How useful are monographs of herbal extracts of the European Pharmacopoeia for the development of herbal medicinal products?

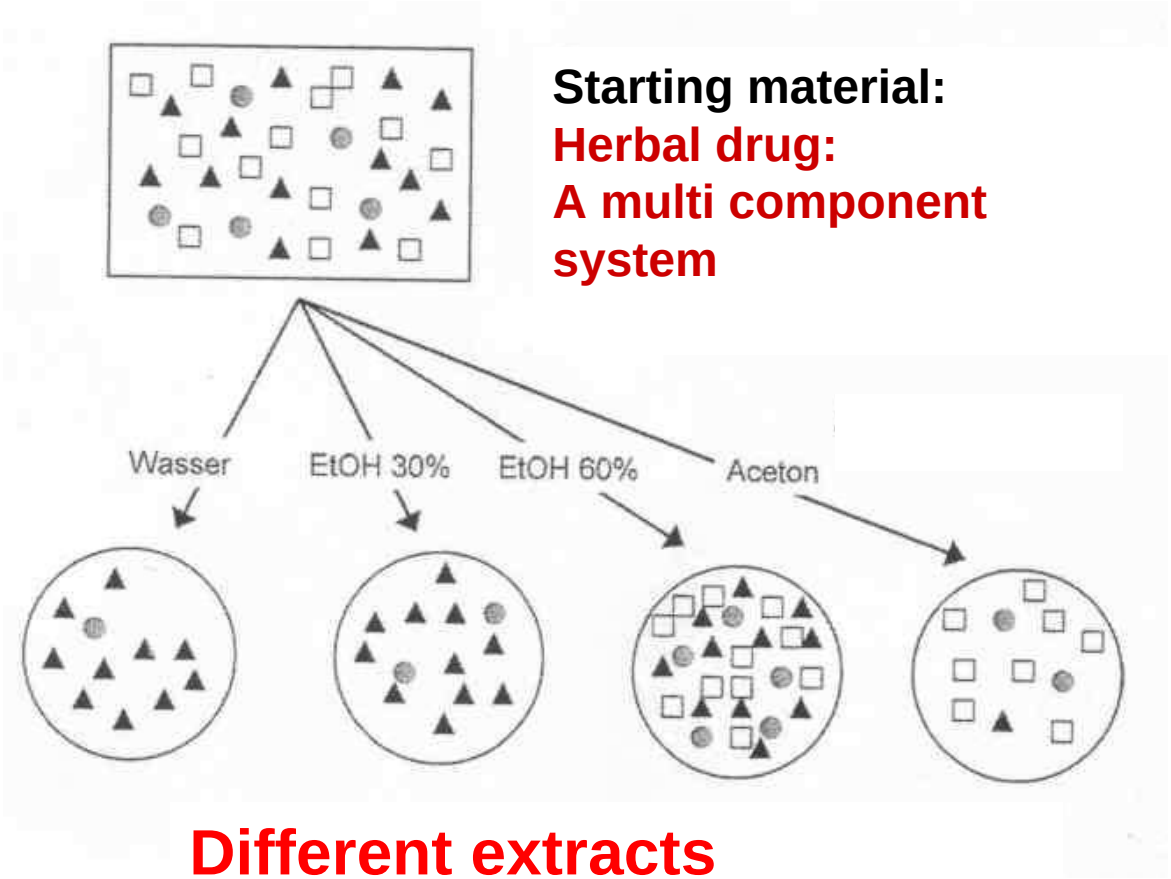
Workshop of the GA-Permanent Committees on
Manufacturing and Quality Control of Herbal Medicinal Products
and
Regulatory Affairs on Herbal Medicinal Products

How useful are herbal extracts of the European Pharmacopoeia for the development of herbal medicinal products?

Topic 1:

Solvents of herbal extract monographs of Ph Eur. with some selected phytochemical profiles and the consequences for the equivalence of herbal medicinal products.

The selectivity of solvents



Starting material:
Herbal drug:
A multi component system

Different extracts

– really?

St. John’s wort: Clinical data

Different solvents – similar clinical data

St. John's wort: Clinical data

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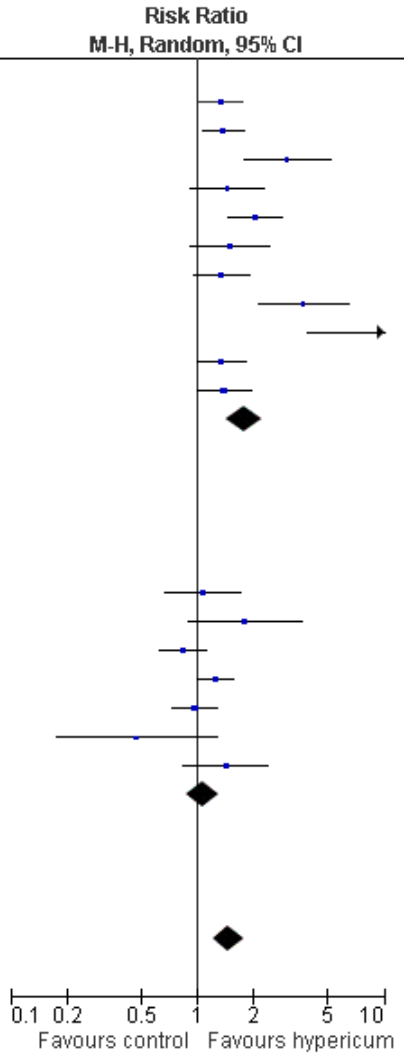
Study or Subgroup	Hypericum Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.5.1 Studies from German-speaking countries						
Bracher 2001	64	109	48	109	7.0%	1.33 [1.02, 1.74]
Gastpar 2006	71	131	51	130	7.0%	1.38 [1.06, 1.80]
Hänsgen 1996	35	53	12	55	4.8%	3.03 [1.77, 5.17]
Kalb 2001	23	37	15	35	5.4%	1.45 [0.92, 2.29]
Kasper 2006	159	243	26	81	6.5%	2.04 [1.47, 2.83]
Laakmann 1998	24	49	16	49	5.1%	1.50 [0.92, 2.46]
Philipp 1999	67	106	22	47	6.4%	1.35 [0.96, 1.89]
Schrader 1998	45	80	12	79	4.6%	3.70 [2.12, 6.46]
Uebelhack 2004	41	70	4	70	2.4%	10.25 [3.88, 27.09]
Volz 2000	46	70	34	70	6.8%	1.35 [1.01, 1.82]
Witte 1995	34	48	25	49	6.5%	1.39 [1.00, 1.93]
Subtotal (95% CI)		**996**		**774**	**62.5%**	**1.78 [1.42, 2.25]**
Total events	609		265			
Heterogeneity: $Tau^2 = 0.11$; $Chi^2 = 40.02$, df = 10 ($P < 0.0001$); $I^2 = 75\%$						
Test for overall effect: $Z = 4.92$ ($P < 0.00001$)						
1.5.2 Studies from other countries						
Bjerkenstedt 2005	22	54	21	55	5.3%	1.07 [0.67, 1.70]
Fava 2005	17	45	9	43	3.7%	1.80 [0.90, 3.60]
HDTSG 2002	46	113	56	116	6.8%	0.84 [0.63, 1.13]
Lecrubier 2002	98	186	80	189	7.4%	1.24 [1.00, 1.54]
Montgomery 2000	55	123	57	124	6.9%	0.97 [0.74, 1.28]
Moreno 2005	4	20	11	26	2.4%	0.47 [0.18, 1.27]
Shelton 2001	26	98	19	102	4.9%	1.42 [0.84, 2.40]
Subtotal (95% CI)		**639**		**655**	**37.5%**	**1.07 [0.88, 1.31]**
Total events	268		253			
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 10.91$, df = 6 ($P = 0.09$); $I^2 = 45\%$						
Test for overall effect: $Z = 0.70$ ($P = 0.48$)						
Total (95% CI)		**1635**		**1429**	**100.0%**	**1.48 [1.23, 1.77]**
Total events	877		518			
Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 68.87$, df = 17 ($P < 0.00001$); $I^2 = 75\%$						
Test for overall effect: $Z = 4.21$ ($P < 0.0001$)						



