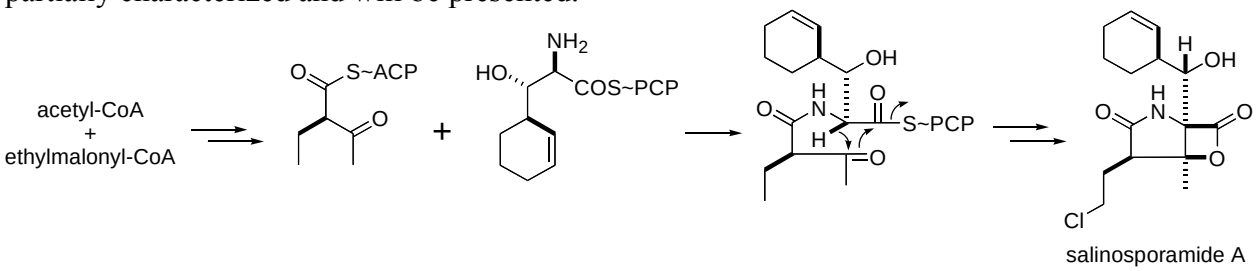
Neurosporaxanthin β-D-glucopyranoside was identified as a new carotenoid from the strain. A yield of carotenoid in 1g freeze-dried fungus body was found to be 0.25 mg. Main carotenoids of the strain were neurosporaxanthin (45% out of the all carotenoids), γ-carotene (32%) and the new carotenoid neurosporaxanthin β-D-glucopyranoside (11%). β-Carotene (5%) and torulene (3%) were minor constituents**.**

P:417

PROPOSED BIOSYNTHESIS OF THE MARINE NATURAL PRODUCT SALINOSPORAMIDE A:A NOVEL 20S PROTEASOME INHIBITOR

Laura L. Beer and Bradley S. Moore* Pharmacology and Toxicology and Division of Medicinal Chemistry, University of Arizona, 1703 East Mabel, Tucson, AZ 85721

A series of 13C-labeled precursors were fed to Salinospora sp. CNB476. NMR spectroscopy demonstrated that salinosporamide A is derived from acetyl-coenzyme A, an unknown four-carbon unit possibly derived from ethylmalonyl-CoA, and possibly a novel non-proteinogenic amino acid residue (2R,3S,4R)-3-(cyclohex-2'-ene)-3-hydroxyalanine. Biosynthesis of this novel amino acid, which we have demonstrated to be a product of the shikimate pathway, has been partially characterized and will be presented.



Proposed biosynthesis of salinosporamide A by a mixed PKS-NRPS involving enzyme-bound intermediates on acyl- and peptidyl carrier proteins (ACP and PCP)

P:418

THE ISOLATION OF AINIGMAPTILONE DERIVATIVES FROM THE ANTARCTIC GORGONIAN CORAL *AINIGMAPTILON ANTARCTICUS*

Scott M. Haake, Katrin B. Iken, and Bill J. Baker*
Department of Chemistry, University of South Florida, 4202 E. Fowler Ave SCA 400, Tampa, FL 33620, USA

The gorgonian coral *Ainigmaptilon antarticus* was collected from the Weddell Sea of Western Antarctica. This coral appears to be chemically defended, as opposed to other octocorals of the region that display physical defenses. Fractionation of the bioactive extract was performed in an attempt to isolate derivatives of the sesquiterpenes Ainigmaptilone A and B. These compounds were previously isolated in a similar study. Ainigmaptilone C was isolated from a more polar fraction and is similar to Ainigmaptilone A except for an additional double bond between carbons 7 and 8. Studies continue in an attempt to isolate more derivatives.

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ADDITIONAL BROMOTERPENES FROM THE RED ALGA *LAURENCIA LUZONENSIS*

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Species of the genus *Laurencia* contain a variety of characteristic metabolites, mainly halogenated terpenes and C_{15} acetogenins. Many of these compounds are toxic and often found also from sea hares that feed on *Laurencia*. Sea hares are believed to accumulate the toxic constituents of the algae for their own defense. The alga *Laurencia luzonensis* is a tropical species which had not been chemically explored until our recent work. Since it grows in the coral reefs of Okinawa and can be collected in substantial amounts in season, we examined its constituents and reported discovery of new metabolites, an unusual diterpene and several sesquiterpenes.[1] Our continuing work on this species gave rise to additional new bromoterpenes including a diterpene of an unprecedented skeleton and five sesquiterpenes. In this presentation we report the isolation and structures of these compounds. Also presented is a biosynthetic relationship among the sesquiterpenes including those known from other species of *Laurencia* and sea hares, all of which were found in *L. luzonensis*.

1. Kuniyoshi, M.; Marma, M. S.; Higa, T.; Bernardinelli, G.; Jefford, C. W. *J. Nat. Prod.* **2001**, *64*, 696-700.

P:420

MARINE SESQUITERPENOIDS THAT INHIBIT THE LYASE ACTIVITY OF DNA POLYMERASE β

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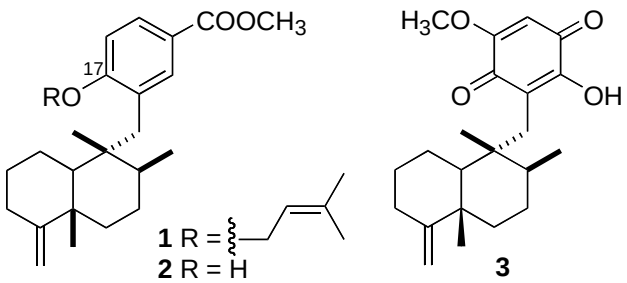
Bioassay-directed fractionation of an extract of the marine species *Spongia* sp. ntm 15 (Spongiidae) led to the discovery of the new sesquiterpernoid hydroquinone 17-*O*-isoprenyldictyoceratin-C (**1**), the known sesquiterpernoid hydroquinone dictyoceratin-C (**2**), and the sesquiterpernoid quinone ilimaquinone (**3**), in addition to the nucleoside 2′-deoxyuridine. The structure of the new compound **1** was determined on the basis of spectroscopic methods.



P:421

1-*O*-SULFATOHEMIBASTADINS 1 AND 3 FROM *IANTHELLA BASTA* (PALLAS). ANTAGONISTS OF THE RYR_1-FKBP12 Ca^{2+} CHANNEL

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The release of Ca^{2+} from stores of the sacroplasmic reticulum (SR) is the trigger that stimulates contraction of striated muscle fibers through ATP hydrolysis coupled to induced conformational changes of the actin-myosin protein aggregate. In 1994, we discovered that bastadin-5,[1] from the marine sponge *Ianthella basta,* stimulates the release of Ca^{2+} from the SR by binding to the RyR_1-FKPBP12 Ca^{2+} channel through a novel mechanism that is not understood.[2] Examination of polar extracts from the sponge *Ianthella basta* (Mangilao, Guam) now reveals a series of new sulfated esters of the bastadins. Two new compounds– 1-*O*-sulfatohemibastadin-1 (**1**) and 1-*O*-sulfatohemibastadin-3 (**2**)– were isolated, characterized, and their structures established by interpretation of their spectral data. To our surprise, **1** and **2** exhibited *antagonistic* activity toward the RyR_1-FKBP12 complex (IC_{50} 13 and 29 μM, respectively). Antagonism by bastadin derivatives suggests a bimodal mechanism of action upon a common, but as-yet unidentified, bastadin effector site of the ~2 MDalton channel complex.

a, Chemistry; *b,* Molecular Biosciences.

1. Kazlauskas, R.; Lidgard, R. O.; Murphy, P. T.; Wells, R. J.; Blount, J. F. *Aust. J. Chem.* **1981**, *34*, 765-786.
2.(a) Mack, M.; Molinski, T. F.; Buck, E. D.; Pessah, I. N. *J. Biol. Chem.* **1994**, *269*, 23236-23349. (b) Chen, L.; Molinski, T. F.; Pessah, I. N. *J. Biol. Chem.* **1999**, *274*, 32603-32612. (c) Pessah, I. N.; Molinski, T. F.; Meloy, T. D.; Wong, P.; Buck, E. D.; Allen, P. D.; Mohr, F. C.; Mack, M. M. *Am. J. Physiol.* **1997**, *41*, C601-C614.

P:422

AURANTOSIDES G, H AND I: THREE NEW TETRAMIC ACID GLYCOSIDES FROM A PAPUA NEW GUINEA THEONELLA SP.

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Lithistid sponges of the family Theonellidae have been recognized as a rich source of structurally novel secondary metabolites with potent and varied biological activities. Among these are the chlorine-containing cytotoxic orange pigments: aurantosides A-F and rubrosides A-H. Recently three other new cytotoxic orange pigments aurantosides G-I were isolated from the lithistid sponge *Theonella* sp. from Papua New Guinea. These cytotoxic constituents were discovered in the process of screening the crude extract for HIV active principals.

The gross structures were established by the application of spectroscopic methods. Compounds G-I represent new monochloropentaenoyl tetramic acids with mono-, di-, and tri-N-saccharide substituents, respectively. All three compounds were recovered as bright orange solids in their pure form.

The identities of the sugar moieties were confirmed by methanolysis followed by HPLC and TLC comparison with authentic material. The absolute configuration of aurantosides G-I as well as that of their sugar moieties were identical to those reported for the known aurantosides.

P:423

HYRTIOSENOLIDES A AND B, TWO NEW SESQUITERPENE γ-METHOXY-BUTENOLIDES AND A NEW STEROL FROM A RED SEA SPONGE *Hyrtios* SPECIES

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[1]Department of Pharmacognosy, Faculty of Pharmacy, Suez Canal University, Ismailia 41522, Egypt, [2]Department of Pharmacognosy, Faculty of Pharmacy, Ain Shams University, Abbasia, Cairo, Egypt, and Institution for Systematics and Ecology, [3]The University of Amsterdam, P.O. Box 94766, 1090 GT Amsterdam, The Netherlands, and [4]Laboratory of Aquatic Natural Products Chemistry, Graduate School of Agricultural and Life Sciences, The University of Tokyo, Bunkyo-ku, Tokyo 113-8657, Japan.

Two new sesquiterpene γ-methoxybutenolides, hyrtiosenolides A (**1**) and B (**2**), together with a new 4α-methyl polyoxygenated steroid hyrtiosterol (**3**), were isolated from a Red Sea sponge, *Hyrtios* species. Their structures were elucidated by analysis of their 1D and 2D NMR spectra and HRFABMS. Biological activities of the compounds will be presented.

P:424

HYBRIDIZATION IN SOFT CORALS: GENETIC RECOMBINATIONS RESULT IN NOVEL BIOGENIC METABOLITES

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[1]Department of Pharmacognosy and [2]National Center for Natural Products Research, Research, RIPS, School of Pharmacy, The University of Mississippi, University MS 38677, [3]Department of Biology, University of Alabama at Birmingham, Birmingham AL 35294.

Hybridization and its consequences have attracted scientists for centuries. An important effect of hybridization is the generation of qualitative and quantitative variation in secondary metabolite chemistry. Although hybridization is common phenomenon in the sea, very little attention has been paid to its effects and consequences. The tropical Pacific soft corals *Sinularia maxima* and *S. polydactyla* have formed a hybrid zone on the reefs of Guam, USA. These broadcast spawning species have some degree of overlap in their reproductive periodicity, and this has apparently resulted in the development of these hybrid zones. Chemical studies of the extract of the hybrid resulted in the isolation of several compounds including a novel metabolite with a biosynthetically mixed skeleton linking a cembrane-type diterpene and an africanane-type sesquiterpene. The production of this compound, and at least 5 other new compounds, suggests that genetic crosses between different species have the potential to produce novel natural products not found in the parent species. This study represents the first chemical investigation of a hybrid marine invertebrate and our data indicates that hybridization among marine organisms represents a novel chemical and biological resource in the marine environment.

P:425

A NEW ANTIBIOTIC FROM A *STREPTOMYCES* SP. ISOLATED FROM MARINE SEDIMENT COLLECTED IN LA JOLLA, CA

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Marine actinomycetes are a rich source of new antibiotics and cytotoxic agents. In an ongoing effort to discover drugs for the treatment of infectious diseases and cancer, we are continually mining ocean sediments for marine microorganisms that produce new chemistry with therapeutic potential. This effort led us to undertake a local expedition to the Scripps Canyon in La Jolla, California, a narrow gorge extending from the coastal cliffs seaward for about one mile. The canyon topography is conducive to collecting marine sediments at a wide range of depths spanning a short distance, over which we conducted a transect, taking sediments at depths ranging from 15 to 650 feet. From one of these sediment samples, we isolated a strain of *Streptomyces* sp. that produced a new antibiotic along with new cytotoxic agents. The structures of the new compounds were established by complete spectroscopic analysis.

P:426

DISCOVERY OF (-)-SPIROLEUCETTADINE: THE FIRST NATURAL PRODUCT CONTAINING A FUSED 2-AMINOIMIDAZOLE OXALANE

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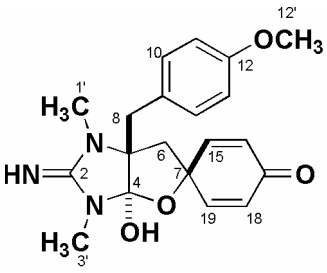

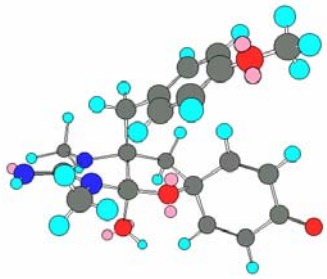

Sponges belonging to the class Calcarea are widespread in most coral reef habitats, yet as a group they have not been the subject of a great deal of chemical study. The information accumulated in the literature on these sponges to date showed that the genus *Leucetta* and its associated nudibranchs has received the most attention. Recently we reported the first nonorganometallic spiral imidazole alkaloids from a Fijian collection of *Leucetta* species. Further studies on this collection of *Leucetta* sp. containing the spirocalcaridines yielded (-)-spiroleucettadine, the first natural product to contain a fused 2-aminoimidazole oxalane ring along with the known compounds *N, N*-dimethylnaamidine D and isonaamine B. NMR analysis allowed the unambiguous assignment of the structure of (-)-spiroleucettadine and its absolute stereochemistry was determined by ORDCD spectroscopy. (-)-Spiroleucettadine also showed moderate antibacterial activity against *Eschericia coli* and *Staphylococcus epidermitis* and potent activity against *Enterococcus durans* with an MIC of less than 6.25μg/mL. Possible anticancer activity of this compound is currently under investigation.

P:427

TRUNGAPEPTINS A-C, NEW CYCLODEPSIPEPTIDES FROM THE MARINE CYANOBACTERIUM *LYNGBYA MAJUSCULA*

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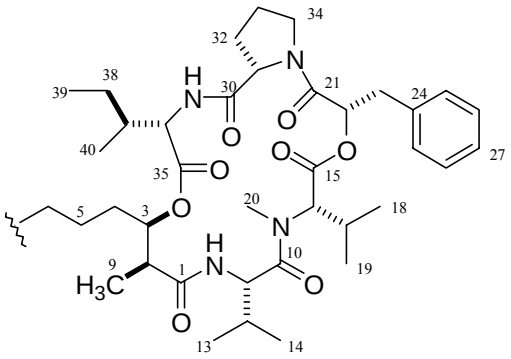
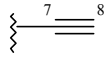
Trungapeptins A-C (**1-3**) were isolated from the marine cyanobacterium *Lyngbya majuscula* collected from Trung Province, Thailand. Their gross structures were elucidated by interpretation of spectroscopic data. The absolute configurations of the amino acids and phenyllactic acid were determined by Marfey's and chiral HPLC analyses, respectively. The relative stereochemistry of 3-hydroxy-2-methyl-7-octynoic acid (Hmoya) of trungapeptin A was elucidated by application of the *J*-base configuration analysis and its absolute stereochemistry was established to be 2*S* and 3*R* by Mosher's method. The structures of compounds **1-3** are closely related to the antanapeptins, a series of depsipeptides isolated a Madagascan collection of *L. majuscula*.



R =  Trungapeptin A (**1**)

R =  Trungapeptin B (**2**)

R =  Trungapeptin C (**3**)

P:428

THREE NEW HALOGENATED FURANONES FROM THE ANTARCTIC RED ALGA *DELISEA PULCHRA*

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Marine red algae from the family Bonnemaisoniaceace have been shown to produce a wide range of halogenated metabolites including butenones, acetones, octenones and from the genus *Delisea*, halogentaed furanones. Halogenated compounds from *D. pulchra* interfere with Gram-negative bacterial signaling systems, affect the growth of Gram-positive bacteria and inhibit quorum sensing and swarming motility of marine bacteria (inhibit bacterial communication). They also inhibit surface colonization by marine bacteria and exhibit antifouling properties. Chemical investigation of the *D. pulchra* collected near Palmer station, Antarctica, yielded three new halogenated furanones pulchralide A-C along with the previously reported fimbrolide, acetoxyfimbrolide, hydroxyfimbolide and a halogenated ketone. The reported compounds were characterized by comparison of their ^{1}H and ^{13}C NMR data with that previously published. Pulchralide A-C were characterized by both 1D (^{1}H NMR, ^{13}C NMR, DEPT, ^{1}H-^{1}H COSY) and 2D (gHMBC, gHMQC) NMR techniques, supported by HREIMS/HRESIMS data. The absolute stereochemistry of Pulchralide A was determined by X-ray crystal analysis. Acetoxyfimbrolide, Hydroxyfimbrolide and fimbrolide are found to be active against *Staphylococcus aureus, Micrococcus luteus* and *Bacillus subtilis.*

P:429

MANADOMANZAMINES A AND B, A NOVEL ALKALOID RING SYSTEM WITH POTENT ACTIVITY AGAINST MYCOBACTERIA AND HIV-1

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[a]Department of Pharmacognosy and National Center for Natural Products Research, [b]Department of Medicinal Chemistry, University of Mississippi, MS 38677, USA. [c]Center of Marine Biotechnology, University of Maryland Biotechnology Institute, MD 21202, USA. [d]Institute of Tuberculosis Research, College of Pharmacy, University of Illinois, IL 60612, USA. [e]Department of Pediatrics, Emory University/VA Medical Center, GA 30033, USA. [f]National Institute of Water & Atmospheric Research Ltd., Auckland, New Zealand. [g]The Faculty of Pharmacy, Gadjah Mada University, Yogyakarta, Indonesia.

Two novel alkaloids, named manadomanzamines A (**1**) and B (**2**), were isolated from an Indonesian sponge *Acanthostrongylophopra* sp. Their structures were elucidated and show to be a novel organic skeleton related to the manzamine type alkaloids. Their absolute configuration and conformation were determined by CD, NOESY, and molecular modeling analysis. The microbial community analysis for the sponge that produces these unprecedented alkaloids has also been completed. Manadomanzamines A (1) and B (2) exhibited strong activity against *Mycobacterium tuberculosis* (Mtb) with MIC values of 1.9 and 1.5 μg/mL. Manadomanzamines A and B also exhibit activities against human immunodeficiency virus (HIV-1), and AIDS opportunistic fungal infections.

P:430

TWENTY-SEVEN NEW DITERPENES AND SESQUITERPENES FROM THE JAMAICAN SPONGE *MYRMEKIODERMA STYX*

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Thirty diterpenes, cyanthiwigins A-AD (**1-30**), and five sesquiterpenes were isolated from the Jamaican sponge *Myrmekioderma styx*. The diterpenes cyanthiwigins E-AD (**5-30**) and sesquiterpenes, styxone A (**31**) and styxone B (**32**), are unreported natural products and their structures were elucidated by detailed analysis of ^{1}H, ^{13}C, DEPT, COSY, NOESY, HMQC and HMBC NMR spectra. Cyanthiwigins AC, AD, and styxone A represented novel skeletons for diterpene and sesquiterpene.
Cyanthiwigins A, C, D, E, F, I and Z (**1, 3, 4, 5, 6, 10, 26**) are active against human primary tumor cell lines. Cyanthiwigin C exhibited moderate activity against HBV and Mtb. and cyanthiwigin B exhibited activity against HIV-1. Interestingly, an activity enhancement by cyanthiwigin B (7) to curcuphenol was observed in the antimicrobial assays when the two compounds were administered together.

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MARINE SPONGES WITH ANTI-INFLAMMATORY ACTIVITY

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The only defence of marine sponges is chemical and therefore these organisms are prime candidates to possess bioactive metabolites. Their chemical defence cannot be equated with biomedical activity, but these two correlate well. In this work *in vivo* barnacle anti-fouling assay and *in vitro* neutrophil elastase release assay are combined. They are representative models for the host defence in primitive marine invertebrates and in humans respectively. In the anti-fouling assay settling of barnacle cyprids (*B. improvisus*) together with sponge extracts in fresh seawater is studied. The elastase assay is a multi target human neutrophil assay, where released elastase together with a substrate forms a coloured product, which is photometrically measured. Four extracts from eight marine sponges have been tested for their elastase inhibition; six of these have shown activity. Further work has been concentrated on the Indonesian sponges *Niphates olemda* and *Haliclona* sp., from which steroids and fatty acids have been isolated. Anti-fouling assay results will be compared to the already obtained elastase inhibition assay results.
This work is a cooperation between Uppsala University, Sweden and Heinrich-Heine University (HHU), Düsseldorf, Germany, and is a part of a larger marine project of HHU. Isolation and structure elucidation are performed in Düsseldorf and the bioassays in Uppsala.

P:432

LONG-CHAIN AMINOPOLYKETIDES FROM A MICRONESIAN TUNICATE

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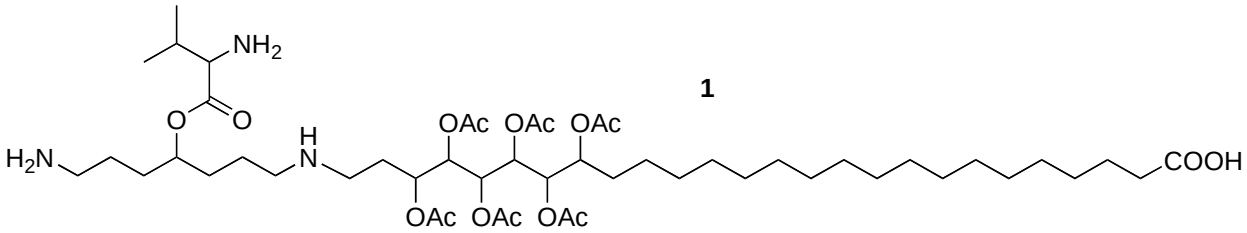
Examination of the organic extracts of an unidentified tunicate from Pohnpei, Micronesia, yields a series of novel poly-acetoxylated aminopolyketide carboxylic acids. The most abundant compound is hexa-*O*-acetyl-4'-*O*-valinyl-26-(7'-amino-4'-hydroxy-heptylamino)-19,20,21,22,23,24-hexahydroxyhexacosanoic acid (**1**). The novel structural characteristics of **1**, including the *O*-hexacetyl-1,2,3,4,5,6-hexaol-functionality and unusual 1,7-diaza chain segment, were identified by a combination of mass spectrometry and 1D and 2D NMR. Partial relative and absolute stereochemistry of the new compounds are addressed using Kishi's universal NMR database[1] and Edman degredation[2].



1

1. Higashibayashi, S.; Czechtizky, W.; Kobayashi, Y.; Kishi, Y. *J. Am. Chem. Soc.* **2003**, *125*, 14379-14393
2. Edman, Pehr *Acta Chem. Scan.* **1950**, *4*, 277-282

.P:433

MANZAMINE-TYPE ALKALOIDS AND THEIR ACTIVITY AGAINST INFECTIOUS DISEASES

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The Department of Pharmacognosy and National Center for the Development of Natural Products, School of Pharmacy, The University of Mississippi, University, MS 38677

The marine environment represents an enormous resource for the discovery of potential chemotherapeutic agents. In recent decades, the importance that the secondary metabolites from the marine ecosystem play in the control of infectious and parasitic organisms has largely been overlooked. As infectious diseases evolve and share resistance to existing pharmaceuticals, the marine environment provides a huge molecular diversity and represents a valuable ecosystem for the identification of novel leads against fungal, parasitic, bacterial, and viral diseases. One of the most promising antiinfective leads to be discovered from the oceans is the manzamine-type alkaloids. They are complex polycyclic alkaloids with an unprecedented biosynthetic pathway. Manzamine A is the first isolated congener from the Okinawan sponge of the genus Haliclona in 1986 by Higa and co-workers. In order to isolate manzamine analogs with more potency and selectivity against *Plasmodium falciparum*, a new species of a manzamine-producing sponge was investigated. Several new analogs have been isolated and the structure activity relationship of this type of alkaloids will be presented.

P:434

A NEW PHLOROGLUCINOL DERIVATIVE ISOLATED FROM A *HYPERICUM* SPECIES NATIVE TO THE SOUTHEASTERN UNITED STATES (*H. DOLABRIFORME* VENT., SECTION *MYRIANDRA*)

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Fractionation of the dichloromethane extract of the aerial parts of *H. dolabriforme* Vent. (Straggling St. John's Wort; Clusiaceae), a species native to the southeastern United States that belongs to the taxonomic section *Myriandra*, led to the isolation of a new phloroglucinol derivative. On the basis of 1D and 2D NMR experiments, as well as x-ray diffraction analysis, the structure was established as 3-benzoyl-4-hydroxyl-5,6,6-trimethyl-1,7-bis(3-methylbut-2-enyl)bicycle[3.3.1]non-3-ene-2,9-dione and its corresponding tautomer, and was named dolabriformin.

P:435

A SPIROLACTONE ISOLATED FROM A *HYPERICUM* SPECIES NATIVE TO THE SOUTHEASTERN UNITED STATES (*H. LLOYDII* (SVENSON) P. ADAMS, SECTION *MYRIANDRA*)

Sara L. Crockett[1], Wolfgang Schühly[2], Ferdinand Belaj[3], Ikhlas A. Khan[1, 4]*
[1]Department of Pharmacognosy, University of Mississippi, University, MS 38677 U.S.A. [2]Institut für Pharmakognosie. [3]Institut für Chemie, Karl-Franzens-Universität Graz, A-8010 Graz, Austria. [4]National Center for Natural Products Research, Research Institute for Pharmaceutical Sciences, University of Mississippi, University, MS 38677 U.S.A.

Fractionation of the dichloromethane extract of the aerial parts of *H. lloydii* (Svenson) P. Adams (Sandhill St. John's Wort; Clusiaceae), a species native to the southeastern United States and belonging to the taxonomic section *Myriandra*, led to the isolation of a spirolactone. The structure of this compound was deduced through spectral analyses, as well as x-ray diffraction analysis, as the known hyperlactone C (1,7-dioxaspiro[4,4]non-2-ene-4,6-dione-9-ethenyl-9-methyl-2-phenyl (5S, 9S)), previously isolated from *H. monogynum* (published in earlier reports as *H. chinense*, section *Ascyreia*).

P:436

NOVEL SECONDARY METABOLITES OF THREE BARBADIAN HERBS OF THE MINT FAMILY (LAMIACEAE): *HYPTIS*, *LEONOTIS* AND *LEONURUS*

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[a]Laboratory of Bioorganic Chemistry, Department of Biological and Chemical Sciences, University of the West Indies, Cave Hill Campus, P.O. Box 64, Bridgetown, Barbados
[b]Department of Chemistry, University of Toronto, Toronto, Ontario, M5S 3H6, Canada

The mint family (Lamiaceae) is utilized extensively in ethnomedicine in the Caribbean; various species are used for anthelmintic, cathartic, anti-pyretic, astringent and euphoric properties. A chemical investigation of three Barbadian herbs of the mint family was undertaken, and the secondary metabolites characterized on the basis of 1D and 2D NMR experiments.
From *Hyptis pectinata*, three α-pyrones - pectinolides D-F (1-3) and pectinolide G (4) - a 2(5H)-furanone were identified. A labdane diterpenoid, leonotinic acid (5) was isolated from *Leonotis nepetaefolia*. A number of prefuranoditerpenoids were isolated from *Leonourus sibiricus*-sibiricinones A-C (6-8), in addition to six stereochemically related diterpenes-sibiricinones D-F (9, 11 and 13) and 15-*epi*-sibiricinones D-F (10, 12 and 14), as C-15 epimeric mixtures.

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ANTI-TUBERCULOSIS COMPOUNDS FROM *MICROMELUM HIRSUTUM*

Cuiying Ma[1], Ryan Jay Case[2], Yuehong Wang[2], Hong-Jie Zhang[1], Ghee Teng Tan[1], Nguyen Van Hung[3], Nguyen Manh Cuong[4], Guido F. Pauli[2], Scott G. Franzblau[2], Djaja Djendoel Soejarto[1], Harry H. S. Fong[1*]
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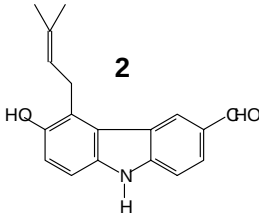

Anti-TB bioassay-directed fractionation of a CH_2Cl_2 extract of the stembark of *Micromelum hirsutum* led to the isolation of six carbazole alkaloids, as well as a γ-lactone derivative of oleic acid. The carbazoles include the new micromeline (**2**) and five known alkaloids: lansine (**3**), 3-methyl-carbazole (**4**), methyl carbazole-3-carboxylate (**5**), 3-formyl-carbazole (**6**), and 3-formyl-6-methoxy-carbazole (**7**). The lactone derivative of oleic acid, identified as (-)-*Z*-9-octadecene-4-olide (**1**) for which the trivial name micromelide was suggested, showed *in vitro* anti-TB activity with MIC value of 5.5 μM and a selectivity index of 63, appeared worthy of further evaluation as a potential anti-TB agent. Isolates **2**, **3**, **6** and **7** demonstrated moderate *in vitro* anti-TB activities with MIC values of 59-217 μM respectively, while compounds **4** and **5** were inactive. Structure elucidation and identification were based on spectroscopic data interpretation, including 1D, 2D NMR and full spin system analysis.

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A NEW NON-TOXIC CHROMAN DERIVATIVE FROM *PHYLLANTHUS AMARUS*

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2.Department of Chemistry, Virginia Polytechnic Institute & State University, Blacksburg VA 24061, U.S.A.

Phyllanthus amarus Schum. et Thonn is synonymous with *P. niruri* L. It is a Euphorbaceous plant shrub indigenous to the tropical and Asian Pacific regions. It is highly valued among traditional healers for antimicrobial, antiviral antimalarial properties. The antiviral property in the treatment of Hepatitis B and HIV virus infection has further created an upsurge on investigations on the plant. Previous studies on this plant species have furnished ellagitannins, amariinic acid and alkaloids from the polar fractions of the plant.
Chemical and cytotoxicity examinations of the methanol extract of the aerial parts of *Phyllanthus amarus* led to the isolation of a new chroman derivative, from the dichloromethane fraction. On the basis of spectroscopic nuclear magnetic resonance and mass spectral data, the structure of the chroman was established as 2-(methylene), 6 dimethoxy, 4-methyl, 8-hydroxy chroman. The chroman did not exhibit significant *in vitro* cytotoxicity property in the bioassay led fractionation and isolation using the human A2870 ovarian cancer cell line with an IC_{50} of 16.2 μg/ml.

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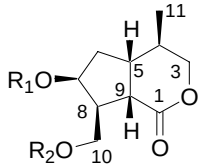
ANTITUBERCULAR CONSTITUENTS OF *VALERIANA LAXIFLORA* DC.

Jian-Qiao Gu,[1] Yuehong Wang,[2] Scott G. Franzblau,[2] Gloria Montenegro,[3] Barbara N. Timmermann*,[1].
[1]Department of Pharmacology and Toxicology, College of Pharmacy, University of Arizona, Tucson, AZ 85721. [2]Institute for Tuberculosis Research, College of Pharmacy, University of Illinois at Chicago, Chicago, IL 60612. [3]Departamento de Ciencias Vegetales, Facultad de Agronomía e Ingeniería Forestal, Pontificia Universidad Católica de Chile, Avenida Vicuña Mackenna 4860, Santiago, Chile

As part of a collaborative search for novel antitubercular agents from Latin American plants, the *n*-hexane and CH_2Cl_2 extracts of the above-ground biomass and roots of *Valeriana laxiflora* were found to inhibit the growth of *Mycobacterium tuberculosis* H37Rv with minimum inhibitory concentrations (MICs) of 50 and 100 μg/mL, respectively. Bioassay-guided fractionation of these extracts led to the isolation of a new iridolactone (**1**) and a new lignan, (+)-1-hydroxy-2,6-diepipinoresinol (**2**), along with betulin (**3**), betulinic acid (**4**), 5,7-dihydroxy-3,6,4'-trimethoxyflavone (**5**), 23-hydroxyursolic acid (**6**), oleanolic acid (**7**), tricin (**8**), ursolic acid (**9**), ferulic acid, (+)-1-hydroxypinoresinol, prinsepiol, and 5,7,3'-trihydroxy-4'-methoxyflavone. Structures of **1** and **2** were elucidated on the basis of spectroscopic evidence. The absolute stereochemistry of **1** was determined by chemical transformations and Mosher ester procedures. Among these isolates, compounds **2**-**9** exhibited MICs of 15.5-127 μg/mL in a microplate alamar blue assay. In addition, all the isolates were tested for cytotoxicity against the African green monkey Vero cells in order to evaluate for their selectivity potential. (Supported by ICBG grants 5 UO1 TW000316-10 and 3 UO1 TW000316-10S1 from NIH, NSF, and USDA to B.N.T.).



1 $R_1 = R_2 = H$
1a $R_1 = H$, $R_2 = COCH_3$
1s $R_1 = (S)$-MTPA, $R_2 = COCH_3$
1r $R_1 = (R)$-MTPA, $R_2 = COCH_3$

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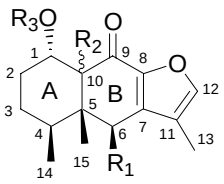
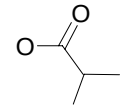
POTENTIAL ANTITUBERCULAR CONSTITUENTS OF *SENECIO CHIONOPHILUS*

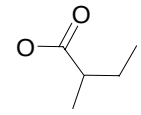
Jian-Qiao Gu,[1] Yuehong Wang,[2] Scott G. Franzblau,[2] Gloria Montenegro,[3] Barbara N. Timmermann*,[1].
[1]Department of Pharmacology and Toxicology, College of Pharmacy, University of Arizona, Tucson, AZ 85721. [2]Institute for Tuberculosis Research, College of Pharmacy, University of Illinois at Chicago, Chicago, IL 60612. [3]Departamento de Ciencias Vegetales, Facultad de Agronomía e Ingeniería Forestal, Pontificia Universidad Católica de Chile, Avenida Vicuña Mackenna 4860, Santiago, Chile

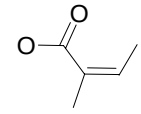
As part of a collaborative search for novel antitubercular agents from Latin American plants, the *n*-hexane and CH_2Cl_2 extracts of the above-ground biomass and roots of *Senecio chionophilus* were found to inhibit the growth of *Mycobacterium tuberculosis* H37Rv with minimum inhibition concentrations (MICs) of 50 and 100 μg/mL, respectively. Fractionation of these extracts led to the isolation of two new 9-oxofuranoeremophilanes **1** and **2**, along with 21 known constituents. The chemical structures of **1** and **2** were elucidated on the basis of spectroscopic evidence and chemical transformation methods. The absolute stereochemistry of **1** was determined by Mosher ester methodology. Among these isolates, compounds **2**, **3**, and 4′-hydroxyacetophenone (**4**) were found to exhibit mild antitubercular activity at MIC values of 119, 114, and 121 μg/mL, respectively, in a microplate alamar blue assay. (Supported by ICBG grants 5 UO1 TW000316-10 and 3 UO1 TW000316-10S1 from NIH, NSF, and USDA to B.N.T.).



