

# **E/S/C/O/P MONOGRAPHS**

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EUROPEAN SCIENTIFIC COOPERATIVE  
ON PHYTOTHERAPY



**Thieme**

# HEDERAE HELICIS FOLIUM

## Ivy Leaf

### DEFINITION

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Ivy leaf consists of the dried leaves of *Hedera helix* L. It contains three main saponins: hederasaponin C (hederacoside C), hederasaponin B and hederasaponin D (saponin k10), with not less than 2.5% of hederasaponin C.

The material complies with the monograph of the Pharmacopée Française [1].

Fresh material may also be processed provided that when dried it complies with the monograph of the Pharmacopée Française.

### CONSTITUENTS

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Triterpene saponins (2.5-6%), predominantly bidesmosidic glycosides of hederagenin with hederasaponin C (hederacoside C) as the main saponin, and a small amount of the monodesmosidic saponin  $\alpha$ -hederin [2,3]. Other saponins present, in decreasing order of concentration, are hederasaponins B,D,F,G,E,H and I.

Other constituents include phytosterols, polyines such as falcarinol and didehydrofalcarinol, essential oil, flavonoids and other phenolic compounds such as caffeoylquinic acids [2,3].

### CLINICAL PARTICULARS

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#### Therapeutic indications

Coughs, particularly when associated with hypersecretion of viscous mucus; as adjuvant treatment of inflammatory bronchial diseases [4-11].

#### Posology and method of administration

##### Dosage

Note: Most preparations from ivy leaf contain hydro-ethanolic dry extracts incorporated into ethanol-containing or ethanol-free oral liquids, or suppositories. The following recommendations are:

Daily doses expressed as the corresponding amounts of dried ivy leaf

##### ORAL USE

##### *Ethanol-containing preparations*

Adults: 250-420 mg [5].

Children 4-12 years: 150-210 mg [8,9].

Children 1-4 years: 50-150 mg [12].

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Children 0-1 year: 20-50 mg [12].

### *Ethanol-free preparations*

Adults: 300-945 mg [10,11,13].

Children 4-12 years: 200-630 mg [6,7,10,11,13,14].

Children 1-4 years: 150-300 mg [10,11,14].

Children 0-1 years: 50-200 mg [10-12].

### RECTAL USE

#### *Suppositories*

Children 4-10 years: 960 mg [8].

### **Method of administration**

For oral administration in liquid or solid dosage forms; for rectal application as suppositories.

### **Duration of administration**

If symptoms persist or worsen medical advice should be sought.

### **Contra-indications**

None known.

### **Special warnings and special precautions for use**

None required.

### **Interaction with other medicaments and other forms of interaction**

None reported.

### **Pregnancy and lactation**

No human data available. In accordance with general medical practice, the product should not be used during pregnancy or lactation without medical advice.

### **Effects on ability to drive and use machines**

None known.

### **Undesirable effects**

Fresh ivy leaf and the leaf sap can cause allergic contact dermatitis [15-17]. Falcarinol and didehydrofalcarinol have been reported to be allergenic [18,19].

### **Overdose**

Overdosage can provoke nausea, vomiting, diarrhoea and excitation [20]. In these cases a physician should be consulted immediately.

## **PHARMACOLOGICAL PROPERTIES**

### **Pharmacodynamic properties**

#### ***In vitro* experiments**

##### *Spasmolytic activity*

Saponins and phenolic compounds isolated from a 30%-ethanolic extract of ivy leaf (6:1) exhibited spasmolytic activity against acetylcholine-induced

contractions of isolated guinea pig ileum. Spasmolytic activity equivalent to that of 1 mg of papaverine was exerted by 169 mg of hederacoside C, 18 mg of  $\alpha$ -hederin and 21 mg of their aglycone, hederagenin, which was not present in the extract ( $p < 0.05$  for all three compounds); 7 mg of kaempferol and 18 mg of quercetin ( $p < 0.01$ , although less than 0.01% of each of these flavonol glycosides was present in the extract); and 46 mg of 3,5-dicaffeoylquinic acid ( $p < 0.05$ ; about 0.5% present in the extract). Taking into account the amounts of such constituents present in the extract in relation to their activity, the saponins  $\alpha$ -hederin and hederacoside C appeared to contribute most of the spasmolytic activity, with  $\alpha$ -hederin the more prominent in this respect. Each of 5 fractions of the extract, in total representing over 90% of the original extract, had spasmolytic activity (all  $p < 0.05$ ) [21,22].