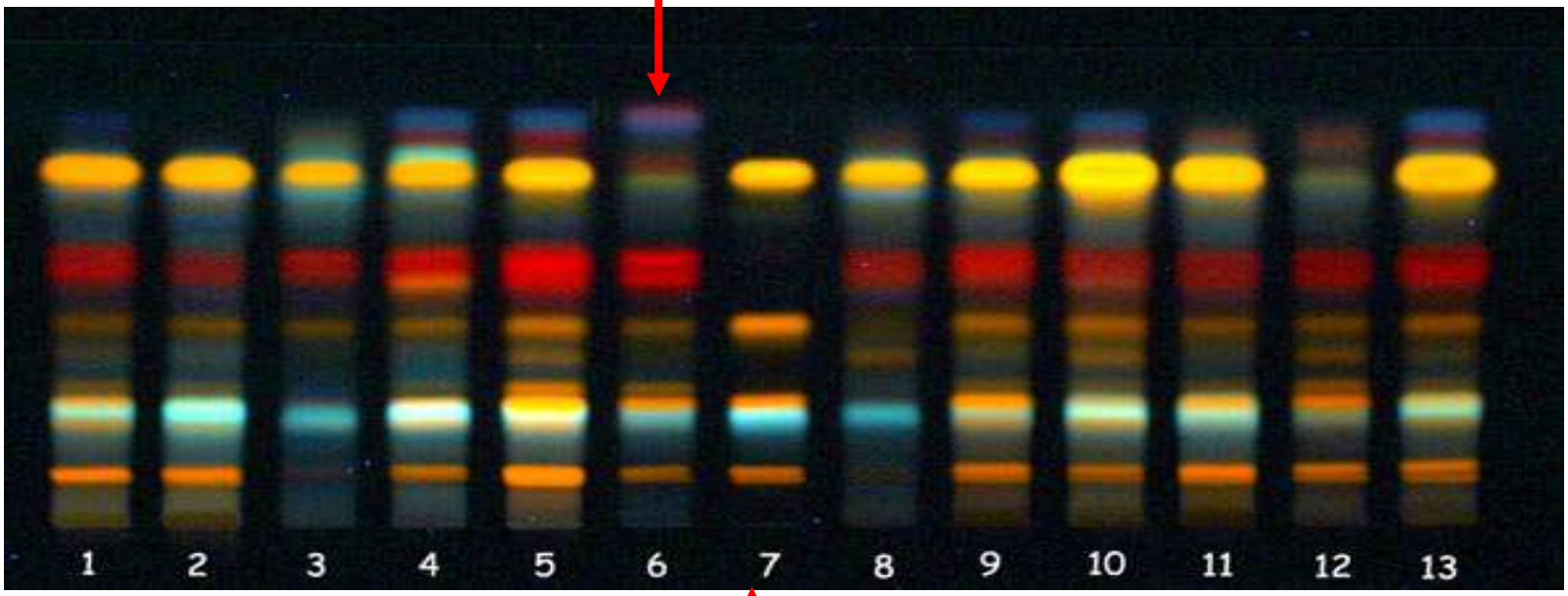
St. John's wort: Clinical data

Different solvents – equal clinical data

Methanol 80%
Ethanol 50%
Ethanol 60%
Ethanol 68%
Ethanol 70%
Ethanol 80%

St. John's wort: TLC of Tinctures in Switzerland

Trace 6: Herbal drug



Trace 7: Reference compounds.

Extraction solvents: Ethanol 44-70 Vol%

Questions to the Pharmacopeia

- **How specific are solvents ?**

- Should toxic solvents like methanol be avoided for dry extracts ?

- Do we need new clinical and toxicological studies after a small change in solvent mixtures ?

Ph Eur Monographs for Extracts

- General Monograph 0765 Extracts

Tinctures

- Standardised Tinctures (4)
- Tinctures (9)

- Liquid extracts (4)

- Dry extracts (24)

The Ph Eur monograph 0765 extracts….

…is generally a useful tool for the manufacturer.

Remarks concerning solvents

No restriction concerning solvents
(ethanol or other suitable solvents)

Recovered or recycled solvents may be used

Potable water may be suitable*

Solvents have to be declared

***A new monograph „Water for extraction“ has been published in PharmEuropa 21.2.**

Solvents for Standardised Tinctures

1812 Belladonna leaf tincture stand.	70 per cent *V/V* ethanol
2337 Capsicum tincture stand.	70-85 per cent *V/V* ethanol
1530 Ipecacuanha tincture stand.	70 per cent *V/V* ethanol
1841 Opium tincture standardised.	Equal volumes of 70 per cent *V/V* ethanol and water

Solvents for Tinctures

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1809 Arnica Tincture 1:10	60-70 per cent *V/V* ethanol
1604 Bitter-orange-epicarp and mesocarp tincture 1:5	70 per cent *V/V* ethanol
1819 Cinnamon tincture 1:5	70 per cent *V/V* ethanol
1870 Gentian tincture 1:5	70 per cent *V/V* ethanol
1877 Myrrh Tincture 1:5	90 per cent *V/V* ethanol
1888 Rhatany tincture 1:5	70 per cent *V/V* ethanol
1889 Sage tincture 1:10	70 per cent *V/V* ethanol
1895 Tormentil tincture 1:5	70 per cent *V/V* ethanol
1899 Valerian tincture 1:5	60-80 per cent *V/V* ethanol

Solvents for Liquid Extracts

1818 Cinchona liquid extract standardised	30-90 per cent *V/V* ethanol **or** a mixture of diluted hydrochloric acid, ethanol 96 per cent V/V, glycerol, water 1:2:5:20
1536 Liquorice ethanolic liquid extract standardised	70 per cent *V/V* ethanol
1864 Hawthorn leaf and flower liquid extract, quantified	30-70 per cent *V/V* ethanol
1544 Matricaria liquid extract	2.5 volumes of a 10 per cent m/m solution of ammonia (NH_3), 47.5 volumes of water und 50 volumes of ethanol (96 per cent).

Ethanol as solvent for dry extracts

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1294 Belladonnae leaf dry extract, standardised	70 per cent *V/V* ethanol
1214 Frangula bark dry extract, standardised	50-90 per cent *V/V* ethanol
1875 Ipecacuanha liquid extract, standardised	60-80 per cent *V/V* ethanol
2313 Olive leave dry extract	65-96 per cent *V/V* ethanol
1261 Senna leaf dry extract, standardised	50-80 per cent *V/V* ethanol).
2309 Vitex agnus castus dry extract (published in Pharmeuropa)	40-80 per cent *V/V* ethanol.

Water as solvent for dry extracts

0259 Aloes dry extract, standardised	Boiling water
2389 Artichoke leaf dry extract	Water of minimum 80℃
2378 Liquorice dry extract for flavouring purposes	Water
1839 Opium dry extract, standardised	Water
2400 Valerian dry aqueous extract	Water not less than 60°C

Ethanol and methanol as solvents for dry extracts

2394 Fresh bilberry fruit dry extract, Refined and standardised	Ethanol 96 per cent *V/V* Methanol minimum 60 per cent *V/V*
1882 Passion flower dry extract	Ethanol 40-90 per cent *V/V* Methanol 60 per cent *V/V* Acetone 40 per cent *V/V*
1874 St.John‘s wort dry extract, quantified	Ethanol 50-80 per cent *V/V* Methanol 50-80 per cent *V/V*
1898 Valerian dry hydroalcoholic extract	Ethanol 65-80 per cent *V/V* Methanol 40-55 per cent *V/V*

Water and alkanols as solvents for dry extracts

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1816 Boldo leaf dry extract	Hot water not less than 65℃ or a hydroalcoholic solvent equivalent in strength to ethanol 45-75 per cent *V/V*
1844 Cascara dry extract, standardised	Boiling water or a hydroalcoholic solvent at least equivalent in strength to ethanol 60 per cent *V/V*
1871 Devil‘s claw dry extract	Water or a hydroalcoholic solvent that is at most equivalent in strength to ethanol 95 per cent *V/V*
1898 Hawthorn leaf and flower dry extract	Water or a hydroalcoholic solvent equivalent in strength to a minimum of 45 per cent *V/V* ethanol

Water and alkanols as solvents for dry extracts (2)

2524 Melissa leaf dry extract	Hot water not less than 70℃ or a hydroalcoholic solvent that is at most equivalent in strength to ethanol 70 per cent *V/V*
2382 Peppermint leaf dry extract	Water of minimum 60℃ or ethanol 30-50 per cent *V/V*
2312 Willow bark dry extract	Water or a hydroalcoholic solvent equivalent in strength to a maximum of ethanol 80 per cent *V/V*

Organic solvents for dry extracts

1827 Ginkgo dry extract, refined and quantified	Organic solvents and their mixtures with water
2071 Milk thistle dry extract, refined and standardised	Ethyl acetate Acetone or mixture of acetone and water Ethanol or mixture of ethanol and water Methanol or mixture of methanol and water

Ph Eur Monographs for Extracts

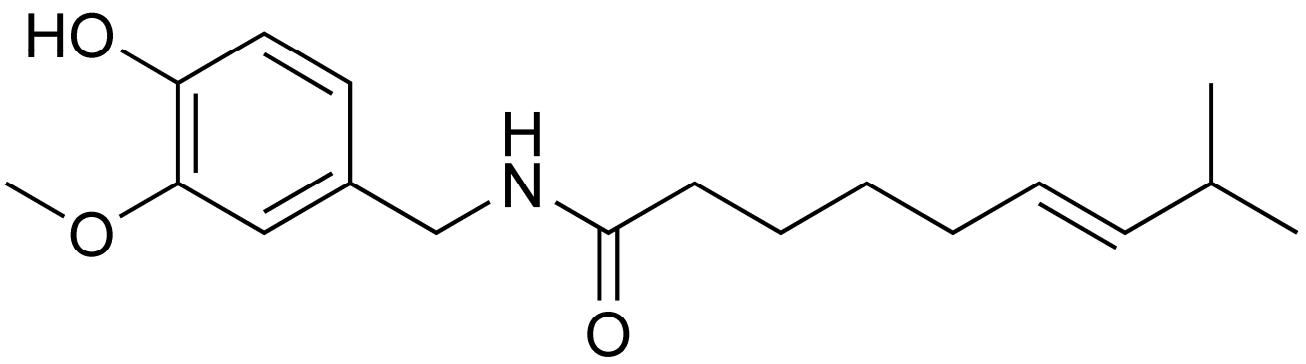
- **Are the solvents proposed in Ph Eur justified?**

2337 Capsicum tincture standardised

Production:

Solvent: 70-85 per cent *V/V* ethanol

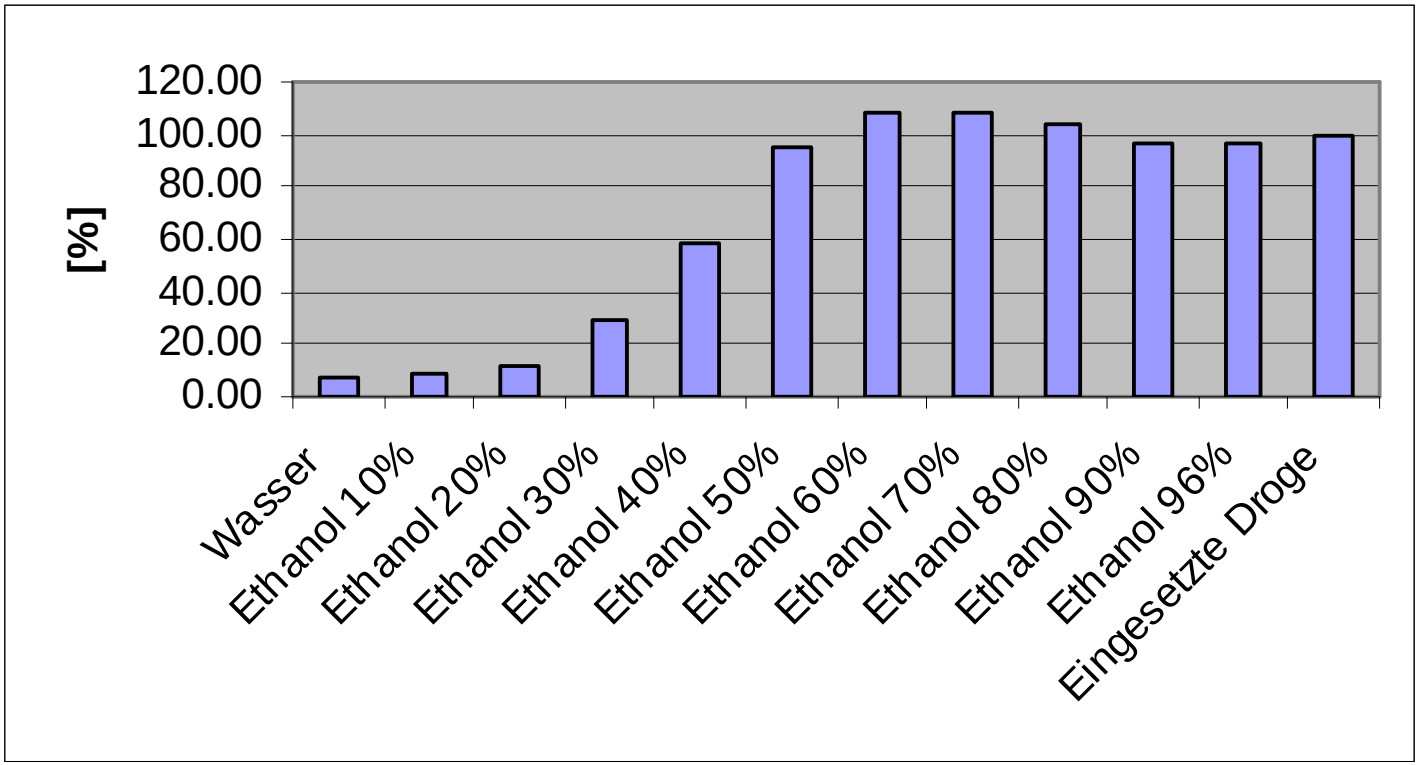
Active compounds: Capsaicin(s)



2337 Capsicum tincture standardised

Production:

Solvent: 70-85 per cent *V/V* ethanol



2337 Capsicum tincture standardised

Solvent: 70-85 per cent *V/V* ethanol

Conclusion

The solvent for capsicum tincture standardised is justified.

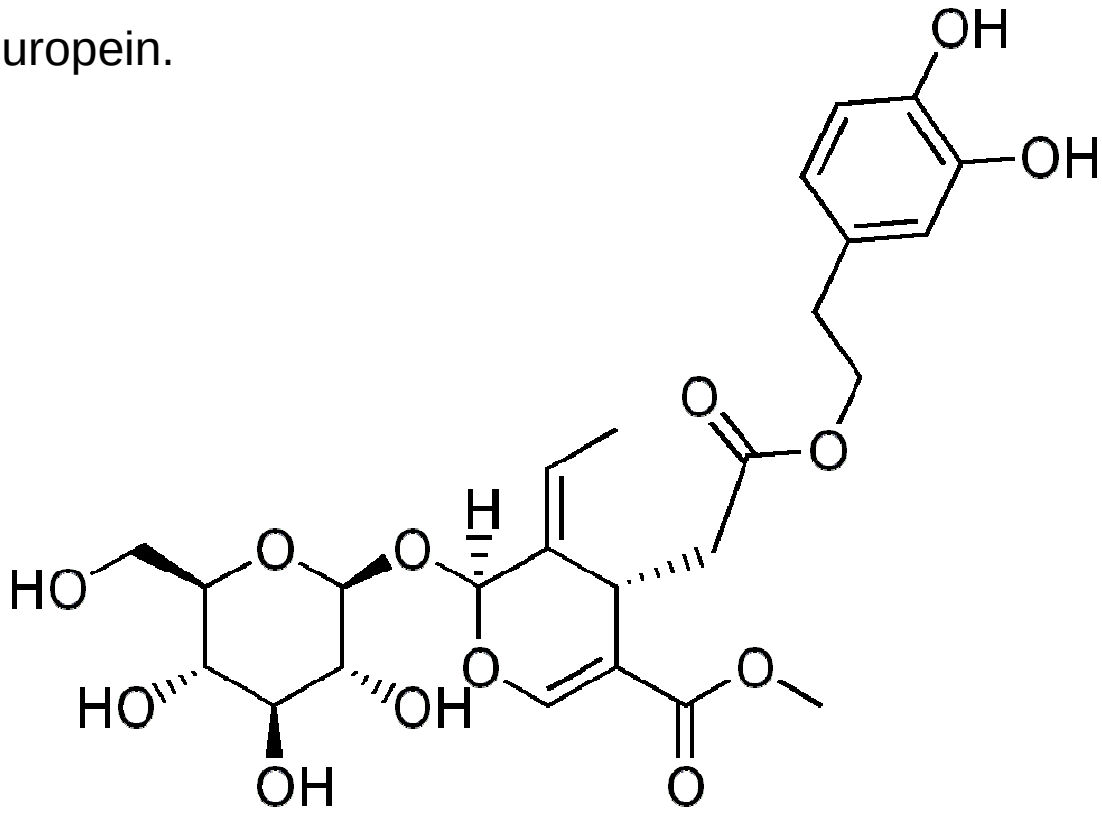
96 per cent V/V ethanol will be used for Capsicum oleoresin.
Capsicum extractum spissum will be published in Pharmeurope with 80 per cent V/V ethanol

2313 Olive leave dry extract

Production:

Solvent: 65-96 per cent *V/V* ethanol

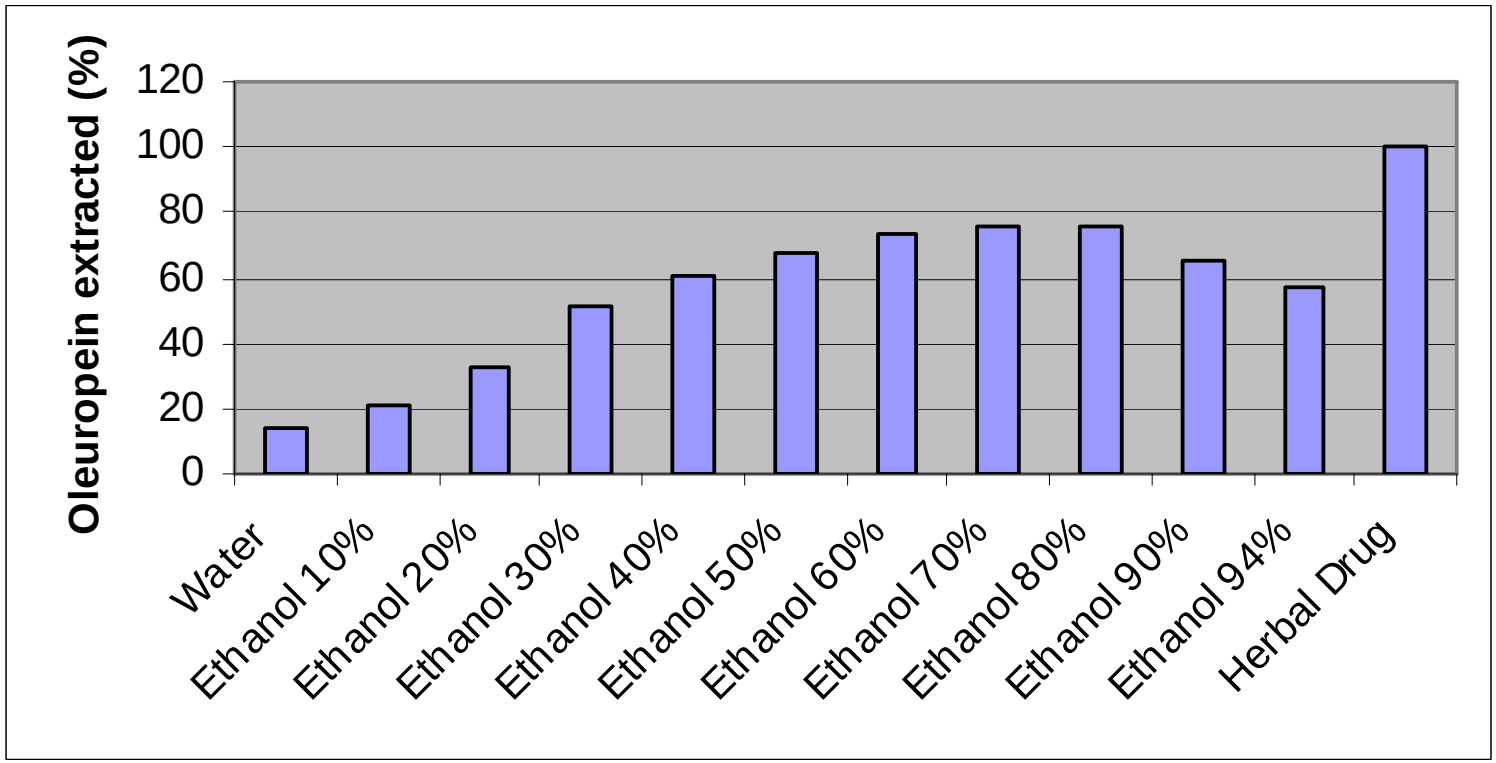
Lead compound: Oleuropein.



2313 Olive leave dry extract

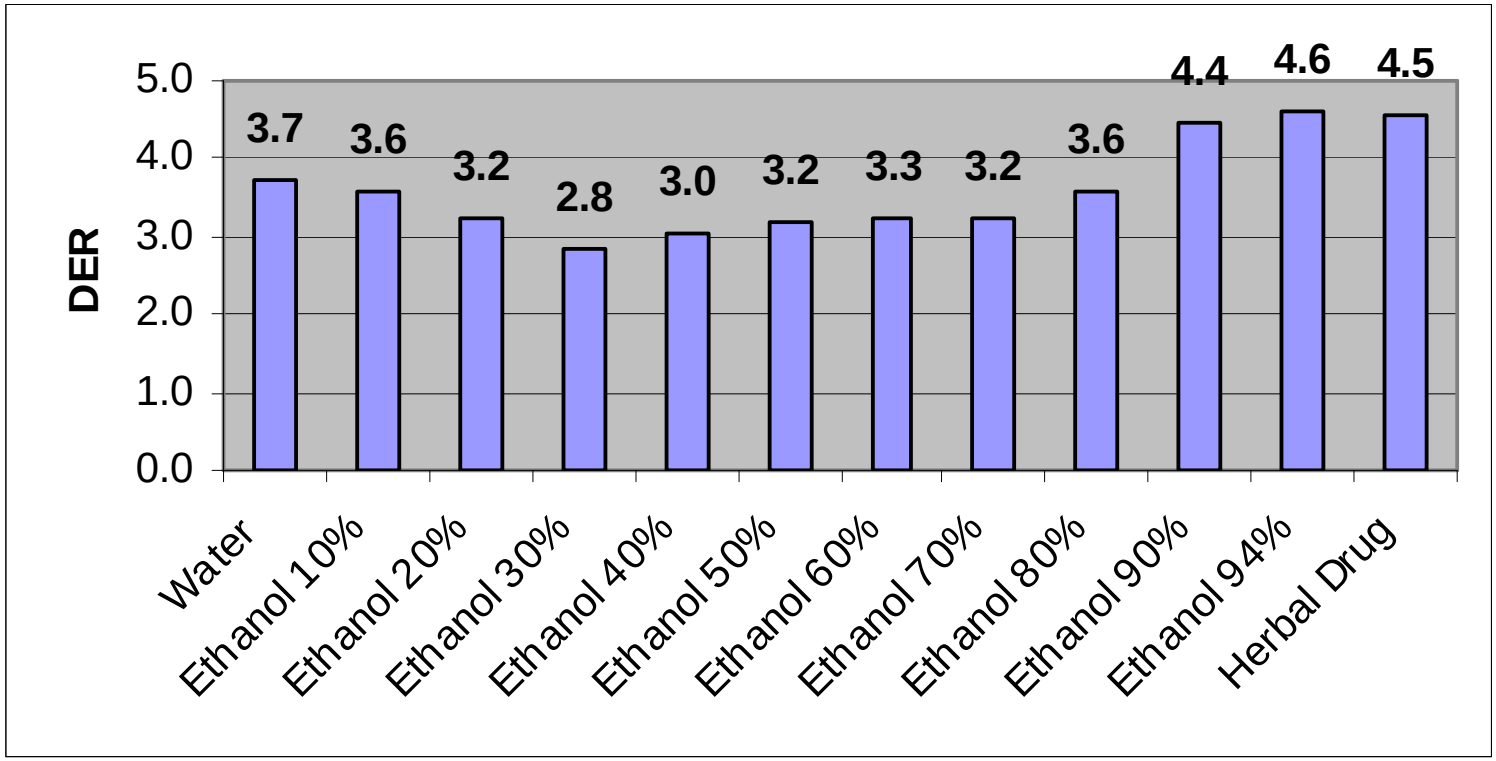
Solvent: 65-96 per cent *V/V* ethanol

Extraction profile for oleuropein



2313 Olive leave dry extract

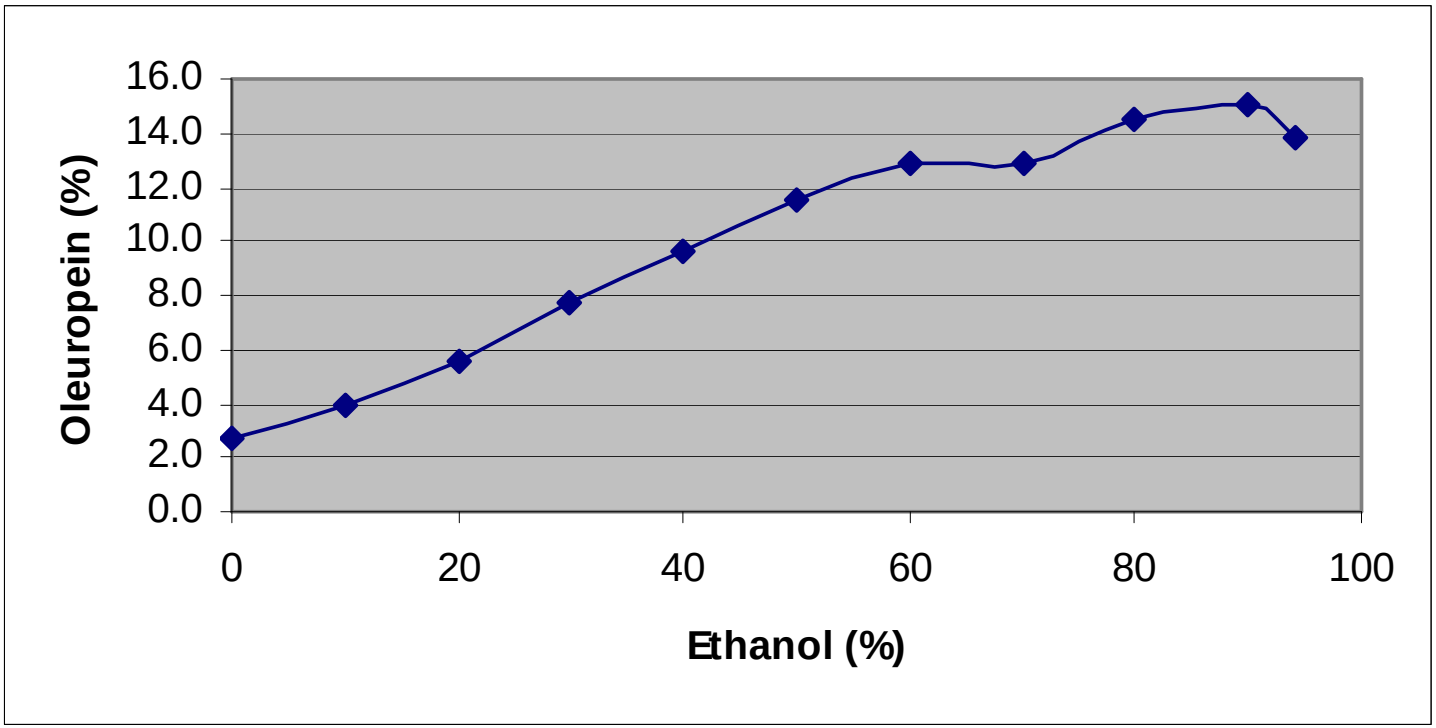
Solvent: 65-96 per cent *V/V* ethanol



2313 Olive leave dry extract

Solvent: 65-96 per cent *V/V* ethanol

Calculated Content of Oleuropein in Dry Extract



2313 Olive leave dry extract

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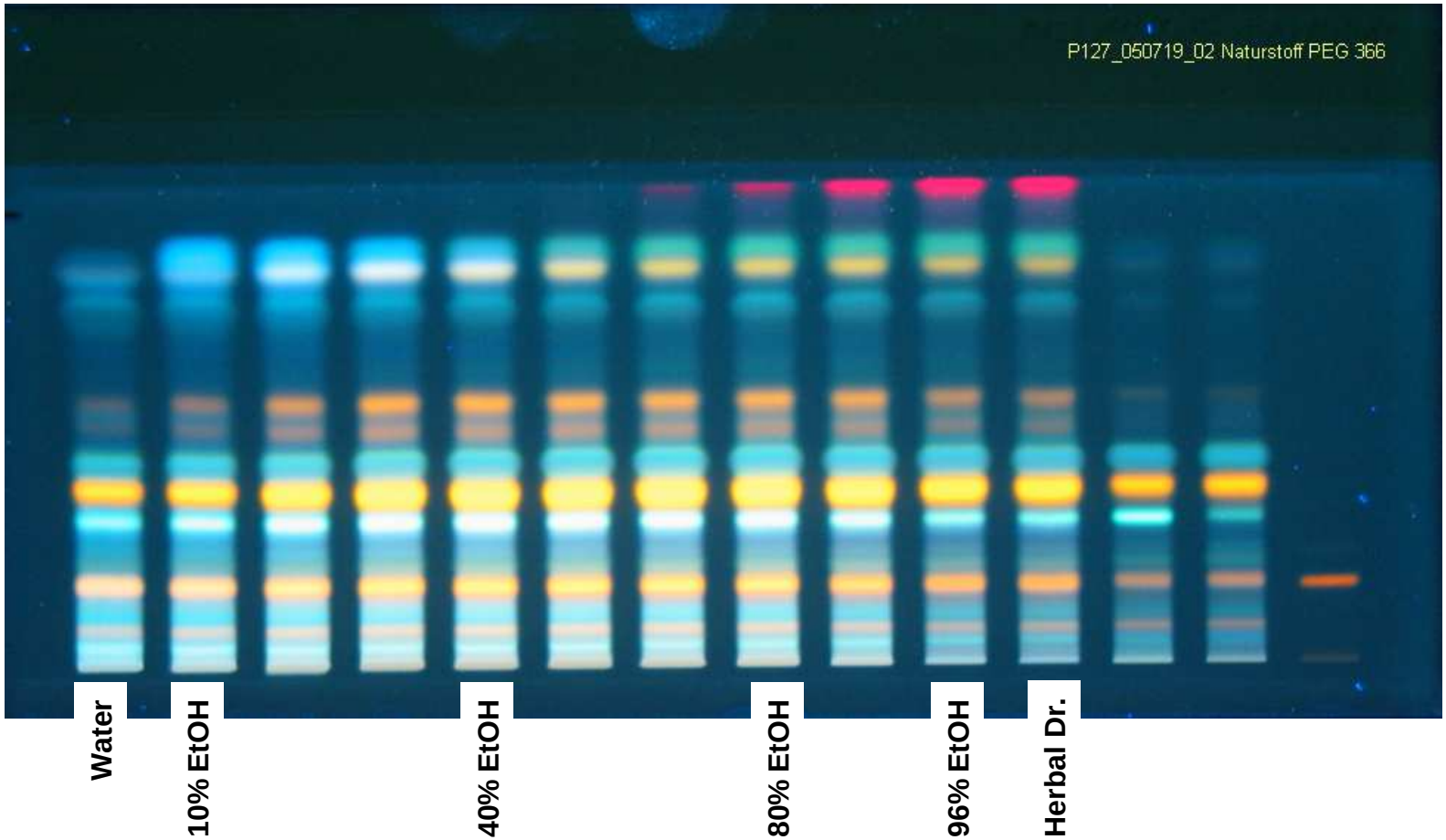
Solvent: 65-96 per cent *V/V* ethanol

HPTLC-Fingerprint of Flavonoids



2313 Olive leave dry extract

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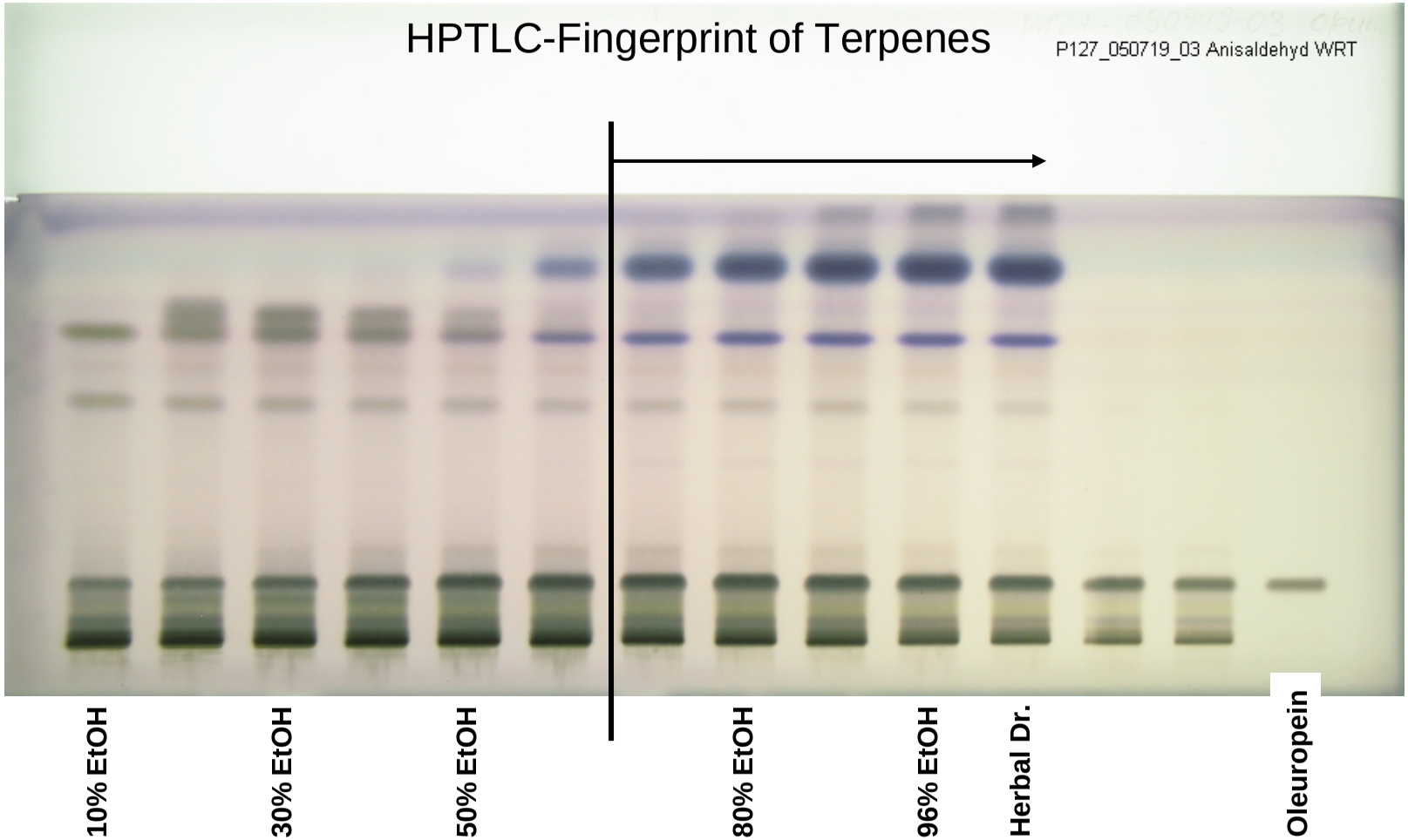
Solvent: 65-96 per cent *V/V* ethanol



2313 Olive leave dry extract

Solvent: 65-96 per cent *V/V* ethanol

Conclusion

The solvent for olive leave dry extract is justified.

1882 Passion flower dry extract

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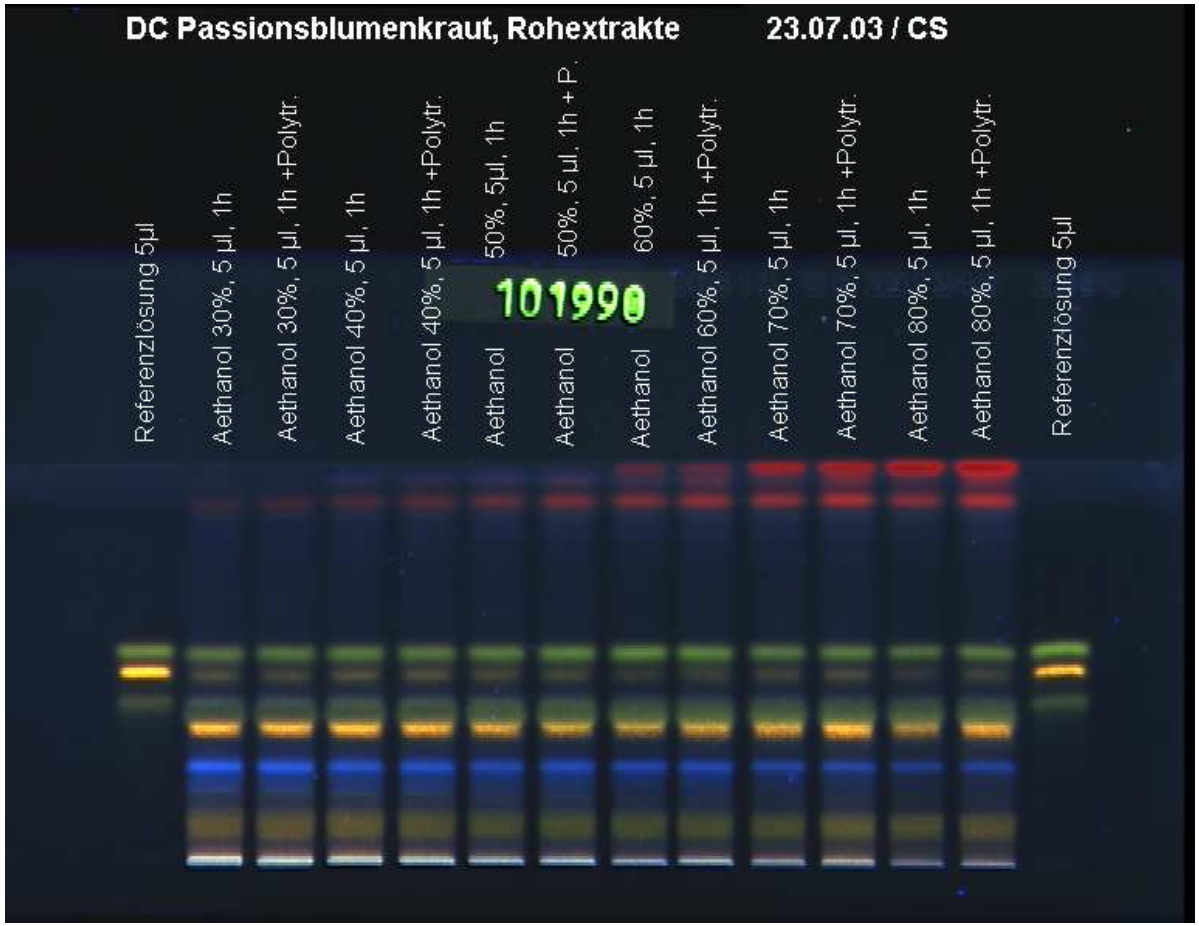
Production:

Solvent: 65-96 per cent *V/V* ethanol



1882 Passion flower dry extract

Solvent: 65-96 per cent *V/V* ethanol

Conclusion

65-96% ethanol as solvent for passion flower dry extract is justified.

30-65% ethanol is equivalent concerning flavon-C-glycosides and similar compounds.

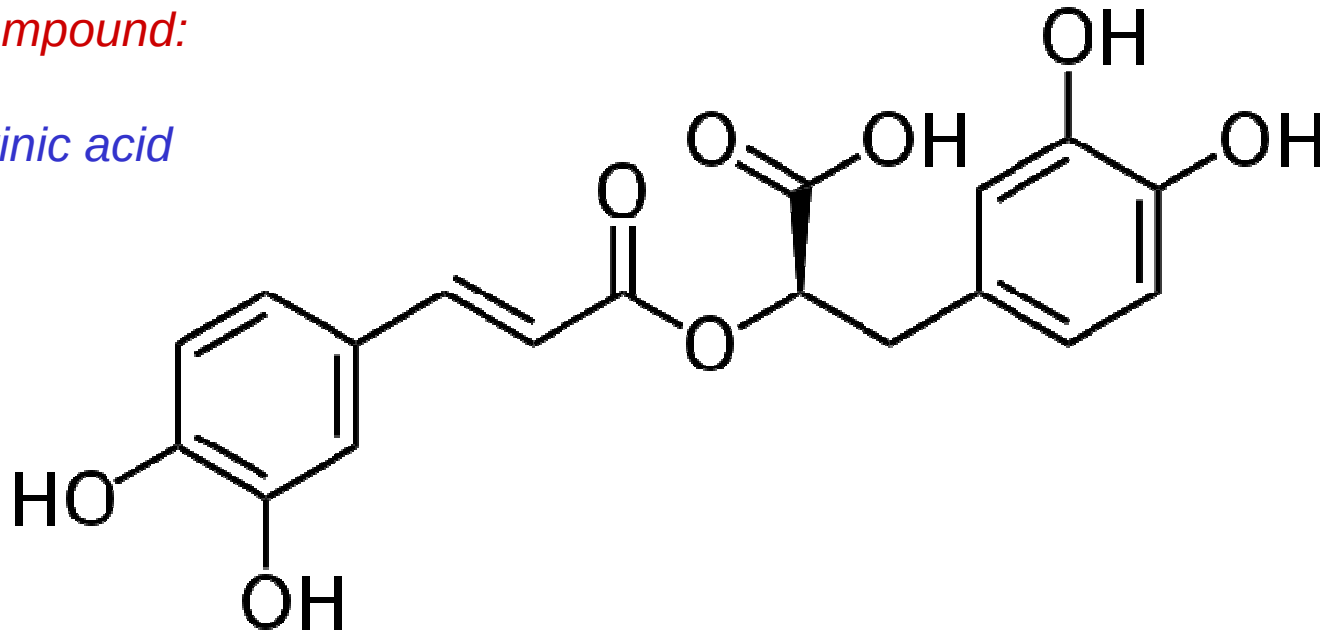
2524 Melissa leaf dry extract

Production

Hot water not less than 70℃
or a hydroalcoholic solvent that
is at most equivalent in strength to ethanol 70 per cent *V/V*

Lead compound:

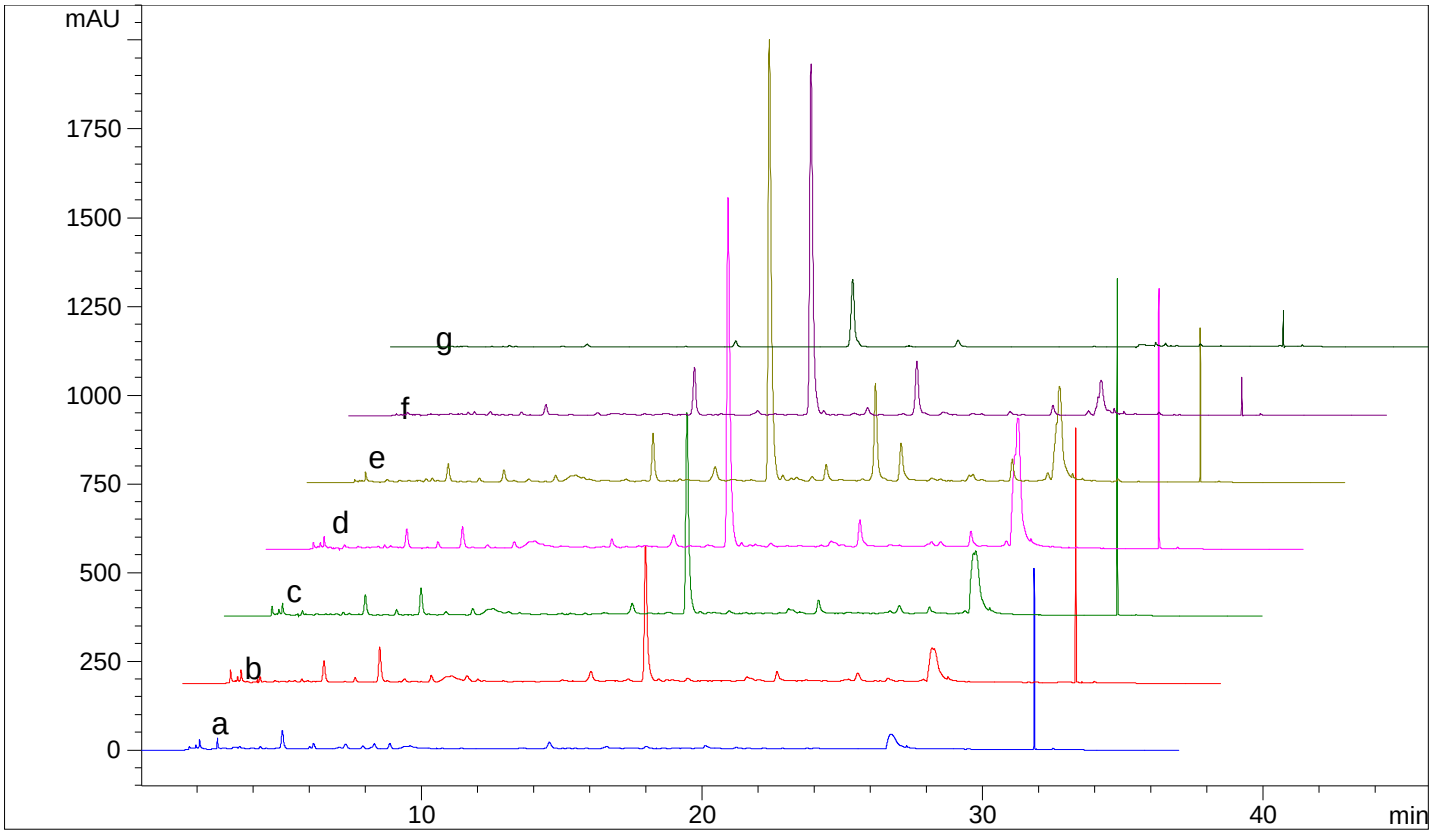
Rosmarinic acid



2524 Melissa leaf dry extract

A hydroalcoholic solvent
that is at most equivalent in strength to ethanol 70 per cent *V/V*

Extraction of rosmarinic acid with ethanol



2524 Melissa leaf dry extract

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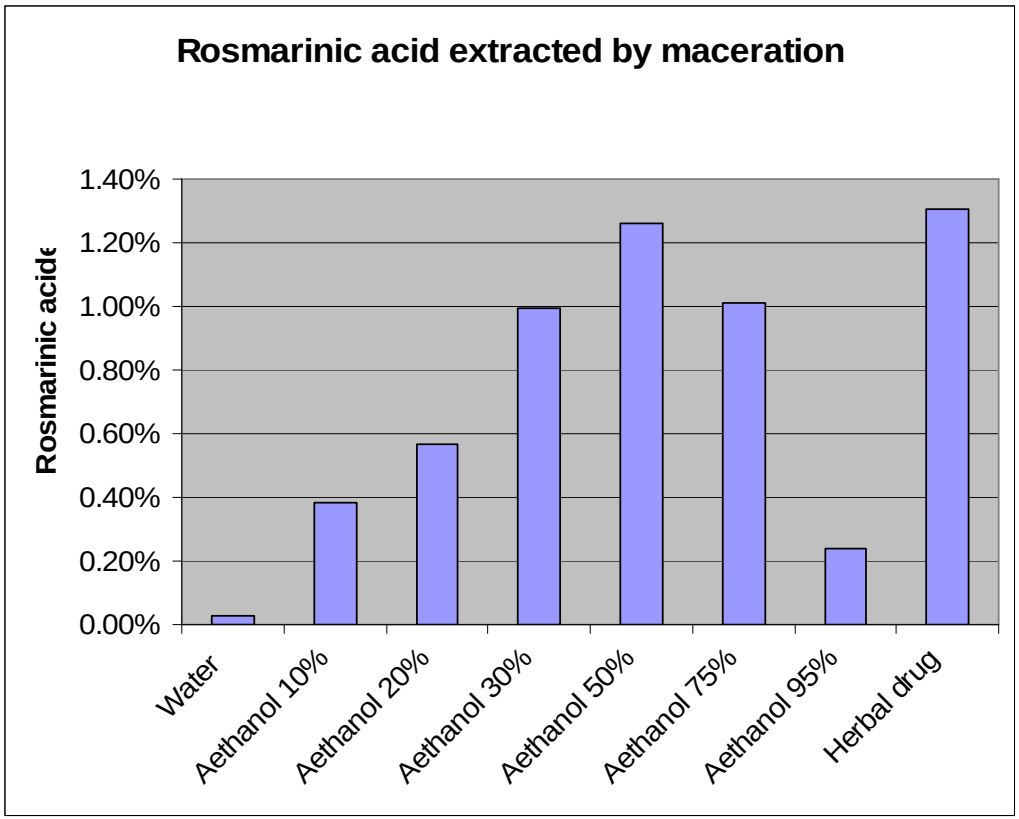
Extraction of rosmarinic acid with ethanol

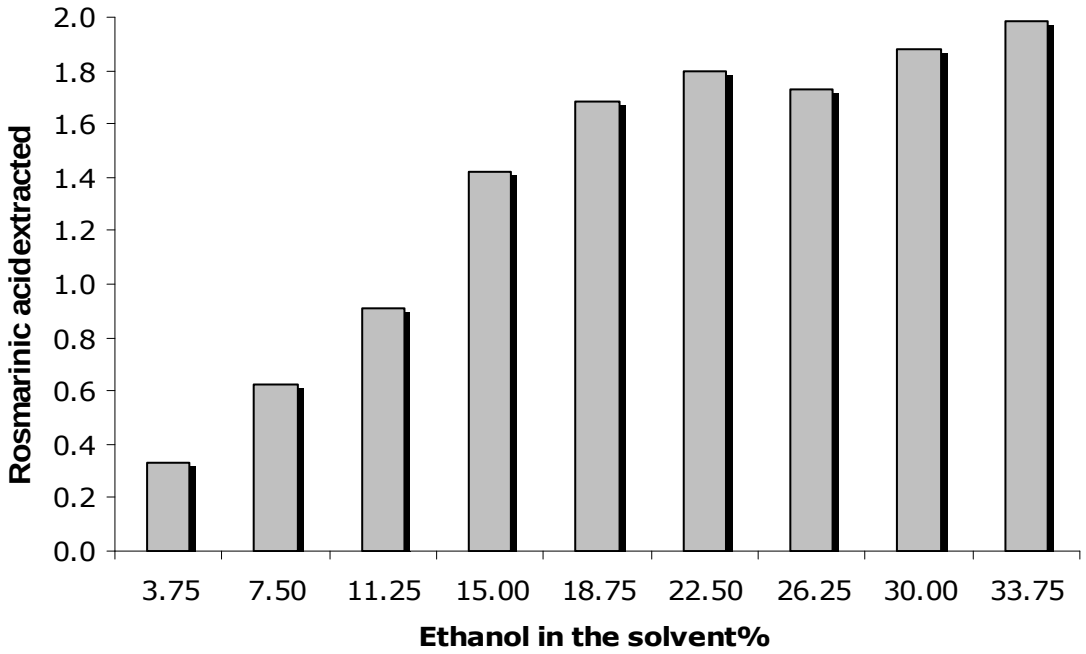


Yield

Wasser	**2.3%**
Aethanol 10%	**29.5%**
Aethanol 20%	**43.3%**
Aethanol 30%	**75.9%**
Aethanol 50%	**96.6%**
Aethanol 75%	**77.4%**
Aethanol 95%	**18.2%**

2524 Melissa leaf dry extract

Extraction of rosmarinic acid with water



The herbal drug contained 1.9% of rosmarinic acid

2524 Melissa leaf dry extract

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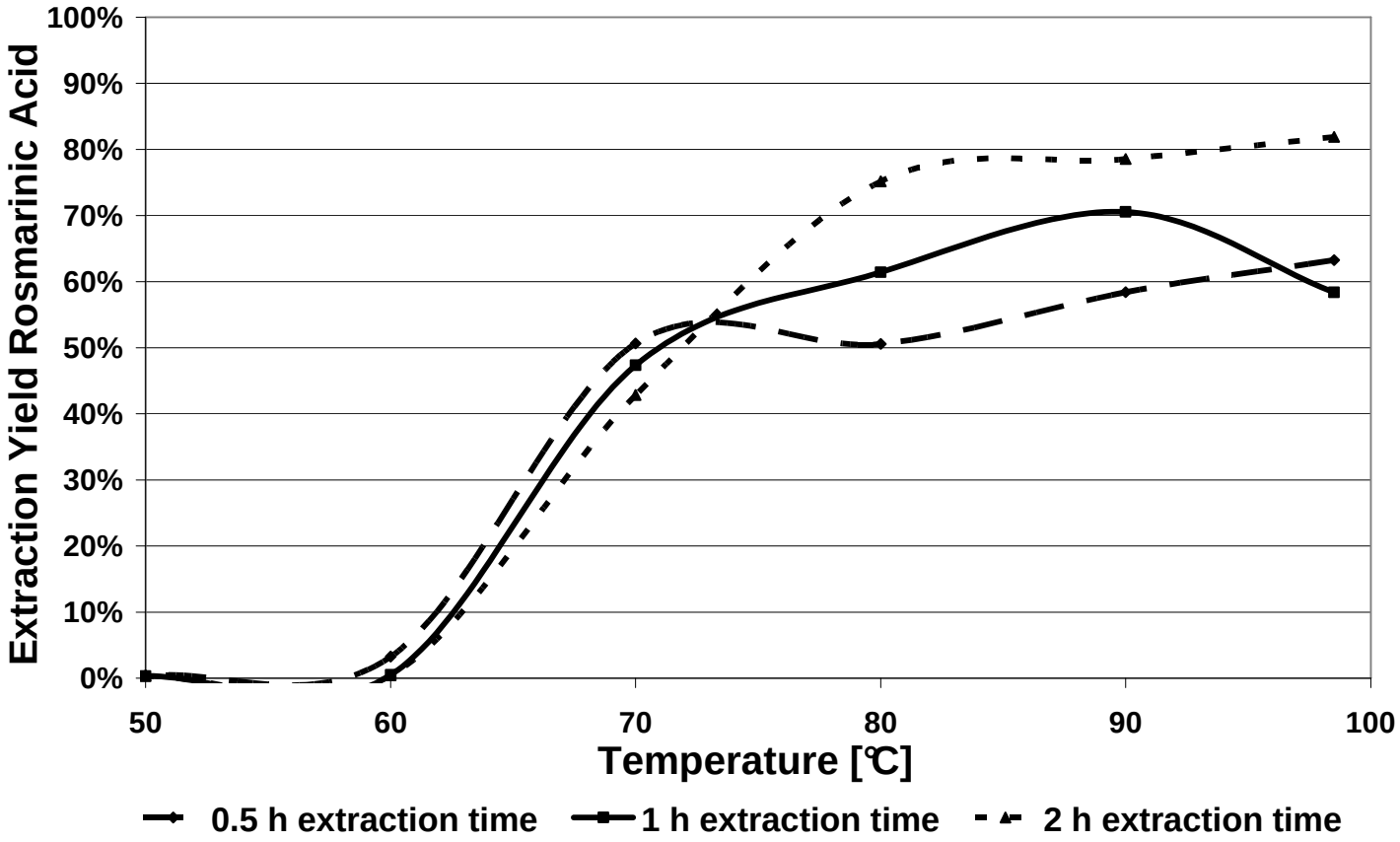
Extraction of rosmarinic acid with hot water



2524 Melissa leaf dry extract

Production
Hot water not less than 70℃
or a hydroalcoholic solvent that
is at most equivalent in strength to ethanol 70 per cent *V/V*

Conclusion

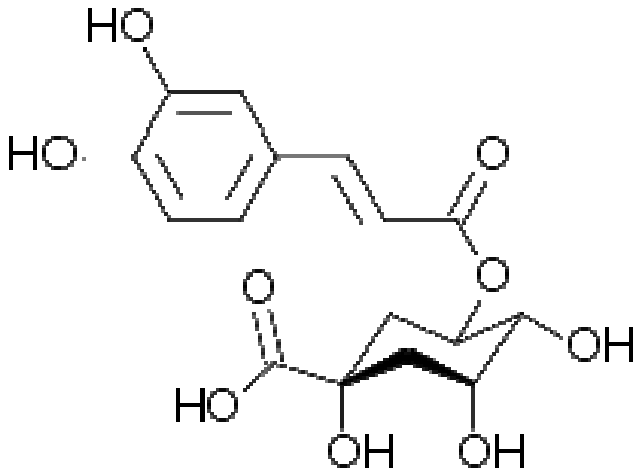
Hot water and
Ethanol/Water mixtures in a
wide variety are
justified.

2389 Artichoke leaf dry extract

Production
Hot water not less than 80℃

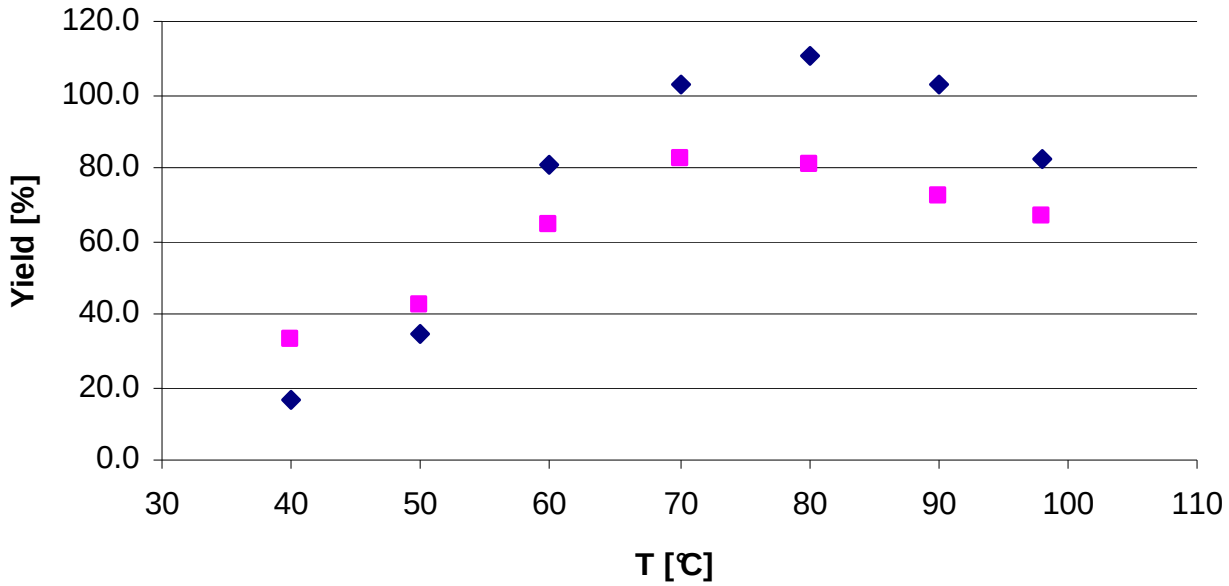
Lead compound:

Chlorogenic acid



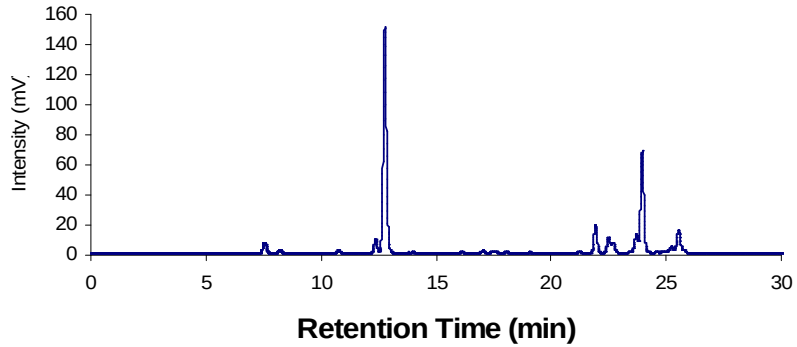
Herstellung eines Artischockenblattextraktes

Hot water not less than 80℃



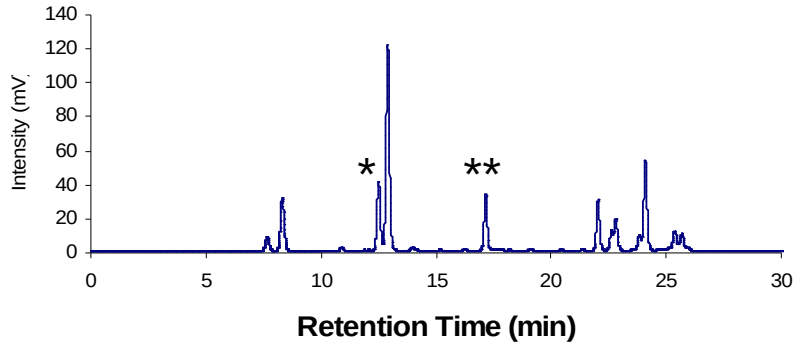
Herstellung eines Artischockenblattextraktes

Hot water not less than 80℃



70 ℃

98



98 ℃ Two additional peaks

2389 Artichoke leaf dry extract

Hot water not less than 80℃

Conclusion

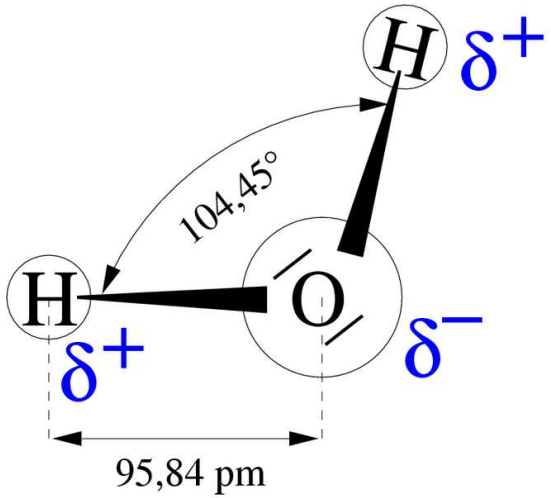
Hot water is justified. Temperature could or should be reduced.

Water as solvent

Dielectricity constant water

0 ℃	87,69
10 ℃	83,82
20 ℃	80,08
25 ℃	78,25
30 ℃	76,94
40 ℃	73,02
50 ℃	69,70
60 ℃	66,51
70 ℃	63,45
80 ℃	60,54
90 ℃	57,77
100 ℃	55,15

Methanol	25 ℃	32,63
Ethanol	25 ℃	24,30
Glycerin	25 ℃	42,5



Overall conclusions

- It is worth to think about solvents
- Solvent strength of ethanol/water mixtures is often not very specific.
  - Therefore not very specified solvents of Ph Eur are justified.
- Equivalent herbal drug preparations can result of different solvents
- Hot water has a strongly increased solvent strength compared to cold water

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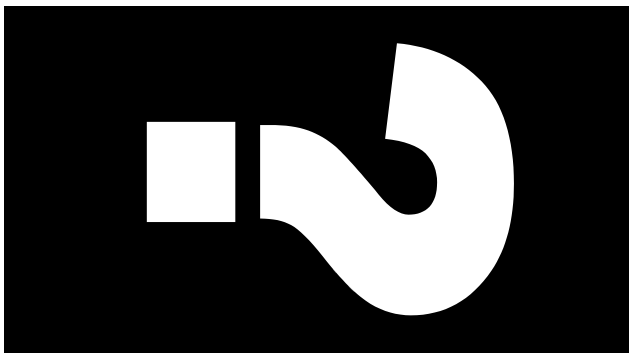
How useful are herbal extract monographs:



Thanks

I thank

Swissmedic

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I thank
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(Pharmacognosy and Phytochemistry)
of the
European Pharmakopöe
especially Dr Keith Helliwell and Dr Eike Reich
for usefull discussions.

How useful are herbal extracts of the European Pharmacopoeia for the development of herbal medicinal products?

Topic 2:

The importance of extract monographs of the European Pharmacopoeia for the quality reviewer in Switzerland