1 R_1 = a, R_2 = β-H, R_3 = H
1s R_1 = a, R_2 = β-H, R_3 = (*S*)-MTPA
1r R_1 = a, R_2 = β-H, R_3 = (*R*)-MTPA
2 R_1 = b, R_2 = α-H, R_3 = H
2a R_1 = b, R_2 = α-H, R_3 = $COCH_3$
3 R_1 = c, R_2 = α-H, R_3 = H

a = 

b = 

c = 

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G.U.E.S.S.WORK HELPS SEPARATE BIOACTIVE NATURAL PRODUCTS

J. Brent Friesen[a] and Guido F. Pauli[b,c]
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In order to take advantage of support-free liquid-liquid (i.e., CCC) separations, solvent choice must be a vital step in the purification of bioactive natural products. Our practical approach using a "*Generally Useful Estimation of Solvent Systems*" (G.U.E.S.S.) predicts CCC retention volumes based on TLC R_f values. Targeted towards the high sample diversity of natural products, G.U.E.S.S.WORK allows a major reduction in workload by direct use of routine TLC information performed in fraction control or primary screening. Matching TLC data with partition coefficients (P) is largely an empirical exercise, since the general trend of TLC R_f values relates only approximately to P values. There is, therefore, a need to compare TLC R_f values directly with those of reference compounds, for which P is known. This presentation describes the relationship of partition coefficients, measured by UV/vis, TLC and HSCCC retention volumes for 20 diverse and commercially available natural products in the two popular and useful CCC solvent systems HEMWat (Hexane:Ethyl Acetate:Methanol:Water) and ChMWat (Chloroform:Methanol:Water). In order to quickly determine suitable CCC conditions, a mixture of reference standards may be (a) run on the same TLC plate as the target compounds or (b) compared to target compounds run under identical conditions in two or three different TLC solvent systems. The G.U.E.S.S. method has been shown to be readily applicable to natural products isolation and purification projects currently in progress in our laboratory.

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A NOVEL ANTIMICROBIAL INDOLIZINIUM ALKALOID FROM *ANIBA PANURENSIS*

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Activity-guided fractionation of an *Aniba panurensis* organic solvent extract has led to the isolation of the novel alkaloid 6,8-didec-(1Z)-enyl-5,7-dimethyl-2,3-dihydro-1*H*-indolizinium, trifluoroacetic acid salt (1). Its structure was determined by NMR and mass spectrometry. Bioassays performed in vitro demonstrated toxicity of compound 1 to a drug resistant strain of *Candida albicans*.

The content of this publication does not necessarily reflect the views or the policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government. This project has been funded in whole or in part with Federal funds from the National Cancer Institute, National Institutes of Health, under Contract No. NO1-CO-12400.

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NOVEL BIOGENETICALLY SIGNIFICANT UNUSUAL CYCLOPROPANOID REARRRANGEMENT REACTION PRODUCT OF GEDUNIN.

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Gedunin,1 has been reported to have exhibit a number of biological activities[1 – 7]. It also undergoes a number of rearrangement reactions[1,8,9] to give various products that could have interesting biological activities.

Recently, we treated 7-deacetoxy-7-hydroxy gedunin,2 with acid and obtained new reaction products including the novel[10] cyclopropane acid,3 which were isolated along with the previously described[9] 7,9-diene derivative, 4.

The cyclopropane compound,3 is biogenetically significant because it is structurally related to the naturally occurring[11] cneorins and the tricoccins,5.

The reaction is unusual in converting a methyl group into a cyclopropane ring member.

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NOVEL PREGNANE AND 14,15-SECOPREGNANE GLYCOSIDES WITH ANTIPROLIFERATIVE ACTIVITY FROM SOLENOSTEMMA ARGEL .

Alberto Plaza[1], Ciro Balestrieri[2], Maria Luisa Balestrieri[2], Giuseppe Bifulco[1], Francesca Felice[2], Arafa I. Hamed[3], Angela Perrone[1], Sonia Piacente[1], Cosimo Pizza[1,*].

[1] Dipartimento di Scienze Farmaceutiche, Università degli Studi di Salerno, Via Ponte don Melillo 84084 Fisciano (Sa), Italy. [2] Dipartimento di Biochimica e Biofisica, Seconda Università di Napoli, Italy, [3] Faculty of Science, South Valley University, Aswan 81528, Egypt.

Four new pregnane glycosides stemmoside C - F and seven novel 14,15-secopregnane glycosides namely argeloside C - I were isolated from the pericarps and seeds of *Solenostemma argel* (Asclepiadaceae). Stemmosides C – F possess an unusual C-17α side chain, while stemmosides D and F display in addition an unusual 14β proton configuration, apparently being the first pregnane isolated from plants known to have a 15 keto, *cis* CD ring junction. Argelosides C - I show a novel unusual secopregnane skeleton characterized by the opening of ring D between C-14 and C-15, and the presence of two hemiketal functions on C-14 and C-20. The structures of these compounds were elucidated by extensive spectroscopic methods including 1D- (^{1}H and ^{13}C) and 2D-NMR experiments (DQF-COSY, HSQC, HMBC, HOHAHA and ROESY) as well as ESIMS analysis. The relative configurations of stemmosides C and D have been defined combining the NMR data with DFT calculations of ^{1}H and ^{13}C chemical shifts, and ^{1}H homonuclear spin-spin coupling constants. Moreover, we tested the role of these compounds on the proliferation of KS cells. Results indicate that these compounds inhibit the VEGF-induced KS cell proliferation in a dose dependent manner and the highest inhibition occurs at 10μM (50% of VEGF-stimulated KS cells).

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CYTOTOXIC PRINCIPLES FROM THE LEAVES OF *PIPER BARBATUM*

Catherina Caballero-George, Yelkaira Vásquez, Ángela Calderón, Roberto Pinzón, Pablo N. Solís, Mahabir P. Gupta*
Center for Pharmacognostic Research on Panamanian Flora (CIFLORPAN), Estafeta Universitaria, Apdo. 10767, College of Pharmacy, University of Panama, Panama, Republic of Panama.

In our on-going research on Latin-American biodiversity, the hexane extract of the dried ground leaves of *Piper barbatum* Kunth (Piperaceae) showed high cytotoxicity in three cell lines MCF-7 (breast), H-460 (lung) and SF-268 (CNS), GI_{50}=1.5, 1.7, 1.5 μg/ml, respectively. ***P. barbatum*** is a Colombian medicinal plant which is used in the treatment of ulcers and as wound healing.
Bioassay-guided fractionation of the active extract led to the isolation of three known compounds (2'E,6'E)-2-farnesyl-1,4-benzoquinone[1], (2'E,6'E)-2-farnesylhydroquinone[1] and dictiochromenol. Their chemical structures were determined by spectral means (1D, 2D NMR, MS) and chemical data. Among these three, (2'E,6'E)-2-farnesyl-1,4-benzoquinone was the most active (MCF-7 GI_{50}= 1.8 μg/ml; H-460 GI_{50}=4.8 μg/ml; SF-268 GI_{50}= 3.5 μg/ml).

Reference:

[1]*Revista Colombiana de Química* (2000), 29(2): 25-37.

Acknowledgement: Organization of American States, Project SEDI/AICD/AE-106-03

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SEARCH FOR ANTICANCER, ANTIPARASITIC AND ANTIFUNGAL BIOACTIVE MOLECULES FROM LATINAMERICAN BIODIVERSITY IN A MULTINATIONAL PROJECT

Mahabir P. Gupta[a,*], Pablo N. Solís[a], Angela I. Calderón[a], Yelkaira Vásquez[a], Nelson Rodríguez[a], Susana Zacchino[b], Alberto Giménez[c], Roberto Pinzón[d], Armando Cáceres[e], Eduardo Ortega[f]. [a]CIFLORPAN, College of Pharmacy, University of Panama, [b]Universidad Nacional de Rosario, Rosario, Argentina, [c]Instituto de Investigaciones Farmacobioquímicas de Bolivia, La Paz, Bolivia, [d]Universidad Nacional de Colombia, Bogota, Colombia, [e]Universidad de San Carlos, Guatemala, Guatemala, [f]Instituto de Investigaciones Avanzadas y Servicios Tecnológicos e Innovación (INDICASAT), Panama, Panama.

This collaborative multinational OAS project aimed at discovering novel bioactive molecules during 2001-2003 has resulted in the generation of an ethnomedical database PLAN MEDIA® with a total of 4129 entries corresponding to 1152 species (167 families and 692 genera). In addition, 300 plant species collected, 382 extracts were prepared and tested in a panel of bioassays. Twenty-one (5.4%) extracts showed relevant antifungal, 49 (13%) anti-*Trypanosoma*, 42 (11%) anti-*Leishmania*, 143 (37%) anti-malarial and 15 (4.0%) cytotoxic activities. Ninety compounds were isolated from which 10 were new: (4 benzophenones, 1 flavonol, 1 flavanone, 2 caffeic acid derivatives, 1 quinone and 1 benzoic acid derivative).

Acknowledgements:
OAS through the Multinational project (SEDI/AICD/106/01) and Convenio Andrés Bello

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CLERODANES DITERPENOIDS FROM *MICROGLOSSA ANGOLENSIS*

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[c]*Chemistry Department, University of Glasgow, Glasgow G12 8QQ, Scotland*

Microglossa angolensis Oliv. et Hiern (syn. *Conyza pyrrhoppapa* Sch. Bip. Ex A. Rich; *Microglossa pyrrhoppapa* A. Rich) (Compositae) is an erect undershrub of 60 to 120 cm growing in Africa and Madagascar[1]. The whole plant is used for treatment of malaria[1]. Previous studies led to the isolation of clerodanes diterpenoids[2]. Chemical investigation of the CH_2Cl_2 extract of the aerial parts of this plant yielded two novel clerodanes diterpenoids 10β-hydroxy-3α,4α,15,16-bis-epoxy-8βH-6-oxo-cleroda-13(16),14-diene-20,12-olide and 6β-(2-methylbut-2-enoyl)-3α,4α,15,16-bis-epoxy-8βH-cleroda-13(16),14-diene-20,12-olid, together with two oleanane triterpenoids and for flavonoids. The isolation as well as elucidation of the new metabolites will be dicussed.

References
1- Kokwaro, O; 1976. *Medicinal Plants of East Africa*; East African literature Bureau, Kampala, Nairobi, Dar es salaam.
2- Zdero, C., Bohlmann, F., and Mungai, G. M.; 1990. Rearranged clerodanes and other diterpenes from *Microglossa pyrrhopappa*; *Phytochemistry*, 29, 3233-3241

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CYTOTOXIC TRITERPENES FROM THE AERIAL ROOT OF *FICUS MICROCARPA*

Yi-Ming Chiang, Yueh-Hsiung Kuo*
Department of Chemistry, National Taiwan University, Taipei, 106, Taiwan, ROC

Six new triperpenes, 3β-acetoxy-12,19-dioxo-13(18)-oleanene, 3β-acetoxy-19(29)-taraxasten-20α-ol, 3β-acetoxy-21α,22α-epoxytaraxastan-20α-ol, 3,22-dioxo-20-taraxastene, 3β-acetoxy-11α,12α-epoxy-16-oxo-14-taraxerene, 3β-acetoxy-25-methoxylanosta-8,23-diene along with nine known triperpenes were isolated from the aerial roots of *Ficus microcarpa*, and their structures were elucidated by spectroscopic methods. The *in vitro* anti-tumoral cytotoxic efficacy of these triperpenes against three human cancer cell lines, namely, nasopharyngeal carcinoma HOME-1, oral epidermoid carcinoma KB, and colorectal carcinoma HT29 cells, were investigated. One lanostane derivative and seven pentacyclic triperpenes (including oleanane, lupane, ursane, friedelane) that bearing a carboxylic acid at C-28 showed significant cytotoxic activities against these cell lines and gave IC_{50} values in the range 4.0-21.2 μM.

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GROWTH INHIBITION OF *MYCOBACTERIUM TUBERCULOSIS* BY THE CONSTITUENTS OF *MYRCIANTHES COQUIMBENSIS*.

Smriti Khera[1*]
Gloria Montenegro[3], Barbara N. Timmermann[2]. [1]Department of Pharmaceutical Sciences, [2]Department of Pharmacology and Toxicology, University of Arizona, Tucson, AZ. [3]Departmento de Ciencias Vegetales, Pontificia Universidad Catolica de Chile, Santiago, Chile.

As a part of an International Cooperative Biodiversity Group Program (ICBG) we investigate Latin American plants for new biologically active agents. We report here a bioassay guided chemical investigation of a Chilean plant *M. coquimbensis* (Barn.) Landrum et Grifo (Myrtaceae). The CH_2Cl_2-MeOH (1:1) extract of *M. coquimbensis* was found to inhibit the growth of *Mycobacterium tuberculosis* H37 R_v by 73% at a concentration of 50 μg/ml. Partitioning of this extract with various solvents based on solvent polarity resulted in a Hexane, CH_2Cl_2, BuOH, and H_2O fractions. The CH_2Cl_2 fraction was found to inhibit growth by 98% and the BuOH fraction by 51% at concentrations of 50 μg/ml each. These extracts were combined based on similar TLC profiles. Bioassay guided fractionation of the CH_2Cl_2-BuOH fraction thus far has led to the isolation of oleanolic acid, (+)-trans-sobrerol, catechin and *epi*-catechin. This is the first report of non-volatiles from this genus.

This work was supported by the "Bioactive Agents from Dryland Biodiversity of Latin America" ICBG grant U01 TW 00316-09 from NIH, NSF and USDA to B.N.T.

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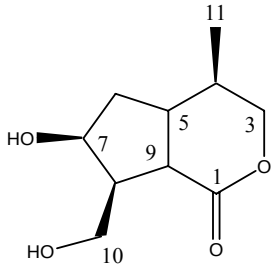
(4*R*,5*R*,7*S*,8*S*,9*S*)-7-HYDROXY-8-HYDROXYMETHYL-4-METHYL PERHYDROCYCLOPENTA[*c*]PYRAN-1-ONE FROM *VALERIANA LAXIFLORA*

Smriti Khera[1*], Michael Carducci[2], Barbara N. Timmermann[3]. [1]Department of Pharmaceutical Sciences, [2] Department of Chemistry, [3] Department of Pharmacology and Toxicology, University of Arizona, Tucson AZ 85721.

Bioassay guided fractionation led to the isolation of a new iridolactone **1** from a methanolic antitubercular extract of the Chilean *Valeriana laxiflora* (Valerianaceae). X-Ray diffraction of a single crystal of **1** was carried out to unequivocally establish its structure as well as its relative stereochemistry. It was observed that the two rings were *cis*-fused. The δ-lactone ring was a slightly twisted half-chair and the cyclopentane ring adopted an envelope conformation. The hydroxy group at C(7) and the methyl hydroxy group at C(8) both were β oriented, as was the C(4) methyl group. The lactone group C(9)-C(1)O(2)-O(1)-C(3) was determined to be almost planar. As a result of the adventitious inclusion of chloroform in the crystal lattice the anomalous dispersion data was used to arrive at an absolute configuration of 4*R*,5*R*,7*S*,8*S*,9*S* for the compound. This to our knowledge is the first report of the absolute configuration of an iridolactone based on X-ray data. An interesting arrangement of molecules of **1** in the crystal lattice with $P2_1$ symmetry was observed. Further details about this unique assembly and specifics of the hydrogen bonds will be discussed at the meeting. Through this work we were able to study in great detail, making comparisons with existing literature where possible- the ring conformation, bond distances, planarity of the lactone group, hydrogen bonding and absolute configuration of compound **1** and gain a wealth of information on the three dimensional structures of iridolactones.



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This work was supported by the "Bioactive Agents from Dryland Biodiversity of Latin America" ICBG grant U01 TW 00316-09 from NIH, NSF and USDA to B.N.T.

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HIGH-THROUGHPUT NATURAL PRODUCTS CHEMISTRY METHODS LEAD TO THE DISCOVERY OF A NOVEL ANTIBACTERIAL INDOLOSESQUITERPENE FROM *GREENWAYODENDRON SUAVEOLENS*

Jin-Feng Hu,* Hye-Dong Yoo, Caroline T. Williams, Peadar A. Cremin, Lu Zeng, Eliane Garo, Helene C. Vervoort, Chris M. Lee, Shane M. Hart, Matt G. Goering, Mark O'Neil-Johnson and Gary R. Eldridge
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Utilizing high-throughput isolation, purification and analysis methods applied to our natural products libraries from plants, a mass-limited novel indolosesquiterpene, suaveolindole (**1**, 300 micrograms), was obtained from *Greenwayodendron suaveolens*.
The structure and relative stereochemistry of **1** was elucidated by interpretation of mass and NMR spectral data acquired via the CapNMR™ probe. Compound **1** was found to possess significant *in vitro* antibacterial activity against Gram-positive bacteria *Bacillus subtilis* (ATCC 43223), *Staphylococcus aureus* (ATTC 6538P) and methicillin-resistant *Staphylococcus aureus* (ATTC 33591).

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ANTIBACTERIAL ALKYLATED SUGARS FROM *ARCTOSTAPHYLOS PUMILA* VIA THE HIGH-THROUGHPUT NATURAL PRODUCTS CHEMISTRY METHODS

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High-throughput isolation, purification and analysis methods applied to natural products libraries gave rise to the discovery of two mass-limited novel alkylated glucoses (**1**, **2**) produced by *Arctostaphylos pumila*.
The NMR spectra were acquired using the CapNMR™ probe, which enabled us to elucidate the structures of pumilopyranoside A (**1**, 200 micrograms) and pumilopyranoside B (**2**, 70 micrograms). The pumilopyranosides exhibited antibacterial activity against Gram-positive methicillin-resistant *Staphyllococcus aureus*.

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NEW CYTOTOXIC ISOFLAVONE FROM THE ROOT BARK *BROSIMUM UTILE*

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A new isoflavone 5,7,4'-trihydroxy-3'-(3-hydroxy-3-methylbutyl)isoflavone (isowigtheone hydrate) (**1**), together with six known isoflavones 2-7 and (-) epicatechin, were isolated from the root barks of *Brosimum utile*. Their structures were established on the basis of spectroscopic evidence. The *in vitro* cytotoxic activity of the new compound **1** was evaluated against cell lines MCF7 (human breast carcinoma), PC3 (human prostate carcinoma), HT29 (human colon cancer) and human dermis fibroblasts**.**

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QSAR STUDIES ON ACETYLCHOLINESTERASE ENZYME INHIBITORY EFFECTS OF AMARYLLIDACEAE ALKALOIDS

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Twenty-three Amaryllidaceae alkaloids having several different ring types were evaluated for their acetylcholinesterase enzyme (AChE) inhibitory activity. The alkaloid 1-O-acetyllycorine (IC_{50}: 0.96±0.04 μM) showed significant AChE inhibitory activity, two-fold more active than the currently used drug, galanthamine (IC_{50}: 1.9±0.16 μM). QSAR studies of these Amaryllidaceae alkaloids as acetylcholinesterase inhibitors were carried out using physicochemical properties as descriptors. Multiple linear regression analysis of the data has shown that energy, molecular weight, heat of formation and substituents at both the aromatic ring and ring C play an important role in the development of the QSAR model. The contribution of substituents at ring C to the model was further supported when energy was omitted from the model and ring-type based QSAR analysis for crinine- and lycorine-type alkaloids were performed.

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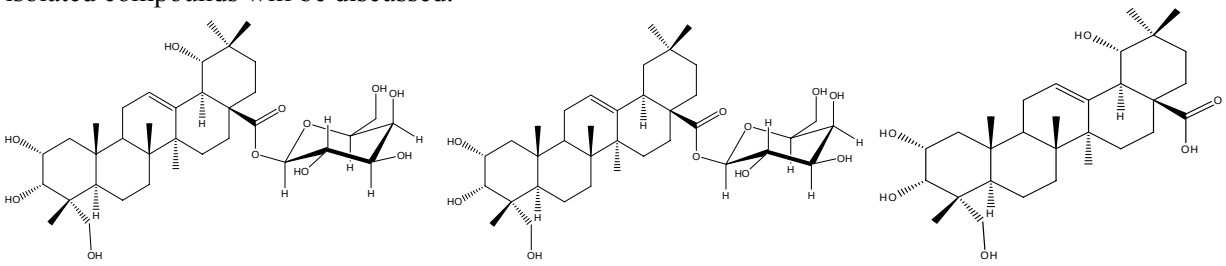
TRITERPENOIDS AND LIGNANS FROM *PICRORHIZA KURROA* SEEDS

Yanjun Zhang[1], Sorimuthu Murugesan[2] and Muraleedharan G. Nair[1]. [1]Bioactive Natural Products and Phytoceuticals, Department of Horticulture and National Food Safety and Toxicology Center, Michigan State University, East Lansing, MI, 48824. [2]Institute of Forest Genetics and Tree Breeding, Coimbatore, India.

The bitter rhizomes and seeds of *Picrorhiza kurroa* have been used for thousands of years in the Ayurvedic system of medicine in India and traditional medicines in China to treat disorders of liver and upper respiratory tract. Iridoids, acetophenones and cucurbitacins were reported from the rhizomes of *P. kurroa*. We have recently reported cyclooxygenase-2 enzyme and lipid peroxidation inhibitory compounds from EtOAc extracts of *P. kurroa* seeds. The active compounds reported were mainly tannins. As a continuation of our research on *P. kurroa* EtOAc seed extract, we have now identified several polyhydroxy triterpenoids, lignans and sterols. The structures of compounds were identified by extensive NMR experiments. The compounds isolated will be tested for their cyclooxygenase enzyme and lipid peroxidation inhibitory activities. Details of purification, structure elucidation and bioactivities of the isolated compounds will be discussed.



P:456

BIOACTIVE DITERPENES FROM *COMMIPHORA MUKUL* RESIN

Jayaraj A. Francis[1], [2]Srinivsa N. Raja and Muraleedharan G. Nair[1].
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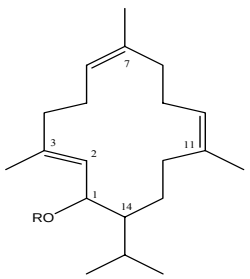
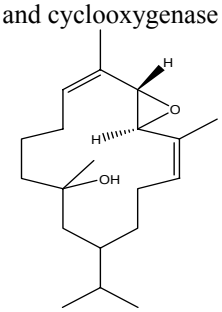
Guggulu, the gum resin from *Commiphora mukul* has been used in various systems of traditional medicine for treating inflammation, obesity and lipid disorders. Bioassay guided extraction and isolation of compounds from the hexane soluble portion of the methanol extract of the gum resin of *C. mukul* yielded diterpenes **1**-**7**. The structures of these compounds were identified by spectroscopic methods. Compounds **5**, **6** and **7** are novel. At 100 ppm, these compounds inhibited lipid peroxidation and cyclooxygenase enzymes (COX-1 and COX-2) activities.



4 **R=H**
5 **R=OMe**



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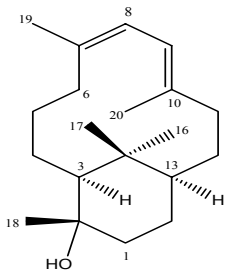

7

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BIOACTIVE TERPENOIDS FROM STINKING TOE (*HYMANAEA COURBARIL*) FRUITS

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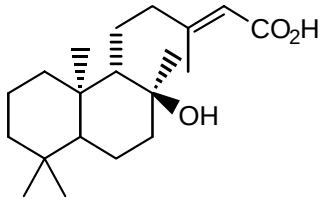
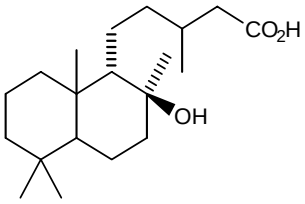
Hymanaea Courbaril, commonly called as Stinking toe or Jatoba, belongs to the family leguminosea and widely distributed in southern Mexico, Central America, West Indies, Brazil, Bolivia, and Peru. In traditional medicine, various parts of the plant were used as antibacterial, antifatigue, antifungal, anti-inflammatory, antioxidant, anti-spasmodic, antiyeast, astringent, decongestant, diuretic, expectorant, hemostatic, hepatoprotective, hypoglycemic, laxative, molluscicidal, stimulant, stomachic, tonic, and vermifuge. Earlier chemical investigations of this plant yielded several diterpenoids. A systematic bioassay directed purification of extracts from *H. courbaril* fruits yielded several known labdanes and sesquiterpenoids. Isolation, characterization and bioactivities of these terpenoids will be presented.



1



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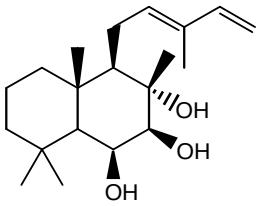

3

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BIOACTIVE CONSTITUENTS FROM *CORNUS KOUSA*

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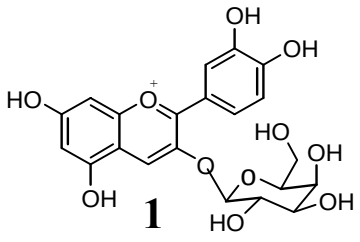
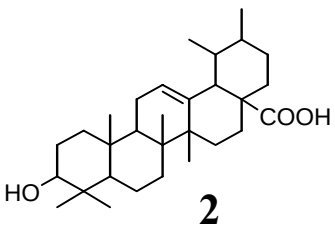
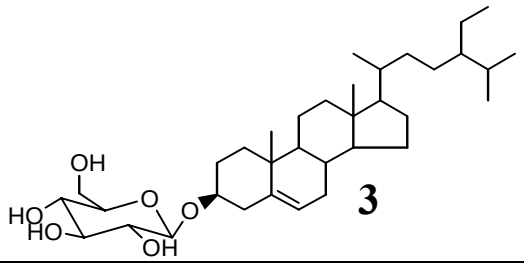
Dogwood trees (*Cornus*) are grown for its attractive flowers and fruits. The fruits from dogwood have been used in China as antiviral, antiinflammatory, antimicrobial, antidiabetic and antifungal agents for more than 2000 years. *Cornus kousa*, one of the dogwoods grown in Michigan, is an ornamental tree. The fruits from *C. kousa* were not investigated for its constituents and bioactivity. We have collected *C. kousa* fruits at Michigan State University campus grounds and sequentially extracted with H_2O, MeOH and EtOAc. Our preliminary studies with MeOH and EtOAc extracts inhibited lipid peroxidation by 100 and 68%, respectively, at 250 ppm. The EtOAc extract showed 58% inhibition of cyclooxygenase (COX-2) enzyme at 250 ppm. Purification of the MeOH extract yielded cyanidin 3-*O*-galactoside (**1**), ursolic acid (**2**) and β-sitosterol glucoside (**3**). Details of purification, chemical characterization and bioactivities of these compounds will be presented.



1



2



3

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NEW CYANOPYRIDONES FROM *ACALYPHA INDICA* L.

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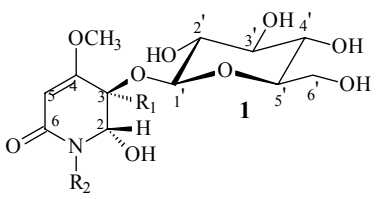
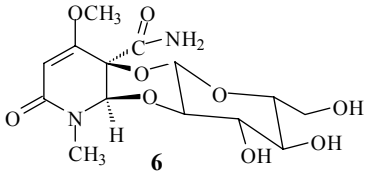
Acalypha indica L. (Euphorbiaceae), an annual weed growing in arid zones, is used in folk medicine against pneumonia, as an anthelminthic and homoeopathic drug. In addition to acalyphin, the major cyanogenic compound (**1**), and its C2-epimer (**2**), we isolated further cyanopyridones from the methanolic extract of the dried leaves and flowers. They represent two new epimeric pairs of cyanopyridones, the complete structures being established by ESI-MS, 2D-NMR, CD and X-ray crystallography.
One pair represents noracalyphin and its C2-epimer (**3**, **4**). The other pair was elucidated as acalyphinamide (**5**) and a corresponding C2 epimeric compound that represents a new glucosyl-fused pyridone with an intramolecular dioxane structure (**6**). These amides can only be detected in air-dried plant material.



1

	C-2*	R_1	R_2
1	S	CN	CH_3
2	R	CN	CH_3
3	S	CN	H
4	R	CN	H
5	S	$CONH_2$	CH_3



6

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DETERMINATION OF THE MINIMUM ENERGY CONFORMATION OF GLABRESCOL BY MOLECULAR MODELLING.

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University of the West Indies, Mona, Kingston 7, Jamaica

Molecular modeling of the remarkable natural product, glabrescol, both in its native form and when complexed to metal, using PCMODEL™ version 6.0, has led to the conclusion that this compound is more stable in its unbound state and therefore formation of a glabrescol-metal complex is not feasible. From these studies it is also evident that this compound assumes an extended rather than folded conformation; this extended conformation does not readily lend itself to complexation with metal ions.

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SCREENING OF YUCATECAN PLANTS AND ISOLATION OF A NEW FUNGISTATIC COMPOUND FROM *ACACIA PENNATULA* TO CONTROL *COLLETOTRICHUM GLOEOSPORIOIDES*

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Colletotrichum gloeosporioides (Penz.) is the causal agent of anthracnose in diverse tropical fruit trees (*e.g*. papaya, avocado, mango), which causes low yield and poor quality of the fruits. The damages caused by this fungus are present mainly after harvest. This pathogen has a great capacity of genetic variability, which has permitted the fungus to create resistance to some synthetic chemical fungicides, principally those in the group of benzimidazoles. For that reason, it is of the most importance to find new strategies to combat this phytopathogen. Based on this premise and in the use of non-contaminant, renewable natural resources, we carried out the screening of native Yucatecan plants. Chromatographic purification of the methanolic extract of one of the most active plants, *Acacia pennatula* (Chan. & Schltdl.) Benth., resulted in the isolation of the new compound 15,16-dihydroxi-8(14)-pimaren-3-one (**1**), which showed to have fungistatic activity in the *in vitro* bioassay "dilution in agar". RMN spectroscopic techniques were used to elucidate its structure.

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STRUCTURE AND BIOLOGICAL ACTIVITY OF NEW DIMERIC CARBAZOLE ALKALOIDS FROM *MURRAYA KOENIGII*

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Toukai Gakuen University, Tempaku, Nagoya 468-8514, Japan
Faculty of Pharmacy, University of Dhaka, Dhaka-1000, Bangladesh

Murraya plants (Rutaceae) are one of the richest sources of carbazole alkaloids. In 1983, we isolated the first dimeric carbazole alkaloid, murrafoline-A, from the plant *M. euchrestifolia* HAYATA collected in Taiwan. Since then, we have reported the isolation of many kinds of dimeric carbazole alkaloids from this plant.
This time, we studied the chemical constituents of leaves of *M. koenigii* (L.) SPRENG collected in Bangladesh and isolated five new dimeric carbazole alkaloids along with two new monomeric and known carbazoles.
The structures of the new dimeric carbazoles were elucidated on the basis of spectroscopic analyses.
Cytotoxic activities against HL-60 cells of some carbazole alkaloids will also be presented.

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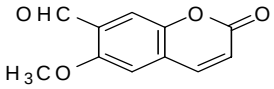
PHYTOCHEMICAL AND BIOLOGICAL STUDIES ON *ZANTHOXYLUM FLAVUM*

Samir A. Ross,[1,2,*] Kesanapalli S. Krishnaveni,[1] Charles L. Burandt,[3] Mahmoud A. ElSohly[1,3]
[1]National Center for Natural Products Research, Research Institute of Pharmaceutical sciences, [2]The Department of Pharmacognosy, [3]The Department of Pharmaceutics, School of Pharmacy, The University of Mississippi, University, MS 38677-1848

The genus *Zanthoxylum,* commonly called prickly-ash, is the largest genus in the family Rutaceae and comprises about 200 species of trees and shrubs, with a worldwide, but predominantly tropical distribution. *Zanthoxylum* species are reported to have many medicinal properties and phytochemical studies on the genus have shown it to be a rich source of coumarins, lignans, and alkaloids with febrifuge, sudorific, and diuretic properties.

Previous studies on the root and stem bark of *Zanthoxylum flavum* Vahl. led to the isolation of three alkaloids and four coumarins and our phytochemical reinvestigation on the roots of *Z. flavum* led to the isolation of a new coumarin (**1**) together with a group of known coumarins, sterols and alkaloids. Among the twenty known compounds isolated, ten compounds constitute the first report from this species. The structure of the new compound (**1**) has been assigned on the basis of IR, ^{1}H and ^{13}C NMR, DEPT, HMQC, HMBC and Mass spectroscopy. The biological activities of the isolated coumarins and alkaloids will be presented.



1

P:464

THE ISOLATION AND OPTICAL ROTATION MEASUREMENTS OF (+) AND (-) AMMODENDRINE

Stephen T. Lee*,[†], Russell J. Molyneux[‡], Kip E. Panter[†], Cheng-Wei Tom Chang[§], Dale R. Gardner[†], Massoud Garrossian[†]
[†] Poisonous Plant Research Laboratory, Agricultural Research Service, United States Department of Agriculture, 1150 E. 1400 N., Logan, Utah 84341, USA
[‡] Western Regional Research Center, Agricultural Research Service, United States Department of Agriculture, 800 Buchanan Street, Albany, California 94710, USA
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Ingestion of *Lupinus formosus* by pregnant cows at specific gestational periods can result in calves with cleft palate and front limb contractures, commonly known as crooked calf disease. Ammodendrine, a piperidine alkaloid, found in *L. formosus* is a reported teratogen. In this study, chromatographic methods were developed for the separation and analysis of ammodendrine enantiomers in *L. formosus* and in other *Lupinus* plants. In addition, a mixture of ammodendrine enantiomers was isolated from *L. formosus* and the enantiomers separated and isolated allowing optical rotation measurements and toxicological characterization of the enantiomers.

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PHENYLPROPANOID AND IRIDOID GLYCOSIDES FROM *SCROPHULARIA NINGPOENSIS*

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[a] Lab. of Pharmacognosy, [b] Lab. of Physiology and Pharmacology Fundamentals, [d] Lab. of NMR High Resolution, Université Libre de Bruxelles, B-1050 Brussels, Belgium
[c] Lab. of bio-organic mass spectrometry, University of Antwerp, B-2610 Wilrijk, Belgium

Scrophularia ningpoensis is a well-known traditional Vietnamese herbal medicine. The roots have been used as antipyretic, antifebrine, and antibacterian; they are a remedy for evening fever, erythema, mouth dryness, constipation, prurigo, furunculosis, sore throat, ulcerous stomatitis and tonsillitis.
A preliminary investigation showed that the dichloromethane and ethyl acetate extracts of the roots are cytotoxic on several human cancer cell lines. We report here the isolation of two novel phenylpropanoid and iridoid glycosides from the active extracts by using different chromatography techniques: ningposide D (3-*O*-acetyl-2-*O*-*p*-methoxycinnamoyl-α-L-rhamnopyranose) (**1**) and scrophuloside B_4 (6-*O*-(2''-*O*-acetyl-3''-*O*-*p*-methoxycinnamoyl-4''-*O*-cinnamoyl)-α-L-rhamnopyranosyl catalpol) (**2**) along with the known compounds: oleanonic acid (**3**), ursolonic acid (**4**), cinnamic acid (**5**), 3-hydroxy 4-methoxy benzoic acid (**6**), 5-(hydroxymethyl)-2-furfural (**7**) and β-sitosterol (**8**). The structure of new compounds was elucidated by spectral data (1, 2-D NMR, EI, ESI-MS and MS/MS).
Cytotoxicity of the isolated compounds against different human cancer cell lines using the MTT assay indicates that oleanonic (**3**) and ursolonic acid (**4**) are the main cytotoxic compounds of the plant: (IC_{50} = 5.6, 15.5 µM on MCF7; 4.0, 14.5 µM on K562; 15.3, 44.3 µM on Bowes; 24.9, 43.6 µM on T24S; 64.5, 151.5 µM on A549 for (**3**) and (**4**) respectively). Scrophuloside B_4 (**2**) was active on K562 and Bowes cell lines with IC_{50} = 63.4 and 65.7 µM respectively.

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LAEVISANONE, A NEW AND RARE FLAVANONE GLYCOSIDE FROM *NEWBOULDIA LAEVIS* (BEAUV.) SEEM.EX BUREAU

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2.Za fur Chemie Analytik & Endokrinologie der Tieratzlichen Hochschule, Bischofscholer Damm 15, 30173 Hannover, Germany.

New bouldia laevis (Beauv.) Seem. ex Bureau (Bignoniaceae) is a common tree of West African origin well known for its ethnomedical uses. The leaves, bark and roots are used in the treatment of conjunctivitis, arthritis, dysentery, enlarged spleen, heart burn, wounds and various forms of architis. Recently cytotoxic pentacyclic triterpenoids were isolated from the leaves.
We now report the isolation of a new and rare flavanone glycoside – laevisanone and β – sitosterol from the root extract of the plant.
Laevisanone has been characterized as 4^1-C-phenyl-8-methyl-flavanone-7-α-L-rhamnopyranoside. The structure has been determined mainly by spectral data, colour reactions and the use of 2D correlation experiments.
Keywords: Laevisanone, *Newbouldia Laevis*, flavanone, rhamnopyranoside

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A NEW VHR DUAL-SPECIFICITY PROTEIN TYROSINE PHOSPHATASE INHIBITOR FROM *DENDROBIUM MONILIFORME*

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[1] Korea Research Institute of Bioscience and Biotechnology (KRIBB), Daejeon, South Korea
[2] Dept. of Food and Nutrition, Chungnam National University, Daejeon, South Korea
[3] The Institute of Physical and Chemical Research (RIKEN), Wako-shi, Saitama, Japan
[4] These authors contributed equally to the work

The vaccina open reading-frame H1-related protein phosphatase (VHR) is the first DS-PTPase identified in humans and is known to have a central role in cell cycle regulation and intracellular signaling processes mediated by the mitogen-activated protein (MAP) kinase.

Bioassay-guided fractionation of the EtOAc-soluble extract of *D. moniliforme* afforded a new phenanthraquinone-type metabolite, 7-hydroxy-5,6-dimethoxy-1,4-phenanthrenequinone (**1**), along with the previously reported 5-hydroxy-3,7-dimethoxy-1,4-phenanthrenequinone (**2**). The structures of the compounds were identified mainly by analysis of MS and NMR data. Compound **1** inhibited VHR dual-specificity protein tyrosine phosphatase (DS-PTPase) activity in a dose-dependent manner, displaying an IC_{50} value of 3.0 ± 0.2 μM.

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X-RAY STRUCTURE OF (-) ISTANBOLIN A FROM SENECIO AEGYPTIUS

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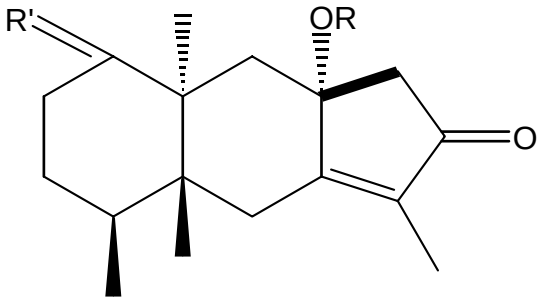
Pharmacognosy Department, Faculty of Pharmacy, Alexandria University, Alexandria, Egypt.

A sesquiterpene **(I)**from *Senecio aegyptius L*. showed it's close semblance to (Istanbolin A) isolated from *Smyrnium* and *Senecio.* Minor differences and the opposite rotation prompted intensive spectral scrutiny and consequently single crystal X-ray analysis; that established (**I**) as;
(-) Istanbolin A. It showed weak cytotoxic activity against A 2780 human ovarian cancer cells.
Experimental: Material, extraction, isolation and chemical derivatization will be discussed.
Results and Discussion: Physical and chemical properties, IR, UV, ^{1}HNMR and ^{13}CNMR are discussed. NMR Evidence of absolute structure is presented.
Single crystal X-Ray diffraction analysis; data and figure are presented that provided conclusive evidence of the absolute structure of **(I)** as (-) Istanbolin A ;

	R	R'
I	H	O
Ia	$COCH_3$	O
Ib	H	NOH



P:469

8,15-EPOXYLABDANES. NEW LABDANES FROM ERAGROSTIS VISCOSA

Dina I. M. D. Mendonça[1]*, N'Soki N. Sebastião[2], Carlos Diakanamwa[3]
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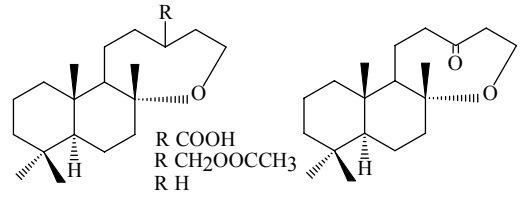
[2]Chemistry Dept, [3]Biology Dept, Agostinho Neto University, Luanda, ANGOLA

Eragrostis genera (*Gramineae, Eragrostoideae* subfamily) are well known by its nutritive value and local people feed the cattle with these grasses as green fodder. Nevertheless *Eragrostis viscosa* it's considered poisonous and must be remove from pasture. In folk medicine it's used as poison to snakes.
Eragrostis viscosa was collected at Lubango district, dried and extracted, in a Soxhlet apparatus, with hexane for 24h. The hexane extract was dewaxed and chromatographed and afforded several diterpenes with a labdane skeleta, as epoxy derivatives that to yours best knowledge are new natural compounds. Compounds were characterised by mono and bidimentional NMR techniques (HSQC, HMBC, COSY H,H and NOESY) using a 600 MHz apparatus.



This work was funded by the project POCTI/QUI/39380/2001 of Fundação para a Ciência e Tecnologia (FEDER) and the Textile and Paper Materials Centre. One of the authors (N'S. S.) gratefully acknowledges an ICCTI PhD scholarship and INABE (Angola) for financial support.

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NEW KAURANE FROM *PARINARI PUMILA*

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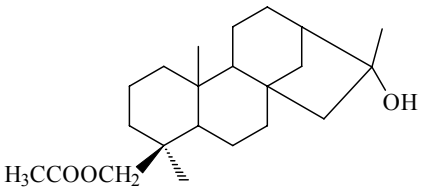
Parinari pumila it's a medicinal plant used in Angola folk medicine to treat tuberculosis. The Parinari genera is small, with only 25 species spread in Africa, Asia and America and studies of this genera are almost inexistent. Bibliographic sources indicate the presence of flavonoids and kaurane compounds as major constituents.
Parinari pumila was collected at Huíla district; leaves were dried and extracted, in a Soxhlet apparatus, with hexane for 24h. The hexane extract was dewaxed and chromatographed and afforded cholesterol, 3-epi-α-amirine and a new kaurane. The new natural product was characterised by mono and bidimentional NMR techniques (HSQC, HMBC, COSY H;H and NOESY) using a 600 MHz apparatus.



This work was funded by the project POCTI/QUI/39380/2001 of Fundação para a Ciência e Tecnologia (FEDER) and Textil and Paper Materials Center. One of the authors (C.B.) gratefully acknowledges an ICCTI PhD scholarship and INABE (Angola) for financial support.

P:471

NEW COMPOUNDS FROM *EUPHORBIA CONSPICUA*

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Interviews were made at Luanda markets S. Paulo and Prenda and the Euphorbia conspicua was indicated as a traditional medicinal plant that is used by traditional healers as treatment to dermatitis and leprosy wounds.
Euphorbia conspicua latex was collected and fractionated in 3 fractions, two irritant and one triterpenic. The triterpenic fraction afforded euphol and other compounds with a euphane skeleton and a new tirucallane euphorbol cinamate, as well as cycloartanes such as 24-methylen-cycloartan-3β-ol and boeticol an ent-euphane. The two irritant fractions afforded several diterpenes with ingenane an ingol skeleta, to our best knowledge two of them are new natural compounds.
The compounds were fully characterised by means of 1H NMR, 13C NMR, bidimentional techniques such as HSQC, HMBC, COSY H,H and NOESY.

This work was partially funded by the project POCTI/QUI/39380/2001 of Fundação para a Ciência e Tecnologia with FEDER funding and Textile and Paper Materials Center.
by the Textile and Paper Materials Centre.

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INDOLOQUINAZOLINE ALKALOIDS FROM ARALIOPSIS TABOUENSIS AUBREV. ET PELLEGR (RUTACEAE)

Christopher O. Ezugwu*[a], Erdal Bedir[a], Chuck Dunbar [a], Ikhlas A. Khan[a,b], Christopher O. Okunji[c,d], Brian M. Schuster[d] and Maurice M. Iwu[c,d].
[a]National Center for Natural Products Research, Research Institute of Pharmaceutical Sciences (Now, Department of Pharmacognosy, Faculty of Pharmaceutical Sciences, University of Nigeria, Nsukka), [b]Department of Pharmacognosy, School of Pharmacy, University of Mississipi, MS 38677, USA, [c]International Center for Ethnomedicine and Drug Development, Nsukka Nigeria; and Bioresources Development & Conservation Programme 11303 Amherst Avenue Suite # 2, Silver Spring, MD 20902 and [d]Division of Experimental Therapeutics, Walter Reed Army Institute of Research, Washington DC, 20307-5100, USA.

Three new indoloquinazoline-type alkaloids, 2-methoxy-8,13-dihydro-7H-indolo[2',3':3,4]pyrido[2,1-b]quinazolin-5-one **(1)** 2-methoxy-13-methyl-8,13-dihydro-7H-indolo[2',3':3,4]pyrido[2,1-b]quinazolin-5-one **(2)**, and 2-methoxy-14-methyl-7,8,13,14-tetrahydroindolo[2',3':3,4]pyrido[2,1-b]quinazolin-5-one **(3)** were isolated from *Araliopsis tabouensis*, together with three known compounds. The structures of the new compounds were determined primarily from 1D- and 2D-NMR analysis. The antimalarial activities of compounds **1-5** were evaluated against *Plasmodium falciparum* D_6 and W_2 clones. The IC_{50} values in antimalarial bioassay for compounds **2-5** varied from 1.8 to 4.7 μ/ml. The antifungal activities range from 10 – 50 μ/ml.

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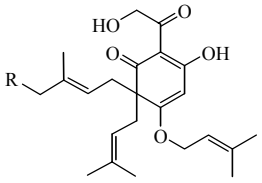
PRENYLATED ACETOPHENONES FROM *MELICOPE* SPECIES FROM RÉUNION ISLAND

Henrik T. Simonsen*, Nina K. Schwerin, Rikke A. Petersen, Anne Adsersen, Dan Stærk, Jerzy W. Jaroszewski, Ulla W. Smitt
The Danish University of Pharmaceutical Science, Universitetsparken 2, 2100 Copenhagen, Denmark.



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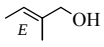
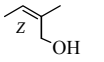
2: R = 

3: R = 

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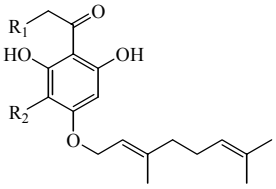

5: R_1 = H, R_2 = H

6: R_1 = OH, R_2 = 

7: R_1 = H, R_2 = 

From *Melicope coodeana* T.G. Hartley (syn. *Euodia simplex* Frappier ex Cordem.) four new non aromatic, prenylated acetophenones, 1, 2, 3, and 4, were isolated. From *M. obscura* (Cordem.) T.G. Hartley two known prenylated acetophenones, 5 and 6 were isolated. The later was also isolated from *M. obtusifolia* ssp. *obtusifolia* var. *arborea* (Coode) T.G. Hartley along with 7.

The non aromatic acetophenones from *M. coodeana* are unusual constituents of the genus and are interesting due to *in vitro* antimalaria activity. The IC_{50} value of 2 was determined to 42,8 μM, and by membrane incorporation experiments it was found not to have any toxic effect towards the erytrocytes.

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NEW FATTY ACID ESTERS ORIGINATE DURING STORAGE BY THE INTERACTION OF COMPONENTS IN PRASAPLAI, A THAI TRADITIONAL MEDICINE

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[2]Institute of Pharmaceutical Biology and Phytochemistry, Westfälische Wilhelms-Universität, Münster, Germany.

Prasaplai is a Thai traditional preparation composed of 10 medicinal plants and two chemical compounds. It has commonly been used by Thai traditional practitioners as a remedy for relieving dysmenorrhea and adjusting the cycle of menstruation. Recently, it has been found active against inflammation and uterine muscle contraction. During a study on the standardization of the mixture, we observed 3 newly emerging peaks by HPLC whose structures were determined as the new (E)-4-(3,4-dimethoxyphenyl)but-3-en-1-yl linoleate, (E)-4-(3,4-dimethoxyphenyl)but-3-en-1-yl oleate and the known (E)-4-(3,4-dimethoxyphenyl)but-3-en-1-yl palmitate on the basis of spectral data and chemical evidence. The artificial esters could be investigated already after 1 day storage of the freshly prepared dry mixture, and steadily increased during a storage period of 30 days and more. Systematic search indicated that the three esters originated from the interaction of compounds present in the rhizomes of *Zingiber cassumunar* and the seeds of *Nigella sativa*.

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ANTI-INFLAMMATORY EVALUATION OF CRUDE EXTRACTS AND ISOLATED CONSTITUENTS OF *SPHENOCENTRUM JOLLYANUM* Pierre

[1]Robert A. Victoria*, [1]Moody O. Jones and [2]Connolly D. Joseph. [1]Department of Pharmacognosy, Faculty of Pharmacy, University of Ibadan,Nigeria. [2]Department of Chemistry, University of Glasgow, UK.

Sphenocentrum jollyanum Pierre (Menispermaceae) are mostly found in the forest zones of southern Nigeria where the roots are used as chewing sticks, the leaf twigs has been reported to have aphrodiasic activity. It is prepared with piper guineese and mixed lime juice as cough medicine. The root hair is used with other antimalaria plants as remedies against fever.
The anti-inflammatory activity of *S. jollyanum* extractives was evaluated using carrageenan-induced hind paw oedema of healthy adult albino rat, utilising the oral route of administration. The results showed that the crude methanolic fruit extract (82.5% inhibition at 200 mg kg^{-1}) gave a highest anti-inflammatory activity, flavonoid fraction gave 81.2% at 200 mg/kg, root (68.2% inhibition) and leaf (60.3% inhibition). Further purification of the most active crude methanolic fruit extract led to the isolation of an active principle identified as columbin (UV, IR, NMR, and MS) with anti-inflammatory activity (58.9% inhibition at 20 mg kg^{-1}) in comparable range with reference acetylsalicylic acid (80.3% at mg kg^{-1}). The result justified the use of S. jollyanum in the treatment of anti-inflamatory based disease across the West Africa sub region.

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NEW ACYLATED IRIDOID GLUCOSIDES FROM *VITEX ALTISSIMA*

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§Laila Impex R & D Centre, Unit-I, Phase-III, Jawahar Autonagar, Vijayawada-520 007, ‡Department of Pharmaceutical Chemistry, Sri Padmavathi School of Pharmacy, Tirupati-517 507, and ⊥Organic Chemistry Division-I, Natural Products Laboratory, Indian Institute of Chemical Technology, Hyderabad-500 007, India

Six new iridoid glucosides, 6′-*O*-*trans*-feruloylnegundoside **(1)**, 6′-*O*-*trans*-caffeoylnegundoside **(2)**, 2′-*O*-*p*-hydroxybenzoyl-6′-*O*-*trans*-caffeoylgardoside **(3)** 2′-*O*-*p*-hydroxybenzoyl-6′-*O*-*trans*-caffeoyl-8-epiloganic acid **(4)**, 2′-*O*-*p*-hydroxybenzoylgardoside **(5)**, and 2′-*O*-*p*-hydroxybenzoyl-8-epiloganic acid **(6),** along with two known iridoids, agnuside and negundoside, have been isolated from the ethyl acetate extractives of leaves of *Vitex altissima*. Details of structural elucidation and antioxidant activity studies of these compounds will be presented.

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HOMOISOFLAVONES FROM MUSCARI COMOSUM GROWING IN EGYPT

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Pharmacognosy Department, Faculty of Pharmacy, Alexandria University, Alexandria, Egypt.

The homoisoflavanones 3,9-dihydro-autumnalin **(I)** and E 6-hydroxy-4'-demethyl-eucomin (**II**) are reported; **(I)** for the first time from Muscari comosum, and **(II)** for the first time from a natural source .

Experimental:

Muscari comosum bulbs; collected from North Mediterranean Strip, West to Alexandria, Egypt. Partition of the alcoholic extract with petroleum ether, ether, ethyl acetate and butanol afforded 10.4g of ether + ethyl acetate extracts (similar TLC pattern) . Chromatography (silica column and petroleum ether + increments of chloroform, then chloroform + gradual increments of methanol) afforded 20mg of **(I)** from the pet. ether : chloroform (4:6) fractions and 30mg of **(II)** from the chloroform: methanol (9:1) fractions.

Results and Discussion :

Compound (I), C17H16O6 (**FABMS**), **m. p**.; 202-204 ^{0}C; **UV max**: (Me OH), (Me OH + NaOCH3), (MeOH +ALCL3), (MeOH+ALCL3+HCL), (MeOH+NaOAc) in **Table 1**. **IR v** (KBr): 3390, 2940, 1640, 1610, 1440, 1290, 1160 cm-1. **FABMS**; (in Text). ^{1}**H-NMR** (270 MHz) and ^{13}**CNMR** (67.5 MHz) in **Table 2.**
Compound (II); **m. p**. > 300 ^{0}C; **FABMS**, C16H12O6; **UV max** (in all the above shift reagents), **Table 1**. **IR v** (KBr); 3380, 2910, 1650, 1605, 1480,1510 cm-1. ^{1}**HNMR** (270 MHz) and ^{13}**C-NMR** (67.5 MHz), **Table 2.**
Spectral results established **(I)** as 3, 9-dihydro-autumnalin (first time from M. comosum); while intensive **MS**, ^{1}**HNMR**,^{13}**CNMR** and **UV** established **(II)** as 6-hydroxy-4`-demethyl-eucomin(for the first time from nature).

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IN VITRO EFFECTS OF THE ETHYL ACETATE EXTRACT AND ISOLATED COMPOUNDS FROM *MOMORDICA FOETIDA* BASED ON A GSH-HAEMIN INTERACTION ASSAY

S. Frölich [a], *K. Siems* [b], *B. Onegi* [c], *K. Jenett-Siems* [a] *
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[b] Analyticon Discovery GmbH, Hermannswerder Haus 17, D-14473 Potsdam, Germany
[c] Department of Pharmacy (Pharmacognosy Unit), Makerere University, Kampala, Uganda

Momordica foetida Schum. (Cucurbitaceae), a perennial climbing herb with cream coloured flowers is found in sub-Saharan Africa. Based on ethnobotanical information, either from the literature or directly from personal communication with traditional healers, *M. foetida* preparations are locally used for the treatment of malaria. Previous studies resulted in the isolation and identification of sitosteryl glucoside, 5,25-stigmastadien-3ß-yl glucoside and 1ß-hydroxyfriedel-6-en-3-one. During our ongoing phytochemical research on antiplasmodial plant species from Africa, we investigated extracts of different polarity from the leaves of *M. foetida* and tested them on a multiwell assay based on the inhibition of the GSH-dependent haemin degradation with chloroquine as standard. The ethyl acetate extract showed the most promising *in vitro* activity in this screening and was further analysed to isolate the active compounds. Finally the *in vitro* cytotoxicity of extracts and pure compounds (e.g. 5,7-dihydroxychromone 7-glucoside, prunin) against the cell line ECV-304 was evaluated.

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ALKALOIDS OF *CORYDALIS* SPECIES AND THEIR ANTIFUNGAL ACTIVITY

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Banaras Hindu University,Varanasi-221 005, INDIA

Corydalis species have been reported as a rich source of isoquinoline alkaloids and various medicinal properties are attributed to them. No medicinal value and chemical substances has earlier been reported from *C chaerophylla* and *C longipes* collected from Nepal. We report here the isolation of a new alkaloid chaerophylline together with (-)-corypalmine, berberine chloride,(-)-isocorypalmine, (-)-corydalmine,(±)-bicuculline from *C chaerophylla* and a new alkaloid longicine together with (±)-α-hydrastine,(±)-β-hydrastine, N-methylhydrasteine hydroxyl lactam, 1-methoxyberberine chloride and berberinium hydroxide from *C.longipes*.
The alkatoids chaerophylline, longicine, (-)-corypalmine, (±)-bicuculline and barberinium hydroxide, (±)- α -hydrastine and (±)- β-hydrastine exhibited potent antifungal activity against spore germination of some fungi.
The details of the isolation and characterisation of new alkaloids and their antifungal activity will be discussed.

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INVESTIGATIONS OF ALKALOIDS FROM PLANTS OF THE FAMILY *ELAEOCARPACEAE*

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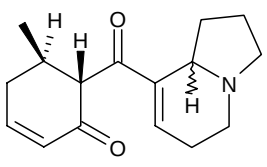
Plants from the family *Elaeocarpaceae* are found in tropical to temperate regions and are typically large rainforest trees. Previous chemical investigations of this family have been limited to five *Elaeocarpus* species from Papua New Guinea (PNG), a species from India, and several *Aristotelia* species from southern Australia. Queensland contains a unique diversity of *Elaeocarpaceae*, of which only one species has been investigated previously. Indole alkaloids and indolizidine alkaloids have been isolated from *Aristotelia* species and *Elaeocarpus* species, respectively. The chemistry of a large proportion of *Elaeocarpaceae* remains unknown. Therefore, the family is a potential source of novel alkaloids.

We have conducted a phytochemical survey of plant parts from *Elaeocarpaceae* species collected in Queensland, PNG and China. Screening of extracts with an alkaloid-detecting reagent, and positive ESIMS has identified five new alkaloid producing species. Alkaloids were purified by ion-exchange and reverse-phase chromatography and their structures elucidated by 2D NMR experiments. Fourteen alkaloids, nine of which are new, have been isolated and will be presented. These include the indolizidine alkaloid elaeograndisine 2 (**1**) and the pyrrolidine alkaloid habbenine (**2**).



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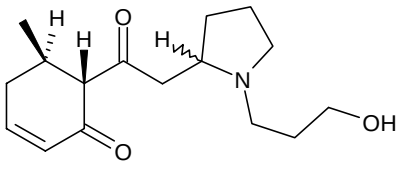

2

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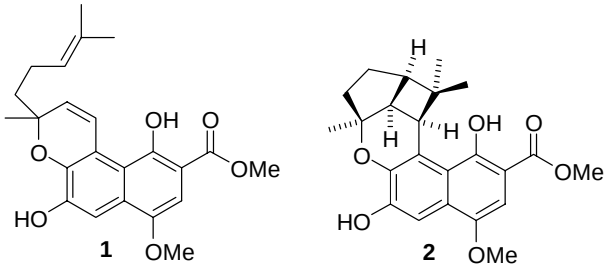
ISOLATION AND STRUCTURE ELUCIDATION OF SEVEN NEW NATURAL PRODUCTS FROM THE ROOTS OF *PENTAS BUSSEI* K. KRAUSE

Jaques Bukuru, Sven Claessens, Norbert De Kimpe*
Department of Organic Chemistry, Faculty of Agricultural and Applied Biological Sciences, Ghent University, Coupure Links 653, Ghent, B 9000, Belgium

Seven novel natural products were isolated from the roots of *Pentas bussei* K. Krause, a plant collected in the bush land of Kenya. A decoction of its roots has been used as a remedy against gonorrhoea, syphilis and dysentery.
The dried roots were extracted with *n*-hexane, dichloromethane, ethyl acetate and methanol. Subsequent MPLC analysis was performed for the fractionation of the *n*-hexane, dichloromethane and ethyl acetate extracts. CPC analysis was used for the methanol extract.



The first known phytochemical study of this species revealed the presence of two new highly oxygenated naphthohydroquinones and five new naphthohydroquinones of the benzochromene type, among which the homoprenylated benzochromene **1** and the pentacyclic cyclol-type naphthohydroquinone **2**. This is the first report on a reduced quinonic cyclol-type natural product.

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BIOLOGICAL AND PHYTOCHEMICAL INVESTIGATIONS ON PAVETTA OWARIENSIS

A.M. Baldé[*1,2], F. Camara[2], N. Mahomou[2], R. Barry[1,2], M. Claeys[3], L. Pieters[3], D. Vanden Bergh[3], E. Van Marck[3], L. Kestens[4], S. Geerts[4], A.J. Vlietinck[3]
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In view to promote a scientific support to the use of guinean traditional drugs, an ethnopharmacological survey has been conducted on plants which are supposed to cure human helminthes and/or microbial infections. From the selected plants, the shrub *Pavetta owariensis* P. Beauv (Rubiaceae) was submitted to a series of ethnobotanical, therapeutical, biological and phytochemical surveys. The antischistosomal (*Schistosoma mansoni*), molluscicidal (*Biomphalaria glabrata*), antibacterial (*Staphylococcus aureus, Streptococcus pneumoniae* and *Neisseria gonorhoeae*), and antiviral (*herpes simplex* and *coxsackie B2*) activities of the extracts of ***Pavetta owariensis*** P. Beauv (Rubiaceae) were demonstrated. Bioassay guided fractionation resulted in the isolation of the chemotherapeutically active components which were identified as phenolics ones. Chemical investigations on the stem-bark led to the isolation and identification of a series of proanthocyanidins possessing a doubly-linked structure, quinic acid esters, fatty acids, fatty alcohols, fatty esters, ferulic esters, sterols and ketosteroids. The toxicity of the extracts of the plant were also assessed.

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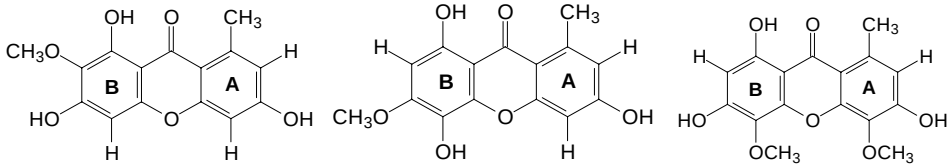
NOVEL XANTHONES FROM THE SOUTH AFRICAN HYACINTHACEAE

Chantal Koorbanally[1], Dulcie A. Mulholland[1] and Neil R. Crouch[1,2]
[1]Natural Products Research Group, School of Chemistry, University of KwaZulu-Natal, Durban, 4041, South Africa
[2]Ethnoy Unit, National Botanical Institute, P.O. Box 52099, Berea Road, 4007, Durban, South Africa

A recent survey has ranked the Hyacinthaceous plants second only to the Aloaceae with regard to their popularity in cultivation by traditional healers[1]. One of the plants in this investigation, *Drimiopsis maculata*, is widely used in traditional medicine. Bulbs are reported to treat stomach ailments[2], are administered as enemas and decoctions are also used traditionally to treat a condition known as *ipleyti*[2]. In this investigation, *Drimiopsis maculata* has yielded six novel xanthones. One of the most commonly known fungal metabolites is lichexanthone, a 3,8-dihydroxy-6-methoxy-1-methylxanthone, which is widely associated with antibiotic activity. The xanthones isolated in this work are of the same skeletal structure and biological assays on these compounds are currently being undertaken.



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A NOVEL SESQUITERPENE DILACTONE FROM *MIKANIA NATALENSIS* DC.

Koorbanally, N.A[1*], Nathoo, M[1], Dlamuka, B.[2] and Mulholland, D.A. [1]
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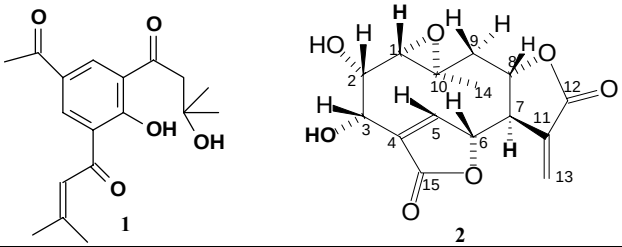
Mikania natalensis is used in traditional medicine in South Africa to alleviate HIV related symptoms. The leaves of this plant are the major constituent in a specially prepared medicine, which also contains aerial parts of other unknown species in minor quantities. The effects of this medicine are noticed six weeks after daily doses are administered.
A phytochemical investigation of the aerial parts of *Mikania natalensis* DC. resulted in the isolation of dehydroisostoebenone, **1**, whose structure has been revised and a novel sesquiterpene dilactone, 1,10-epoxy-2,3-dihydroxy-4,11(13)-germacradiene-12,8:15,6-diolide, **2** (natalenolide). Biological screening of these compounds against HIV strains still need to be carried out.



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THE STRUCTURAL ELUCIDATION OF LIMONOIDS AND LIMONOID DERIVATIVES FROM THE MELIACEAE

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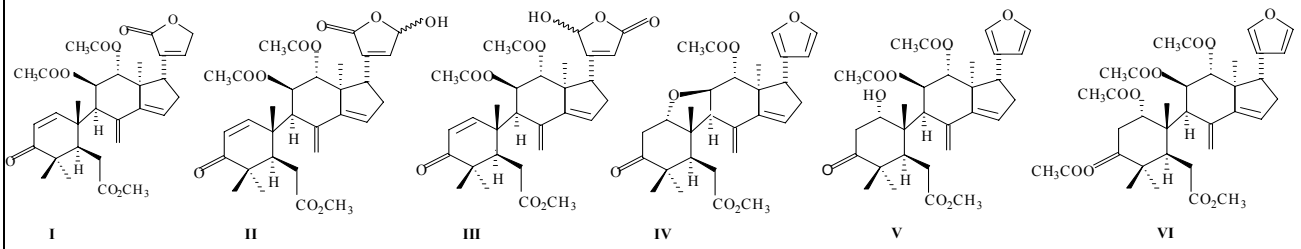
The Meliaceae family is known to produce a variety of compounds of which limonoids are the most important. The genus *Turraea*, from the subfamily Melioideae, is found widely in Africa and the Indian Ocean islands and to a lesser extent in Asia and Australia. An investigation into the hexane and methylene chloride extracts of the seeds of *Turraea floribunda* yielded eight limonoids and limonoid derivatives of the toonafolin class of which six have not been isolated before. These six new compounds will be presented.



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NOVEL ALKALOIDS FROM *CRINUM STUHLMANNII* (AMARYLLIDACEAE)

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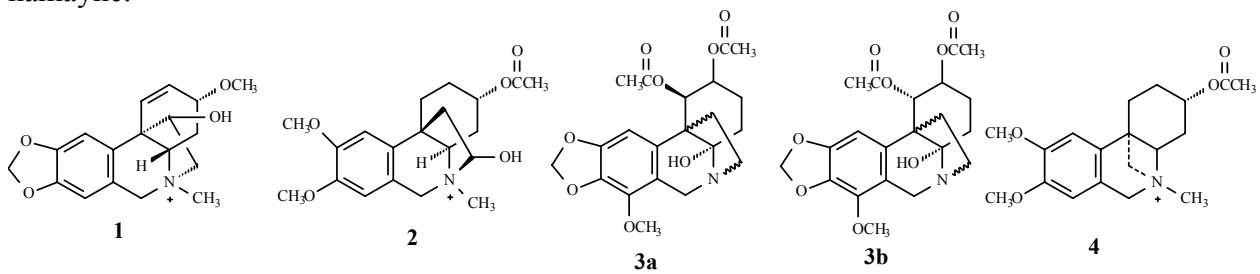
Crinum stuhlmannii Baker (syn. *C. delagoense* I.Verd.) (Amaryllidaceae) is used in traditional medicine to treat urinary tract problems and by others to treat cattle.[1] Species within the genus C*rinum* are considered capable of causing dermatitis.

A phytochemical investigation of the bulbs of *C. stuhlmannii* resulted in the isolation of ten alkaloids, five of which have not been reported previously. These are stuhlmanine A (**1**), delagoenine A (**2),** stuhlmanine B and C (**3A** and **3B**),), and stuhlmanine D (**4**). Also isolated were lycorine, 8,9- methylenedioxophenanthridine, 6-hydroxycrinamine, haemanthamine and hamayne.



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ALKALOIDS FROM *TECLEA NATALENSIS* (RUTACEAE)

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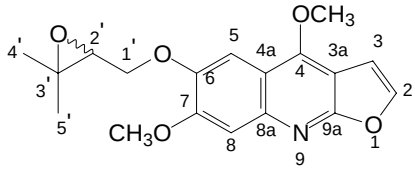
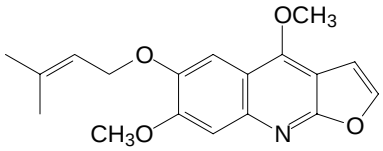
Teclea natalensis (Sond) Engl., or the Natal Cherry-Orange, or uMozane is a member of the Rutaceae family. A decoction of the crushed root bark is used for chest irritations associated with coughs and colds in KwaZulu-Natal.

The chloroform and ethyl acetate extracts of the leaves of *T. natalensis* have yielded two novel furoquinoline alkaloids, tecleanatalensines A **1** and B **2**, and the known alkaloids *iso*haplopine prenyl ether, flindersiamine and dictamnine.



tecleanatalensine A **1**



tecleanatalensine B **2**

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EXTRACTIVES FROM *SAMADERA MADAGASCARIENSIS* (SIMAROUBACEAE)

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Samadera madagascariensis Jussieu (locally known as "fatriana") belongs to the Simaroubaceae family and is endemic to Madagascar. The leaves of *S. madagascariensis* are used in Madagascar for the treatment of stomache aches and dysentry, and the juice of the fresh leaves is used to treat wounds and burns.

S. madagascariensis leaves were investigated in this work for the presence of quassinoids. Seven quassinoids: samaderine A, the novel 5β,6-dihydrosamaderine A, the novel 2-chlorosamaderine A, the novel samaderine DN, samaderine B, cedronin and the novel 3,4β-dihydrosamaderine C were isolated from the *S. madagascariensis* leaves.

The quassinoids isolated in this work are of the C_{18} and C_{19} classes, and only five of the C_{18} type have been published previously. Quassinoids exhibit a range of biological activities such as antileukemic, antiviral, antimalarial, anti-inflammatory, antifeedant and amoebicidal. 2-Chlorosamaderine A, cedronin and 3,4β-dihydrosamaderine C were found to have anticarcinogenic properties. The novel compounds will be discussed.

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FLAVONOIDS FROM *Diplotropis ferruginea* BENTH (FABACEAE)

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Diplotropis ferruginea Benth is a species native to Northeastern Brazil, where it is popularly know as "sucupira". It is used in folk medicine for the treatment of rheumatism, arthritis and diabetes.
Phytochemical investigation of this species resulted in the isolation two flavonoids, a new 3-methoxyflavone - 3-methoxy-6-*O*-prenyl-6",6",dimethylchromene-(7,8,2",3")-flavone and the known 3,6-dimethoxy-6",6"-dimethylchromene-(7,8,2",3"). These compounds received the vernacular names of diploflavone A and diploflavone B respectively. Their structures were elucidated on the basis of their spectral data (IR, MS and NMR), mainly 1D and 2D NMR. Cytotoxic activity of the isolated compounds was tested against the cells NCI-H292 (lung carcinoma), HEp-2 (larynx carcinoma) and KB (oral epidermoid carcinoma). The cells HEp-2 were the most affected by the tested substances.

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PHYTOCHEMICAL INVESTIGATION OF *Nymphaea caerulea* Savigny.

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Flower extracts of the ancient Egyptian sacred plant, the Blue Lily of the Nile (*Nymphaea caerulea* Savigny, Nymphaeaceae), were analyzed by GC/MS, LC/MS and NMR. Eight compounds were identified: one flavone: 7-hydroxyflavone; 2 aurones: 4',7-dihydroxyaurone and 4'-hydroxyaurone; and 4-methoxybenzyl alcohol, benzamide, methyl 4-hydroxybenzoate, methyl vanillate and cinnamyl alcohol. Two substances, 4',7-dihydroxyaurone and 4'-hydroxyaurone are reported for the first time as natural compounds.