#### *Antimicrobial activity*

A saponin mixture (predominantly hederacoside C) from ivy leaf exhibited antibacterial activity against Gram-positive bacteria (*Bacillus* spp., *Staphylococcus* spp., *Enterococcus* spp., *Streptococcus* spp.) with minimum inhibitory concentrations (MICs) of 0.3-1.25 mg/ml and against Gram-negative bacteria (*Salmonella* spp., *Shigella* spp., *Pseudomonas* spp., *Escherichia coli*, *Proteus vulgaris*) with MICs of 1.25-5 mg/ml [23]. An ethanolic extract from ivy leaf completely inhibited the growth of *Staphylococcus aureus* and *Pseudomonas aeruginosa* and partially inhibited the growth of *E. coli* [24].

$\alpha$ -Hederin at 0.5 mg/ml exhibited antifungal activity against *Candida albicans* and the dermatophyte *Microsporum canis* (0.05 mg/ml), but hederacoside C and crude saponin mixtures from ivy leaf were ineffective against these and other dermatophytic fungi [25]. Other experiments confirmed the antifungal activity of  $\alpha$ -hederin (MIC: 0.25 mg/ml) [26].

Hederacoside C has been reported to have antiviral activity against influenza virus A2/Japan-305 [27].

#### *Other activities*

*In vitro* experiments have demonstrated inhibition of hyaluronidase activity by hederagenin (but not by hederacoside C or  $\alpha$ -hederin) [28], anthelmintic activity of ivy leaf extracts [29], antileishmanial activity of ivy leaf saponins [30-32] and anti-trypanosomal activity of  $\alpha$ -hederin and hederagenin (but not hederacoside C) [33].

### **In vivo experiments**

#### *Spasmolytic activity*

In the compressed air model in conscious guinea pigs, an orally administered ethanolic extract from ivy leaf at 50 mg/kg body weight dose-dependently inhibited bronchoconstriction induced by inhalation of ovalbumin (57% inhibition,  $p = 0.01$ ) or platelet

activating factor (43% inhibition,  $p = 0.03$ ) [34].

*Anti-inflammatory activity*

An orally administered ethanolic extract from ivy leaf at 162 mg/kg body weight inhibited carrageenan-induced rat paw oedema by 39% after 1 hour and by 5% after 5 hours [34]. A saponin mixture isolated from ivy leaf, administered intravenously, inhibited ovalbumin-induced rat paw oedema with an  $ED_{50}$  of 0.32 mg/kg [35].

*Antifungal activity*

*Candida albicans* infections, as abscesses on the backs of mice, were eliminated after oral administration of a saponin mixture (60% hederasaponin C) from ivy leaf at 50 mg/kg body weight for 10 days. At the same dose level and duration,  $\alpha$ -hederin eliminated the infection in 90% of animals and hederasaponin C in 40% of animals. In comparison, the infections were eliminated by oral amphotericin B at 2.5 mg/kg within 6 days [25].

*Other effects*

Anthelmintic properties of ivy leaf [29] and hepatoprotective properties of  $\alpha$ -hederin [36,37] have been demonstrated in mice.

*Clinical studies*

In early clinical studies, ivy leaf extracts were used in the treatment of children and adults suffering from various respiratory complaints involving coughing. Reductions were observed in the frequency of coughs [38-44].

In a randomized, double-blind, comparative study, 99 patients (aged from 25 to 70 years) with mild to moderate, simple or obstructive, chronic bronchitis were treated daily for 4 weeks with either an oral liquid containing ivy leaf dry extract (5-7.5:1, ethanol 30% m/m; 2 g of dry extract per 100 ml) [3-5  $\times$  20 drops of the oral liquid and 3  $\times$  1 placebo tablet] or ambroxol [3-5  $\times$  20 drops placebo and 3  $\times$  1 ambroxol 30 mg tablet]. Improvements in spirometric and auscultation parameters were observed in both groups with no significant differences between groups. The patients' diaries indicated a tendency towards greater decreases in frequency of coughing, sputum production and dyspnoea in the ivy leaf extract group [5].

In a randomized, comparative, crossover study, 26 children (aged 5 to 11 years) suffering from bronchial asthma were treated for 3 days with preparations containing a 30%-ethanolic dry extract (5-7.5:1) from ivy leaf: 2  $\times$  25 drops of an oral liquid preparation daily (= 35 mg of the extract daily) and then, after a wash-out interval, 2 suppositories daily (= 160 mg of the extract daily), or vice versa. Compared to initial values, reductions of 31% (oral liquid) and 23% (suppositories) in obstruction of the airways was observed. Both dosage forms were well tolerated [8].

In a randomized, double-blind, placebo-controlled, crossover study, 24 patients aged 4-12 years suffering from bronchial asthma were treated with an oral liquid containing ivy leaf dry extract (2  $\times$  25 drops, corresponding to 35 mg of the extract or 210 mg of crude drug daily) for 3 days and, over a separate 3-day period, with placebo drops. A significant reduction in airway resistance was observed in the verum group ( $p = 0.0361$ ) in comparison with the placebo group [9].

In an open multicentre study involving 52 children (aged up to 12 years) suffering from bronchial complaints, the above-mentioned oral liquid preparation containing ivy leaf dry extract (5-7.5:1; ethanol 30% m/m) was compared with another containing ivy leaf dry extract (3-6:1; ethanol 60%; 200 mg of hederacoside C per 100 ml). The daily dose was: children up to 4 years, 2  $\times$  5 ml daily; 4-10 years, 2  $\times$  7.5 ml daily; 10-12 years, 2  $\times$  10 ml daily. Treatment for 10 days led to improvement of symptoms in both groups with no significance differences between groups [14].

In an open pilot study, 26 children (aged 4-10 years) with chronic, obstructive bronchitis were treated with an ethanol-free oral preparation of ivy leaf extract (4  $\times$  1-2 teaspoonsful daily) for 4 weeks. Spirometry results, auscultatory findings and symptoms such as cough, sputum and dyspnoea improved after the first week in most of the children. Good to very good efficacy was reported in more than two-thirds of the children and no adverse reactions were reported [4].

In a multicentre surveillance study, 113 children (aged 6-15 years) suffering from recurrent obstructive respiratory complaints were treated with an ethanol-free oral preparation of ivy leaf extract for up to 20 days (in some cases up to 30 days). As the daily dose the majority took 6  $\times$  2.5 ml, one-third took 8-10  $\times$  2.5 ml and a few took only 3-4  $\times$  2.5 ml. Compared to baseline, improvements were observed in lung function and accompanying symptoms of coughing and expectoration. The physicians concluded that the optimal daily dosage was 6  $\times$  2.5 ml [6].

In a randomized, double-blind, crossover study involving 25 children (aged 10-15 years) with chronic obstructive pulmonary complaints, changes in lung function were examined after treatment over separate 10-day periods with two oral liquid preparations based on the same ivy leaf dry extract: an ethanol-free preparation (3  $\times$  5 ml daily, corresponding to 3  $\times$  35 mg of dry extract or 630 mg of crude drug daily) and an ethanol-containing preparation (3  $\times$  20 drops daily, corresponding to 3  $\times$  14 mg of dry extract or 252 mg of crude drug daily). Comparable improvements in spirometric and body-plethysmographic parameters were observed after both treatments. However, higher dosages of the ethanol-free preparation were required

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to achieve a therapeutic effect equivalent to that of the ethanol-containing preparation [7].

In an open comparative study, children aged 10-14 years suffering from chronic obstructive bronchitis were treated daily for 3 days with two different oral liquid preparations containing ivy leaf dry extract, both dosages corresponding to 250 mg of dried ivy leaf per day: an ethanolic preparation and an ethanol-free preparation. The spirometry results showed that, despite identical dosages in terms of crude drug, improvements in lung function after taking the ethanolic preparation were clearly superior to those after the ethanol-free preparation, with increases in 1-second capacity (FEV<sub>1</sub>) of 18% and 8.2% respectively ( $p < 0.05$ ) [13].

In an open study 372 children (aged from 2 months to over 10 years, average 5.7 years) suffering from respiratory tract infections were treated for 7 days with an ethanol-free oral liquid preparation containing a dry extract from ivy leaf (6-7:1, ethanol 40%; 2 ml of preparation contained 18 mg of extract corresponding to 108-126 mg of crude drug). Depending on age, average daily doses ranged from 2.8 ml to 6.7 ml. Compared to baseline, substantial improvements were observed in lung function and cough symptoms, and the physicians rated efficacy as good to very good in 94.4% of patients [10].

In an open study, 1024 children suffering from acute infections of the upper respiratory tract (52.4%), acute bronchitis/bronchiolitis (26.6%) or bronchitis (not further specified, 22.2%) were treated with an ivy leaf dry extract. Compared to initial values, significant reductions were observed in coughing, expectoration and airway resistance ( $p < 0.01$ ) [11].

### Pharmacokinetic properties

No data available.

### Preclinical safety data

#### Single dose toxicity

The oral LD<sub>50</sub> of several ivy leaf extracts in mice was determined as  $> 3$  g/kg body weight [45]. Oral administration of a dry extract of ivy leaf (ethanol 66% V/V) to rats at up to 4.1 g/kg body weight caused no deaths within 72 hours; only diarrhoea was observed [3,46].

Oral LD<sub>50</sub> values in mice of saponin mixtures from ivy leaf containing 60% and 90% of hederacoside C, and of hederasaponin C and  $\alpha$ -hederin, were all  $> 4$  g/kg body weight; the intraperitoneal LD<sub>50</sub> values for  $\alpha$ -hederin and the saponin mixture containing 60% of hederacoside C were 1.8 and 2.3 g/kg respectively [25]. In an earlier study, oral and intravenous LD<sub>50</sub>

values in rats for crude saponins from ivy leaf were reported as  $> 100$  mg/kg and 13 mg/kg respectively [35].

#### Repeated dose toxicity

Daily oral administration of an ivy leaf dry extract to rats at 1.5 g/kg body weight for 100 days caused no toxic effects; haematological and biochemical parameters, histological findings and kidney and liver weights were normal compared to those of control animals [47]. Haemolytic effects were detected after oral administration of a hydroethanolic dry extract from ivy leaf to rats at 4 g/kg body weight for 90 days [45].

#### Mutagenicity and cytotoxicity

$\alpha$ -hederin,  $\beta$ -hederin and  $\delta$ -hederin isolated from ivy leaf showed no mutagenic potential in the Ames test using *Salmonella typhimurium* strain TA 98, with or without S9 activation. These three saponins showed dose-dependent antimutagenic effects against benz[a]pyrene at levels between 80 and 200  $\mu$ g/plate in the Ames test [48]. In another study,  $\alpha$ -hederin prevented gene mutations caused by doxorubicin in human lymphocytes [49].

Cytotoxic properties of  $\alpha$  and  $\beta$ -hederin have been demonstrated in mouse 3T3 non-cancer fibroblasts, mouse B16 melanoma cells and human HeLa tumour cells [50,51]. In the presence of serum albumin, the cytotoxic effect decreased.  $\alpha$ -Hederin also induced vacuolisation of the cytoplasm and membrane alterations leading to cell death [51].

#### Reproductive toxicity

No data available on ivy leaf or extracts from it.

Intoxication of the maternal animal causes an acute phase reaction characterized by redistribution of the trace elements zinc, copper and iron, and by an increase in various plasma and liver proteins (e.g. metallothionein,  $\alpha_1$ -acid glycoprotein and ceruloplasmin), associated with non-specific malformations in the embryo. Subcutaneous administration of  $\alpha$ -hederin at 3 to 300  $\mu$ mol/kg body weight to pregnant rats on gestation days 8 and/or 11 induced an acute phase response indicated by decreased concentrations of Fe and Zn and increased concentrations of Cu,  $\alpha_1$ -acid glycoprotein and ceruloplasmin in plasma along with a dose-dependent increase in the concentration of maternal hepatic metallothionein (MT). The maximum induction of MT was 11- to 15-fold greater than in controls after doses of 30  $\mu$ mol/kg or higher. Doses of both 30 and 300  $\mu$ mol/kg significantly increased resorption incidence ( $p = 0.05$ ), and 300  $\mu$ mol/kg body weight also decreased fetal weight and increased the incidence of abnormal fetuses [52].

In another study  $\alpha$ -hederin was subcutaneously administered to rats at 20 and 30  $\mu$ mol/kg body

weight daily on gestation days 6-15, resulting in sustained elevation of hepatic metallothionein and subsequent redistribution of zinc. This led to a decrease in the zinc available to the embryo and ultimately to adverse development of the offspring. Repeated dosing throughout organogenesis increased the severity of the effects previously observed with single large doses of  $\alpha$ -hederin administered during mid-gestation [53].

Addition of  $\alpha$ -hederin to an embryo culture, directly (300  $\mu$ mol) or as serum collected 2 hours after administration of  $\alpha$ -hederin to the maternal rat (i.e. before the onset of MT synthesis), had no embryotoxic effect. However, after addition of serum obtained at the peak of metallothionein synthesis (18 hours after application of  $\alpha$ -hederin to the maternal animals), the embryos developed normally only after addition of zinc [52].

The above studies showed that single high toxic doses, or repeated low doses, of  $\alpha$ -hederin alter (as do many other substances) systemic zinc distribution in the pregnant rat, which is associated with abnormal embryo development. Abnormalities of embryogenesis due to the amount of  $\alpha$ -hederin orally administered in therapeutic doses of ivy leaf extracts (with absorption to a lesser extent) cannot be deduced from these results.

REFERENCES

1. Lierregrimant - Hedera helix. Pharmacopée Française.
2. Willuhn G. Hederae folium - Efeublätter. In: Wichtl M, editor. Teedrogen und Phytopharmaka. Ein Handbuch für die Praxis auf wissenschaftlicher Grundlage, 4th ed. Stuttgart: Wissenschaftliche Verlagsgesellschaft, 2002: 274-7.
3. Horz KH, Reichling J. Hedera. In: Hänsel R, Keller K, Rimpler H, Schneider G, editors. Hagers Handbuch der Pharmazeutischen Praxis, 5th ed. Volume 5: Drogen E-O. Berlin: Springer-Verlag, 1993:398-407.
4. Gulyas A, Lämmlein MM. Zur Behandlung von Kindern mit chronisch-obstruktiver Bronchitis. Prospan-Kindersaft, ein altbewährtes Produkt in neuer Darreichungsformen - Ergebnisse einer klinischen Prüfung. Sozialpädiatrie 1992;14:632-4.
5. Meyer-Wegener J, Liebscher K, Hettich M, Kastner H-G. Efeu versus Ambroxol bei chronischer Bronchitis. Eine Doppelblindstudie zum Vergleich der klinischen Wirksamkeit und Verträglichkeit von Efeublätter-trockenextrakt und Ambroxol. Z Allg Med 1993;69:61-6.
6. Lässig W, Generlich H, Heydolph F, Paditz E. Wirksamkeit und Verträglichkeit efeuhaltiger Hustenmittel. Prospan® Kindersaft bei rezidivierenden obstructiven Atemwegserkrankungen. TW Pädiatrie 1996;9:489-91.
7. Gulyas A, Reppes R, Dethlefsen U. Konsequente Therapie chronisch-obstruktiver Atemwegserkrankungen bei Kindern. Atemw-Lungenkrkh 1997; 23:291-4.
8. Mansfeld H-J, Höhre H, Reppes R, Dethlefsen U. Sekretolyse und Bronchospasmodolyse. Klinische Studie: Behandlung von Kindern mit chronisch obstruktiven Atemwegserkrankungen mit Prospan®. TW Pädiatrie 1997;10:155-7.
9. Mansfeld H-J, Höhre H, Reppes R, Dethlefsen U. Therapie des Asthma bronchiale mit Efeublätter-Trockenextrakt. Münch Med Wschr 1998;140:26-30.
10. Jahn E, Müller B. Efeublättertrockenextrakt. Pädiatrische Therapie-studie zur Wirksamkeit und Verträglichkeit. Dtsch Apoth Ztg 2000;140:1349-52.
11. Roth R. Anwendungsbeobachtung bestätigt Wirksamkeit der Behandlung mit Efeublätter-Trockenextrakt. Efeublätter wirken sekretolytisch und bronchospasmodolytisch. Pädiatrische Nachrichten, September 2000.
12. Dorsch W, Loew D, Meyer-Buchtela E, Schilcher H. Hederae helicis folium (Efeublätter). In: Kooperation Phytopharmaka, editor. Kinderdosierung von Phytopharmaka, 3rd ed. Teil I. Empfehlungen zur Anwendung und Dosierung von Phytopharmaka, monographierte Arzneidrogen und ihren Zubereitungen in der Pädiatrie. Bonn: Kooperation Phytopharmaka, 2002:76-7.
13. Hecker M. Efeublättertrockenextrakt: Hustentropfen mit Ethanol - deutlich bessere Wirksamkeit; Verschiedene Zubereitungen von Efeublättertrockenextrakt. Dosisanpassung erforderlich. T & E (Therapie & Erfolg) Pädiatrie 1997;10:648-50.
14. Unkauf M, Friederich M. Bronchitis bei Kindern: klinische Studie mit Efeublätter Trockenextrakt. Der Bayerische Internist 2000;(4)(Beilage, 29 June 2002):1-4.
15. Boyle J, Harman RM. Contact dermatitis to Hedera helix (common ivy). Contact Dermatitis 1985;12:111-2.
16. García M, Fernández E, Navarro JA, del Pozo MD, Fernández de Corrés L. Allergic contact dermatitis from Hedera helix L. Contact Dermatitis 1995;33:133-4.
17. Sánchez-Pérez J, Córdoba S, Hausen BM, Moreno de Vega MJ, Aragüés M, García-Díez A. Allergic contact dermatitis from common ivy confirmed with stored allergens. Contact Dermatitis 1998;39:259-60.
18. Hausen BM, Bröhan J, König WA, Faasch H, Hahn H, Bruhn G. Allergic and irritant contact dermatitis from faltarinol and didehydrofaltarinol in common ivy (Hedera helix L.). Contact Dermatitis 1987;17:1-9.
19. Gafner F, Epstein W, Reynolds G, Rodriguez E. Human maximization test of faltarinol, the principal contact allergen of English ivy and Algerian ivy (Hedera helix, H. canariensis). Contact Dermatitis 1988;19:125-8

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20. Von Mühlendahl KE, Oberdisse U, Bunjes R, Ritter S, editors. Vergiftungsunfälle mit pflanzen. In: Vergiftungen im Kindesalter, 3rd ed. Stuttgart: Ferdinand Enke Verlag, 1995:347.
21. Trute A, