RISK PROFILE

Hedera Helix (Ivy) extracts

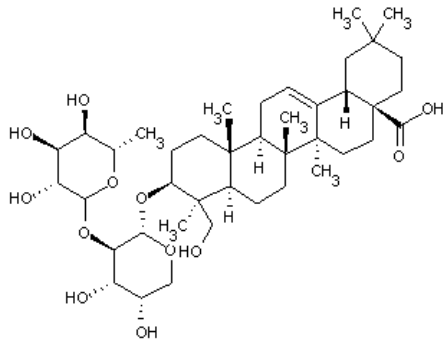
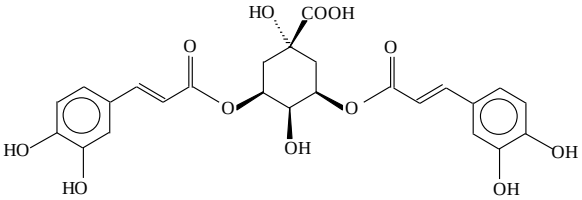
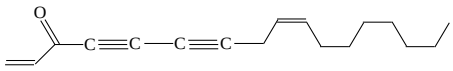
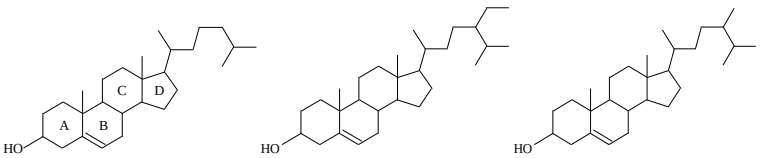
CAS No.84082-54-2

Date of reporting 04.06.2012

Content of document

1. Identification of substance

Chemical name (IUPAC):	Not applicable
INCI	*Hedera helix* extracts
Synonyms	Hedera Helix is a plant material derived from the dried leaves and stems of the Ivy, Hedera helix L., Araliaceae
CAS No.	84082-54-2
EINECS No.	282-000-2
Molecular formula	The extract of *Hedera helix* contains various bio-active substances. The more important constituents are described below.

Chemical structures (the more important constituents)	 Alfa-hederin (CAS No: 27013-91-8)  3,5-Dicaffeoylquinic acid (3,5-DCQA) (CAS No: 2450-53-5) Isochlorogenic acid A  Falcarinol (CAS No: 21852-80-2)  Cholesterol CAS No 57-88-5 β-Sitosterol CAS No: 83-46-5 Campesterol CAS No: 474-62-4 Cholestrol and β-Sitosterol also are used as cosmetic products ingredients on their own (CosIng)
Molecular weight (g/mol)	Alpha –hederin: 751 3,5-DCQA: 516,5 Falcarinol: 244,4 Cholesterol 386,7 β-Sitosterol 414,7 Campesterol 400,7
Contents (if relevant))	Professor Hanns Häberlein and co-workers at the Department of Physiological Chemistry at the University of Bonn in Germany have

	conducted much work on pharmacological properties of ivy extracts. This research group has prepared a monograph on medicinal and borderline cosmetics use (Häberlein H – see Annex I). They provide a fairly detailed description of the chemical composition of the ivy leaves. *Saponins*: Alpha-, Beta-, Gamma-Hederin, others: 5-8 % Alpha-Hederin : 1.5-2.5 % 3,5-DCQA): 0.5-1 % 7-Hydroxy-6-methoxycumaringlucoside (scopoline) *Polyalkynes*: Falcarinon: 0.05 % Falcarinol: 0.03 % 11,12-dehydrofalcarinol: 0.005 % Didehydrofalcarinol: 0.0025 % Another source mentions that the leaves contain the phytosterols Beta-sitosterol, Cholesterol and Camperesterol (Schöpke T). Probably, Beta-sitosterol possesses ability to exert an anti-inflammatory effect. However, the content of these molecules have not been mentioned by Häberline *et al*, so, most probably, they are present at such a low level that they attract only inferior interest therapeutically (herbalists). Häberline *et al* informed that current investigations show that the alkaloids emetin and cephalin are not present as earlier postulated.
Physiochemical properties	Council of Europe in a monograph from 2002 convey that there are two types of preparations: 1): Hydro alcoholic dry extract (Water less than 5 %. pH: 4,5 – 6) 2): Glycolic extract (E/D = 2:1)(Water less than 10 %, pH: 4,5 – 5,5)

2. Uses and origin

Uses	➢ Cosmetic products *Functions according to* • CosIng database: "Skin conditioning: maintains the skin in good condition" • Council of Europe 2002 Tonic, astringent, lentive Up to 3 % dry extract Up to 10 % glycolic extract in creams, lotions, gels for body massage Other effects: Astringent, micro vessel protector, anti-oedema

Frequency of use and types of products involved

The EWG database contains 27 products the Codecheck database 165 products that contain HHE. A series of different types of cosmetics contain the extract. The following ones are mentioned in the EWG database:

Around-the-eye-cream, anti-age, facial cleanser, sunscreen, stylig gel, anti-itch, moisterizer, exfoliant scrub, shampoo, foot moisturizer.

The Codecheck database additionally also mention some other stay-on products that are used over large parts of the body like body lotions, massage oils and soap, skin firming creams for body and bosom, foot and leg creams.

Eight (8) of the HHE products listed in the Codecheck database are called *"cellulite"* products. These products claim they smooth mattress looking skin. The condition is erroneously called *"cellulite"* .It has nothing to do with the medicinal condition of the same name that involves a skin infection. There are all together 470 *"cellulite"* products being mentioned in the Codecheck database. Only 8 contain HHE.

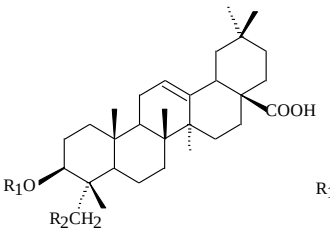
Importance of hederin as active ingredient

In addition to HHE also three other botanicals function as active ingredient relative to the *"cellulite"* claim and are also otherwise much used in cosmetic because of containing constituents similar to *hederin*. This concern extracts of the following three other herbs:

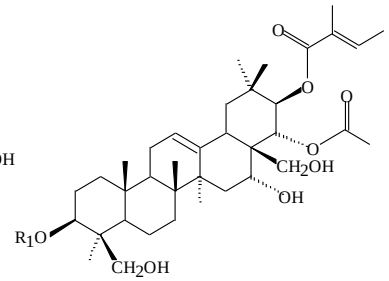
Herb extract	Function (CosIng)	Number of products mentioned in Codecheck that contain extract	
		All types of cosmetics	"Cellulite" products
Ruscus aculeatus root extract (Butcher's broom)	Astringent Refreshing Skin conditioning Soothing Stabilizing Tonic	192	16
Aesculus hippocastanum seed extract[1]	Skin conditioning	376	9
Centella asiatica Extract	Cleansing Skin conditioning Smoothing Soothing Tonic	507	9

All four botanical extracts contain saponins and sapogenins that inhibit the anti-elastase and anti-hyaluronidase catabolic enzymes (Facino *et al*., 1995). The involved molecules share structural traits:

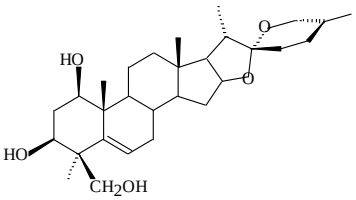
[1] These extracts contain up till 20% of the constituent called Escin



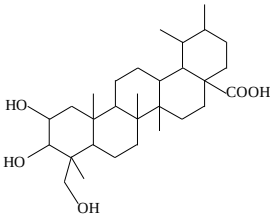
Hederinsaponins



Escin (R_1 is glucoronic acid and 2 D-glucose)



Ruscogenin



Asiatic acid (Centella asiatica)

In the *"cellulite"* products these constituents are present in high concentration. The HHE normally employed is used in the concentration range 3 – 10% (CoE 2002). Escin is used at strength of 2 % (CoE 2006). The Centella Asiatica standardised botanical extract contains 3% asiaticoside (Handa fine chemicals).

As concerns the HHE ingredient the Bonn-group researchers inform that in different *in-vitro* assays, there was inhibition of elastase and hyaluronidase activity observed. Apparently, according to the group, certain *in vivo* efficiency studies relative to *"cellulite"* have been "successful". Some clinical parameters were: roughness, skin elasticity, pain on pressure, skin tautness.[2]

Typically, the HHE *"cellulite"* products also contain abundant amounts of powerful vehicles like ethanol, propylene glycol and butylene glycol. The same goes for other stay-on products rich in HHE and that are meant to be used on larger parts of the body; massage oils and cream, breast firming creams etc.

- Medicinal products

Professional use

Especially in Germany leaf ethanol extracts are used therapeutically for the alternative treatment of obstructive respiratory tract diseases due to expectorial and spasmolytical characteristics. The assumed active principle is the group of hedera saponins. Apparently, due to approval (1988) of this herbal-medicinal use by the German Commission E, it has become one of the most popular prescribed herbal monopreparations in that country.

Some authors have remarked that there is lack of placebo controls. Further research — particularly long-term – are needed according to them (Milot B 2003). This pertains to the efficacy of the product.

Mechanism of action

[2] Different studies also show that many products do not live up to the promises

	The producer of the product presented in the behind, claims that the molecular mechanism behind the anti-coughing effect of their product has been cleared up. It's said that in the lung especially the saponin Alpha-Hederin prevents inactivation of beta-2-receptors. It thereby increases the numbers of active such receptors on the cell surfaces. This, in its turn, indirectly increases the effect of the symphatic nervous system (Engelhard Arznemittel GmbH 2003). *Disproved indication* It should be mentioned that another indication of HHE has been disproved in the past. Some years ago, ivy's purported use as an alternative treatment for chronic venous insufficiency (CVI) was disproved, and its saponins were found to be ineffective for this indication (Facino et al., 1995). *Contra-indication* Children under 2 years of age because of the risk of aggravation of respiratory symptoms. (EMA 2011) *Folk medicinal use* The HHE also found some folk medicinal use in elderly times – and, apparently, to some extent, even today in some countries. On the Internet herbalists mention pain removal remedies in the form of ointments, lotions, baths (Heilpflanzen-welt February 2006). There has been some use of it as corn cure for the feet (ref in BODD).
Origin Natural (exo / endo) Synthesis	Hedera helix (Common Ivy, English Ivy) is a species of ivy native to most of Europe and western parts of Asia. Hedera helix extract is an extract of the stems and leaves of the ivy, Hedera helix.

3. Regulation

Norway	No regulation[3].
EU	No regulation in relation to cosmetics
Rest of the world	No regulation in relation to cosmetics

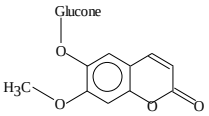
4. Relevant toxicity studies

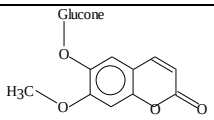
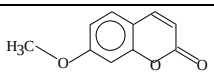
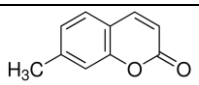
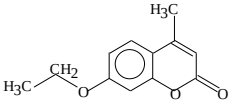
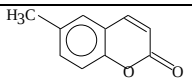
Absorption Skin GI tractus	There is reason to believe that the active ingredients, the hederin-saponins, penetrate skin to a substantial degree. This is anticipated because the related escin molecule has been shown to be taken up in the body through skin in an amount of up to 2.5% (CoE 2006).

[3] The Norwegian medicinal products agency considers ivy extracts medicinal remedies. Because of that up till 2008 topical products containing these extracts were considered medicines – meaning a topical product containing the extract were automatically classified a medicine. Applications for allowance to use the extract for other purposes (cosmetics) were rejected. This regime has since been lifted.

<table>
<tr><td>Distribution</td><td>No data available</td></tr>
<tr><td>Metabolism</td><td>No data available</td></tr>
<tr><td>Excretion</td><td>No data available</td></tr>
<tr><td>Local toxic effects
Irritation
Sensitivity</td><td>
The Commission E states that the HHE is irritative to skin.
The Hedera helix plant has long been recognized as a cause of dermatitis. There is a comparatively long series of case reports – confer, for example, those cited in the reference BODD.
The clinical features of the dermatitis as described suggest that allergic sensitization may occur. The lesions may be linear and vesicular as in poison ivy (ref in BODD).

Experimental and chemical investigations revealed that HHE contains 3 polyacetylenic compounds which are powerful irritants and moderate sensitizers. Two of these are falcarinol and didehydrofalcarinol. 4 patients were patch tested. Even in low concentrations (0.03%), the main allergen falcarinol elicited strong reactions in all of them (Hausen et al 1987).

HHE also contains certain amounts (seemingly not determined) of the coumarin derivative scopoline.


This molecule is structurally related to some other simple derivatives of coumarins that all possess photo allergenic properties:
<table>
<tr><th>Name</th><th>Structural formula</th><th>Comment</th></tr>
<tr><td>Scopoline</td><td> 
</td><td></td></tr>
<tr><td>7-Methoxycoumarim</td><td> 
</td><td>Not allowed in cosmetic products as a fragrance ingredient because of photo allergenic effect</td></tr>
<tr><td>7- Methylcoumarin</td><td> 
</td><td>Not allowed in cosmetic products as a fragrance ingredient because of photo allergenic effect</td></tr>
<tr><td>4-Methyl-7-ethoxycoumarin</td><td> 
</td><td>IFRA[4] Code of practice: Not to be used in cosmetic products because of photo allergenic effect</td></tr>
<tr><td>6-Methylcoumarin</td><td> 
</td><td>Allowed only in oral hygiene products as</td></tr>
</table>
</td></tr>
</table>

[4] The international fragrance association

			concerns cosmetic products – and not in a higher concentration than 30 ppm**.** IFRA Code of practice: Not to be used in cosmetic products because of photo allergenic effect

It will not be a daring hypothesis to say that like the other coumarines shown, also scopoline possess a photo allergenic property so powerful that it qualifies for a ban in cosmetic products.

Systemic toxic effects Acute and repeated	Escin shows nephrotoxic effects in man and acute renal failures have occurred in clinical settings. A low NOAEL of 0.3 mg/kg bw in man has been determined (CoE 2006). The hederin saponins share important molecular traits with Escin and possess, like Escin does, anti-elastase and anti-hyaluronidase properties *(in vitro*). It would not come as a total surprise, therefore, if eventual further studies reveal a nephrotoxic effect also as concerns the hederin-saponins.
Reprotoxicity	Investigations have revealed that upon single dose subcutaneous administration of Alpha-hederin on gestational day 8, the compound shows pronounced teratogenic effects in Sprague-Dawley rats. These would be foetal abnormalities, including hydrocephaly and delayed ossification of sternebrae and vertebrae. These effects were observed in more than 38% of the foetuses from 20 micromole /kg bw and upwards. The effect is mediated via disturbance of the Zn status in the body. Alpha- hederin is a potent metallothionein. A NOAEL value of 10 micromole/kg bw can be determined for the teratogenic effect on the basis of these studies (Duffy JY et al 1996). 10 micromole/kg bw correspond to 7.5 mg /kg body weight. This dose is close to the daily curative dose prescribed for the mentioned coughing medicine; 5 mg/ kg body weight. The risk for foetal abnormalities in pregnant women taking the medicine seems unacceptably high because of the Duffy study. We question why the producer – as far as we can see – hasn't put the contraindication; "pregnancy" on his product. We also question why the mentioned researchers at the University of Bonn haven't mentioned the serious and pronounced teratogenic effect documented by Duffy et al.
Mutagenicity	Using the Salmonella tester strain TA98 +/- S9 mix α-Hederin, ß-hederin and δ-hederin isolated from ivy leaf was not found to be toxic or mutagenic for doses of 400 micrograms (Elia R *et al* 1990).

5. Exposure estimate and critical NOAEL/NOEL

NOAEL/NOEL critical	7.5 mg/kg bw in rats
Exposure cosmetic products	As mentioned above Alpha-hederin shows pronounced teratogenic effects in Sprague-Dawley rats. We performed a rough risk analysis for the cellulite use on the basis of this effect: *Premises*: • NOAEL (teratogenic effect in rat): 7.5 mg /kg body weight • Amount of cellulite product applied to the skin on the back of the thighs: 1600 mg [5] two times a day. • Worst case: A firm selling a cellulite product on the internet advise customer to use 15 ml pr single treatment. This covers the thighs, waist and the buttocks according to the company. It's assumed that 15 ml corresponds to 15 000 mg. • Concentration of alpha-hederin in extract: 2.5 % (measurements) • Skin penetration rate: 2.5 % (as for Escin) • Body weight: 60 kg (standard used by the EU scientific committee) Systemic exposure dose/ back of thighs only: (SED_t): 1600 x 0.025 x 0.025 x 2 /60 = 0,034 mg /kg bw Systemic exposure dose /worst case: (SED_{worst}) = 15 000 x 0.025 x 0.025 /60 = 0.156 mg/kg bw
Margin of Safety (MoS)	MOS (thighs only) = NOAEL / SED_t = 7.5 / 0.034 = 220 MOS (worst case) = NOAEL / SED_{worst} = 7.5 / 0.156 = 48 The MOS that can be accepted is normally above 100. Customary within toxicology, when serious teratogenic effects are concerned – as in this case – safety factors should exceed 1000. These are rough calculations since the rate of skin penetration is uncertain and illustrative. The normal procedure when data are missing for this rate is, however, to assume a rate of 100%. In light of this our estimation for the MOS may be considered conservative. Clearly, there are strong indications that this use is not safe.

6. Other sources of exposure than cosmetic products

Food stuffs	No data available
Pharmaceuticals	No data available
Other sources	No data available
Adverse side effects - from uses other than cosmetics	It seems beyond question that HHE, when used as an expectorant, exhibit certain pharmaceutical properties. As is well known, whenever there is a pharmaceutical effect there also, with few exceptions, are side effects. Therefore, we would expect this to be the case also as concerns medicinal use of HHE. Ivy is a poisonous plant and intoxications have occurred upon accidental intakes in children; vomiting, diarrhea, and nervous depression. There is report of a death. Besides, clipping or just

[5] Rule of 9 – and a thickness of 1 mg/ cm^2

	handling the plant may result in a skin rash and even blistering and inflammation (ref to Watt & Breyer-Brandwijk 1962 in BODD). We observe that different sources express that caution ought to be exercised in medicinal oral administration. We observe that the German Commission E and, therefore, also marketers claim that no adverse effect in expectorant use is known. Considering the pronounced capability of the contained saponins to irritate the epithelia of the stomach, we find this surprising. We wonder whether an explanation could be that the remedy is prepared as a controlled-release product. This technique is applied in order to make the saponin Escin usable as an internal drug against CVI. Ivy show allergenic properties, so, might not also allergy be an issue in medicinal practice, we question. As concerns topical administration, seemingly, no modern medicinal use is involved – and adverse side effects are, therefore, not described in the scientific literature. There is no mention of adverse side effects in connection with the lay uses (except for dermatitis in the corn cure). This doesn't mean that there aren't any. Our experience is that among those advocating and promoting the use of the so-called alternative herb-based medicines there is a tendency to ignore or belittle adverse side effects. The main constituent of the ivy-extract, Alpha-hederin, has been investigated somewhat as to its toxicity because it shows anti-mutagenic properties and appears to attract some medicinal interest because of that (Toxline).

7. Assessment

Clipping or just handling the ivy plant easily results in a skin rash and even blistering and inflammation. It is a poisonous plant and death has occurred in children ingesting plant material. The HHE being used in cosmetics contains at least three inherently harmful substances. HHE is used in high concentration in many stay-on cosmetic products like creams, lotions, gels for body massage, "cellulite" creams. These products are mostly used on larger parts of the body to firm the skin. Commonly HHE is employed in these products together with powerful vehicles.

The scopoline constituent possess an inherent photo allergenic property so powerful that it qualifies it for a ban in cosmetic products. Besides, even in low concentrations (0.03%), the allergen falcarinol elicited strong reactions in all patch tested patients. It is normally present at 0.05 % in the HHE.

The HHE might have nephrotoxic effect. HHE also show pronounced teratogenic effects in rats the NOAEL being down low 7.5 mg/Kg bw. The margins of safety estimated on the basis of this NOAEL value is much below the necessary margin of 1000.

The MOS that can be accepted is normally above 100. Customary within toxicology, when serious teratogenic effects are concerned – as in this case – safety factors should exceed 1000.
These are rough calculations since the rate of skin penetration is uncertain and illustrative. The normal procedure when data are missing for this rate is, however, to assume a rate of 100%. In light of this our estimation for the MOS may be considered conservative.

8. Conclusion

In light of the risks for both local and systemic grave heath damage as described in the above we conclude that Hedera helix extracts have no place in cosmetic products and should be prohibited in such products.

9. References

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Company claims like for example: http://www.rxwellnesscenter.com/prod_data/prod_desc_145.pdf

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Schöpke T: Priv.-Doz. Dr. Thomas Schöpke Institut für Pharmazie Ernst-Moritz-Arndt-Universität Greifswald http://www.pharmakobotanik.de/systematik/6droge-f/hedera-f.htm DENNE LINKEN VIRKER IKKE

10. Annex

Monograph prepared by Hanns Häberlein *et al* at the Institute of Biochemistry and Molecular Biology, Rheinische Friedrich-Wilhelms-University, Bonn, Germany.

Hedera helix L.

Hedera helix L.(engl.:Common Ivy or Woodbind; frz.:Lierre commun; dt.:Efeu) is a very widely distributed plant in middle and north europe. It belongs to the genus Hedera, (Fam. Araliaceae), of which there are six different known species in Europe, north and east asia, the Canary Islands and north Africa.There are three varieties described of *Hedera helix L*.: *Hedera helix var. helix*, *Hedera helix var.baltica* and *Hedera helix var. hibernica*. But there are more than 60 cultivated gardenforms of *Hedera helix L.* with a big variety in color and shape of the leaves and in the expression of ornamental venation.[1]

Plant description

Hedera helix L. is an evergreen, often climbing or creeping shrub, whos wooden aerial stems often attach by numerous adventitious roots to trees, rocks, walls and buildings. Through this the branching stem is able to climb up to 30 m in hight to reach climatically beneficial areas.The plant can reach 300 years of age and the stem 60 cm in diameter. The young shoots are densly covered with stellate to peltate hairs with with 6-22 rays and a diameter of about 0.2-0.4 mm. The leaves are dark green with a shiny gloss, often with paler or white veins. They appear in a dimorphic style: those leaves of the juvenile, non-flowering shoots are palmately 3-5 lobed and can measure upto15 cm x 15 cm, but usually much less (7-10 cm x7-10 cm). Those of the mature flowering shoots are narrowly elliptical to rhombical with an entire shape. The fertile, flowering shoots are often absent in shady or cold climates.The hermaphrodite flowers are radially symmetric with 5 yellowish-green petals(3-5 mm). In autumn they appear in sphereical umbels or panicels. The fertilization is done by flies and the fruits, black to orange-red berries with 3-5 seeds, ripen in the following springtime. [3]

Hedera helix L. - juvenile shoots

Hedera helix L. in the traditional medicine

Ivy leaves have been used in the traditional medicine of middle and northern Europe since the antique. The range of application of this drug was various. It was used internally against diseases of the gastro-intestinal tract; especially illnesses of the gall-bladder, like gall-stones, were treated with preparations of this plant. External usage of *Hedera helix L.* was expected to cure inflammtions and burns, cellulite and phlebitis, as well as neuralgia and rheumatism. But the benefits of those traditional uses could not be proven by modern scientific investigations.[3]

Chemistry

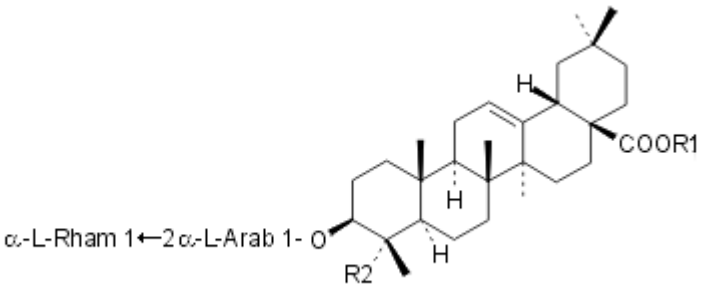
The leaves contain approximatly 5-8 % of saponins. This fraction is mainly composed of bisdesmosidic hederagenin-, oleanolic acid-, and bayogeninglycosides. Hederasaponins B to I are characterized.[4]The ratio between these Saponines is given in *Table 1*.[2] By far the main constituent is hederasaponin C (=hederacoside C) and its level of content varies depending on the season, between 5 and 7% of the saponine fraction. Through fermentation or basic hydrolysis one get alpha-Hederin, the monodesmosidic derivative of hederacosid C. Additionally phenolic compounds were found in Ivy leaves. The composition of this fraction depends on the functional state of the plant. The leaves of the juvenile shoots contain rutoside (=rutine = quercetin-3-rhamnoglucoside). During its transition to the mature state, kämpferol-3-rhamnoglucoside additionally appears in the flavonoid spectrum. Furthermore, in the phenolic fraction chlorogenic acid, coffeeacid and scopoline (=7-Hydroxy-6-methoxycumaringlucoside) have been found.[5]

Ivy contains a small fraction of water destillable components, mainly methylethylketone, methylisobutylketone, capronaldehyde, trans-2-hexenal, trans-2-hexenol, furfurole, maltol as well as the sesquiterpenes germacren B and beta-elemen.[6]

Small amounts of polyalkynes as falcarinon (approx.:0,05%), falcarinol (approx. 0,03%), 11,12-dehydrofalcarinol (approx. 0,005%) and didehydrofalcarinol (approx. 0,0025%) were detected in the Ivy leaves.

Table 1: Distribution of saponines in Ivy leave extract

Compound	rel.ratio
Hederasaponine B	70
Hederasaponine C	1000
Hederasaponine D	45
Hederasaponine E	10
Hederasaponine F	40
Hederasaponine G	15
Hederasaponine H	6
Hederasaponine I	5



Compound	Substituents
α-Hederin	R1 = -H R2 = -CH_2OH
Hederacosid C	R1 = -1 β-D-Gluc 6←1 β-D-Gluc 4←1 α-L-Rham R2 = -CH_2OH
Hederacosid B	R1 = -1 β-D-Gluc 6←1 β-D-Gluc 4←1 α-L-Rham R2 = -CH_3

Fig. 1 main saponines of ivy leave extract

The presence of the alcaloids emetin and cephaelin in the leaves was postulated by Rusche in 1979 [7], but has not be verified in more current investigations.[8]

Pharmacology of ivy leaf extract

Based on its expectorical and spasmolytical characteristics, ethanolic ivy leaf extracts are used therapeuticaly for the treatment of obstructive respiratory tract diseases. The assumed active principle is the group of hederasaponines. Additionally, in different in-vitro assays, there were inhibition of elastase and hyalurinase activity observed, furthermore, protection of the liver and antibiotical and antiparasitical activity could be proven.

1. secretolytical activity

Some newer clinical studies investigated the secretolytical potential of ivy leaf extract in comparison with chemically defined drugs in commercially available preparations. In these studies a clear improvement of syndrome-related parameters like vital capacity, breathway-resistance, intrathorical gas-volume and maximum peak flow, could be shown. Unfortunally no studies analyzing the pharmacological aspects of these preparations exist. The first and only was an investigation by Vogel et al in 1962 [9], describing a higher speed of mucociliar movement of frogs throat epithelium after treating it with various saponines, included Hedera-saponines. The explanation for these results is thought to be found in the surface active property of the saponines. But further investigations are lacking.

2. spasmolytical activity

The spasmolytical activity of ivy leaf extractwas investigated by Trute et al. in 1996[10]. For several compounds they found in the ivy leaf extracts certain activity in comparison to papaverin on the Acetylcholine treated gunea pig trachea. Related to their high concentration in the extract, the saponines obvisiously play the biggest role in antispasmodic action. Their relative strength in relation to papaverin was described by so called PE-value, the papaverin related units. It describes the potential of each tested compound contained in one gram ivy leave extract in relation to the

equivalent amount of papaverin necessary to avail the same effect.

Table 2: papaverine-equivalents of the most active compounds in ivy leave extract

	Compound	Concentration in ivy leaf extract	papaverin equivalent (PE)
1	alpha-Hederin	1.5-2.5%	55 mg
2	Hederagenine	<0.001%	49 mg
3	Quercetrine	<0.001%	54 mg
4	Kämpferol	<0.001%	143 mg
5	3,5-Dicaffeoylquinicacid	0.5-1.0%	2 mg

Related to to their concentration, compound 1 and 5 are relevant for the antispasmodic activity.

3. anti-elastase and anti-hyaluronase activity

The anti-elastase and anti-hyaluronase activity of triterpensaponines is known from horse chestnut saponines, and there especially escin. [11,12]. Following this thought the topical influence of hederasaponines on the enzymatic activity was tested in a clinical study on 40 women with liposclerosis, also called cellulitis, over 30 days in comparison to topically applyed escin. The therapeutical success was marked by clinical parameters like skin roughness, skin elasticity, pain on pressire, skin tautness and the consistancy af subcutaneous tissue.[13]

The topical use of both preparations, hederasaponines and escin, have shown comparable beneficial results after a treatment period of 30 days.

Additionally, an in-vitro enzymatic assay for antihyaluronase activity was carried out. Here a dose-dependent inhibition was investigated with an achieved half-maximum at 0.25 mM for hederasaponine complex, 0.5 mM for Hederacoside C, 0.6 mM Hederacoside B in comparison to escin with 0.25 mM.[14]

A second inhibition assay for elastase out of pig pancreas has shown a inhibition potency for the aglyca oleanolicacid (IC50:5.1 µM) and hederagenin (IC50:40.6 µM). But further experiments should show the potency of the genuine saponines.

4. hepatoprotection aspects

The alpha-hederin contained in ivy leaf extract is known from some other medicinal plants, which were used for treating hepatological illnesses in traditional medicine, so an experiment was performed with alpha-hederin by Liu et al. in 1995[15]. These investigations have shown that alpha-hederin reduced the hepatotoxicity of several agents as acetaminophen, tetrachlorcarbon thioacetamid and others, which are metabolized in the liver by Cytochrome P450 oxidases. So the mechanism may be related to an inhibition of Cytochrome-P450 oxidases; this theory could be supported by activity testing of hepatomicrosomes preparations with several Cyt-P-450 oxidases (inhibition between 30-50%) and additionally cytochrome b5 (inhibition 20-30%) and the NADPH cytochrome-c-reductase (inhibition between 15-25%) . These enzymes were inhibited dose-dependent by alpha-Hederin. The influence to the oxidative enzyme complex seems to be a likely mechanism for the hepatoprotective potential of ivy leaf extract.

5. antibiotical and antimicrobiological activity

alpha-hederin shows activity against several microorganisms and parasites.This spectrum includes gram positive and gramnegative bacterias, yeasts and funghi. This potential has been described by

Hamacher and Kraus in 1986 in detail [16].

Conclusion

There were a lot of investigations carried out elucidating the mechanisms of influence of ivy leaf extract on the human body, but most of the results have their origin in clinical investigative work, and it is not clearly shown yet, which pharmacological and physiological processes are involved in the obviously strong pharmacological activity of *Hedera helix L.* So it is necessary to set the focus on the clarification of the molecular mechanisms of ivy leaf compounds.

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