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STUDY ON THE ACTIVE CONSTITUENTS OF *OPUNTIA DILLENII*

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Opuntia dillenii (KER-GAW.) HAW. is a cactus that grows mainly in the south of China and is called Xian Ren Zhang in Chinese. The stem of this plant is used as a folk medicine for the treatment of diabetes, gastric ulcer, inflammatory and several other diseases, while its reddish fruit is commonly used as coloring agents for foods, drinks and drugs.

In the course of our chemical studies on the bioactive constituents of *O. dillenii*, the 80% ethanolic extract of its stems was found to show potent anti-inflammatory and anti-diabetes effects. The 1-butanol soluble phase of the extract exhibited potenter anti-inflammatory activity than other phase. Scavenging effect on 1, 1-diphenyl-2-picrylhydrazyl (DPPH) radical and superoxide anion radical ($\cdot O_2^-$) generated by the xanthing-xanthine oxidase system was also found in the 80% ethanolic extract.

As for the chemical constituents of this plant, systemic studies lead to the isolation of forty-nine compounds from the extract, and forty-seven of them were identified by spectroscopic analysis. Nine new compounds were characterized, and they were: opuntioside I (**11**), 4-ethoxyl-6-hydroxymethyl-α-pyrone (**14**), (ethyl succinate)-(dimethyl malate)-ester (**22**), 1-butoxyl-(L)-malate (**24**), ethyl α-L-rhamnopyranoside (**26**), opuntioside II (**34**), kaempferol 7-*O*-β-D-glucopyranosyl (1$\rightarrow$4)-β-D-glucopyranoside (**46**), methyl α-D-glucopyranoside-6- (methyl 4-malate)-ester (**47**), and opuntioside III (**48**). Opuntioside I, II, III and 4-ethoxyl-6-hydroxymethyl-α-pyrone belong to the skelecton of α-pyrone. Twenty-eight known constituents were isolated from the genus of *Opuntia* for the first time, their names were listed as below: daucosterol (**4**), kaempferide (**5**), *p*-hydroxybenzoic acid (**6**), 3-*O*-methyl isorhamnetin (**12**), (*E*)-ferulic acid (**13**), 1-heptanecanol (**15**), vanillic acid (**16**), isorhamnetin- 3-*O*-β-D-rutinoside (**17**), ethyl 3, 4-dihydroxybenzoate (**19**), 4- hydroxyaceophenone (**20**), 1-(3-ethylphenyl)-1, 2-ethanediol (**23**), 5-(hydroxymethyl)-2- furaldehyde (**25**), (*S*)-3-hydroxy- 3-methylglutarate (**27**), tetrahydro-5-oxo-2-furancaboxylic acid ethyl ester (**28**), guaiacylglycerol -β-ferulic acid ether (**29**), methyl *p*-hydroxy-(*E*)-cinnamate (**30**), methyl 4-hydroxybenzoate (**31**), ethyl α-D-arabinofuranoside (**35**), piceine (**36**), androsin (**37**), 3,4-dihydroxy benzoic acid (**39**), 3',5'-dimethoxy-4'-*O*-β-D- glucopyranosyl-cinnamic acid (**40**), 9(*S*), 12(*S*), 13(*S*)- trihydroxyoctadeca 10(*E*), 15(*Z*)-dienoic acid (**41**), 9(*S*), 12(*S*), 13(*S*)-trihydroxy-10(*E*)- octadecenoic acid (**42**), 3-*O*-methyl quercetin 7-*O*-β-D- glucopyranoside (**43**), kaempferol 7-*O*-β-D-glucopyranoside (**44**), manghaslin (**45**), and ethyl β-D-fructopyranoside (**49**). Eight compounds separated for the first time from the title plant were: aromadenerin (**2**), opuntiol (**3**), kaempferol (**7**), 3-*O*-methyl quercetin (**8**), quercetin (**10**), rutin (**18**), isorhamnetin (**21**), and benzoic acid (**38**).

The compounds of α-pyrone type and flavonol type with large amount were subjected to bioactive studies. The scavenging effects on DPPH and $\cdot O_2^-$, inhibitory effects on nitric oxide generation, on aldose reductase, and on α-glucosidase were carried out. Flavonol type ingredients showed good activities on the aspects described above, expect for on α-glucosidase, while α-pyrone type compounds didn't show any activity. Flavonol type components maybe play an important role in *O. dillenii*'s pharmacological effects. On the base of chemical and pharmacological works, a study on quality standardization of Yi-Jin-Jiang-Tang oral liquid consisted of *O. dillenii* was conducted. The methods for TLC identifications with 3-*O*-methyl quercetin (8) and opuntiol (3) as authentic samples, and quantitative determination were established. Base on the result of content tests, the contents of opuntiol ($C_7H_8O_4$) in an ampoule of Yi-Jin-Jiang-Tang Oral Liquid (20 ml) should not lower than 20 mg.

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STUDYING *COLCHICUM* SPECIES IN JORDAN

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A systematic study to investigate nine *Colchicum* species growing wild in Jordan is under taken. Colchicine content was determined in five species using new acid-based reverse phase PDA-HPLC method. Among plant parts of *C. steveni* and at flowering time, leaves showed the highest colchicine content of 0.204 (wt/wt) g%, while corms of *C. hierosolymitanum* showed the highest colchicine content of 0.126 (wt/wt). Colchicne content was also determined using prep-TLC-UV spectrophotometric method, results were not significantly different and within 20 % of these measured by PDA-HPLC; indicate an acceptable alternative method.

In another study aimed dereplication, LC/MS analysis of corms of *C. hierosolymitanum* was conducted using a single quadruple mass analyzer equipped with (+)-APCI as an ionizing interface. Colchicine and eight other natural analogues were identified in the alkaloid rich fraction.

Phytochemical studies were also conducted for *C. stevenii*, *C. brachyphllum*, *C. tunicatum* and *C. tauri*. Three new compounds, (-)-3-demethyl-*N*-methyldemecolcine, (-)-2,3-didemethyldemecolcine and (-)-colchicinone and eighteen known colchisides were identified. Structural elucidation was based on 1D- and 2D-NMR and EI and APCI mass analysis. Compounds showed potent activity against BST and MCF-7wk, H460 and SF268 cancer cell lines.

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NEW TETRANORDITERPENOID DILACTONE OF FUNGAL ORIGIN

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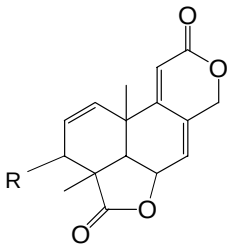
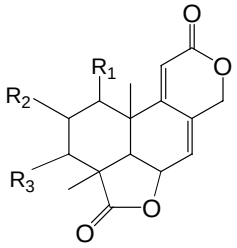
National Center for Natural Products Research, The University of Mississippi, University, MS 38677

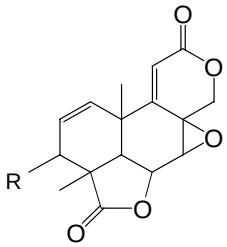
Eight new (**1 - 8**) and three other previously reported (**9 – 11**) tetranorditerpenoids dilactones were isolated from the ethyl acetate extract of the culture medium of a tentatively identified fungus *Oidiodendrum sp*. The structures of the new tetranorterpenoids (**1 – 8**) were determined using high-resolution NMR and mass spectroscopic data.



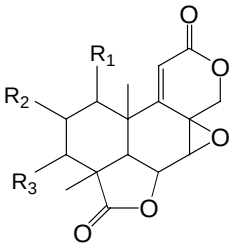
1 R = OH
2 R = H



3 R_1=R_2=H, R_3= OH
7 R_1=OH, R_2= R_3= H
9 R_1=R_2= R_3= H
11 R_1=R_3=H, R_2= OH



5 R = H
10 R = OH



4 R_1=R_3=H, R_2= OH
6 R_1=R_2=H, R_3= OH
8 R_1=OH, R_2= R_3= H

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A NEW FLAVONOIDAL TRIGLYCOSIDE AND STRUCTURAL CHARACTERIZATION OF FLAVONOIDS FROM FARSETIA AEGYPTIA BY LIQUID CHROMATOGRAPHY – ELECTROSPRAY IONIZATION MASS SPECTROMETRY AND COLLISION-INDUCED DISSOCIATION

Abdelaaty A. Shahat[+]*, Filip Cuyckens[+], Khaled A. Abdel-Shafeek*,[++] Husseiny A. Husseiny[*], Sandra Apers[+], Sabine Miert[+], Magda Claeys[+], Luc Pieters[+], and Arnold J.Vlietinck[+]

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A new flavonoid, isorhamnetin-3-O-α -L-arabinoside- 7-O-[β- D-glucosyl-1 3]– α-L-rhamnoside, in adition to two known flavonoids rhamnetin and isorhamnetin 3-0-α L – rhamnosyl 7-O- β - D- glucoside were isolated by column chromatography from *F. aegyptia* and the structure established by MS, 1D and 2D NMR spectroscopy, including DEPT, DQF-COSY,TOCSY,HSQC and HMBC experiments,
The flavonoid fraction of the methanolic extract of the *Farsetia aegyptia* Turra. herb, (Crucifereae) was studied using high-performance liquid chromatography simultaneously coupled to a photodiode array detector (LC/UV-DAD)and a mass spectrometer equipped with an electrospray source (LC/ESI-MS) . collision-induced dissociation (C/D)mass spectral data were obtained off-line by nanospray (nano-ESI) analysis

References : 1. Loatfy, Boulos. " flora of Egypt " volume l, AL hedra. Publishing, Cario, Egypt, 1999. 2. Ma, Y.L., Li, Q., Van den Heuvel, M.H.and Claeys, M., characterization of flavone and flavonol aglycones by collision- induced dissociation tandem mass spectrometry, Rapid Commun. Mass Spectrom. 11,1357-1364,1997.
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NATURAL ALGICIDES FROM TWO RUTACEAE SPECIES

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The cyanobacterium (blue-green alga) *Oscillatoria perornata* is a pest in commercial catfish production ponds in the southeastern region of the USA. 2-Methyl isoborneol (MIB) is produced by *O. perornata* and accumulates in the flesh of pond-raised channel catfish (*Ictalurus punctatus*) causing a musty "off-flavor" that results in an unpalatable and unmarketable product. As part of our continuing efforts to discover natural product-based algicides, ethyl acetate extracts of the roots of *Ruta graveolens* and the stems of *Amyris texana* were investigated. Preliminary bioassays of the extracts and the silica-gel-column chromatographic fractions indicated the presence of constituents selectively toxic towards *O. perornata*, with relatively little toxicity towards the green alga *Selenastrum capricornutum.* An acridone alkaloid and a chromene amide were isolated from *R. graveolens* and *A. texana* by bioassay-guided fractionation with a lowest-complete-inhibition concentration (LCIC) towards *O. perornata* of 0.3 μM and 10 μM, respectively.

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ISOLATION AND CHARACTERISATION OF 1,2,3,4,6-PENTAGALLOYL GLUCOSE AN ANTIMYCOBACTERIAL AGENT FROM THE LEAVES OF *ENTANDROPHRAGMA ANGOLENSE.*

Orisadipe, Abayomi T.[a]; D'Ambrosio Michele[b]; Joseph I. Okogun*[a]; Peters Oladosu[a]; Uford S. Inyang [a]; Akinbobola A. Adesomoju[c]; Helena Boschoff[d]; Cynthia Dowd[d]; Clifton Barry III[d].

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c. Chemistry department, University of Ibadan, Ibadan, Nigeria.
d. Tuberculosis Research section, National Institute for Allergy and Infectious Diseases, NIH, Parklawn drive, Rockville, MD, USA.

Tuberculosis (TB) has been declared one of the leading killer infectious diseases worldwide. The emergence of multi-drug resistant strains of *Mycobacterium tuberculosis* has raised an urgent need for new chemotherapies for the treatment of such MDR strains.
The methanolic extract of the leaves of *E. angolense* , a Nigerian medicinal plant was found to be active against M.tuberculosis (H_{37RV}) in our evaluation of some Nigerian medicinal plants for antimycobacterial activity. Fractionation of the extract yielded pentagalloyl glucose. Its structure was determined by LC-MS, and ^{1}H,^{13}C NMR techniques. Pentagalloyl glucose exhibited activity against M. tuberculosis at a concentration of 0.665mM. This compound is reported for the first time from this plant.

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ESTROGENIC ACTIVITY OF ISOLATED COMPOUNDS AND ESSENTIAL OILS OF *PIMPINELLA* SPECIES FROM TURKEY, EVALUATED USING A RECOMBINANT YEAST SCREEN

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Several plants and plants derived pure compounds, designated as phytoestrogens, have been reported to cause estrogenic effects. They have been used for alleviation of menopausal symptoms, prevention of osteoporosis, heart disease and cancer. There is an increased interest in studying phytoestrogens such as isoflavones and lignans for their use as replacements for synthetic estrogens. In this study, the estrogenic activity of essential oils of eleven *Pimpinella* species and the compounds isolated from these species were evaluated using the yeast estrogen screen (YES) assay. The essential oils from different species varied in their estrogenic potencies and efficacies with EC50 ranging from 45 □g/ml to 650 □g/ml. Among different plant parts, the fruit oils of most species were more active followed by aerial parts without fruits and root oils.

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NOVEL ANTIMICROBIAL DITERPENOIDS FROM *TURRAEANTHUS AFRICANUS* (MELIACEAE)

Simplice Tatsimo Ndendoung Joel[1], Jacob Melissa[2], Pierre Tane[3], Beiba L. Sondengam[1], Christopher O. Okunji[4,5], Brian G. Schuster[5], Maurice M. Iwu[4,5], Ikhlas A. Khan [2]
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Turraeanthus africanus (Welw. ex C. DC.) Pellegr. is a member of the Meliaceae found in Cameroon where the stem bark is used as anthelmentic. The dichloromethane-methamol extract from stem bark of *T. africanus* showed remarkable antimicrobial activity against *Cryptococcus neoframans, Staphylococcus aureus* and *methicillin resistant S. aureus*. Phythochemical investigation of the stem bark afforded several diterpenoids. These include the seven new compounds,(+)-16-acetoxy-12,15-epoxylabda-8(17),12,14-tiene(**1**),(12ς,15ς)-16-acetoxy-12,15-epoxy-15-isopropoxylabda-8(17),13(16)-diene (Turraeanin A and B) (**2** and **3**), (12ς,15ς)-16-acetoxy-12,15-epoxy-15-methoxylabda-8(17),13(16)-diene (Turraeanin C and D) (**4** and **5**), (12ς,15ς)-12,15-epoxy-15-methoxylabda-8(17)-en-16-al (Turraeanin E) (**6**) and (12ς,15ς)-16-acetoxy-12,15-epoxy-15-hydroxylabda-8(17),13(16)-diene (Turraeanin F) (**7**), as well as the known compounds, 15,16-epoxy-*ent*-labda-8(17),13(16),14-triene (**8**), (+)-Pumiloxide (**9**), *ent*-labda-8(17),12(E)-dien-15,16-dial (**10**). Antimicrobial activity essays of the isolates, including the 15-acetoxy of compound **7** (**7a**) have been carried out and compounds **6, 7a** and **10** exhibited significant activities.

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ANTIMICROBIAL ACTIVITY GUIDED FRACTIONATION OF *AFRAMOMUM LONGIFOLIUS* (ZINGIBERACEAE)

Simplice Tatsimo Ndendoung Joel[1], Jacob Melissa[2], Pierre Tane[3], Beiba L. Sondengam[1], Christopher O. Okunji[4,5], Brian G. Schuster[5], Maurice M. Iwu[4,5], Ikhlas A. Khan [2,]
[1] Department of organic chemistry, University of Yaounde, Box 812, Yaounde, Cameroon. [2]National Center for Natural Products Research, The University of Mississippi, University, MS, 38677, USA. [3]Department of Chemistry, University of Dschang, Box 67, Dschang, Cameroon. [4]International Centre for Ethnomedicine and Drug Development, Nsukka Nigeria; and Bioresources Development & Conservation Programme 11303 Amherst Avenue Suite # 2, Silver Spring, MD 20902. [5]Division of Experimental Therapeutics, Walter Reed Army Institute of Research,Washington DC, 20307-5100, USA.

Many species of *Aframomum* (Zingiberaceae) are used in Cameroon for medicinal, ethnodietary and spiritual purposes. The genus *Aframomum* was found to contain flavonoids and diterpenoids (Kimbu et *al*., 1979; Tsopmo et *al*., 1996; Tomla et *al*., 2002). Antimicrobial activity directed fractionation of the seeds of *Aframomum longifolius* (Zingiberaceae) afforded two new labdane-type diterpenoids, 15-hydroxy-15-methoxylabda-8 (17), 12 (E)-dien-16-al (AframolinA) (**1**) and 8β(17)-epoxy-15, 15-dimethoxylabd-12 (E)-en-16-al (AframolinB) (**2**), together with the known diterpenes labda-8 (17), 12 (E)-dien-16-al (**3**) and aframodial (**4**). Their structures were determined by spectroscopic methods. Compound **4** showed significant antimicrobial activities against *Cryptococcus neoformans, Staphylococus aureus* and *methicillin-resistant S. aureus (MRS*) while **1**, **2** and **3** were found to be inactive.

P:500

CHEMICAL AND BIOLOGICAL INVESTIGATION OF *EPHEDRA VIRIDIS*

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Various species belonging to the genus *Ephedra* are widely used in medicinal preparations. They are prescribed for the cure of ailments such as fever, pain cough etc. Among the various species belonging to the genus ephedra, *E. viridis* is native to North America. In our effort to standardize medicinal plants, we have identified that the alkaloid content in *E. viridis* is minimal. This prompted us to carryout a detailed phytochemical investigation of *E. viridis*, an hitherto phytochemically unexplored taxon. The dried plant material was successively extracted with hexane and chloroform. Hexane extract on GC-MS analysis showed the presence of several long chain aliphatic acids such as n-hexadecanoic acid, oleic acid, octadecanoic acid, eicosanoic acid, docosanoic acid, tricosanoic acid and tetracosanoic acid. The chloroform extract showed a moderate degree of antioxidant and cytotoxic effect in HL-60 cells. Column chromatography of the chloroform extract led to the isolation of several compounds including 9-acetoxyisolariciresino, a new lignan. Besides this, lariciresinol, 9-acetoxylariciresinol, and cyclolariciresinol were also isolated. The structures and stereochemistry were unambiguously assigned by spectroscopic and synthetic evidence. The presence of lignans in the genus ephedra is reported for the first time. All the isolates were tested for their antioxidant and cytotoxic effect in HL-60 cells and were found to be active.

P:501

ISOLATION AND STRUCTURE ELUCIDATION OF MODULATORS OF CNS FUNCTION FROM *DRACAENA MANNII*, A CAMEROONIAN MEDICINAL PLANT.

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Several neuropsychiatric disorders, including depression, psychostimulant dependence and Parkinson's disease, are characterized by derangements in monoamine neurotransmitter systems. Consequently, it is believed that agents that can modulate monoamine neurotransmitter function may be potentially useful in the management of these disorders.
As part of our ongoing search for modulators of CNS function from medicinal plants, a crude methanolic extract of *D. mannii* was bioassayed and found to exhibit significant inhibition of radioligand binding at the serotonin transporter (IC50 = 6.7 ± 0.3 ug/ml). A subsequent assay conducted on the EtOAc and n-BuOH fractions of this extract revealed 100% inhibition of radioligand binding at the Dopamine D3 receptor at a concentration of 80mg/ml. We report herein the isolation and structure elucidation of the bioactive compounds responsible for the observed activity.

P:502

NEW CYTOTOXICITY OBSERVED IN CERBINAL, A KNOWN PRODUCT OF *CERBERA MANGHAS*

Brent J. Yoder,[a] Jennifer K. Schilling,[a] James S. Miller,[b] Rabodo Andriantsiferana,[c] Vincent E. Rasamison,[c] and David G. I. Kingston*,[a]

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The aromatic iridoid cerbinal was first isolated from the bark of *Cerbera manghas* more than 25 years ago. Since that time, various groups have demonstrated that the compound is bioactive as both an antifugal and antioxidative agent. We report here the first known observance of the cytotoxic properties of cerbinal, based upon screening in our A2780 ovarian cell line assay. The bark wood extract of *Cerbera manghas* (Apocynaceae) was obtained from Madagascar as part of an ICBG program and the dichloromethane fraction of the subsequent liquid-liquid partition yielded a bright yellow pigment. Purification of the material by C18 flash chromatography and HPLC led to the identification of the known structure cerbinal. Due to the cytotoxicity observed in our bioassay (IC_{50} = 1 μg/mL), a sample of the isolated compound was sent to NCI for testing in the 60-cell line tumor panel; the results of these assays will be reported.

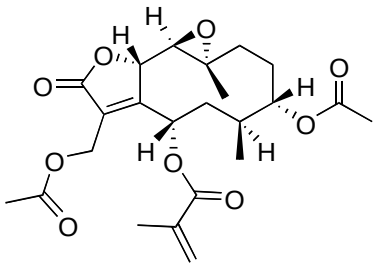
P:503

NEW CYTOTOXIC SESQUITERPENE LACTONES FROM *APODOCEPHALA SP.* FROM THE MADAGASCAR RAINFOREST

Russell B, Williams,[a] Andrew Norris,[a] J. S. Merola,[a] James S. Miller,[b] Rabodo Andriantsiferana,[c] Vincent E. Rasamison,[c] and David G. I. Kingston*,[a]

[a]Department of Chemistry, M/C 0212, Virginia Polytechnic Institute and State University, Blacksburg, VA 24061, [b]Missouri Botanical Garden, P.O. Box 299, St. Louis, MO 63166, and [c]Centre National d'Application et Recherches Pharmaceutiques, B.P. 702, Antananarivo 101, Madagascar

Through a continuing search for anticancer compounds as part of an International Cooperative Biodiversity Grant program, bioassay guided fractionation was carried out on the leaf extract of *Apodocephala* sp. from Madagascar. This has led to the isolation of a series of new sesquiterpene lactones. Their structures were elucidated using 1D and 2D NMR techniques along with single crystal X-ray diffraction. The compounds showed good cytotoxic activity against the A2780 human ovarian cancer cell line.



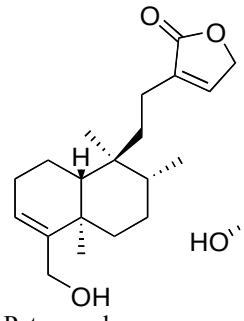
P:504

NEW CYTOTOXIC DITERPENOIDS FROM *HUMIRIANTHERA AMPLA* FROM THE SURINAME RAINFOREST

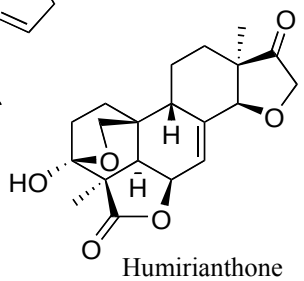
Eba Adou,[a] Russell B. Williams,[a] Jennifer Schilling,[a] Stan Malone,[a] Jan H. Wisse,[c] and David G. I. Kingston*,[a]

[a]Department of Chemistry, Virginia Polytechnic Institute and State University, Blacksburg, Virginia 24061-0212, [b]Conservation International Suriname, Kromme Elleboogstraat No. 20, Paramaribo, Suriname, and [c]Bedrijf Geneesmiddelen Voorziening Suriname, Commissaris Roblesweg, Geyersvlijt, Suriname.

Through a continuing search for anticancer compounds as part of an International Cooperative Biodiversity Grant program, bioassay guided fractionation was carried out on extracts of *Humirianthera ampla* from Suriname. This has led to the isolation of five new diterpenoids and five known diterpenoids. Their structures were elucidated using 1D and 2D NMR techniques along with oxidation for one compound. All ten compounds showed cytotoxic activity against the A2780 human ovarian cancer cell line. Two of the compounds were submitted to the NCI for testing in their 60-cell line.



Patagonol



Humirianthone

P:505

IPOMOEASSINS A-E, FIVE NEW CYTOTOXIC MACROCYCLIC GLYCORESINS, FROM THE LEAVES OF *IPOMOEA SQUAMOSA*

Shugeng Cao,[a] Rebecca C. Guza,[a] Andrew Norris,[a] James S. Miller,[b] Jan H. Wisse,[c] and David G. I. Kingston*,[a]

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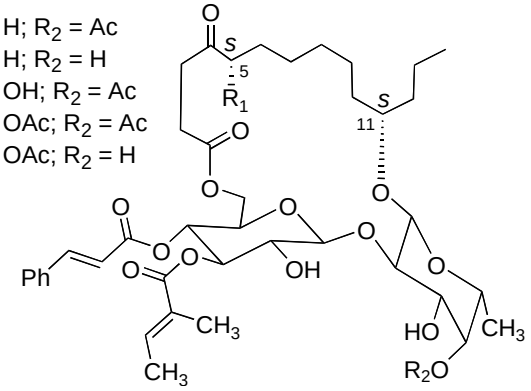
New glycoresins, ipomoeassins A-E (**1**-**5**), have been isolated from the leaves of *Ipomoea squamosa*. The structures were elucidated by spectroscopic analyses and chemical transformations. The absolute configuration of C-5 and C-11 was determined by their double derivatives of (*R*)-MPA and (*S*)-MPA. All the isolates were active in the A2780 assay, and **4** showed significant activity.

1 R_1 = H; R_2 = Ac
2 R_1 = H; R_2 = H
3 R_1 = OH; R_2 = Ac
4 R_1 = OAc; R_2 = Ac
5 R_1 = OAc; R_2 = H

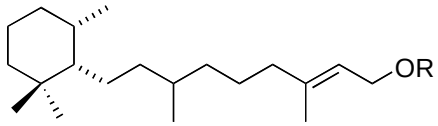


P:506

NEW CYTOTOXIC DITERPENES FROM *CASSIPOUREA* SPECIES FROM THE MADAGASCAR RAINFOREST

V. S. Prakash Chaturvedula,[a] Andrew Norris,[a] James S. Miller,[b] Rabodo Andriantsiferana,[c] Vincent E. Rasamison,[c] and David G. I. Kingston*,[a]
[a]Department of Chemistry, M/C 0212, Virginia Polytechnic Institute and State University, Blacksburg, VA 24061, [b]Missouri Botanical Garden, P.O. Box 299, St. Louis, MO 63166, and [c]Centre National d'Application et Recherches Pharmaceutiques, B.P. 702, Antananarivo 101, Madagascar

As a part of our continuing study in isolating potential anticancer compounds, the combined chloroform soluble portion of the crude extracts of the roots and leaves of *Cassipourea* species was fractionated using A2780 bioassay, which resulted in the isolation of two new diterpenes (**1**-**2**) and three known compounds combretol, 3β,30-dihydroxylup-20(29)-ene and 30-hydroxylup-20(29)-ene-3-one. The structures of the two new compounds were established on the basis of extensive spectral data, followed by chemical conversion studies. The two new compounds exhibited activity in A2780 assay in the range 2.0-3.0 μg/mL.



1 R = OH
2 R = $OCOCH_3$

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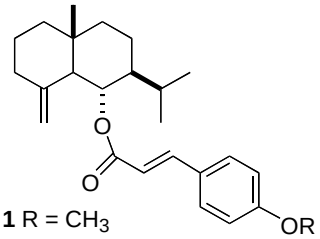
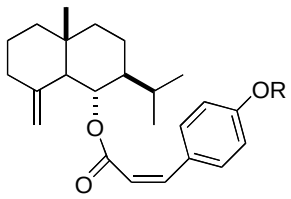
NEW EUDESMANE DERIVATIVES FROM THE LEAVES OF *MELAMPODIUM CAMPHORATUM* FROM THE SURINAME RAINFOREST EXHIBITING ANTIMALARIAL ACTIVITY

V. S. Prakash Chaturvedula,[a] Afgan Farooq,[a] Stan Malone,[b] Jan H. Wisse,[c] and David G. I. Kingston*,[a]
[a]Department of Chemistry, Virginia Polytechnic Institute and State University, Blacksburg, Virginia 24061-0212, [b]Conservation International Suriname, Kromme Elleboogstraat No. 20, Paramaribo, Suriname, and [c]Bedrijf Geneesmiddelen Voorziening Suriname, Commissaris Roblesweg, Geyersvlijt, Suriname.

Six new eudesmane sesquiterpenes (**1**-**6**) and two known compounds 6-*epi*-β-verbesinol and 9-desacetoxyleucanthinin were isolated from the EtOAc extract of the leaves of *Melampodium camphoratum* by the hemin binding bio-assay guided fractionation. The structures of the new compounds **1**-**6** were established on the basis of extensive 1D and 2D NMR spectroscopic data interpretation and chemical modifications.



1 R = CH_3
2 R = $CO(CH_2)_{16}CH_3$
3 R = $CO(CH_2)_{14}CH_3$
4 R = $CO(CH_2)_7CH{=}CH(CH_2)_5CH_3$



5 R = H
6 R = $COCH_3$

P:508

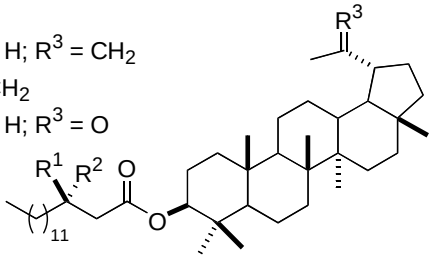
NEW LUPANE TRITERPENOIDS FROM *SOLIDAGO CANADENSIS* THAT INHIBIT THE LYASE ACTIVITY OF DNA POLYMERASE β

V. S. Prakash Chaturvedula,[a] Bing-Nan Zhou,[a] Zhijie Gao,[b] Shannon J. Thomas,[b] Sidney M. Hecht,[b] David G. I. Kingston[a,*]

[a] Department of Chemistry, M/C 0212, Virginia Polytechnic Institute and State University, Blacksburg, VA 24060, USA and [b] Departments of Chemistry and Biology, University of Virginia, Charlottesville, VA 22901, USA

Bioassay-directed fractionation of a methyl ethyl ketone extract of *Solidago canadensis,* using an assay to detect the lyase activity of DNA polymerase β, resulted in the isolation of the four new lupane triterpenoids **1-4** and the seven known compounds lupeol, lupeyl acetate, ursolic acid, cycloartenol, cycloartenyl palmitate, α-amyrin acetate, and stigmasterol. The structures of the new compounds were established as 3β-3*R*-acetyloxyhexadecanoyl-lup-20(29)-ene (**1**), 3β-3-ketohexadecanoyl-lup-20(29)-ene (**2**), 29-*nor*-lup-3β-3*R*-acetyloxyhexadecanoyl-20-one (**3**), and 29-*nor*-lup-3β-3-ketohexadecanoyl-20-one (**4**), respectively, on the basis of extensive 1D and 2D NMR spectroscopic interpretation and chemical modification studies. All eleven compounds were inhibitory to the lyase activity of DNA polymerase β.

1 $R^1 = OCOCH_3$; $R^2 = H$; $R^3 = CH_2$
2 $R^1 = R^2 = O$; $R^3 = CH_2$
3 $R^1 = OCOCH_3$; $R^2 = H$; $R^3 = O$
4 $R^1 = R^2 = R^3 = O$



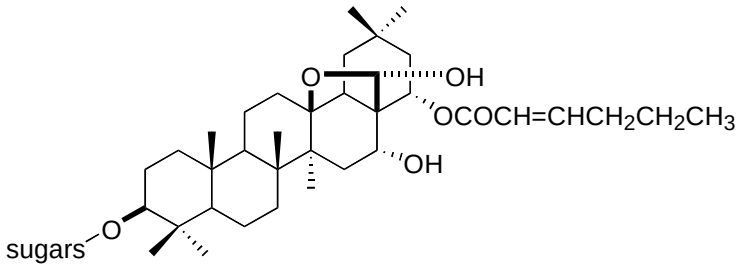
P:509

SAPONINS FROM *SYZYGIUM GUIANEENSE* EXHIBITING CDC25 ACTIVITY

V. S. Prakash Chaturvedula,[a] Sidney M. Hecht,[b] Caleb Foster,[c] John S. Lazo,[c] David G. I. Kingston[a,*]

[a] Department of Chemistry, M/C 0212, Virginia Polytechnic Institute and State University, Blacksburg, VA 24060, USA and [b] Departments of Chemistry and Biology, University of Virginia, Charlottesville, VA 22901, USA and [c] Department of Pharmacology, University of Pittsburgh, PA 15261

Bioassay-directed fractionation of the crude extract of S*yzygium guianeense* using an assay for inhibitors of Cdc25B, resulted in the isolation of three active saponin fractions in addition to the two known triterpenoids 2α,3β,23-trihydroxyurs-12-ene-28-oic acid and 2α,3β,23-trihydroxyolean-12-ene-28-oic acid. The saponins contained the olenane triterpenoid skeleton with different sugar units at the C-3 position. The detailed structures and the evidence for these structures will be presented.



P:510

PHYSALINS ACTIVATE PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR-γ (PPARγ) IN BREAST TUMOR CELLS

Flor D. Mora, Yu-Dong Zhou, Dennis R. Feller, and Dale G. Nagle*
Department of Pharmacognosy, National Center for Natural Products Research, and Department of Pharmacology, Research Institute of Pharmaceutical Sciences, School of Pharmacy, University of Mississippi, University, MS, 38677-1848.

The nuclear hormone receptor/transcription factor peroxisome proliferator-activated receptor-γ (PPAR-γ) regulates the expression of many genes involved in lipid metabolism and adipocyte differentiation. Activation of PPAR-γ has been shown to promote tumor suppression both *in vitro* and *in vivo*.
The annual herb *Physalis angulata* (Solanaceae) is grown worldwide and extracts of this plant have been used to treat tumors, pain, inflammation, fever, and as a diuretic in folk medicines. Leaf extracts of *P. angulata* produced a significantly greater activation of PPARγ (in a breast tumor cell-based bioassay) than the known PPAR-γ activator 15-deoxy-$\Delta^{12,14}$-PGJ_2 (10 μM). Bioassay-guided fractionation yielded physalin B and physalin F, two triterpene metabolites previously known to inhibit tumor cell growth *in vitro.* Activation of PPARγ may, at least in part, contribute to the antitumor effects of physalins B and F.

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NOVEL GLYCOLIPIDS FROM THE LEAVES OF *Solanum lanceolatum* AND THEIR ANTIINFLAMMATORY ACTIVITY

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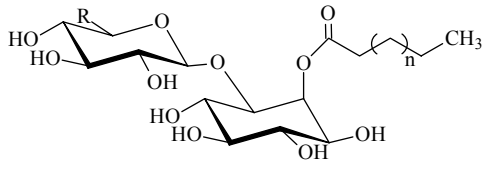
Centro de Investigaciones Químicas, Lab. Productos Naturales. Av.Universidad 1001.Col.Chamilpa. C.P.62210. Cuernavaca, Morelos.

Six new glycolipids **(1-6)** were isolated from the leaves of *Solanum lanceolatum* and shown to possess a novel molecular structure. The chemical structure of these compounds was elucidated by spectroscopic analysis and chemical derivatization. The *in vivo* antiinflammatory evaluation with 12-*O*-tetradecanoyl phorbol 13-acetate (TPA) induced mouse ear edema showed that the mixtures of **1-3** and **4-6** displayed 57.84% and 78.65% of inhibitory activity respectively, against indometacine control. Due to their interaction with inflammatory mediators these natural products represent a new group of potential anti-inflammatory agents.



1 R=H n=8
2 R=H n=9
3 R=H n=10
4 R=CH_2OH n=8
5 R=CH_2OH n=9
6 R=CH_2OH n=10

*Yesenia Herrera Salgado. Centro de Investigaciones Químicas, Lab.10.Tel. (777) 3 297997, Ext.6010.Cuernavaca, Mor. México.

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HUMULENE DERIVATIVES FROM *ZINGIBER ZERUMBET* WITH INHIBITORY ACTIVITY OF LIPPOPOLYSACCARIDE-INDUCED NITRIC OXIDE PRODUCTION

Dae Sik Jang[†], Hye-Young Min[‡], Ah-Reum Han[‡], Gwang-Ho Jeohn[§], Tri Windono[§], Sang Kook Lee[‡], and Eun-Kyoung Seo*[,‡]
[†]Division of Molecular Life Sciences, and [‡]College of Pharmacy, Ewha Womans University, Seoul 120-750, Korea; [§]College of Pharmacy, University of Surabaya, JL. Raya Kalirungkut, Surabaya 60293, Indonesia.

In our ongoing project directed toward the discovery of novel naturally occurring inducible nitric oxide synthase inhibitory agents from higher plants, the rhizomes of *Zingiber zerumbet* were chosen for more detailed investigation. Bioassay-guided fractionation of the *n*-hexane-soluble fraction of the MeOH extract of the rhizomes of *Z. zerumbet*, using the *in vitro* iNOS inhibition assay, led to the isolation of a new humulene derivative, 4-hydroxyzerumbone (4-hydroxy-2*E*,6*E*,10*E*-humulatrien-1-one) (**2**) and two known sesquiterpenoids, zerumbone (**1**) and zerumboneoxide (**5**) as the active constituents, along with two new natural products, 3-methoxy-6,10-humuladien-1-one (**3** and **4**) and a known steroid, stigmast-5-ene-3-one as the inactive constituents. The structures of **2**-**4** were determined by spectroscopic data measurement such as 1D and 2D-NMR experiments.

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ANTITUBERCULAR CONSTITUENTS FROM THE ROOT OF FORMOSAN *ENGELHARDIA ROXBURGHIANA*

Ih-Sheng Chen[1], Wen-Yu Lin[1], Chien-Fang Peng[2], Ian-Lih Tsai[1], Jih-Jung Chen[3], Ming-Jen Cheng[1]
[1] Graduate Institute of Natural Products, College of Pharmacy, Kaohsiung Medical University, Kaohsiung, Taiwan 807, Republic of China
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[3] Department of Pharmacy, Tajen Institute of Technology, Pingtung, Taiwan 907, Republic of China

Tuberculosis and the incidence of multidrug-resistant TB have become an increasing world health problem. Searching for new structural types of effective drug against this infectious disease has also become important. Recently about 200 species of Formosan plants were screened on antitubercular activity and *Engelhardia roxburghiana* Wall. (*E. chrysolepis* Hance; *E. formosana* (Hay.) Hayata; *E. spicata* Bl. *var*. *formosana* Hayata) (Juglandaceae) was shown to be one of the active species. *E. roxburgiana* is a deciduous tree growing in India, Indochina, China, and Taiwan. Leaves of this plant have been used as a sweet tea to prevent obesity and to treat abdominal pain and fever in China. The bark and the leaves are also used as fish poison. Past studies have revealed dihydroflavonol glycosides and flavonol glycosides were the major constituents of leaves and stem bark of this species. Examination of the root has led to the isolation of three new compounds, engelhardione (**1**), (-)-5-hydroxy-4-methoxy-1- tetralone (**2**), and 3-carbomethoxy-1,5-dihydroxyanthraquinone (**3**), together with twelve known compounds. In this congress, the structural elucidation of **1**-**3** and the antitubercular activity of the isolates will be discussed.

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LIMNOPHILASPIROKETONE, A HIGHLY OXYGENATED STRUCTURALLY NOVEL PHENOLIC DERIVATIVE FROM *LIMNOPHILA GEOFFRAYI*

Dae Sik Jang,[1,4] Bao-Ning Su,[1,5] Alison D. Pawlus,[1,5] William P. Jones,[1,5] Robert A. Kleps,[2] Nuntavan Bunyapraphatsara,[3] Harry H. S. Fong,[1] John M. Pezzuto,[1,6] and A. Douglas Kinghorn[1,5,*]
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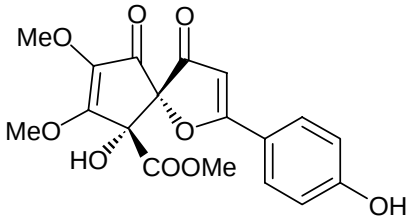
A highly oxygenated spiroketone functionalized phenolic compound, limnophilaspiroketone (**1**), along with nine known compounds, betulinic acid, 4-*epi*-hederagenin, 3-farnesyl-4-hydroxybenzoic acid, gardenin B, 6β-hydroxyoleanolic acid, isothymusin, nevadensin, rotungenic acid, and uncaric acid, was isolated and characterized from the EtOAc-soluble partition of a MeOH extract of the aerial parts of *Limnophila geoffrayi* Bon. (Scrophulariaceae), collected in Thailand. The structure of limnophilaspiroketone (**1**) was determined based on extensive 2D NMR and HRMS studies, and confirmed by chemical transformation. Limnophilaspiroketone (**1**) was verified as a racemic mixture from the ^{1}H NMR data of its (*R*)-MTPA-ester, which is consistent with its optically inactive nature. All isolates obtained in the present study were evaluated for their potential cancer chemopreventive activity utilizing an *in vitro* assay to determine quinone reductase induction.



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(Supported by grant P01 CA48112 from the National Cancer Institute, NIH, Bethesda, MD).

P:515

BIOACTIVE COMPOUNDS FROM ATLANTIC FOREST SPECIES *ALCHORNEA GLANDULOSA* AND *A. SISIFOLIA*

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Plants of the family Euphorbiaceae have been used as traditional medicines in several parts of the world. In Africa, *Alchornea cordifolia* has been used mainly to treat amoebiasis and malaria. The bioassay guided fractionation of extracts of *Alchornea* species collected in the Atlantic Forest – Brazil using TLC test revealed with β-carotene or DPPH solutions for the detection of antioxidant compounds led to the isolation of flavonoids 3-*O*-β-glucosyl-kaempferol from *A. glandulosa* leaves and astilbin from *A. sisifolia* leaves and the ellagitannin corilagin from *A. sisifolia* fruits. Additionally, the bioassay-guided fractionation of *A. glandulosa* leaves, using mutant strains of *Saccharomyces cerevisae* led to the isolation of the potential antitumoral guanidine alkaloids pterogynine and pterogynidine, besides two new triisoprenylated derivatives. The citotoxicity of the isolated guanidine alkaloids has been evaluated by the MTT test using five tumor cell lines, HCT-8, MCF-7 (human breast tumor), HL60 (human promyelocytic leukemia), CEM (human acute lymphoblastic leukemia) and B16 (murine melanoma) in which the triisoprenylated alkaloids showed moderate activity whereas pteroginine and pteroginidine showed intense activity (IC_{50} < 0,69 μg/mL). (Granted by Biota-FAPESP Program)

P:516

FRACTIONATION OF THE BARK OF *ELMERILLIA OVALIS* USING A HISTONE DEACETYLASE INHIBITION ASSAY

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Histone deacetylase inhibitors are of great interest because of their ability to arrest cell growth, induce cell differentiation, and they may also induce apoptosis of cancer cells (**1**). As part of an ongoing collaborative search for novel plant-derived anticancer agents, evaluation of over 200 hundred chloroform-soluble extracts from plants in a fluorogenic histone deacetylase inhbition assay provided several active leads, with one of the most active being *Elmerillia ovalis* (Magnoliaceae), collected in Indonesia. Fractionation of the chloroform-soluble extract of the bark of *Elmerillia ovalis* was guided using a fluorogenic histone deacetylase inhibition assay and led to the isolation of a new trisubstituted cinnamyl aldehyde derivative, three benzaldehyde derivatives, and a benzoic acid derivative. The structures of these isolates were characterized based on their physical and spectroscopic data, especially 2D-NMR data. (Supported by grant U19 CA52956-14S1 from NCI, NIH).

(**1**) Takai, N., Desmond, J. C., Kumagai, T., Gui, D., Said, J. W., Whittaker, S., Miyakawa, I., Koeffler, H. P. *Clin. Cancer Res*. **2004**, 10: 1141-49.

P:517

CONSTITUENTS OF *ZANTHOXYLUM PIPERITUM* FRUITS AND THEIR EFFECTS ON METHICILLIN-RESITANT *STAPHYLOCOCCUS AUREUS*

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Pericarp of *Zanthoxylum piperitum* fruit has been used for treatment of intestinal disorder and also as an anthelmintic in Japan. Our investigation on the constituents led to the isolation of several aliphatic acid amides including new compounds. Structures of the amides were elucidated to be (6*RS*)-(2*E*, 7*E*, 9*E*)-6-hydroxy-*N*-(2-hydroxy-2-methylpropyl)-11-oxo-2,7,9-dodecatrienamide, (11*RS*)-(2*E*, 7*E*, 9*E*)-11-hydroxy-*N*-(2-hydroxy-2-methylpropyl)-6-oxo-2,7,9-dodecatrienamide, (10*RS*, 11*SR*)- and (10*RS*, 11*RS*)-(2*E*, 6*Z*, 8*E*)-10,11-dihydroxy-*N*-(2-hydroxy-2-methylpropyl)-2,6,8-dodecatrienamides and (6*RS*, 11*SR*)- and (6*RS*, 11*RS*)-(2*E*, 7*E*, 9*E*)-6,11-dihydroxy-*N*-(2-hydroxy-2-methylpropyl)-2,7,9-dodecatrienamides. Although the amides did not show distinctive antibacterial effects on the methicillin-resistant *Staphylococcus aureus* (MRSA) strains used, monoterpenes (geraniol and citronellal) and a polymeric proanthocyanidin fraction showed suppression of the antibiotic resistance of MRSA.

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PHYTHOTOXIC COMPOUNDS FROM *HOFMEISTERIA SCHAFFNERI* (A. GRAY) KING & ROBINSON (ASTERACEAE)

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[a]Facultad de Química and [b]Instituto de Biología, Universidad Nacional Autónoma de México, Mexico City 04510, México.

A CH_2Cl_2-MeOH (1:1) extract prepared from the aerial parts of *Hofmeisteria schaffneri* (Asteraceae) inhibited radicle growth of *Amarathus hypochondriacus* (IC_{50}=52.54 μg/mL) when tested by the petri dish assay. Accordingly, the phytotoxic extract was selected for bioassay-guided fractionation. This process led to isolation of the novel natural compound **1** which was given the trivial name of hofmeisterin, and **2**. Compound **2** inhibited radicle elongation of *A. hypochondriacus* seedlings. The calculated IC_{50} value of $1x10^{-5}$ μM.

This work was supported by a grant of CONACyT C01-018 and DGAPA IN200902

P:519

ANTIMYCOBACTERIAL COUMARINS FROM *ARRACACIA TOLUCENSIS* VAR *MULTIFIDA*

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Arracacia tolucensis (H.B.K). var multifida Hemsl (S. Wats.) Mathias & Constance (Umbelliferae) has been traditionally used for the treatment of cough and bronchitis as well as a condiment. Bioassay-guided fractionation of the CH_2Cl_2-MeOH (1:1) extract obtained from the aerial parts of the plant led to the isolation of eight coumarins identified as isoimperatorin (**1**), suberosin (**2**), osthol (**3**), 8-methoxypsoralen (**4**), umbelliferone (**5**), herniarin (**6**), scoparone (**7**) and oxypeucedanin hydrate (**8**). Antimycobacterial activity was determined against *Mycobacterium tuberculosis* $H_{37}Rv$ (ATCC 27294) using the Microplate Alamar Blue Assay (MABA). Compounds **1-3** showed significant anti-TBC activity.

This work was supported by the "Bioactive Agents from Dryland Biodiversity of Latin America" grant U01 TW 00316 from the NIH, NSF and USDA (to B. N. T.). CONACyT C01-018 (to R. M.).

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ADDITIONAL COMPOUNDS FROM THE LEAVES OF *PIPER SANCTUM*.

Isabel Rivero-Cruz[a], Isolda Enríquez[a], Laura Acevedo[a], Iliana Morales[a], Robert Bye[b], Scott Franzblau[c], Barbara N. Timmermann[d], and Rachel Mata[a]
[a]Facultad de Química, and [b]Instituto de Biología, Universidad Nacional Autónoma de México, Mexico City 04510, México. [c]College of Pharmacy, University of Illinois at Chicago, Chicago, Illinois 60612-7231, USA. [d]College of Pharmacy, The University of Arizona, Tucson, Arizona, 85721, USA.

Reinvestigation of the anti-TBC extract of the leaves of *Piper sanctum* afforded three new additional compounds identified as 2-oxo-16-phenyl-3-hexadecene, methyl-(6-tridecanyl)tetrahydro-2-pyran-2-yl-acetate and methyl-(5-tetradecanyl)tetrahydro-2-furan-2-yl-acetate. In addition, 2-oxo-14-(3′,4′-methylenedioxyphenyl)-3-tetradecene, 2-oxo-16-(3′,4′-methylenedioxyphenyl)-3-hexadecene, 2-oxo-16-phenyl-3-hexadecane, 2-oxo-12-(3′,4′-methylenedioxyphenyl)-dodecane, 2-oxo-14-(3′,4′-methylenedioxyphenyl)-tetradecane (**1**), 2-oxo-16-(3′,4′-methylendioxyphenyl)-hexadecane (**2**), 2-oxo-18-(3′,4′-methylenedioxyphenyl)-octadecane and methyl[6-(10-phenyldecanyl)tetrahydro-pyran-2-yl]acetate. Compounds **1** and **2** showed noted anti-TBC activity.The X-ray-structure of compound **2** is also reported.

This work was supported by the "Bioactive Agents from Dryland Biodiversity of Latin America" grant U01 TW 00316 from the NIH, NSF and USDA (to B. N. T.). CONACyT C01-018 (to R. M.).

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ANTIMYCOBACTERIAL COMPOUNDS FROM THE STEM OF *PIPER SANCTUM*.

Isabel Rivero-Cruz[a], Isolda Enríquez[a], Laura Acevedo[a], Iliana Morales[a], Robert Bye[b], Scott Franzblau[c], Barbara N. Timmermann[d], and Rachel Mata[a]
[a]Facultad de Química, and [b]Instituto de Biología, Universidad Nacional Autónoma de México, Mexico City 04510, México. [c]College of Pharmacy, University of Illinois at Chicago, Chicago, Illinois 60612-7231, USA. [d]College of Pharmacy, The University of Arizona, Tucson, Arizona, 85721, USA.

Bioassay-guided fractionation of the anti-TBC extract of the stem of *Piper sanctum* yielded eugenol, methyleugenol, *Z*-piperolid, demethoxyyangonin (**1**), 5,6-dehydro-7,8-dihydrometisticin (**2**), cepharanone B (**3**), cepharadione A, piperolactame A (**4**), N-*trans*-feruloyltyramine, and N-*trans*-p-coumaryltyramine (**5**), were obtained from the anti-TBC stem extract of the plant. Compounds **1**-**5** inhibited the growth of *Mycobacterium tuberculosis* when tested by the MABA assay with MIC values ranging from 2 to 64 μg/mL. GC-MS analysis of the essential oils prepared from the leaves and stems revealed that in both cases the major component was safrol [86.75 and 83.90 %, respectively]. Other important constituents identified in both oils were bicyclo [4,1,0]hept-3-ene, 3,7,7-trimethyl, myristicin, benzenepropanoic acid methyl ester and bezenepropanoic acid ethyl ester.

This work was supported by the "Bioactive Agents from Dryland Biodiversity of Latin America" grant U01 TW 00316 from the NIH, NSF and USDA (to B. N. T.). CONACyT C01-018 (to R. M.).

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PHYTOCHEMICAL CONSTITUENTS OF *DIOSCOREA OPPOSITA* RHIZOMES

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Dioscorea opposita THUNB (= *D. batatas* DECNE) (Dioscoreaceae) is a tropical food yam which is widely cultivated in Asia. This plant is also widely used in Traditional Chinese Medicine for the treatment of anorexia, chronic diarrhoea, diabetes, seminal emission and excessive leukorrhea. A phytochemical investigation of the MeOH extract of the rhizome of *D. opposita* has led to the isolation by successive VLC on Si RP_{18} and MPLC on normal Si gel of a new phenanthrene glycoside, 3,4,6-trihydroxyphenanthrene-3-*O*-*β*-D-glucopyranoside (**1**), and five known compounds, soyacerebroside I (**2**), adenosine (**3)**, β-sitosterol (**4**), palmitic acid (**5**) and palmitoyloleoylphosphatidylcholine (**6**). Their structures were determined mainly by 1D- and 2D-NMR experiments (COSY, TOCSY, HSQC and HMBC) and by HRESIMS. Compounds **1-6** exhibited no antifungal activity against the human pathogenic yeasts *Candida albicans*, *C. glabrata* and *C. tropicalis*.

The isolation, structural elucidation and antifungal bioassay of **1-6** will be presented.

P:523

FOUR NOVEL GLYCOSIDES FROM THE ROOTS OF *CUCURBITA FOETIDISSIMA*

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[a] Laboratoire de Pharmacognosie, Unité de Molécules d'Intérêt Biologique (UMIB EA 3660), Faculté de Pharmacie, Université de Bourgogne, 7 Bd Jeanne d'Arc, BP 87900, F-21079 Dijon Cedex, FRANCE, [b] Graduate School of Pharmaceutical Sciences, Kyushu University, Fukuoka, JAPAN

Cucurbita foetidissima H.B.K. (Syn. *C. perrenis*, A. Gray, *Cucumis perrenis* E. James) (Cucurbitaceae) is an indigenous plant to Texas, Arizona, New Mexico and California. North American Indians used the roots as laxative. Our previous phytochemical studies on the MeOH extract of *C. foetidissima* roots led to the isolation of two new triterpene saponins, foetidissimosides A and B, and the identification of cucurbitacins.

The crude saponin mixture obtained from the MeOH extract of the roots of *C. foetidissima* was fractionated by repeated MPLC over normal Si gel and semi-preparative high pressure liquid chromatography (HPLC) on reversed-phase Si RP 18 yielding the pure echinocystic acid glycosides foetidissimosides C (**1**), D (**2**), and the 1:1 inseperable mixture of cucurbitane glycosides, foetidissimosides E and F (**3**,**4**). Their structures were elucidated mainly by 1D and 2D NMR experiments (COSY, TOCSY, ROESY, NOESY, HSQC and HMBC) and by FABMS.

This communication deals with the isolation and structural elucidation of **1-4.**

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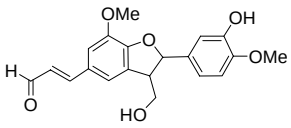
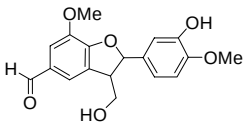
CHEMICAL CONSTITUENT STUDY ON *VITEX AGNUS-CASTUS*

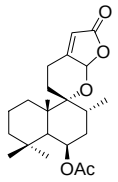
Shao-Nong Chen, Guido F. Pauli, Harry H. S. Fong, Stephanie Schlecht, Norman R. Farnsworth*
UIC/NIH Center for Botanical Dietary Supplements Research and Department of Medicinal Chemistry and Pharmacognosy, University of Illinois at Chicago, Chicago, IL 60612



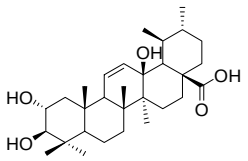
Vitagnusin A



Vitagnusin B



Agnolide A



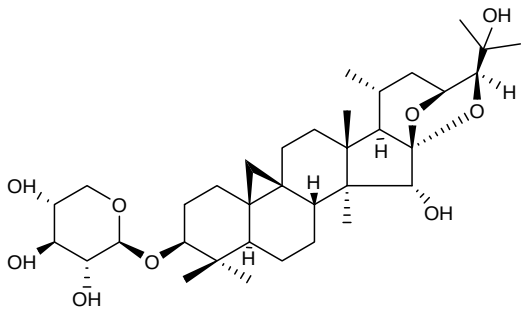
Vitexolic acid A

An extract of chaste berry (*Vitex agnus-castus* L.) has long been used in Western countries as a remedy for the relief of symptoms of premenstrual syndrome (PMS). As part of our Center's efforts to chemically characterize and standardize defatted MeOH extracts of *V. agnus-castus* fruits, two new lignans named vitagnusin A and B, the new diterpene agnolide A, the new triterpene vitexolic acid A, and 21 known compounds were isolated from bioactive fractions under activity guided fractionation using opioid δ_2 and μ bioassay models. Structural elucidation and identification of all compounds were accomplished by detailed NMR spectral analysis.

P:525

3-O-β-D-XYLOSIDE-16-EPI-CIMIGENOL, A NEW STEREOISOMERIC TRITERPENE GLYCOSIDE FROM *CIMICIFUGA RACEMOSA*

Shao-Nong Chen, Daniel S. Fabricant, Zhi-Zhen Lu, Harry H. S. Fong, Guido F. Pauli, Norman R. Farnsworth*
UIC/NIH Center for Botanical Dietary Supplements Research and Department of Medicinal Chemistry and Pharmacognosy, University of Illinois at Chicago, Chicago, IL 60612



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Cimicifuga racemosa (L.) Nutt. (syn. *Actaea racemosa* L., Ranunculaceae) known as black cohosh, is widely used as an herbal dietary supplement for the relief of symptoms related to menopause. In our studies on the chemical characterization and standardization of *C. racemosa* extracts, a new stereoisomeric triterpene glycoside, 3-O-β-D-xyloside-16-epi-cimigenol (**1**), was isolated and its structure elucidated by 1D and 2D NMR, especially NOESY spectral analysis. This finding resolves potential confusion with the HPLC fingerprinting of triterpene glycosides for standardization purposes

P:526

QUASSINOIDS FROM THE LEAVES AND TWIGS OF *CASTELA MACROPHYLLA* (SIMAROUBACEAE)

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[b]*Department of Chemistry, University of Toronto, 80 St. George Street St., Toronto, Canada M5S 3H6*

Eight quassinoids have been isolated from acetone and methanol extracts of the endemic Jamaican plant *Castela macrophylla* (Simaroubaceae). The structures and stereochemistry of these compounds were established using a combination of spectroscopic methods including 2D NMR.

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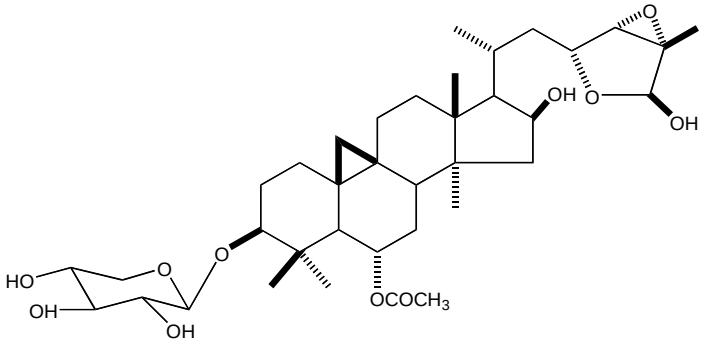
TRITERPENE GLYCOSIDES FROM *ASTRAGALUS TOMENTOSUS* .

Mohamed M. Radwan,[1,2] Nadia A. El-Sebakhy,[2] Aya M. Asaad,[2] Soad M. Toaima,[2] and David G. I. Kingston.[1,]*
[1]Department of Chemistry, M/C 0212, Virginia Polytechnic Institute and State University, Blacksburg, Virginia 24061, USA, [2]Department of Pharmacognosy, Faculty of Pharmacy, University of Alexandria, Alexandria, Egypt

Six new cycloartane-type saponins, tomentosides V-X (**1-6)**, in addition to the known glycosides astrasieversianin X, astrasieversianin XIV, and soyasaponin I methyl ester, were isolated from the aerial parts of *Astragalus tomentosus.* The structures of the new compounds were determined by spectral and chemical methods. All compounds exhibited very weak cytotoxicity against the A2780 ovarian cancer cell line.



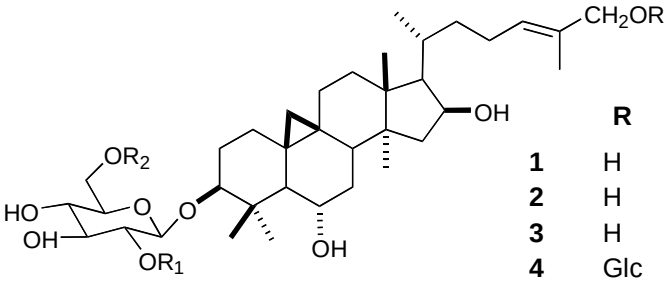
Tomentoside V (1)

P:528

NEW CYCLOARTANE-TYPE TRITERPENES FROM *ASTRAGALUS KAHIRICUS*.

Mohamed M. Radwan,[1,2] Nadia A. El-Sebakhy,[2] Aya M. Asaad,[2] Soad M. Toaima,[2] and David G. I. Kingston [1,*].
[1]Department of Chemistry, M/C 0212, Virginia Polytechnic Institute and State University, Blacksburg, Virginia 24061, USA, [2]Department of Pharmacognosy, Faculty of Pharmacy, University of Alexandria, Alexandria, Egypt

Five new cycloartane-type saponins, kahiricoside II-VI (**1-4**), were isolated along with the known triterpene lupeol from the aerial parts of an Egyptian collection of *Astragalus kahiricus*. Their structures were elucidated by chemical and spectroscopic evidence. All compounds exhibited very weak cytotoxicity against the A2780 ovarian cancer cell line.



	R	R_1	R_2
1	H	H	H
2	H	$COCH_3$	H
3	H	H	$COCH_3$
4	Glc	H	H

P:529

NEW CYTOTOXIC MONOTETRAHYDROFURANIC ANNONACEOUS ACETOGENINS FROM *ANNONA MONTANA*

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The family Annonaceae is regarded as an important source of edible fruits, fragrance oils, and folk medicine for various purposes in the world. Recently, some Annonaceae became important in pharmaceutical research because of the antifungal and cytotoxic activities of some chemical constituents of the leaves and bark, such as *ent*-kaurene diterpenoids and Annonaceous acetogenins. Among them, the Annonaceous acetogenins was regarded as one of the most potential drugs due to their potential activities in anticancer, cytotoxic, antiparasitic, insecticide, and immunosuppressive effects.

In continuation of our studies on acetogenins from Formosan annonaceous plants, eleven monotetrahydrofuranic Annonaceous acetogenins, montalicins A-J (**1-10**) and *cis*-annoreticuin (**11**), along with ten known acetogenins, were isolated from the seeds of *Annona montana* by a high performance liquid chromatographic (HPLC) method. The structures of all new isolates were elucidated and characterized by spectroscopic and chemical methods.

These mono-THF Annonaceous acetogenins showed selectively potent cytotoxicity against two human cancer cell lines, 1A9 and Hep G2.

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ANTI-PLATELET AGGREGATION OF NEW APOTIRUCALL TYPE SAPONINS FROM THE GALLS OF *SAPINDUS MUKOROSSI*

Hui-Chi Huang,[†‡§] Wei-Jern Tsai[§], Yao-Haur Kuo,[§*] and Yang-Chang Wu[‡*] [†]Graduate Institute of Pharmaceutical Sciences, Kaohsiung Medical University, Kaohsiung 807, Taiwan. [‡]Graduate Institute of Natural Products, Kaohsiung Medical University, Kaohsiung 807, Taiwan. [§]National Research Institute of Chinese Medicine, Taipei 110, Taiwan, R.O.C.

The plants of *Sapindus murkorossi* has been traditionally used as an expectorant, as well as a source of natural surfactants rather than for medicinal purpose. We have been reported that several hederagenin-based acetylated saponins were isolated from the pericarp of this plant. Galls are abnormal growths of plant tissue induced by insects and other organisms. Further investigation of the galls of *S. mukorossi* by column chromatography and HPLC led to the isolation and characterization of five new apotirucall-type saponins, **1**-**5** and two new dammarane-type saponin, **6** and **7**. The structures of these saponins were elucidated on the basis of spectroscopic analyses including 1D and 2D NMR techniques. Biological evaluation showed that **1** and **2** demonstrated anti-platelet aggregation induced by AA (IC_{50}= 12.5±0.1 μM for **1**, 6.7±0.4 μM for **2**), U46619 (IC_{50}= 5.4±0.2, 3.4±0.7), PAF (IC_{50}= 13.5±0.3, 7.7±0.2), and thrombin (IC_{50}= 8.9±0.4, 8.4±0.2), respectively.

P:531

THE NEW C_{18} DIBENZOCYCLOOCTADIENE LIGNANS AND ANTI-HEPATITIS C_{19} HOMOLIGNANS FROM *KADSURA JAPONICA*

Yao-Haur Kuo[1,*], Ming-Der Wu[1,2], Chia-Ching Liaw[1,3], Ya-Wen Hsu[1], Ray-Ling Huang[1], Li-Ming Yang Kuo[1], Chia-Cheng Hung[1], Ya-Ching Shen[3], Chi-Wi Ong[2,*]
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We have recently reported the isolation of two kinds of C_{19} homolignans including 5,4-butano-2, 4-cyclohexadienone-6-spiro-3-(2,3-dihydrobenzo[*b*]furan) skeleton and a 3, 4-{1-[(Z)-2-methoxy-2-oxoethylidene]}-pentano- (2,3-dihydrobenzo[*b*]furan) –3 (2-oxoacetate) skeleton, as well as C_{18} dibenzocyclooctadiene lignans from *Kadsura matsudai* and *Schizandra arisanensis*. Further investigation of EtOAc extract of *Kadsura japonica* by column chromatography and HPLC has led to the isolation of six new C_{18} dibenzocyclooctadiene lignans, schizanrins I (**1**), J (**2**), K (**3**), L (**4**), M (**5**), N (**6**), along with four known C_{19} homolignans, taiwanschirin A (**7**), B (**8**), C (**9**), and heteroclitin F (**10**). The elucidations of new structures **1-6** were based on the spectral analysis including 2-D NMR techniques. Bioassay evaluation for against human type B hepatitis exhibited that taiwanschirin A and B showed strong activity for anti-HBsAg, and medium effect for anti-HBeAg, at 25 μg/mL.

P:532

CHROMANOES, DIHYDROCOUMARINES AND PYRANOXANTHONES FROM TAIWANESE *CALLOPHYLLUM BLANCOI*

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Chromatographic fractionation of the acetone extract of the seeds of *Calophyllum blancoi* yielded six pyranochromanone derivatives; apetalic acid, isoapetalic acid, apetalic acid methyl ester, apetalic acid 5-*O*-acetate, isoapetalic methyl ester, isoapetalic acid 5-*O*-acetate. In addition, one new dihydrocoumarin derivative, isorecedensolide, was also isolated together with recedensolide. Phytochemical investigation of the roots of *C. blancoi* resulted in the isolation of five pyranoxanthone derivatives. Three of the isolated xanthones are novel, blancoxanthones A-C. The structures of the isolated compounds were established through analysis of NMR spectral data including 2 D techniques as well as other physical and spectroscopic methods. Blancoxanthone A and apetalic acid exhibited significant anti-coronavirus activity

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ANTIFUNGAL CYCLOPENTENEDIONES FROM *PIPER CORUSCANS*

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In our search for new prototype antifungal agents, preferably with novel mechanisms of action, from higher plants, the ethanol extract of the whole Peruvian plant, *Piper coruscans* demonstrated antifungal activity against *Candida albicans* with IC_{50} of 2 μg/mL. No previous phytochemical or biological studies have been reported on this plant. A subsequent antifungal bioassay-guided fractionation of this extract led to the identification of two new cyclopentenedione derivatives, coruscanones A and B. Their structures were elucidated by spectroscopic analysis and total synthesis. Coruscanone A exhibited significant antifungal activity against *C. albicans* and its azole-resistant strains, comparable to amphotericin B and fluconazole. Owing to its strong antifungal potency, selectivity, acceptable *in vitro* cytotoxicity, unique structural feature, and easy accessibility by total synthesis, coruscanone A may serve as a template for a new class of antifungal agents. In addition, synthesis of 2-methoxy-5-methyl-3-styryl-1,4-benzoquinone as part of the coruscanone A structure elucidation provides an alternative method for preparation of styryl benzoquinone derivatives.

P:534

ISOLATION AND CHARACTERISATION OF 1,2,3,4,6-PENTAGALLOYL GLUCOSE AN ANTIMYCOBACTERIAL AGENT FROM THE LEAVES OF *ENTANDROPHRAGMA ANGOLENSE.*

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Tuberculosis (TB) has been declared one of the leading killer infectious diseases worldwide. The emergence of multi-drug resistant strains of *Mycobacterium tuberculosis* has raised an urgent need for new chemotherapies for the treatment of such MDR strains.
The methanolic extract of the leaves of ***E. angolense*** , a Nigerian medicinal plant was found to be active against M.tuberculosis (H_{37RV}) in our evaluation of some Nigerian medicinal plants for antimycobacterial activity. Fractionation of the extract yielded pentagalloyl glucose. Its structure was determined by LC-MS, and ^{1}H,^{13}C NMR techniques. Pentagalloyl glucose exhibited activity against M. tuberculosis at a concentration of 0.665µmoles/ml. This compound is reported for the first time from this plant.

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ANTI-STAPHYLOCOCCAL AND CYTOTOXIC COMPOUNDS FROM HYPTIS PECTINATA

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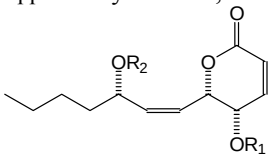
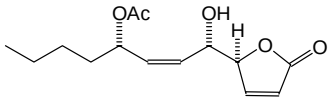
Bioassay-guided fractionation of a $CHCl_3$ extract prepared from *Hyptis pectinata* led to the isolation of four pyrones, pectinolides A-D (**1–4**). Activity was tracked using multidrug-resistant strains of *Staphylococcus aureus*. The absolute stereochemistry of the novel compound pectinolide D was established as 5*S*-[(4*S*-acetyloxy)-(1*S*-hydroxy)-2*Z*-octenyl]-2(5H)-furanone on the basis of spectral, chiroptical and chemical correlation with pectinolide A. Mosher ester derivatives were used with pectinolide B (**2**) for the stereogenic center C-3'.

This research was partially supported by DGAPA, UNAM (IN2009022) and The Royal Society.



1 $R_1 = R_2 = Ac$
2 $R_1 = Ac,\ R_2 = H$
3 $R_1 = H,\ R_2 = Ac$
5 $R_1 = Ac,\ R_2 = MTPA$



4

P:536

CHEMICAL ANALYSIS OF THE LIPOPHYLIC RESIN GLYCOSIDES FROM IPOMOEA PES-CAPRAE

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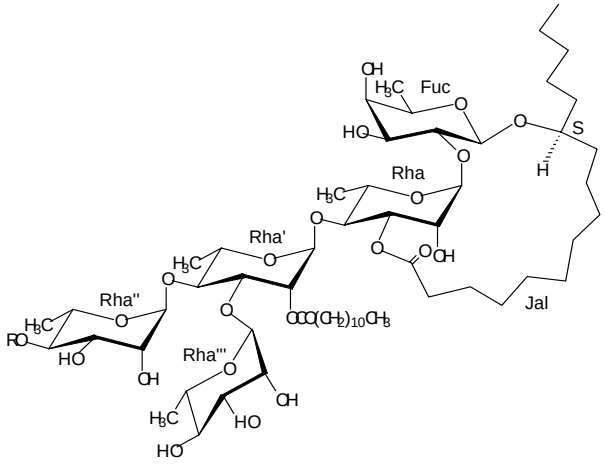

Pesacaprein I R = H
Pesacaprein II R = 2-methylpropanoyl
Pesacaprein III R = (2*S*)-methylbutanoyl
Pesacaprein IV R = *n*-hexanoyl

This research was supported by DGAPA, UNAM (IN2009022 and IX234504).

P:537

PHENOLIC METABOLITES OF THE 'SMOKE TREE' *DALEA SPINOSA* (FABACEAE) POTENTIATE ACTIVITY AGAINST MULTI-DRUG RESISTANT ORGANISMS

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As part of a continuing investigation of the genus *Dalea*, extraction and chromatography of *Dalea spinosa* (Fabaceae) A. Gray (syn: *Psorothamnus spinosus*), collected in the Anza-Borrego Desert of California, was undertaken. This study has resulted in the isolation of phenolic compounds, including a new aldehyde-containing 2-arylbenzofuran, with multi-drug resistant (MDR) inhibitory activity against bacteria. The morphology of *Dalea* spp. typically progresses from herbs, in the Eastern United States, to shrubs, in the West. *D. spinosa* the 'smoke tree' grows up to 25 feet in height and is the largest member of this genus. The metabolites observed in *D. spinosa* are consistent with those found in other *Dalea* spp. Our methods of purification consisted of open column chromatography and selective precipitation, with the guidance of thin layer chromatography and ^{1}H NMR spectroscopy. Compound structures were determined primarily by NMR spectroscopy and mass spectrometry. Details of this work will be described in this poster, as well as the results of testing for antibiotic and antifungal activity against multi-drug resistant organisms.

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PHARMACOGNOSICAL STUDIES ON NATURAL PRODUCT (I) - STUDIES ON EFFICACY COMPONENT ISOLATION AND STRUCTURAL DETERMINATION OF HOVENIAE SEMEN CUM FRUCTUS

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According to the traditional herbal medicine, *Hovenia dulcis* is neutral in nature, sweet and sour in flavor, and has biological effects like defervescence, diuresis, and alcohol detoxification. Two known compounds, ferulic acid (**1**) and myricetin (**2**), have been isolated from fractionated 70% methanolic extracts of Hovenia dulcis. To facilitate further pharmacological research and develpoment in this area, we have summarized the progress of phytochemical and pharmacological research on the plants of the *Hovenia dulcis*. Compounds **1** and **2** are known but are first isolated from the *Hovenia dulcis*. In MTT bioassay, compound **2** exhibited activity.

P:539

CHEMICAL CONSTITUENTS FROM THE NEUTRAL FRACTION OF *OCOTEA LEUCOXYLON*

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Ocotea leucoxylon, collected in Jamaica, is a member of the Lauraceae family and the bark of this plant is a source of aporphine and oxoaporphine alkaloids. The neutral extract isolated from the stem of this plant did not show biological activity, but phytochemical investigation of this fraction resulted in the isolation of 1-hydroxy-3, 6-dimethoxy-8-methylxanthone, sitosterols and two oxoaporphine alkaloids in minute amounts. The isolation procedure and structural determination of these compounds by spectral methods will be presented.

P:540

A NEW DAMMARANE TRITERPENE FROM *RHUS CHINENSIS* MILL.

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Rhus chinensis Mill. (Anacardiaceae) is widely distributed in Korea, Japan and China. Its barks and leaves have been used traditionally as dysentery and diarrhea remedies in Korea. Recently antioxidative, postprandial hypoglycemic, hepatoprotective and antineoplastic effects of *R. chinensis* Mill have been studied. During phytochemical studies on *R. chinensis* Mill., a new dammarane triterpene, 3-oxodammar-20,24*E*-dien-26-oic acid, was isolated together with the known compounds semialactone and β-sitosterol from the ethyl acetate extract of the stems. We report here on the isolation and structure elucidation of them.

The compounds were isolated and purified by silica gel column chromatography using hexane/ethyl acetate. Their structures were determined by the means of mass and NMR spectral techniques including ^{1}H, ^{13}C, ^{1}H-^{1}H COSY, HMQC and HMBC.

P:541

CYTOTOXIC ISOPRENYLATED COUMARINS FROM *MAMMEA AMERICANA*

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Activity-guided fractionation of *Mammea americana* seeds resulted in the identification of three new isoprenylated coumarins, mammea B/BA hydroxycyclo F (**1**), mammea E/BC (**2**), and mammea E/BD (**3**). In addition, twelve known isoprenylated coumarins, mammea B/BA (**4**), mammea B/BB (**5**), mammea B/BC (**6**), mammea B/BD (**7**), mammea B/BA cyclo F (**8**), mammea E/BA (**9**), mammea E/BB (**10**), mammea A/AA (**11**), mammea A/AA cyclo D (**12**), mammea A/AA cyclo F (**13**), mammea A/AC cyclo D (**14**), and mammea A/AD cyclo D (**15**), as well as two known flavonols, (+)-catechin and (-)-epicatechin, were identified. The coumarin compounds **2**, **3**, **4**, **5**, **9**, **10**, and **13** display high cytotoxicity in the SW-480 and HT-29 human colon cancer cell lines (IC_{50} range 4.8 – 10.5 μg/mL). The cytotoxicity of the remaining 8 coumarin compounds are being tested currently. This research was supported by the funds from the NIH-National Institute of General Medical Sciences SCORE award S06GM08225 and the Professional Staff Congress of The City University of New York (PSC-CUNY) award 669662.

P:542

NOVEL BIOACTIVE BENZOPHENONES FROM GARCINIA XANTHOCHYMUS FRUITS

Scott Baggett,[1] Petr Protiva,[2] Eugene P. Mazzola,[3] Hui Yang,[1] Elizabeth T. Ressler,[3] Margaret J. Basile,[4] I. Bernard Weinstein,[2] and Edward J. Kennelly*,[1]

[1]Department of Biological Sciences, Lehman College and The Graduate School and University Center, The City University of New York, Bronx, NY 10468, [2]Herbert Irving Comprehensive Cancer Center, College of Physicians and Surgeons of Columbia University, New York, NY 10032, [3]Department of Chemistry and Biochemistry, Joint Institute for Food Safety and Applied Nutrition, University of Maryland, College Park, MD 20742, [4]Department of Neurology, University of Miami School of Medicine, Miami, FL 33136

A MeOH extract of *Garcinia xanthochymus* fruits was subjected to activity-guided fractionation yielding two new benzophenones guttiferone H (1) and gambogenone (2). Compound 1 contains a 7-membered ring attached to the bicyclo[3.3.1]nonane ring system at positions 7 and 8 and displayed cytotoxicity in the SW-480 colon cancer cell line (IC_{50} = 12 μM). Compound 2 has a novel benzophenone bicyclo[3.3.2]decane ring system and a IC_{50} = 188 μM. The structures of compounds 1 and 2 were established by extensive 1D and 2D NMR data analysis. Eleven known compounds, aristophenone A, xanthochymol, guttiferone E, cycloxanthochymol, isoxanthochymol, alloathyriol, amentoflavone, 3,8″-biapigenin, (+/-)-fukugetin, (+/-)-fukugiside, and (+/-)-volkensiflavone were also obtained. This work is supported in part by the NIH-NIGMS SCORE award S06GM08225. Scott Baggett is supported by NIH-NCCAM NRSA F31-AT00062.

P:543

SCREENING AND DEREPLICATING A PLANT EXTRACT LIBRARY FOR SKIN WHITENING AGENTS

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The presentation implements a strategy that combines a tyrosinase inhibition assay with a chemical dereplication process to identify active compounds within plant extracts that specifically inhibit tyrosinase protein function and may lead to reduction of melanin production and effect of skin lightening. A total of 1144 plant extracts were screened for their ability to inhibit mushroom tyrosinase. This primary screen identified 20 plant extracts (1.75% hit rate) with potent tyrosinase inhibition activities in dose responses that have been further fractionated and dereplicated. A total of seven active extracts were chosen for bioassay guided large-scale isolation and purification. Three diarylalkanes were isolated and identified from two different species of plants as novel and potent inhibitors of tyrosinase enzyme with IC_{50} values from 0.25 to 24μM. Molecular mechanics (MM2) was utilized to calculate energy minimization for locating stable conformation of the active diarylalkanes that had shown a very unique 3-dimentional conformation with two aromatic rings superimposed to each other. It was hypothesized that diarylalkanes would tightly bind to dual copper ions [Cu^{II}-O2—Cu^{II}] at the active site of the binuclear enzyme. This theory was further evaluated by synthesized diarylalkane derivatives. Compound isolation, identification, synthesis, evaluation of structure and activity relationships, and kinetics of enzyme inhibition will be presented in details.

P:544

MOLECULAR-TARGETED ANTITUMOR AGENTS: *SAURURUS CERNUUS* DINEOLIGNANS ARE POTENT INHIBITORS OF HYPOXIA-ACTIVATED HIF-1

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Department of Pharmacognosy, National Center for Natural Products Research, RIPS, School of Pharmacy, University of Mississippi, University, MS, 38677-1848.

The transcription factor hypoxia-inducible factor-1 (HIF-1) is a key regulator of tumor cell adaptation and survival under hypoxic conditions. Selective HIF-1 inhibitors represent an important new class of potential molecular-targeted antitumor therapeutic agents. Extracts of plants and marine organisms were evaluated using a T47D human breast tumor cell-based reporter assay for HIF-1 inhibitors. Bioassay-guided fractionation of the lipid extract of *Saururus cernuus* resulted in the isolation of dineolignans known as manassantins. Manassantins also show an high level of tumor cell-specific growth inhibitory effect in NCI 60-cell line evaluation. Manassantins are among the most potent small molecule HIF-1 inhibitors discovered, to date, with IC_{50} values as low as 3 nM. Manassantins selectively inhibit hypoxia-activated HIF-1 in contrast to iron chelator-activated HIF-1. Further study revealed that these compounds selectively block the induction of HIF-1α protein, the oxygen regulated HIF-1 subunit that determines HIF-1 activity. Manassantins also inhibit hypoxic induction of the angiogenic factor VEGF.

P:545

PHYTOCHEMICAL INVESTIGATION OF ZANTHOXYLUM SYNCARPUM

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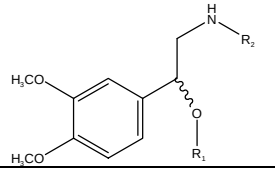
The genus *Zanthoxylum* comprises about 200 species distributed worldwide. Z. species are used medicinally as antimalarial, antihelminthic and other uses in cosmetics and in insecticides. *Zanthoxylum sncarpum* is known as little lemon. Previous studies on the leaves and roots of Z. syncarpum resulted in the identification of several compounds including alkaloids, coumarins, terpenes and glycosides.
Recently, a new antiplasmodial (+) Norepinephrine derivative (an alkaloid, Syncarpamide) was isolated from the bark of *Zanthoxylum syncarpum.* Our work focuses on the leaves and we have isolated a new compound (**1**), and its structure was determined by X-ray crystallography, 1D and 2D NMR, IR, UV, CD, Optical rotation and mass spectrometry. Syncarpamide (**2**) was also isolated from the leaves. The third compound that was isolated is also a new alkaloid; its structure was also elucidated on the basis of spectral data and chemical correlation. Acetylation of **1** yielded a compound identical to **3.** Biological activities of the three isolated compounds will be presented if available.



1 R_1= H, R_2= Cinnamoyl
2 R_1= R_2= Cinnamoyl
3 R_1= Acetate, R_2= Cinnamoyl

P:546

DPPH, NITRIC OXIDE AND PGE2 PRODUCTION INHIBITORY ACTIVITIES OF PHENOLIC COMPOUNDS FROM *SOPHORA JAPONICA* LINNE

H.-J. Kim, M.-G. Kim, J.-G. Shim, H.-W. Lim and M.-W. Lee*
College of Pharmacy, Chung-Ang University, Seoul, 156-756, Korea

Purpose. Investigation of anti-oxidation, anti-inflammation, anti-cancer effects of isolated compounds from *Sophorae Fructus*.
Methods. Several isoflavonoids, flavonoids and gallotannin including genistein **(1)**, sophoricoside **(2)**, genistein-4'-O-α-L-rhamnopyranoside **(3)**, genistein-4'-O-α-L-rhamnopyranosly-(1→2)-β-D-glucopyranoside **(4)**, kaempferol-3-O-β-D-sophoroside **(5)**, kaempferol-3-O-β-D-glucopyranosyl-(1→2), α-L-rhamnopyranosly-(1→6)-β-D-glucopyranoside **(6)**, rutin **(7)**, gallic acid 4-O-β-D-(6'-O-galloyl)-glucopyranoside **(8)** were isolated and characterized its chemical structures by UV, NMR, MS etc. Cell viability on RAW 264.7 cell was measured by MTT assay. Inhibitory activities for nitric Oxide (NO) and PGE_2 production inhibitory activities in Raw 264.7 cell stimulated by INF-γ(murine recombinant Interferon-γ, 10 ㎕) and LPS (lipopolysaccharide, 10 ㎕) were examined. NO and PGE_2 level in RAW 264.7 cell were assayed to verify the effect of isoflavonoids, flavonoids and gallotannin on NO and PGE_2 synthesis inhibition.
Results. MTT assay showed that non-cytotoxic ranges of these isoflavonoids, flavonoids and gallotannin on RAW 264.7 cell were 0 – 100 μg/ml. Compound **1 (IC_{50} = 55.99 μg/ml and 8 (IC_{50} = 50.53 μg/ml)** showed significant NO production inhibitory activity in RAW 264.7 cell stimulated by IFN-γ, LPS compared with positive control, L-NMMA **(IC_{50} = 45.17 μg/ml)**. Compound **1 (IC_{50} = 32.93 μg/ml)** and **8 (IC_{50} = 33.52 μg/ml)** also showed significant PGE_2 production inhibitory activity in IFN-γ, LPS stimulated RAW 264.7 cell compared with positive control, indomethacin **(IC_{50} = 42.57 μg/ml)**. Especially, compound **8 (IC_{50} = 9.11 μg/ml)** exhibited the potent anti-oxidative effect in all concentrations compared with positive control, L-ascorbic acid **(IC_{50} = 8.74 μg/ml)**.
Conclusions. These results suggest that the phenolic compounds that were isolated from the fruits of *Sophora japonica* might be developed as a anti-inflammatory and anti-oxidative agents.

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ANTICANCER CONSTITUENTS WITH CYTOTOXICITY AND TOPOISOMERASE INHIBITORY ACTIVITY FROM THE ROOTS OF *RUBIA CORDIFOLIA* L.

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From the screening experiment. Rubia cordifolia L. exhibited anticancer activity. MeOH extract of the roots of this plant was subsequently fractionated into four parts; CH_2Cl_2, EtOAc, n-BuOH and H_2O fractions. CH_2Cl_2 fraction showed the strongest cytotoxicity against HT-29 and MCF-7 cell lines, and DNA topoisomerases□ and □ inhibitory activities. We isolated furomollugin (**1**), mollugin(**2**), methyl 2,2-dimethyl-3,4-epoxy-6-Hydroxy-2H-naphtho[1,2-b] pyran-5-carboxylate(**3**), 3,3′-bis (3,4-dihydro-4-hydroxy-6-methoxy-2H-1-benzopyran(**4**) and 1-acetoxy-3-methoxy-9,10-anthraquinone(**5**) from the CH_2Cl_2 fraction. **3** and **5** were first isolated from natural source. In DNA topo I and □ assay, **5** showed 86.6 % and 86.2 % inhibition at the concentration of 50 ㎍/mL (equivalent to 10.96 ㎛), respectively. And In DNA topo □ assay, **2** and **3** exhibitied 95.7 and 74.4 % inhibition at the concentration of 50 ㎍/mL. IC_{50} value of **1** was obtained at 16.2 ㎍/mL for HT-29 cell line, that of **2** was at 17.1 ㎍/mL for HepG2 cell line, and that of **3** was at 12.4 ㎍/mL for MCF-7 cell line.

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CYTOTOXIC XANTHONES AND BIPHENYLS FROM THE ROOT OF *GARCINIA LINII*

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Garcinia linii C. E. Chang (Guttiferae) is a small endemic evergreen tree which grows on Lanyu Island and Green Island of Taiwan. The plants of genus *Garcinia* are rich in xanthonoids, depsidones, and benzophenones, some of which have demonstrated cytotoxic activities. However, the chemical constituents and biological activities of this plant have never been studied. In our continuing studies on the cytotoxic constituents of Formosan plants, over 1000 species have been screened for *in vitro* cytotoxicity to date, and *Garcinia linii* has been found to be one of the active species. Investigation on chloroform-soluble fraction of the root of this species has led to the isolation of three new xanthones, linixanthones A–C (**1**–**3**), two new biphenyls, garcibiphenyl A (**4**), garcibiphenyl B (**5**), and a new benzopyran, garcibenzopyran (**6**), together with twelve known xanthones and a known biphenyl. Among the isolates, linixanthone B, linixanthone C, globulixanthone D, 1,6-dihydroxy-5-methoxyxanthone, and 1,7-dihydroxyxanthone exhibited effective cytotoxicities (ED_{50} values < 4 μg/ml) against P-388 and HT-29 cell lines. In this congress, the structural elucidation of **1**–**6** and the cytotoxic activities of the isolates will be discussed.

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CYTOTOXIC DIHYDROCHALCONE AND FLAVONOIDS FROM THE LEAVES OF *MUNTINGIA CALABURA*

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Muntingia calabura L. (Tiliaceae) is an evergreen tree, distributed in tropical America and introduced and cultivated in southern Taiwan. Among the constituents of the Tiliaceae, the flavonoids are an important group of compounds. The plant is rich in flavones, flavanones, flavans, and biflavans. As a series of studies on the active constituents of cytotoxic principles of Formosan plants, *M. calabura* was one of the active species. Investigation on $CHCl_3$-soluble fraction of the leaves of Formosan species led to the isolation and characterization of a new dihydrochalcone: 2',4'-dihydroxy-3'-methoxydihydrochalcone (**1**), and a new flavonoid, 8-hydroxy-10-methoxy-6a,12a-dihydro-5*H*-isochromeno[4,3-b]chromen-7-one (**2**), along with ten known compounds, including seven flavonoids: 5-hydroxy-7-methoxyflavone (**3**), 3,7-dimethoxy-5-hydroxy- flavone (**4**), 5-hydroxy-3,6,7-trimethoxyflavone (**5**), 6,7-dimethoxy-5-hydroxyflavone (**6**), 3,5-dihydroxy-6,7-dimethoxyflavone (**7**), 3,5,7-trihydroxyflavone (**8**); three steroids: β-sitostenone (**9**), a mixture of β-sitosterol (**10**) and stigmasterol (**11**); and one benzoquinone: α-tocopheryl quinone (**12**). The structural elucidation of **1**–**2** and the cytotoxic activities of the isolates will be discussed in this congress.

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CYTOTOXIC CONSTITUENTS FROM STEM BARK OF *JUNIPERUS VIRGINIANA* L.

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Bioassay-guided extraction and fractionation of the stem bark of ***Juniperus virginiana*** L. (*Cupressaceae* family), using a panel of human cancer cell lines [lung carcinoma (A549), colon adenocarcinoma (HT29), breast adenocarcinoma (MCF-7), melanoma (RPMI7951), gliobastoma multiforme (U251)] and a DNA topoisomerase inhibition assay, resulted in the isolation of twelve compounds of which eleven were known diterpenes including abietatriene, agathic acid, communal, communic acid, continentalic acid, 6,7-dehydroferruginol methyl ether, didehydroferruginol, ferruginol, hinokione, isocupressic acid, sugiol, and one lignan, deoxypodophyllotoxin. Compounds were identified by spectral analysis (including IR, UV, MS, and NMR). Using for MCF-7 cell line and DNA topoisomerase inhibition, we measured the activity of fractions and compounds from the active dichloromethane fraction. Based on this, it was concluded that the activity was due to the presence of the known cytotoxic agent, deoxypodophyllotoxin.

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NOVEL AND BIOLOGICAL ACTIVE DITERPENOIDS FROM DIFFERENT EUPHORBIA

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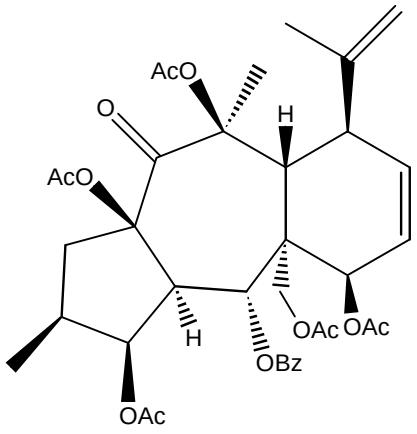
Plants of the genus *Euphorbia* have been investigated for different bioactive natural products. I have isolated several new diterpenoids from different species of *Euphorbia* of Iran with myrsinane type skeleton.
In this paper I will describe isolation and structure elucidation of Decipinone and related diterpenoids from E. decipiens, E. teheranica, E. cheiradenia and E. Marschalliana.
Some of them showed enzyme inhibitory activity against α-glucosidase, prolyl endopeptidase, analgesic activity, DNA damaging activity and anti-HIV-1 reverse transcriptase



decipinone

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NEW CARDENOLIDE AND PREGNANE GLYCOSIDES FROM *PERIPLOCA GRAECA*

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Periploca graeca L. (Asclepiadaceae) is a perennial liana occurring wild in South-East European and West-Asian countries.[1] The decoction of the plant's leaves and bark is used in folk Italian medicine to prepare cardiotonic, hypertensive, diuretic, and purgative remedies.[2] Previous study on the aerial parts of the plant led to the isolation of flavonoids,[3] while cardenolides and pregnane glycosides, of which some showed antitumoral activity, have been reported from the genus *Periploca*.[4] In this work we report the isolation and structural characterization of some new and known cardenolide and pregnane glycosides from the aerial parts of *P. graeca* by means of 1D- and 2D-NMR experiments. The antiproliferative activity of cardenolides was evaluated on human prostate cancer cell lines. A significant antiproliferative activity on the PC3 cell line, which is insensitive to the action of androgens, has been shown.

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NEW PHENOLIC DERIVATIVES FROM *VERNONIA MAPIRENSIS*

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Vernonia genus (Asteraceae family) comprises tropical and sub-tropical species widespread through both the hemispheres.[1] Previous phytochemical studies on this genus led to the isolation and characterization of flavonoids, stigmastane glycosides, and sesquiterpenes.[2,3] *V. mapirensis* (synonymous *Lepidaploa densipaniculata*) is a species native to Bolivia where is used traditionally for the preparation of anti-inflammatory remedies. In this work we report the isolation and structural characterization by means of spectroscopic analyses (NMR and MS data) of some new phenolic derivatives, from the aerial parts of the plant. Pure isolated compounds were tested for their antioxidant activity on lipid peroxidation and on TEAC test. The possible protective role played by compounds on injurious effects of reactive oxygen metabolites on the intestinal epithelium, using Caco-2 human cell line, was investigated. The H_2O_2-induced alterations were prevented by preincubation with compounds.

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IRIDOID GLUCOSIDES FROM *STRYCHNOS SPINOSA*

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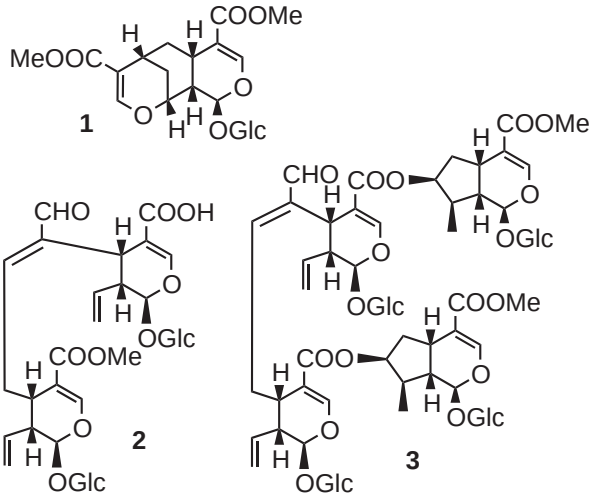
The genus *Strychnos* (Loganiaceae) is well known to contain various bioactive indole alkaloids represented by strychnine. *S. spinosa* is a thorny shrub or small tree distributed in Africa. Various parts of the plant have been used in African traditional medicine. From our interests in indole alkaloids and the related glycosides, we examined the glycosidal fraction of *S. spinosa.*
An investigation of the methanol extract of the branches of *S. spinosa* cultivated in Kyoto led to isolation of three new iridoid glucosides **1** - **3** along with several known iridoid, aromatic, and flavonoid glycosides. The structures of **1** - **3** were elucidated by means of spectroscopic methods, such as SIMS, ^{1}H-NMR, ^{13}C-NMR and 2D-NMR techniques.



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PHENOLIC CONSTITUENTS FROM *CEPHALOTAXUS KOREANA*

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Cephalotaxus spp. is well known for possessing ester type cephalotaxus alkaloids and a number of ester type alkaloids have been reported from *Cephalotaxus harringtonia*. However, there is little information about other constituents such as phenylpropanoids, and norisoprenoids isolated from *Cephalotaxus* spp. Hence, we report two new flavonoids and one lignan, 8-methyl aromadendrin-3-*O*-*β*-D-glucopyranoside (**1**), apigenin-5-*O*-*β*-D-(2-*O*-*a*-L-rhamnopyranosyl)glucopyranoside (**2**), 3,4,7,9,9'-pentahydroxy-3'-methoxy-8-*O*-4'-neolignan (7*S*,8*R* erythro form) (**3**), respectively, and five known compounds, junipediol A (**4**), junipediol A 8-*O*-*β*-D-glucopyranoside (**5**), roseoside (**6**), 4,7,9,9'-tetrahydroxy-3,3'-dimethoxy-8-*O*-4'-neolignan (7*S*,8*S* threo form) (**7**) and 4,7,9,9'-tetrahydroxy-3,3'-dimethoxy-8-*O*-4'-neolignan (7*S*,8*R* erythro form) (**8**) from *Cephalotaxus koreana* Nakai.

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TWO NEW IRIDOIDS FROM THE AERIAL PARTS OF *PAEDERIA SCANDENS*

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Paederia scandens (Lour.) Merr. is a climbing plant, distributed in southern region of Korean Peninsula, Vietnam, India, China, Japan, the Philippines, and the USA. The roots, leaves, bark, and fruits of this plant have been used to treat jaundice, dysentery and dyspepsia in Korea. Also, it was reported that paederoside and asperuloside from this plant exerted an inhibitory effect on Epstein-Barr virus activation. In this paper, we report the isolation and structural elucidation of two new acylated iridoids along with the six known iridoids from the aerial parts of this plant. The MeOH extract of the aerial parts of *P. scandens* was suspended with water, and then partitioned with *n*-hexane, CH_2Cl_2, EtOAc, and *n*-BuOH, successively. The *n*-BuOH soluble fraction was separated by a series of SiO_2, reversed-phase C_{18} MPLC, Sephadex LH-20, and reversed-phase C_{18} HPLC to give two new acylated iridoids (**1** and **2**) and six known iridoids that were identified as daphylloside (**3**), paederoside (**4**), paederosidic acid methyl ester (**5**), deacetylasperuloside (**6**), 6α-hydroxygeniposide (**7**), and paederosidic acid (**8**), with the aid of spectroscopic methods.

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CYTOTOXIC FLAVONOIDS AND NEW CHROMENES FROM *FICUS FORMOSANA* F. *FORMOSANA*

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Ficus formosana Maxim. f. *formosana* (Moraceae) is a small evergreen tree with long obovate leaves, which is distributed in Mainland China, Hong Kong, Vietnam and in the broadleaved forests throughout Taiwan.
Investigation of the cytotoxic $CHCl_3$-soluble layers from stems of this plant led to the isolation of ten compounds, including three chromenes: alloptaeroxylin (**1**), ficuformodiol A (**2**), ficuformodiol B (**3**); five flavonoids: carpachromene (**4**), 5-hydroxy-8,8-dimethyl-2-phenyl-8*H*-pyrano[3,2-*g*]chromen-4-one (**5**), apigenin (**6**), steppogenin (**7**), glabranin (**8**); one benzopyran: chromenylacrylic acid (**9**); one isocoumarin: (*R*)-(-)-mellein (**10**). The structures of these compounds were determined by spectroscopic analysis.
Among these isolates, ficuformodiol A (**2**) and B (**3**) are new chromenes from nature.
Carpachromene (**4**) and apigenin (**6**) exhibited cytotoxicity against HepG2 [human hepatoma: HBV Ag (-)], PLC/PRF/5 [human hepatoma: HBV Ag (+)] and Raji (lymphoma) cancer cell lines *in vitro*.

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MELANOGENESIS INHIBITORS ISOLATED FROM THE RHIZOMES OF *CURCUMA LONGA*.

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Melanogenesis is a physiological process resulted in the synthesis of melanin pigment at the melanocyte, it involves a metabolic pathway beginning with the oxidation of tyrosine to an orthoquinone, dopaquinone, followed by a series of divergent steps that give rise to a predominantly indolic pigment (eumelanin) and a closely related pigment containing benzothiazine subunits (phaeomelanin). The current view is that most human pigmentation involves a combination of these pathways giving rise to mixtures of varying composition (α-MSH, TRP-1,TRP-2 etc.).
We have focused on research of rate-limiting enzyme, tyrosinase inhibitors and furthermore inhibition of melanogenesis induced by α-MSH in B-16 mouse melanoma cell.
Curcuma longa was found out persuasive inhibition on tyrosinase activity and melanogenesis B-16 mouse melanoma cell lines.
Eleven compounds were isolated and elucidated as 4-Hydroxy-3-methoxycinnamaldehyde(1), Methyl 3,4-dihydroxycinnamate(2), *p*-Hydroxycinnamic acid(3), 4-(3',4'-Dimethoxyphenyl)-3-buten-2-one(4), Bidemethoxycurcumin(5), Demethoxycurcumin(6), Curcumin(7), 2,10-Bisaboladien-1,9-dione(8), 2-Hydroxy- 1,3,5,10-bisabolatetraen-9-one(9), 3-Hydroxy-1,10-bisaboladien-9-one(10), 4-(R)-Hydroxy-1,3(15),10- bisabolatrien-9-one(11) by NMR techniques.

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BIOACTIVITY GUIDED ISOLATION OF POTENTIAL ANTIINFECTIVE PEPTIDE ALKALOID FROM SPHAERANTHUS INDICUS AND EVALUATION OF ITS ANTITUMOR ACTIVITY ON MOUSE EHRLICH ASCITES CARCINOMA IN VIVO

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Sphaeranthus indicus L.(Compositae) is a much branched herb with purple flowers that grows plentifully in the fields of Northern and Southern India. It is used in folk medicine as remedy for various ailments including dysentery, pain in the uterus and vagina, diseases of the chest, purification and enrichment of blood, urinary tract infection, wound healing and several other diseases. We report here the bioactivity guided isolation of novel peptide alkaloid and its efficacy as cytotoxic agent.
Dichlormethane: methanol (1:1) (DCM) extract of various parts of *S. indicus* was evaluated for antimicrobial activity against a battery of microorganisms including bacteria and fungi by agar streak method. Chemoprofiles of the extract were established by High Performance Thin Layer Chromatography. Bioautographic studies were carried using various test and clinical isolates of microorganisms.
Cytotoxicity and inhibition of cell proliferation was evaluated against HepG2, HEp2 and HeLa cell lines by MTT assay. Further bioactivity guided fractionation of the extract was carried out and the bioactive compound was isolated. The structure of this isolated compound has been elucidated on the basis of H, C^{13} NMR, Mass, X-ray crystallographic studies and was found to be a peptide alkaloid.
The antitumor activity of this Peptide alkaloid was studied on Ehrlich ascites carcinoma in vivo and was found to be effective in controlling the tumor cell proliferation. Results of these studies will be discussed.

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COMPARISON OF THE VOLATILE OILS OF SATUREJA ATROPATANA BUNGE. AND SATUREJA MUTICA FISCH. ET C. A. MEY. FROM IRAN

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To the genus Satureja (Lamiaceae , tribe Mentheae) belong about 200 species of herbs and shrubs often aromatic,widely diffused in Mediterranean area,Asia and boreal America. The flora of Iran comprises12 species of Satureja, of which 8 are endemic.Some Satureja species are used as flavouring agents and for medical purposes,e.g. an infusion of the aerial parts of S. boliviana is used as a digestive, an anti-spasmodic and in the treatment of colds. An infusion of the aerial parts of S. brevicalix is used as a digestive, a gastralgic, an anti-spasmodic and to help in parturition. S. kitaibelii is used to treat bronchitis in adults and children and skin, respiratory, digestive and Urinary inflammation. An infusion of S. brownei is used as a remedy for respiratory diseases and cough.The oil obtained by hydrodistillation of the aerial parts of Satureja atropatana Bunge., endemic in Iran, and S. mutica Fisch. et C. A. Mey. Was analyzed by GC/MS. Thirty seven compounds representing 99.3% of the oil of S. atropanata were identified, among them carvone (21.5%),menthol (18.1%), 1,8–cineol (13.1%), methyl chavicol (11.1%) and menthone (10.5%) being the major ones. The oil of S. mutica was characterized by higher amount of also menthol (37.4%), menthone (17.2%) and 1,8–cineol (9.3%) among the thirty nine components comprising 95.1% of the total oil detected. Both oils were richer in oxygenated monoterpenes than sesquiterpenes.

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ISOLATION AND IDENTIFICATION OF FLAVONOIDS FROM ACHILLEA BIEBERSTEINII AFAN. POPULATION GOLESTAN,IRAN

Nargess Yassa*, Farnaz Noghreh Nikbakht

The genus Achillea is well known for medicinal properties such as anti-inflammatory and inhibition of bacterial growth. A.biebersteinii Afan. grows widely in the north, northeast and central parts of Iran. In this research we have studied MeOH extract of A. biebersteinii for flavonoids. The plant was collected in June 2001 from Golestan province. The dried and powdered top flowered of plant was extracted by percolation with MeOHl–water (80-20) and solvent was evaporated under reduced pressure. This extract was washed with petrol ether and $CHCl_3$ and the residue was chromatographed on Watman No.3 paper using 15% AcOH and BAW (4:1:5) as solvent respectively. The spots were detected under UV fluorescent at 365 nm. before and after exposure to ammonia fumes, and after isolation were identified by UV, MS and NMR spectroscopic methods as:6-methyl-8-hydroxy kaempferol-7-O-rhamnoglycoside,6-hydroxy-8-methyl kaempferol -4'-O-glycoside and quercetin-7, 4'-diglycoside.

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CONSTITUENTS OF THE ESSENTIAL OILS OF STACHYS PILIFERA BENTH. FROM IRAN

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Stachys is one of the important species in Lamiaceae family. It comprises about 200 species found in mild regions of the Mediterranean and southwest Asia. It is represented by thirty-four species in the flora of Iranica which eighteen of them are endemic species. *Stachys pilifera* Benth (Lamiaceae) is one of the endemic plants of this genus, which has been distributed in many regions of Iran. Aerial parts of *S. pilifera* Benth.were collected from two regions, from Kazeroon in south and Shahr-e-kord in west of Iran.The aerial parts were air dried at ambient temperature in the shade and steam distilled by using a Clevenger-type apparatus for 4 hours. The yield of oil of the plant collected from Kazeroon (1) and Shahr-e-kord (2) were 0.12% and 0.08%, respectively. The composition of the oils of *S. pilifera* (Lamiaceae) was investigated by GC and GC/MS. The main components of the oil of *S. pilifera* collected from Kazeroon (1) in south of Iran were spathulenol (15.8%), cis-chrysanthenol (15.3%), β-caryophyllene (8.4%) and cis-chrysanthenyl acetate (6.9%), while for the plant collected from Shahr-e-kord (2) in west of Iran they were cis-chrysanthenyl acetate (21.8), linalool (18.9%), terpinen-4-ol (11.9%) and cis-chrysanthenol (9.2%).

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NEW CYTOTOXIC NORDITERPENE DILACTONES FROM LEAVES OF *PODOCARPUS MACROPHYLLUS* VAR. *MAKI*

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Eleven new nor- and bisnorditerpene dilactones, S_R-podolactone D (**1**), rakanmakilactones A-J (**2**-**11**), and one new norditerpene dilactone apioside (**12**) were isolated from a MeOH extract of the leaves of *Podocarpus macrophyllus* D. Don var. *maki* Endl. of the family Podocarpaceae.

The structures of these new compounds were established by spectroscopic studies, including 1D and 2D NMR spectral analysis, and single-crystal X-ray crystallographic analysis.

Those rakanmakilactones from this plant were found to have a cytotoxic effect on P388 murine leukemia cells.

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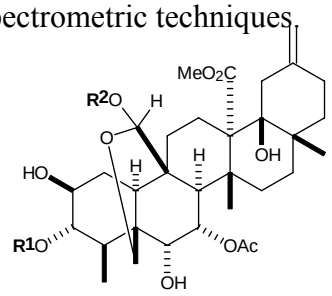
STRUCTURAL ELUCIDATION OF THE NOVEL GLAUCACETALINS A–C, NOR-FRIEDELANES PRODUCED BY HAIRY ROOTS OF THE SEDATIVE PLANT GALPHIMIA GLAUCA

Alexandre T. Cardoso Taketa[1], Blanca L. Nader,[2] María Luisa Villarreal, [2*] Rogelio Pereda-Miranda[1*].
[1]Departamento de Farmacia. Facultad de Química, Universidad Nacional Autónoma de México, Ciudad Universitaria, 04510 DF, Mexico City, MEXICO. [2]Centro de Investigación en Biotecnología, Universidad Autónoma del Estado de Morelos, Av. Universidad 1001, Chamilpa, 62210. Cuernavaca, Morelos, MEXICO.

Hairy roots of the medicinal plant *Galphimia glauca* transformed through infection with *Agrobacterium rhizogenes* produced the novel nor-friedelanes glaucacetalins A–C (**1**–**3**), which were excreted into the nutrient media. These compounds were elucidated by high resolution spectroscopic and spectrometric techniques.



	R^1	R^2
1	Ac	H
2	H	CH_3
3	H	H

This research was supported by Consejo Nacional de Ciencia y Tecnología (35459–B) and Dirección General de Asuntos del Personal Académico, UNAM (IN200902–2).

P:565

CRYSTAL STRUCTURE OF TRICOLORIN A: MOLECULAR RATIONALE FOR THE BIOLOGICAL PROPERTIES OF CONVOLVULACEOUS RESIN GLYCOSIDES

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Tricolorin A is the first natural resin glycoside whose structure has been determined. This major lipopolysaccharide from *Ipomoea tricolor* is singularly complex in that it is assembled from simple metabolic building blocks to create a tetrasaccharide macrolactone with significant mammalian and plant cytotoxicity correlatable to its peculiar amphiphilic structural features. The sample crystals, grown at the interface between PEG200/water solution and mineral oil, belong to the monoclinic space group P21, of which each asymmetric unit has four independent molecules of the glycolipid and 18 water molecules. The conformation of the molecule resulted in the clustering of the hydrophobic groups on one face of the disk-like molecule, facing hydrophobic clusters from other molecules. This arrangement directs the packing so that the hydrophilic faces formed a water channel. This resulting architecture is compatible with the size of any biological membrane and could provide a rationale for the pore-forming-based

cytotoxicity displayed by this class of compounds through a transmembrane insertion model.

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NOVEL ISOCOUMARINS AND A CHROMAN-4-ONE FROM THE RHIZOSPHERE FUNGUS, PARAPHEOSPHAERIA QUADRISEPTATA

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In a study to discover biologically active metabolites from the rhizosphere microflora of Sonoran desert plants, a cytotoxic EtOAc extract of the fungus, *Parapheosphaeria quadriseptata*, occurring in the rhizosphere of the Desert Christmas Cactus (*Opuntia leptocaulis* DC.) was investigated. Bioactivity-guided fractionation of this extract afforded monocillin I as the only cytotoxic constituent. Investigation of the non-cytotoxic fraction afforded three minor but novel isocoumarins, paraphaeosphaerins A – C, biogenetically related to monocillin I, and a new chroman-4-one. Isolation and structure elucidation, including the determination of stereochemistry, of paraphaeosphaerins A – C and the chroman-4-one, and the biosynthetic relationships of monocillin I and paraphaeosphaerins will be presented.

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BIOACTIVE AND OTHER CONSTITUENTS OF *MELAMPODIUM LEUCANTHUM*

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As a part of an ongoing search for bioactive agents from plants of the Sonoran desert, we have investigated a cytotoxic methyl ethyl ketone extract of *Melampodium leucanthum* Torrey & Gray (Asteraceae) collected in the Santa Rita Mountains in Arizona. Bioactivity-guided fractionation of this extract yielded four cytotoxic melampolides (germacranolides) and two non-cytotoxic diterpene lactones. One of the cytotoxic melampolides was new and this was identified as 9-desacetyl uvedalin. Other cytotoxic melampolides included melampodin A, acetyl melampodin A, and leucanthin B whereas the diterpene lactones were identified as 6,7-dihydroxy-1,17-diacetoxymelcantholide and 1,6,7-trihydroxy-17-acetoxymelcantholide. Bioactivity-guided fractionation and structure elucidation of these compounds and the cytotoxic activities of the four melampolides will be presented.

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IN VITRO ANTIPROTOZOAL ACTIVITY OF ETHNOMEDICALLY SELECTED MEMBERS OF THE FAMILY FABACEAE.

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[2]Chemistry Department, University of Dschang, Box 67, Dschang, Cameroon.
[3]Berhanu M. Abegaz, Department of Chemistry, Faculty of Science, University of Botswana, P.O.Box UB0074, Gaborone, Botwana.
[4]Haskins Laboratories and Dept. of Biology, Pace University, New York, NY 10038-1502.
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As part of an ongoing research project, under the auspices of International Cooperative Biodiversity Groups (ICBG), we have collected and identified plant materials used in West and Central African ethnomedicine in the treatment of infectious diseases including, African sleeping sickness, fevers and resistant malaria. Our *in vitro* antiprotozoal assays indicate that members of the family Fabaceae were among those that significantly inhibited the growth of *Plasmodium falciparum* and *Trypanosoma* spp. Out of 35 extracts from 17 species, eighteen extracts exhibited activity against CQ-sensitive (D6) while seventeen were active against CQ-resistant (W2) strains of *Plasmodium falciparum with* IC_{50} < or = 50 μg/mL. The most active extracts on both strains were those of Millettia *griffoniana*, *Glycyrrhiza lepidota*, *Anthonotha crassifolia, Albizia ferruginea* and *Cassia fasciculata* with IC_{50} < or = 5μg/mL. Significant antitrypansomal activity was found for *Erythrina senegalensis* against *Trypanosoma b. brucei*, EATRO 110, *Trypanosoma rhodesiense* KETRI 243, *T. rhodesiense* 243 As 10-3 strains with corresponding IC_{50} values of 7.2, 9.1 and 14.75μg/mL. Bioassay directed-fractionation of the extracts from *Millettia griffoniana,* often cited by traditional medicine practitioners yielded two new isoflavonoid compounds (7-ethoxyebenosin, and griffonianone F) and two known (7-methoxy-8, (3,3-diethylallyl)isoflavone) and Calopogonium isoflavone), which demonstrated strong antiplasmodial and antitrypasomal activities.

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CYTOTOXIC CONSTITUENTS FROM *AVICENNIA GERMINANS*

William P. Jones,[1,4] Tatiana Lobo-Echeverri,[1,2] Heebyung Chai,[1] Qiuwen Mi,[1] Djaja D. Soejarto,[1] Geoffrey A. Cordell,[1] John M. Pezzuto,[1,3] Steven M. Swanson,[1] and A. Douglas Kinghorn[1,4,*]

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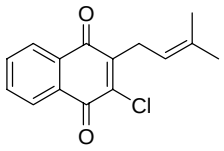
Bioassay-guided isolation of the leaves and twigs of the mangrove tree *Avicennia germinans* (L.) L. (Avicenniaceae), collected from a forest plot in South Florida, led to the isolation of 3-chloro-deoxylapachol (**1**), a new natural product, as well as a number of naphthoquinone and terpenoid cytotoxic constituents. The structures of the isolates were determined by spectroscopic analysis, and the structure of **1** was confirmed by comparison with the synthetically prepared compound. The cytotoxicity of **1**, and the other pure isolates, was evaluated in a panel of human cancer and transformed cell lines. Compound **1** was evaluated in the hollow-fiber *in vivo* model and the NCI 60-cell line panel. (Supported by grant U19 CA52956 from NCI, NIH, Bethesda, MD).



1

P:570

BIOACTIVITY-DIRECTED FRACTIONATION OF *MYRISTICA BECCARIANA* WARB. (MYRISTICACEAE) USING A MECHANISM-BASED PROTEASOME ASSAY TO ISOLATE MALABARICONE C

Sharnelle S. Phifer,[1] Dongho Lee,[1] Rachman Ismail,[2] Soedarsono Riswan,[2] Robert Wild,[3] Naomi Laing,[3] Khalid Benbatoul,[3] Latifa Benmassaoud,[3] Djaja D. Soejarto,[4] Norman R. Farnsworth,[4] A. Douglas Kinghorn,[4,5] David J. Kroll,[1] Nicholas H. Oberlies,[1] and Mansukh C. Wani[1,*]

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The proteasome is a multicatalytic proteinase complex responsible for the degradation of most intracellular proteins, including proteins crucial to cell cycle regulation and programmed cell death. In preclinical models, proteasome inhibitors induce apoptosis, have in vivo efficacy, and sensitize malignant cells to proapoptotic effects of conventional chemotherapeutics and radiation therapy. Moreover, transformed cells appear to display greater susceptibility to proteasome inhibition than nonmalignant cells. Hence, proteasome inhibition is considered an exciting new approach to the treatment of cancer. Using a mechanism-based proteasome assay to direct the purification, malabaricone C was isolated from an extract of the leaves of *Myristica beccariana* Warb. (Myristicaceae). Malabaricone C exhibited potent activity in this assay with an IC_{50} value of 1.4 μM, while little general cytotoxic activity in the KB cell line was observed. Support of this work was provided by grant U19 CA52956, funded by the National Cancer Institute/National Institutes of Health.

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ISOLATION OF DICHAPETALIN A FROM A RECOLLECTION OF THE STEM BARK OF *DICHAPETALUM GELONIOIDES* OBTAINED FROM THE PHILIPPINES

Aiko Ito,[1] William P. Jones,[1] Qiuwen Mi,[1] Hee-Byung Chai,[1] Domingo R. Madulid,[2] Mildred B. Oliveros,[3] Jimmy Orjala,[1] Djaja D. Soejarto,[1] Geoffrey A. Cordell,[1] Steven M. Swanson,[1] and A. Douglas Kinghorn.*[,1,4]
[1]Program for Collaborative Research in the Pharmaceutical Sciences, and the Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, University of Illinois at Chicago, Chicago, IL 60612; [2]Botany Division, National Museum, Manila, Philippines; [3]College of Pharmacy, University of Philippines, Manila, Philippines. [4]Current address: College of Pharmacy, Ohio State University, Columbus, OH 43210

As a part of a program to discover novel plant-derived anticancer agents, the stem bark of *Dichapetalum gelonioides* Engl. (Dichapetalaceae), collected in the Philippines, has been investigated. Earlier activity-guided fractionation using the LNCaP (human prostate cancer) cell line led to the isolation of several dichapetalin-type triterpenoids, which exhibited promising selective activity against the SW626 (human ovarian cancer) cell line (1). In order to obtain larger amounts for follow-up biological testing of dichapetalins A, I, and J, it was necessary to formulate a four-party intellectual property agreement for the specific recollection of *D. gelonioides* stem bark, between the Philippine National Museum, Manila, the University of the Philippines at Manila, the Palawan Council for Sustainable Development, Puerto Princesa, and the University of Illinois at Chicago. The signing of this agreement took several years of continuous effort to effect. In the present work, dichapetalin A has been re-isolated in sufficient quantity for evaluation in the *in vivo* hollow fiber assay at UIC, and the results will be discussed. (Supported by grant U19 CA52956 from NCI, NIH, Bethesda, MD).

(1) Fang, L., Mi, Q., Chai, H.-B., Madulid, D.A., Soejarto, D.D., Cordell, G.A., Pezzuto, J.M., Kinghorn, A.D. 39th Annual Meeting of the American Society of Pharmacognosy, Coronado Springs Resort, Orlando, FL, July 19-24, 1998, Abstract P-43.

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LACTONES AND FLAVONOIDS FROM THE LEAVES OF *LITSEA JAPONICA* AND THEIR ANTI- COMPLEMENT ACTIVITY

Hyeon Kyu Lee,* Byung Sun Min, Sun Young Lee, Jung Hee Kim, Ok Kyoung Kwon, Bo Young Park, Ren Bo An, Joong Ku Lee, Hyung In Moon, Tae Jin Kim, Young Ho Kim, Hyouk Joung
Laboratory of lmmunomodulator, Korea Research Institute of Bioscience and Biotechnology, Daejeon 305-333, Korea;: hykylee@kribb.re.kr

Litsea japonica (Thunb.) Jussieu (Lauraceac) is an evergreen tree, which grows in the southern area of Ko rea and Japan. Lactones and essential oils have been reported from this species. As part of our continuing research to find pharmacologically active compounds from this plant, we isolated five lactones and four flavonoids. This paper describes the isolation, structural determination, and the anti-complement activity of these substances, which include two new natural lactones (Litsealactone A and B), three known compounds (hamabiwalactone A and B and akolactone B) and four flavonoids. Of these two lactones and three flavonoids showed anti-complement activity.

The role of complement components in immune and inflammatory responses continues to be a major field of research. As a resulting of activation the smaller fragments, C3a, C4a, and C5a, are produced and called anaphylatoxins. These can induce the release of strong mediators from the mast cells and lymphocytes, which cause a variety of inflammatory diseases and can be fatal if occurring after organ transplantation. Therefore, modulation of complement activity should be useful in the therapy of inflammatory diseases.

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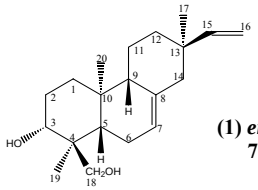
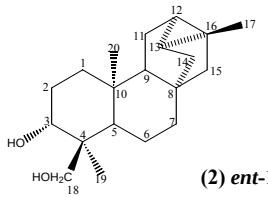
ENT-18-HYDROXY-TRACHYLOBANE-3-β-OL AND ENT-18-HYDROXY-ISOPIMARA-7,15-DIENE-3-α-OL, TWO VASORELAXANT DITERPENES FROM *CROTON ZAMBESICUS* MUELL ARG.

C. Baccelli[1], S. Block[1], B. Van Holle[1], B. Tinant[2], N. Morel[3], J. Quetin-Leclercq[1(*)]
[1]Laboratoire de Pharmacognosie, UCL-CHAM, Av. E. Mounier 72, 1200 Bruxelles, Belgium.
[2]Département de Chimie, UCL-CSTR, Place L. Pasteur, 1348 LLN - Belgium
[3]Laboratoire de Pharmacologie, UCL, Av. Hippocrate 54, 1200 Bruxelles, Belgium.

A mixture of two vasorelaxant diterpenes was isolated by bio-guided fractionation from a dichloromethane extract of *Croton zambesicus* Muell Arg (Euphorbiaceae).
Their structures were determined by X-ray diffraction of crystals containing both compounds and NMR of (ent-18-hydroxy-trachylobane-3-β-ol) **(1)**. One is a trachylobane diterpene (**1**) and the other one is a pimarane derivative (ent-18-hydroxy-isopimara-7,15-diene-3-α-ol) (**2**). The mixture of both compounds inhibits, *in vitro*, the KCl - induced contraction of male Wistar Han rat aorta [1]. Separation was performed after treatment with osmium tetroxide. Compound **1** and hydroxylated compound **2** showed a lower activity than the mixture.



(1) *ent*-18-hydroxy-isopimara-7,15-dien-3β-ol



(2) *ent*-18-hydroxy-trachyloban-3β-ol

1. T.Godfraind, et al. Clinical Science, 1985; 68 (Suppl.10), 65s-71s.

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TWO NEW APOCAROTENOIDS FROM SEEDS OF *Ditaxis heterantha* Zucc. (Azafran de bolita) A FOOD PIGMENT PRODUCING PLANT.

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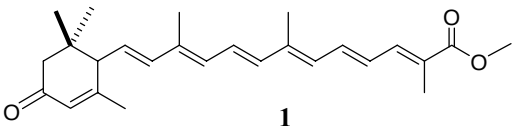
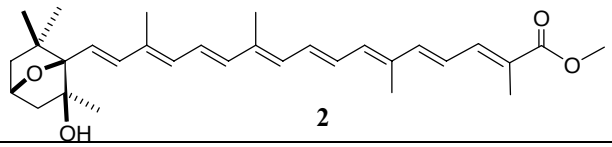
Ditaxis heterantha Zucc., (azafrán de bolita), a plant of the *Euphorbiaceae* family, is found growing wild in the semiarid regions of Mexico. Traditionally, its seeds are used by the inhabitants of the regions where it grows to give color and to enhance the flavor of their food, although in recent years, there has been a growing interest in its cultivation. The endosperm of the seeds has an intense yellow color, indicating the possible presence of pigments of the carotenoid family. We report herein the structure of two new substances, which were isolated as the major components of the pigment. Extraction with hexane and purification by HPLC using a silica gel column afforded the new apocarotenoids **1** and **2**, whose UV spectra showed the three characteristic λ_{max}. 1D and 2D NMR spectroscopy, including COSY, HSQC and HMBC experiments, in combination with MS and IR data established the structure of the two compounds. The stereochemistry of **2** was determined from its NOESY correlation diagram in combination with an analysis of the six-membered ring coupling constants.



1



2

P:575

MARINE NATURAL PRODUCTS AS A SOURCE OF AGENTS THAT REVERSE FLUCONAZOLE RESISTANCE

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Department of Pharmacognosy, The National Center for Natural Products Research, Department of Pharmacology, School of Pharmacy, The University of Mississippi, University, MS, 38677-1848

Azole resistance is an emerging problem in the treatment of opportunistic fungal infections. Over 8200 marine invertebrate extracts from the NCI Open Repository were evaluated in a whole cell, 96-well plate-based assay in the presence of a sub-MIC concentration of fluconazole (FLU) using *Saccharomyces cerevisiae* strains that express *Candida albicans* CDR and MDR-type efflux pumps. Extracts of the sponges *Dysidea arenaria* (Dysideidae), *Psammocinia arenosa* (Ircinidae), *Phyllospongia spp.* (Spongiidae) and the hydroid *Nemalecium lighti* (Haleciidae) were found to be active. The active principle in the *D. arenaria* extract was identified as 9α,11α-Epoxycholest-7-ene-3β,5α,6α,19-tetrol 6-Acetate (ECTA). This is the first marine natural product found to reverse MDR efflux pump-mediated fluconazole resistance. ECTA (3.8 μM) enhances fluconazole activity in resistance mutants of *S. cerevisiae* by 35-fold. *Nemalecium lighti* yielded new active scalarane sesterterpenoids that reverse CDR efflux-mediated fluconazole resistance. *Psammocinia arenosa* yielded (+)–*ent*-ircinianin, a new enantiomeric cyclic furanoseterterpene tetronic acid. This is only the second occurrence of such an enantiomeric sesterterpene.

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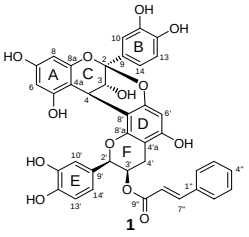
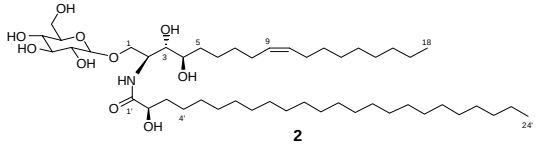
FRACTIONATION OF THE LEAVES OF *ORMOSIA SUMATRANA* USING A PROTEASOME INHIBITORY ASSAY

Bao-Ning Su,[1,5] Bang Yeon Hwang,[1,6] Esperanza J. Carcache-Blanco,[1] Heebyung Chai,[1] Leonardus B. S. Kardono,[2] Johar J. Afriastini,[3] Soedarsono Riswan,[3] Robert Wild,[4] Naomi Laing,[4] Norman R. Farnsworth,[1] Geoffrey A. Cordell,[1] Steven M. Swanson,[1] and A. Douglas Kinghorn[1,5,*]
[1]Program for Collaborative Research in the Pharmaceutical Sciences, Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, University of Illinois at Chicago, Chicago, IL 60612. [2]Research and Development Chemistry, Indonesian Institute of Science, Serpong, 15310 Tangerang, Indonesia. [3]Herbarium Bogoriense, Research and Development Center for Biology, Indonesian Institute of Science, 16122 Bogor, Indonesia. [4]Bristol-Myers Squibb, Pharmaceutical Research Institute, P.O. Box 4000, Princeton, New Jersey 08543. [5]Present address: College of Pharmacy, The Ohio State University, Columbus, OH 43210. [6]Present address: College of Pharmacy, Chungbuk National University, Cheongju, 361-763, Korea.

Using a proteasome inhibitory assay to monitor fractionation, a new A-type proanthocyanidin derivative, 3'-*O*-cinnamoylprocyanidin A-2 (**1**), and a new cerebroside, sumatranoside (**2**), have been isolated from a chloroform-soluble extract of the leaves of *Ormosia sumatrana* (Miq.) Prain. The structures of compounds **1** and **2** were determined as epicatechin-(2β→*O*→7',4β→8')-epicatechin-3'-*O*-cinnamate (**1**) and 1-*O*-(β-D-glucopyranosyl)-(2*S*,3*S*,4*R*)-2*N*-[(2'*R*)-2'-hydroxytetracosanoyl]-9*Z*-octadecene-1,3,4-triol (**2**), respectively, by spectroscopic and chemical methods. Compound **2** exhibited proteasome inhibitory activity with an IC_{50} value of 30 μM. (Supported by NIH grant U19 CA52956).



1



2

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ISOLATION OF A NOVEL ALKALOID FROM *CIMICIFUGA RACEMOSA (*L.) NUTT.

Daniel Fabricant, Dejan Nikolic, Shao-Nong Chen, Harry H.H.S. Fong, Richard van Breemen, Norman R. Farnsworth, Guido F. Pauli
UIC/NIH Center for Botanical Dietary Supplements Research on Womens' Health, College of Pharmacy, Department of Medicinal Chemistry and Pharmacognosy, University of Illinois at Chicago, 833 S. Wood Street, Chicago, IL 60612

Phytochemical investigation of a highly polar butanol soluble fraction of roots/rhizomes of *Cimicifuga racemosa* (L.) Nutt., using innovative non-silica chromatographic techniques yielded known and active constituents, fukinolic acid, cimicifugic acid and one novel compound, {1-[amino(imino)methyl]pyrrolidin-2-yl} acetic acid, a natural guanidine derivative. The first report of such a compound from Black Cohosh. This novel compound exists as a zwitterion in D_2O, resulting in a complex structure elucidation problem by NMR. The structures were elucidated using the NMR, MS, UV and FT-IR spectroscopic techniques. Additionally the use of the ACD™ database in conjunction with assignment of spin systems with the PERCH™ simulation was necessary to elucidate the structure.

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PENTACYCLIC ISOMERS THROUGH REARRANGEMENT OF CARBON SKELETON OF TAXOL

Qingmei Ye, Charles Pathirana, John DiMarco, Rajendra Deshpande, Jack Gougoutas, David Hennings, Karen Tenhuisen, Venkatapuram Palaniswamy*
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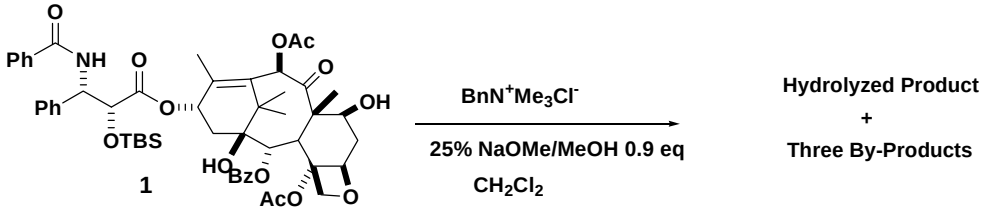
During developmental studies towards the preparation of an analog of taxol, selective hydrolysis of the ester groups of **1** under conditions shown below was investigated. The reaction yielded three by-products that were isolated by preparative HPLC. HPLC and NMR analyses indicated that two of them were hemi-acetal isomers either of which, when isolated by HPLC, readily established an equilibrium mixture containing both compounds. The third by-product was found to be a lactone resulting from the oxidation of the hemi-acetals. Their structures with a rearranged carbon skeleton were identified by the analysis of MS, NMR, and confirmed by single crystal X-ray crystallographic data. The presentation will describe the isolation and structural elucidation of these by-products that posses a rearranged carbon skeleton.



P:579

TRANSFORMED CULTURES OF SOLANUM CHRYSOTRICHUM FOR THE PRODUCTION OF BIOACTIVE SAPONINS

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Callus and cell suspension cultures of the Mexican species *Solanum chrysotrichum* were obtained through transformation of different explants of this species *with Agrobacterium tumefaciens* wild type strains harboring the binay vector pBI121 (C58-pBI121 and B6-pBI121). Nine different putative transformed cell lines were established in which the production of the antifungal saponins SC2-SC6 was tested. The obtained cell lines exhibited the ability to grow in hormone free MS medium and different patterns of saponins production. Some cell lines produce preferentially one of the several active compounds. In the cell line C58-2.2 transformation was confirmed through PCR and Southern blot analysis, and the total production of the active saponins was 3.3 times higher in comparison with untransformed cells from this species.

P:580

NEW TIRUCALLANE TRITERPENE OF *PANDANUS TECTORIUS VAR. LAEVIS ACTIVE AGAINST MYCOBACTERIUM TUBERCULOSIS* $H_{37}Rv$

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One of the Philippines' most pressing health problems is the continuous spread of tuberculosis (TB). About 22 million of the country's population is infected with TB and about 270 thousand per year develops TB infection . A plant worth exploring as potential source of antituberculars is the *Pandanus tectorius var. laevis*, a species which belongs to the *Genus Pandanus*.

Preliminary investigation of the *P. laevis* crude methanolic extract, hexane, chloroform, and n-butanol extracts exhibited a 100%, 100%, 95%, and 57% inhibition, respectively, against the virulent strain of *Mycobacterium tuberculosis* $H_{37}Rv$ using the Microplate Alamar Blue Assay (MABA) method. As of this writing, no literature is available on the anti-TB studies in *P. laevis*.

Bioassay-guided fractionation and isolation of the chloroform extract afforded a new tirucallane-type triterpene 24,24-dimethyltirucall-9(11),25-diene-3-one (Pl-C-A11), squalene (Pl-C-A13a1), and mixture of stigmasterol and β-sitosterol (Pl-C-A13b).

Pl-C-A11 gave an MIC of 64 ug/ml against *MtH_{37}Rv*; Pl-C-A13a1, with a MIC of 100 *u*g/ml while Pl-C-A13b gave a MIC of 128 ug/ml. This is the first report on the antitubercular activity of a tirucallane-type triterpene and squalene.

P:581

SIMULTANEOUS QUANTIFICATION OF A- AND B-TRICHOTHECENE MYCOTOXINS IN PLANTS USING LIQUID CHROMATOGRAPHY-TANDEM MASS SPECTROMETRY

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A selective analytical method based on high-performance liquid chromatography (HPLC) combined with tandem mass spectrometry (MS-MS) has been developed for simultaneous determination of type A- and B-trichothecene. The assay allows the analysis of nivalenol (NIV), deoxynivalenol (DON), HT-2 toxin and T-2 toxin. The method is based on a two-step sample clean-up using MycoSep columns[1]. Quantification was carried out by electrospray ionisation in the negative (NIV, DON) and positive mode (HT-2, T-2), respectively. Verrucarol was used as internal standard. The developed method shows good repeatability for intra- and inter-day precision as well as good linearity of calibration curves (r^2 ranged from 0.991 to 0.996). For the tested compounds average recoveries in the range of 70-100% have been determined in black, fruit and herbal tea. The limits of quantification for the whole method were between 10 ppb and 100 ppb. The utility and practical impact of the assay is demonstrated using different herbal drugs and tea mixtures.

[1] Berger et al; J. Agric. Food Chem. 1999, 47, 4240-4245

P:582

ISOLATION, CHARACERIZATION AND DOCUMENTATION OF HERBAL REFERENCE SUBSTANCES: TEUCRIN A FROM TEUCRIUM CHAMAEDRYS

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Teucrium species (Germander, Lamiaceae) are used in traditional medicine in many regions of the world. But *Teucrium* species also have been associated with liver damage in several cases, e.g., *Teucrium chamaedrys* and *Teucrium polium* (1, 2). Recently, cases of hepatotoxicity have been assigned to adulteration of *Scutellaria* (skullcap) with *Teucrium* (3). Therefore, determination of the toxic neoclerodane diterpene teucrin A, present in some *Teucrium* species, would be useful both to detect skullcap adulteration and limit teucrin content in medically used *Teucrium* preparations.
Because of the presence of a broad variety of neoclerodane diterpenoids in different *Teucrium* species modern analytical methods such as HPLC-MS/MS and HPLC-NMR are useful for classification of the components. Determination of neoclerodane diterpenoids content can be carried out in sum by HPLC-UV when referred to a suitable reference substance. We herein describe isolation, characterization and documentation of Teucrin A for the use as reference standard in *Teucrium* analysis.

1. Mazokopakis E, Lazaridou S, Tzardi M, Mixaki J, Diamantis I, Ganotakis E.: Acute cholestatic hepatitis caused by Teucrium polium L., Phytomedicine. (2004) Jan; 11(1): 83-4.
2. Stickel F, Seitz HK, Hahn EG, Schuppan D.:Liver toxicity of drugs of plant origin, Z Gastroenterol. (2001) Mar; 39(3): 225-32, 234-7.
3. 06/25/99 Draft Report of the FOOD ADVISORY COMMITTEE DIETARY SUPPLEMENT WORKING GROUP On INGREDIENT IDENTITY TESTING RECORDS AND RETENTION U. S. Food and Drug Administration, Center for Food Safety and Applied Nutrition, June 1999.

P:583

DETERMINATION OF THE TOXIC ANTHRAQUINONES LUCIDIN AND RUBIADIN IN COMMERCIAL NONI JUICE BY HPLC

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According to the EU-guideline 2003/426/2003 Noni juice is accepted as novel food or novel food ingredient in pasteurized fruit juices in the European Community. Noni juice is a mixture of the fruit juice of Noni fruit and common grape and blueberry juice concentrates and is traditionally consumed in Polynesia and South East Asia and has been marketed in the USA since July 1st 1996.
With this guideline a compositional profile has been defined with a variety of natural compounds like amino acids, vitamins, minerals, fat, carbohydrates etc. In the roots of the plant Morinda citrifolia L.[1] two genotoxic anthraquinones lucidin and rubiadin could be detected, whilst in the fruits of Morinda citrifolia none of these compounds could be detected[2].
Nevertheless this genotoxic constituents are regulated in this guideline. They are limited to 10 µg/kg in the juice. For the analysis of commercial Noni Juice products we synthesized lucidin and rubiadin as they are not commercially available. Furthermore we developed a HPLC-method with a detection limit of less than 10 µg/kg and an HPLC-MS-MS-technique for the confirmation of the results.
Results of the screening of several commercial products from samoa and fiji are presented.
1 E. Leistner, Planta Med. 27 (1975) 214 - 224
2 MH Zenk, Planta Med. 27 (1975), 79 - 101

P:584

TROPANE ALKALOIDS FROM THE SOUTHAFRICAN PERENNIAL HERB *FALKIA REPENS* (CONVOLVULACEAE)

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[3] Institut für Biologie (Angewandte Zoologie/Ökologie der Tiere), Freie Universität Berlin, Haderslebenerstr. 9, D-12163 Berlin
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Tropane alkaloids are characteristic secondary metabolites in species of many convolvulaceous genera (e.g. *Convolvulus*, *Merremia*). This applies to classical more or less lipophilic tropanes as well as to calystegines, hydrophilic nortropane derivatives. In the present study *Falkia repens* L.f., a member of the tribe Dichondreae s.l., already known as calystegine-positive, has turned out to contain a broad profile of lipophilic alkaloids as well, mainly tropan-3-ol esters. From the roots and rhizoma 3α-acetoxy-, 3α- and 3β-(2-methylbutyryl)oxy-, 3α- and 3β-*trans*-feruloyloxytropane, and furthermore tropan-3-one and 3β-tropanol were isolated. Their structures were elucidated by means of ^{1}H-NMR, H-H-COSY, ^{13}C-NMR, EI-MS, and HR-MS measurements. Moreover, several minor alkaloids could be characterized by GC-MS data. This is the first report on the occurrence of lipophilic tropane alkaloids in the tribe Dichondreae s.l..

P:585

RHIZOME PROPAGATION OF ACTAEA RACEMOSA L. (BLACK COHOSH) AND ANALYSIS OF ASSOCIATED TRITERPENE GLYCOSIDES

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Actaea racemosa (black cohosh) was one of the top ten selling medicinal products in both 2002 and 2003. Due to predicted increases in demand for plant material, it may become necessary to develop large-scale production protocols to replace and/or amend current supply methods. Currently, the majority of raw materials supplied to phytopharmaceutical companies are wildharvested from native populations in North America. There currently exists a lack of replicated data available on specifics of propagation by rhizome division and associated triterpene glycoside analysis.

Objectives of this study were to: 1.) compare yields and triterpene glycoside concentrations between plants grown in various habitats; 2.) compare triterpene glycoside concentrations between individuals originating from a single population; 3.)determine optimal rhizome propagule size for field production; and 4.) to establish which above-ground measurements correlate positively to rhizome yields and triterpene glycoside concentrations after three years of study.

P:586

POTENTIAL THERAPEUTIC LEADS FROM NATURAL PRODUCTS

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Natural products continue to deliver candidates to developmental pipeline. Even the known multinational companies are focusing their R&D towards natural products research for sourcing therapeutic leads.

India is a mega-biodiversity country where traditional knowledge and preparations developed from the Indian Systems of Medicine (ISM) are in use for treating diseases.

Council of Scientific & Industrial Research (CSIR), the largest publicly funded R&D organization of India, mounted about five years back a project on discovering potential new leads from medicinal plants used in formulating traditional and herbal preparations. The objective is to take it up to a stage of Investigational New Drug (IND) and / or Investigational New Herbal Formulations (INHF) for commercialization.

The operational structure evolved to manage such a massive networked programme in a cost effective manner and the diseases for which leads have been generated shall be presented.

The initiative taken by CSIR is shifting the emphasis of R&D carried out in Indian pharma industries, department of universities and other R&D institutes in the country towards product development for various diseases. Experience gained would be shared.

P:587

INVESTIGATION OF RADICAL SCAVENGING OF TEUCRIUM POLIUM L. (LAMIACEAE) ESSENTIAL OIL FROM IRAN, PAPOLATION KERMAN

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Teucrium polium(kalpureh) has been used in traditional medicine for many purposes such as antibacterial, antiinflammatory, analgesic, anti diabetes mellitus and etc. The plant was collected from Kerman province in May 2002 and essential oil of dried and powdered of top flowered plant was prepared by hydro distillation [0.4 ml %(V/W)].It was analyzed by GC and GC/MS on DB1 and DB5 columns. From 86 components 76 ones were identified .The antioxidant activity of ess.oil was investigated by lipid per oxidation (FTC) and free radical scavenging (DPPH) methods. AA% of 30 µl ess.oil in FTC method after 72 hrs (26.74 µg/ml) was more than 10 mg Vite.E and 0.1 mg(100 µg)BHA. IC50 of Ess.oil in DPPH method after 15 min. (5.8µg) was as potent as 5 µg of BHA. The component and antioxidant activity of ess.oil will be discussed.

P:588

COMPARATIVE STUDY OF *DIGITALIS* L. SPECIES FROM PORTUGUESE FLORA

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[1]Centre for Environmental Biology, Pharmacy's Faculty of Lisbon University (FFUL); [2]Pharmaceutical Sciences Research Centre (CECF- FFUL); [3]National Forest Research Station, Oeiras; [4]FFUL, Av. das Forças Armadas, 1649-019 Lisboa, Portugal.

Foxglove, *Digitalis purpurea* L. is a well known medicinal plant with cardiac glycosides, used to treat congestive heart failure and heart rhythm problems. In Portuguese Flora, *D. purpurea* and *D. thapsi* (endemism of Iberian peninsula) are the main species. Some literature references have described the occurrence of a hybrid (*D. purpurea* x *D. thapsi)*, mainly in the North of Portugal as well as among Portuguese herbarium specimens. At this time, we present results of a morphological, molecular and chemical study involving these three plant species. Distinctive and similar anatomic characters were studied. Microscopic analysis on the leaves, by light (LM) and scanning electron microscopy (SEM), showed differences on non-glandular and glandular trichomes of leaf surface. Molecular analysis of leaves DNA, by PCR technology with molecular markers for conserved regions of 23S and 5S rDNA chloroplast genes and nucleotide sequence determinations, have revealed 100% of homology between *D. thapsi* and the so called hybrid *D. purpurea* x *D. thapsi* and 0.88% of divergence between the hybrid and *D. purpurea*. On the other hand, some chemical similarities and differences appear to be found in leaves, mainly regarding lipophilic flavonoids profiles, during different development stages of plants under investigation.

ADDENDUM

P:589 PROANTHOCYANIDINS FROM *APOCYNUM VENETUM* L.

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P:590 GC/MS STUDY OF THE ESSENTIAL OIL OF *DRACOCEPHALUM KOTSCHYI*.FROM BOJNOURD IN KHORASAN PROVINCE- IRAN.

Mani ashrafi *,H.R.Monsef,B.Nikavar,F.Karamkhani.
*Hariseh Pars co. number:112,4th entrance,block B3,Ekbatan complex,Tehran,Iran.

P:591 INDOLE ALKALOIDS FROM *OCHROSIA ACUMINATA* & *ALSTONIA SCHOLARIS*

Angela A. Salim[1,2]*, Mary J. Garson[1] and David J. Craik[2]
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P:592 DEVELOPMENT OF A PROCESS FOR THE PRODUCTION OF THE ANTICANCER LEAD COMPOUND PLEUROTIN BY FERMENTATION OF *HOBENBUEHELIA ATROCAERULEA*

S. M. Shipley*, A. L. Barr*, S. Graf*, R. Collins*, T.G. McCloud*, D.J. Newman#
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P:593 ANTITUMOR INITIATING EFFECT OF *AGARICUS BLAZEIMURILL*

Mutsuo Kozuka,[a] Harukuni Tokuda,[b] Teruo Mukainaka,[b] Hoyoku Nishino,[b] Kuo-Hsiung Lee,[a],* [a]Natural Products Laboratory, School of Pharmacy, University of North Carolina, Chapel Hill, NC 27599-7360, [b]Department of Biochemistry, Kyoto Prefectural University of Medicine, Kamigyo-ku, Kyoto 602-0841, Japan.

P:594 DEVELOPMENT OF ASSAY METHOD OF ANTI-ALLERGIC PROMOTERS BY USING HEL-INDUCED BLOOD FLOW DECREASE

Kyoko Ishiguro*, Hisae Oku, Yoshimi Ueda, Emiko Iwaoka and Yuko Ogawa School of Pharmaceutical Sciences, Mukogawa Women's University, 11-68 Koshienkyuban-cho, Nishinomiya, 663-8179, Japan.

P:595 INHIBITORY EFFECTS OF XANTHONES FROM GUTTIFERAE PLANTS ON PAF-INDUCED HYPOTENSION

Hisae Oku[a]*, Yoshimi Ueda[a] , Munekazu Iinuma[b] and Kyoko Ishiguro [a]

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P:596 CYTOTOXIC FRACTIONS FROM THE LEAVES OF *TACHIA GRANDIFLORA* MAGUIRE &WEA VER (GENTIANACEAE)

TIgre, R.F. [1] ; Cavalcanti, B.C. [1] ; Moraes, M.O. [1] ; Costa-Lotufo, L.V. [1], Moraes, M.E. [1] ; Santos, E.M. [2] ,Morais, S. K. R. [2] , Nunomura, S. M. [3] , Pohlit, A.M. [3] ; Pessoa, C.*
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P:597 COMPARISON OF BIFLORIN CYTOTOXICITY AGAINST HUMAN BREAST CANCER CELLS (MCF-7) AND PERIPHERAL LYMPHOCYTES

Montenegro, R.C.[1]; Porto, LA. [1]; Vasconcellos, M.C. [1]; Fonseca, A.M.[2]; Lemos, T.G.L[1]; Moraes, M.O.[1]; Costa-Lotufo, L.V.[1]; Pessoa C.[1]
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P:598 BIOPROSPECTION OF COMPOUNDS WITH ANTITUMOR ACTIVITY IN EUDISTOMA V ANNAMEI MILLAR, 1977 (TUNICA T A, ASCIDIACEA)

Paula C. Jimenez[1], Diego V. Wilke[1], Claudia Pessoa[1], Manoel Odorico de Moraes[1], Thiago O. Bass0[2], Renata Takeara[2], Norberto P. Lopes[2], Leticia V. Costa-Lotufol*
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P:599 DIFFERENTIATION INDUCTION OF PISOSTEROL FROM *Pisolithus tinetoris* (Pers) Cok. & Couch IN HL60 LEUKEMIA CELLS

Montenegro, R.C.[1]; Nogueira, M.A.S.[1]; Andrade-Neto, M.[2]; Bezerra, F.S[2]; Gomes, A.S.[1]; Souza, M.H.L.p.[1]; Ferreira, F.V.A.[3]; Moraes, M.O. [1]; Pessoa, C. [1]; Costa-Lotufo, L.V.[1]* [1].Departamento de Fisiologia e Farmacologia, UFC, P.O.Box 3157, 60430-270, Fortaleza, CE, Brazil; [2]. Departamento de Quimica Organica e inorganica, UFC. [3]. Departamento de Patologia e Medicina Legal, UFC. *lvcosta{a!,secrel.com.br

P:600 NOVEL NATURAL PRODUCTS FROM BACTERIAL AND FUNGAL STRAINS OBTAINED BY HIGH THROUGHPUT CULTURING

Mustafa Varoglu*, Lisa Rahbaek, Asfia Qureshi, Sasha Marks, Mimi Zhao, Yukiko Sato, Ashish Paradkar, Ken Wong, David Gustafson, Theresa Nibert, Karsten Zengler, Gerardo Toledo, Marion Walcher, Greg Clark, Imke Haller, Martin Keller, Gary Woodnut, Jay Short. Diversa Corp. 4955 Director's Place, San Diego, CA 92121, USA.

P:601 INACTIVATION OF THE CARBAMOYLTRANSFERASE GENE REFINES THE POST-POLYKETIDE SYNTHASE MODIFICATION STEPS IN THE BIOSYNTHESIS OF THE ANTITUMOR AGENT GELDANAMYCIN

Young-Soo Hong,[1] Dongho Lee,[1] Woncheol Kim,[1,2] Jae-Kap Jeong,[1] Chun-Gyu Kim,[3] Jae Kyung Sohng,[4] Jeong-Hyung Lee,[1] Sang-Gi Paik,[2] Jung Joon Lee[1,*]
[1]Korea Research Institute of Bioscience and Biotechnology, Daejeon, Korea, [2]Chungnam National University, Daejeon, Korea, [3]Inje University, Gimhae, Gyeongnam, Korea, [4]Sun Moon University, Asan, Chungnam, Korea

P:602 ANTI-COMPLEMENT ACTIVITY OF NOR-LIGNANS AND TERPENES FROM THE STEM BARK OF *STYRAX japonica*

Byung-Sun Min°, Sei-Ryang Oh, Kyung-Seop Ahn, Jung-Hee Kim, Gil-Saeng Jeong, Joongku Lee, Doo- Young Kim, Hyouk Joung, Hyeong-Kyu Lee*
Korea Research Institute of Bioscience & Biotechnology Daejeon 305-333, Korea

P:603 INCREASE OF CASPASE-3 ACTIVITY BY LIGNANS FROM *MACHI/US THUNBERGII* IN HL-60 CELLS

Bo-Young Park,[o] Byung-Sun Min, Sei-Ryang Oh, Ok-Kyong Kwon, Ki-Hwan Bae, Hyeong-Kyu Lee*
Laboratory ofImmunomodulator, Korea Research Institute of Bioscience and Biotechnology, Daejeon, 305-333, South Korea

P:604 ALKALOIDS FROM *TODDALIOPSIS BREMEKAMPII* (RUTACEAE)

Dashnie Naidoo[1], Dulcie A. Mulholland[1], Philip H. Coombes[1]*, N.R. Crouch[2]
[1] Natural Products Research Group, School of Chemistry, Howard College Campus, University of KwaZulu-Natal, Durban, 4041, South Africa
[2] Ethnobotany Unit, National Botanical Institute, PO Box 52099, Berea Road, 4007, South Africa

P:605 METABOLIC ENGINEERING OF ISOFLAVONOID BIOSYNTHESIS IN ALFALFA

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P:606 AZAPHILONES, FURANOISOPHTHALIDES, AND AMINO ACIDS FROM THE EXTRACTS OF MONASCUS PILOSUS-FERMENTED RICE (RED-MOLD RICE) AND THEIR CHEMOPREVENTIVE EFFECTS

Toshihiro Akihisa, *,[1] Harukuni Tokuda, [2] Ken Y asukawa, [3] Motohiko Ukiya, [1] Ayaka Kiyota, [1]Takashi Suzuki, [3] Hoyoku Nishino[2]
[1]College of Science and Technology, Nihon University, 1-8 Kanda Surugadai, hiyoda-ku, Tokyo 101-8308, Japan, [2] Department of Biochemistry, Kyoto Prefectural University of Medicine, Kamigyo-ku, Kyoto 602-0841, Japan, [3]College of Pharmacy, Nihon University, 7-7-1 Narashinodai, Funabashi-shi,

P:607 USE OF HPLC-SPE-NMR IN DEREPLICATION OF NATURAL PRODUCTS MIXTURES

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Chiba 274-8555, Japan

P:608 EVALUATION OF THE CHEMICAL CONSTITUENTS OF *CLEMATIS LIGUISTICIFOLIA* AND *AKEBIA TRIFOLIATA* FOR THEIR TOXIC EFFECTS ON RENAL CELLS.

Rahul S. Pawar[1], Premlatha Balachandran[1], David S. Pasco[1], Feng Wei[2], Ruichao Lin[2], Ikhlas A. Khan[1,3]*
[1]National Center for Natural Products Research, Research Institute of Pharmaceutical Sciences, and [3]Department of Pharmacognosy, School of Pharmacy, University of Mississippi, University, MS 38677, USA and [2]National Institute for the Control of Pharmaceutical and Biological Products, State Food and Drug Administration (SFDA), Beijing 100050. P.R. China

P:589

PROANTHOCYANIDINS FROM *APOCYNUM VENETUM* L.

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Apocynum venetum L. (Apocynaceae) is a perennial herb growing in mid and north-western of China. Its leaves are used in traditional Chinese medicine in the treatment of several diseases like hypertension, nephritis and neurasthenia.
Recently an ethanolic extract of the leaves showed antidepressant activity in the Forced Swimming Test.
From this extract a range of so far unknown low molecular proanthocyanidins (two dimers and two trimers composed of gallocatechin, epigallocatechin and epicatechin) were isolated and characterized. Furthermore the more abundant soluble polymeric proanthocyanidin fraction was obtained. The chemical properties of this fraction were characterized by ^{13}C-NMR, [α] and acid catalyzed degradation in the presence of phloroglucinol. The results show that the soluble polymers consist of epicatechin, gallocatechin and epigallocatechin as terminating flavan-3-ols. The polymers are mainly built by 2,3-*cis* configurated epicatechin and epigallocatechin extender units. The average degree of polymerization of the polymeric fraction was estimated by ^{13}C-NMR to be nine flavan-3-ol units.

P:590

GC/MS STUDY OF THE ESSENTIAL OIL OF DRACOCEPHALUM KOTSCHYI.FROM BOJNOURD IN KHORASAN PROVINCE- IRAN.

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Dracocephalum kotschyi Boiss(lamiacea) has been used in Iranian traditional medicine as antispasmodicand carminative.
The flowering aerial parts of D.kotschyi were collected in july 2002 from bolnourd and the essential oil obtained from two methods(water and steam distillation) was analyzed by GC/MS ,the composed were identified by retention indices and by computer search using the wiley275.L
Of mass spectral data.
The oils are mainly composed of monoterpenoids, specially oxygenated derivatives.
Sixty-six compounds have been identified in the water distillated oil, the major components are verbenone(21.4%),limonene(14.0%),a-terpineol(8.8%),perilla alcohol(7.9%) and (z)-caryophyll-
ene(7.0%).
In the steam distillated oil, sixty-two compounds was identified, the major components are a-ter-
pineol(27%),verbenone(19.9%),z-caryophyllene(19.4%),limonene(5.2%) and 1,8-cineol(4.4%).

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INDOLE ALKALOIDS FROM OCHROSIA ACUMINATA & ALSTONIA SCHOLARIS

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Extracts from *Ochrosia acuminata* root have been used by the people in Savu island (Indonesia) to treat tumour and ectopic pregnancy, while extracts from *Alstonia scholaris* bark have been used by the people in Timor island to treat malaria. Both plants belong to the Apocynaceae family, which is a rich source of indole alkaloids, many of which are bioactive. Examples of bioactive alkaloids from this family that are currently used as therapeutics include reserpine (antihypertensive), ajmalicine (circulatory stimulant), vinblastine (antitumour) and vincristine (antitumour).
Two new corynanthe type indole alkaloids as well as two antitumour alkaloids (ellipticine & 9-methoxy ellipticine) have been isolated from *O. acuminata* root using bioassay guided isolation. Three other known alkaloids (quebrachidine, voachalotine and isoreserpiline) were also isolated from this plant. The crude alkaloid extract from *A. scholaris* bark gave an IC_{50} of 22 μg/mL against *Plasmodium falciparum* K1. Two new alkaloids (a corynanthe type and an aspidosperma type gluco-indole alkaloid) have been isolated from this extract. Five known alkaloids (echitaminic acid, N_b-demethylalstogustine, N_b-demethylalstogustine N-oxide, echitamidine N-oxide and akkuamicine N-oxide) were also isolated *A. scholaris*. The structural elucidation of the new indole alkaloids by 2D NMR is presented.

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DEVELOPMENT OF A PROCESS FOR THE PRODUCTION OF THE ANTICANCER LEAD COMPOUND PLEUROTIN BY FERMENTATION OF *HOBENBUEHELIA ATROCAERULEA*

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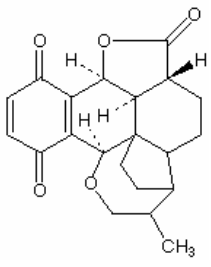
ABSTRACT: Pleurotin is a naphthoquinone antibiotic substance in which there is renewed interest as an anticancer lead compound. To have a reliable supply for continued research, a method had to be developed for production of gram quantities of high purity pleurotin. A strain of *Hohenbuehelia atrocaerulea* was identified, which, on solid substrate fermentation for two months yielded 1-2 mg/liter of the desired compound. This presentation will describe the lengthy series of trials which resulted in a process being developed in which pleurotin is reliably obtained at >100mg/liter from liquid fermentation after four weeks.



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ANTITUMOR INITIATING EFFECT OF *AGARICUS BLAZEIMURILL*

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Agaricus blazei MURILL is a mushroom (basidiomycetous fungus) originating in Brazil, and used as a dietary supplement called "Agaricus". Antitumor, antiviral, blood sugar moderating and cholesterol reducing effects have been reported for this fungus. Previously, we evaluated the aqueous extract of the fungus fruit body, cultivated by Sylvan Inc. and supplied by Atlas World USA, in four *in vivo* assays for antitumor-promoting activity. [1] The extract had strong inhibitory effects on two-stage carcinogenesis of mouse skin caused by 7, 12-dimethylbenz[α]anthracene (DMBA)/12-0-tetradecanoylphorbol-13-acetate (TPA) and by DMBA/UV B.

In the current work, the extract was evaluated *in vivo* for antitumor-initiating activity.

The aqueous extract exhibited a strong antitumor-initiating effect on mouse skin tumors induced by peroxynitrite as an initiator and TPA as a promoter. In the promoting step, the extract delayed the formation of papillomas and reduced the number of papillomas per mouse compared to the control group. Together with our prior results, the data show that the extract has both antitumor-initiating and antitumor-promoting activity on two-stage carcinogenesis.

Both results suggest that *Agaricus blazei* extract could be promising for cancer prevention.

[1]M. Kozuka *et at,* The 43rd Ann. Meeting of the ASP, New Brunswick, NJ, July 2002, P-34.

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DEVELOPMENT OF ASSAY METHOD OF ANTI-ALLERGIC PROMOTERS BY USING HEL-INDUCED BLOOD FLOW DECREASE

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We discovered a phenomenon in which the blood flow in vein microcirculation markably decreased in response to hen egg white (HEL)-sensitization (the stage preceding anaphylaxis) without any change in blood pressure. Using this blood flow decrease as a guide, we developed an *in vivo* assay method to search for substances which can prevent allergies.

Histamine, serotonine and PAF, which are involved in the blood flow decrease in anaphylaxis, were not involved in the blood flow decrease in response to HEL-sensitization. On the other hand, COX-1, COX-2, TXA_2, ET-1, PGI_2 and GE from vascular endothelial cells as well as NO from iNOS affected the blood flow decrease. Thus these substances might injure vascular endothelial cell, and cause the decrease in the blood flow in vein microcirculation. In addition, study of the knockout mouse suggested that the iNOS expression is not indispensable for the blood flow decrease but leads to deterioration of the condition. This mechanism is similar to the disease development mechanism of organ ischemic disease.

Our method can be used to search for preventive agents against allergies involving NO, COX-1, 2 and PGI_2. This is the first report to clarify a correlation between blood flow in vein microcirculation and the promotion (afferent) stage of allergy.

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INHIBITORY EFFECTS OF XANTHONES FROM GUTTIFERAE PLANTS ON PAF-INDUCED HYPOTENSION

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Platelet activating factor (PAF) is a potent mediator involved in many diseases such as allergy, inflammation, pruritus, thrombosis, cardiovascular disease and renal disease. Therefore, inhibitory compounds against PAF-induced reactions should be useful for the treatment of many diseases. We previously developed an *in vivo* assay system to search for inhibitors of exogenous PAF-induced hypotension from natural sources. In this study, we investigated the activities of 22 xanthones isolated from three Guttiferae plants (*Hypericum patulum*, *Calophyllum inophyllum* and *C. austroindium*) against PAF-induced hypotension.

Most xanthones showed inhibitory effects against PAF-induced hypotension**.** Caloxanthone E, patulone, 1,3,5,6-tetrahydroxy-2-isoprenylxanthone, 6-deoxyjacareubin and guanandin showed strong inhibitory activity. Their ID_{50} values were greater than that of ginkgolide B (BN-52021), a natural PAF-antagonist from the *Ginkgo biloba*. The existence of isoprenyl groups in a xanthone skeleton was useful for inhibitory activity. Cyclization of the isoprenyl groups, dimethyl pyran ring, did not reduce inhibitory activity. Xanthones from Guttiferae plants might be effective for the preservation and treatment of PAF-mediated diseases.

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CYTOTOXIC FRACTIONS FROM THE LEAVES OF *TACHIA GRANDIFLORA* MAGUIRE &WEA VER (GENTIANACEAE)

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Stem and leaf extracts were pre-screened using SRB quantification and leaf methanol and ethanol extracts showed appreciable cytotoxicity in human breast (MCF-7) and colon (HCT-8) tumor cell lines. Liquid-liquid partitioning of the leaf ethanol extract yielded hexane, $CHCl_3$, BuOH and H2O-MeOH fractions. Only the hexane and $CHCl_3$ fractions were active, inhibiting murine melanoma (B-16) and HCT -8 cells. These two active fractions suffered sequential column chromatography (CC) on silica gel using different eluent systems and yielded a number of very active sub-fractions. In all, 76 fractions and subfractions were tested and 22 were considered strongly active against either HCT -8 and/or B-16 tumor cells, while 3 samples had only moderate activity against MCF -7 cells. The most active fractions and sub-fractions were tested against five tumor cell lines using the MTT assay, and four fractions demonstrated significant cytotoxicity. Cell lysis was discarded as a possible mechanism for *in vitro* cytotoxicity given that these fractions did not exhibit hemolytic activity. Anti-mitotic potential was confirmed in tests using sea urchin embryos. The greatest anti-proliferative activity was found in the 2nd (2 samples) and 3rd generation (2 samples) cCC sub-fractions of the $CHCl_3$ fraction.**Financial Support: CNPo, FINEP, Bioamazonia-BASA-FEPAD, BNB.**

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COMPARISON OF BIFLORIN CYTOTOXICITY AGAINST HUMAN BREAST CANCER CELLS (MCF-7) AND PERIPHERAL LYMPHOCYTES

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Capraria biflora L. (Scrophulariaceae) is a perennial shrub distributed in North and South America. Its leaves are used as analgesic agent, specifically in menstrual pain and postpartum, and against otitis, hemorrhoids and rheumatic disorders and its roots have antibacterial properties.
Our aim was to compare the cytotoxic activity of biflorin isolated from the roots of *Capraria biflora* against MCF-7 (breast cancer) and peripheral blood lymphocytes *in vitro.* The cytotoxicity was evaluated by MTT test (24 and 72 h), Hematoxilin/Eosin staining and 5-Bromo-2'-deoxyuridine (BrdU) incorporation.
Our results suggest that biflorin was cytotoxic to MCF-7 (IC_{50} = 1.52 and 0.43 µg/mL after 24 and 72 hours, respectively), but non cytotoxic to peripheral lymphocytes (IC_{50} > 25 Ilg/mL). The cytotoxic activity seemed to be related to DNA synthesis inhibition, as revealed by the reduction of incorporation of BrdU after 24 hours of incubation on human breast cancer cells.Financial Support: CNPq, FINEP, CAPES, FUNCAP, BNB.

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BIOPROSPECTION OF COMPOUNDS WITH ANTITUMOR ACTIVITY IN EUDISTOMA V ANNAMEI MILLAR, 1977 (TUNICA T A, ASCIDIACEA)

Paula C. Jimenez[1], Diego V. Wilke[1], Claudia Pessoa[1], Manoel Odorico de Moraes[1], Thiago O. Bass0[2], Renata Takeara[2], Norberto P. Lopes[2], Leticia V. Costa-Lotufol*
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Eudistoma vannamei, a tunicate collected off the coast of Ceará (Brazil), has shown to be active in a number of bioassays performed with the crude extract. This study consisted of the bioguided fractionation of the hydro-methanolic extract and pharmacological characterization of the active fractions. The extract was partitioned by various solvents and fractionated by chromatography in silica gel 60 and sephadex LH-20 columns. The samples' activities were monitored through the MTT assay. The fractions DCM-14 through 17, derived from the CH_2Cl_2 phase were the most active (IC_{50} < 1 J-lg/mL). 6-ethylamino-l-methyl-piperazine-2,5-dione was isolated from the CH_2Cl_2 phase and identified as the major component, however, it lacked activity upon cell proliferation. The H^1RNM spectra of the mentioned fractions showed a number of compounds derived from that diketopiperazine, which were not identified. The fractions effect upon HL-60 cells was understood by studies of viability (exclusion by trypan blue), proliferation (BrdU incorporation and growth curve) and cell death induction (cell morphology, annex in-V and EB/ AO). The active fractions displayed a pronounced inhibitory effect on DNA synthesis and also induced apoptosis. Financial support: CNPq, FUN CAP, FINEP.

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DIFFERENTIATION INDUCTION OF PISOSTEROL FROM *Pisolithus tinetoris* (Pers) Cok. & Couch IN HL60 LEUKEMIA CELLS

Montenegro, R.C.[1]; Nogueira, M.A.S.[1]; Andrade-Neto, M.[2]; Bezerra, F.S[2]; Gomes, A.S.[1]; Souza, M.H.L.p.[1]; Ferreira, F.V.A.[3]; Moraes, M.O. [1]; Pessoa, C. [1]; Costa-Lotufo, L.V.[1]*
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The fungi genus of *Pisolithus* (sc1erodermataceae) has only one member, it is however known by two species names, *Pisolithus tinetorius,* and *Pisolithus arrhizus. Pisolithus* is widely distributed, and is often found in adverse environments. Sites are commonly characterized by high summer soil temperatures, extreme acidity, droughtiness, low fertility, and high levels of toxic metals. In a preview study, we demonstrated its cytotoxic ability against cancer cell lines in vitro.

Our aim was to evaluate the differentiation induction of Pisosterol isolated from *P. tinetorius* in HL60 leukemia cell lines. Analyses were performed by NBT, Hematoxilin/Eosin staining, mieloperoxidase and PAS tests.

Our results suggested that pisosterol induces differentiation in HL60 cells, as observed through NBT analysis, Hematoxylin/Eosin staining and mieloperoxidase activity. PAS analysis gave negative results. Financial support: CNPq, FINEP, FUNCAP, CAPES

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NOVEL NATURAL PRODUCTS FROM BACTERIAL AND FUNGAL STRAINS OBTAINED BY HIGH THROUGHPUT CULTURING

Mustafa Varoglu*, Lisa Rahbaek, Asfia Qureshi, Sasha Marks, Mimi Zhao, Yukiko Sato, Ashish Paradkar, Ken Wong, David Gustafson, Theresa Nibert, Karsten Zengler, Gerardo Toledo, Marion Walcher, Greg Clark, Imke Haller, Martin Keller, Gary Woodnut, Jay Short. Diversa Corp. 4955 Director's Place, San Diego, CA 92121, USA.

Diversa will present its continued optimization and integration of high throughput culturing, dereplication, isolation and structure elucidation techniques for the generation of diverse libraries of biologically active novel and known natural products. Extracts from fermentations of rare and novel bacteria and fungi are fed into our accurate mass based dereplication methods to identify cultures producing novel compounds. The use of advanced preparative HPLC, LC-MS-MS and NMR instrumentation and strategies has allowed us to rapidly isolate and characterize novel biologically active compounds with minimal scale up. These methods have allowed Diversa to generate novel compounds from unique organisms in a timely and cost effective manner.

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INACTIVATION OF THE CARBAMOYLTRANSFERASE GENE REFINES THE POST-POLYKETIDE SYNTHASE MODIFICATION STEPS IN THE BIOSYNTHESIS OF THE ANTITUMOR AGENT GELDANAMYCIN

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[1]Korea Research Institute of Bioscience and Biotechnology, Daejeon, Korea, [2]Chungnam National University, Daejeon, Korea, [3]Inje University, Gimhae, Gyeongnam, Korea, [4]Sun Moon University, Asan, Chungnam, Korea

The post-polyketide synthase modification of geldanamycin biosynthesis is of interest as a means of introducing structural diversity into this compound. From the inactivation of a gene encoding carbamoyltransferase, we demonstrated that the C-17 hydroxylation and C-21 oxidation precede *O*-carbamoylation, and the hypothetical progeldanamycin does not carry double bond at the C-4,5 position. More importantly, our result revealed two new intermediates, indicating that the *O*-carbamoylation occurs prior to the C-4,5 cis-double bond formation in the geldanamycin biosynthesis.

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ANTI-COMPLEMENT ACTIVITY OF NOR-LIGNANS AND TERPENES FROM THE STEM BARK OF *STYRAX japonica*

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Korea Research Institute of Bioscience & Biotechnology Daejeon 305-333, Korea

Repeated column chromatography of a MeOH-soluble fraction from *Styrax japonica* (stem bark) on RP-C18 let to the isolation of three benzofurans and two terpenes. Three new compounds was determined as 5-(3"-hydroxypropyl)-7-methoxy-2 (3' ,4' -dimethoxyphenyl)-benzofuran 3-0-[β-D-xylopyranosyl-(1 ->2)- β -D glucopyranoside] (1, styraxlignolide A), 3 p, 7P-dihydroxy-2-oxomansumbinone 3-0-[BD-glucopyranoside-(1->2)-b-D-glucopyranoside] (2, styraxoside A), and 3β,17β dihydroxy-28-norolean-12-en-16-one *3-0-* α-L-rhamopyranoside-(1 ~2)-P-D glucuronopyranoside] (3, styraxoside B) by spectroscopic means and enzymatic hydrolysis including 2D-NMR..Known compounds were identified as egonol (4) and egonol 3-0-[β-D-xylopyranosyl-(1 ->2)- β-D-glucopyranoside] (5) by comparing their spectral data with those previously reported.
Styraxlignolide A (1), styraxoside B (3), egonol (4), and masutakeside I (5) inhibited the hemolytic activity of the complement system with IC_{50} values of 123, 65, 33, and 166 *mM,* respectively. Of all the compounds tested, egonol (4) was the most active, displaying an IC_{50} value of 33 *mM.*

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INCREASE OF CASPASE-3 ACTIVITY BY LIGNANS FROM *MACHILUS THUNBERGII* IN HL-60 CELLS

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Nine lignans and two butanolides were isolated from stem-bark of *Machilus thunbergii* (Lauraceae) and their structures were identified as machilin A **(1),** licarin B (2), zounin B (3), macelignan (4), secoisolancifolide (5), isolancifolide (6), oleiferin C (7), meso-dihydroguaiaretic acid (8), licarin A (9), machilin F **(10),** and nectandrin (11).

Compounds **1-11** were examined for the their apoptosis-inducing activity in human promyelocytic leukemia HL-60 cells based on caspase-3 activity, and DNA fragmentation. Among them, macelignan (4), oleiferin C (7), meso-dihydroguaiaretic acid (8), licarin A (9) were observed to induce apoptotic activities significantly.

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ALKALOIDS FROM *TODDALIOPSIS BREMEKAMPII* (RUTACEAE)

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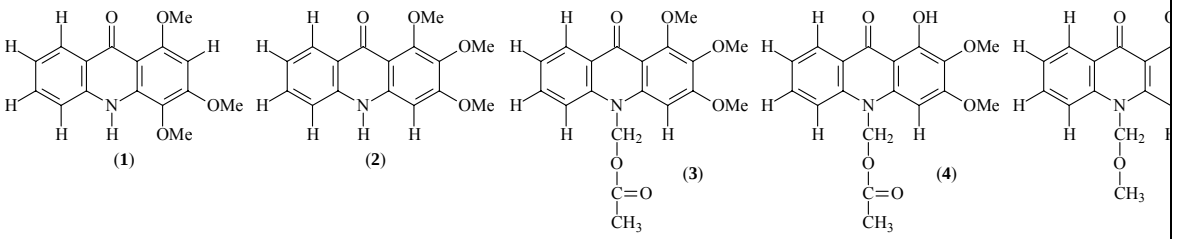
Toddaliopsis Engl. (Rutaceae), is a small African genus comprising only three species, including *T. bremekampii* I. Verd.(Rutaceae), or the Wild-Mandarin, which is widely distributed in south-eastern Africa where it grows as a small evergreen tree in dry woodland and scrub forest.

The dichloromethane extract of the leaves of *T. bremekampii* has yielded five novel acridone alkaloids, toddaliopsins A-E (**1-5**), of which toddaliopsins C-E (**3-5**) are the first reported acridone alkaloids with substituted N-methyl groups. Toddaliopsin D (**4**) in particular displays anti-inflammatory activity.



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METABOLIC ENGINEERING OF ISOFLAVONOID BIOSYNTHESIS IN ALFALFA

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Isoflavone phytoestrogens have generated considerable interest as nutriceuticals due to numerous studies which have linked dietary consumption of isoflavones with lower instances of cancer, improvement of cardiovascular disease, and alleviation of post-menopausal symptoms. However, in the vast majority of these studies it is difficult to conclude whether the observed health benefits are due to isoflavones or whether they are attributable to other dietary constituents. Isoflavones are naturally limited to legumes and major dietary sources include soy. To better address the effects of dietary isoflavones on health, we aim to generate novel plant material with defined levels of isoflavone phytoestrogens for animal feeding studies. The forage legume alfalfa is an excellent model system for this work, since alfalfa pellets are fed to laboratory animals. We have engineered genistein production in alfalfa leaves by expression of the enzyme isoflavone synthase (IFS). In addition to genistein, biochanin A and pratensein were also found to accumulate in leaves of IFS-expressing alfalfa. The engineered isoflavones were present as glucosides, the main form of isoflavones in soybean. Two lines, each harboring a single copy of the introduced transgene, were found to accumulate the highest levels of genistein, which approached 100 nmol/g FW under certain environmental conditions. Microarray analysis was used to detect any unexpected changes in gene expression in these plants in response to IFS-expression.

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AZAPHILONES, FURANOISOPHTHALIDES, AND AMINO ACIDS FROM THE EXTRACTS OF MONASCUS PILOSUS-FERMENTED RICE (RED-MOLD RICE) AND THEIR CHEMOPREVENTIVE EFFECTS

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Six azaphilones, monascin (1), ankaflavin (2), rubropunctatin (3), monascorburin (4), rubropunctamine (5), and monascorburamine (6), two furanoisophthalides, xanthomonasin A (7) and xanthomonasin B (8), and two amino acids, (+)-monascumic acid (9) and (-)-monascumic acid (10), isolated from the extracts of *Monascus pilosus*--fermented rice (red-mold rice) were evaluated for their inhibitory effects on 12-0-tetradecanoylphorbol-13-acetate (TPA)-induced inflammation in mice, on the induction of Epstein-Barr virus early antigen (EBV-EA) by TPA in l cells, and on the activation of *(±)-(E)-methyl-2(E)-hydroxy-imino]-5-nitro-6-methoxy-3-hexemide* (NOR 1), a nit oxide (NO) donor. Among the compounds tested, seven compounds (1-6, and 10) on TPA-induced inflammation, and six compounds (1, 3-5, 9, and 10) on EBV-EA activation, exhibited potent inhibitory effects. All of the compounds tested showed moderate inhibitory effects on NOR 1 activation. Furthermore, compound 1 exhibited remarkable inhibitory effect on an *in vivo* two-stage carcinogenesis test of mouse tumor using peroxynitrite as an initiator and TPA as a promoter.

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USE OF HPLC-SPE-NMR IN DEREPLICATION OF NATURAL PRODUCTS MIXTURES

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Hyphenation ofHPLC with SPE and NMR provides a tool for rapid analysis of complex mixtures, including plant extracts and natural products mixtures without need of preparative isolation of the constituents. HPLC is characterized by high efficiency in analytical separation of practically speaking all families of secondary metabolites. SPE (solid phase extraction) allows sequential trapping of the HPLC peaks directly on a cartridge, prior to desorption with a deuterated solvent and direct transfer to the NMR spectrometer. SPE allows implementation of elaborate HPLC gradients with non-deuterated solvents, as well as up-concentration of minor compounds by multiple trapping. The whole procedure considerably shortens the usually timeconsuming process of natural products identification. Known compounds can be early detected and preparative protocols can be focused on molecules of interest. Dereplication of a total alkaloid extract from *Remijia peruviana* bark (Rubiaceae) will be described as an example of analytical power of the method.

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EVALUATION OF THE CHEMICAL CONSTITUENTS OF *CLEMATIS LIGUISTICIFOLIA* AND *AKEBIA TRIFOLIATA* FOR THEIR TOXIC EFFECTS ON RENAL CELLS.

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Plants belonging to *Akebia*, *Aristolochia* and *Clematis*, genera are commonly mentioned as mutongs in Traditional Chinese medicine and are been widely used. The plants of *Aristolochia* spp., those containing the derivatives of aristolochic acid (AA), are reported to posses nephrotoxic/carcinogenic effects in humans and animals. In the same context, USFDA had banned the use and sale of products/formulation containing AAs. In the present investigation, 4 species of *Clematis* and 2 species of *Akebia* were analysed for their cytotoxic effects on LLC-PK_1 cell, a renal epithelial cell line, using neutral red cell viability assay with AA-1 as a positive control. The plant materials were found to be devoid of AAs during comparative HPLC analysis. Two of the most toxic species from each genus namely *Clematis liguisticifolia* and *Akebia trifoliate*, identified in preliminary toxicity screening, were subjected to bioactivity guided fractionation. The study yielded hederagenin, hederagenin derivatives and their glycosides as the most toxic constituents. The study investigates the mechanisms for the cytotoxicity and the

structural requirements of these constituents for such activity. The study warrants further investigation for their nephrotoxic effects.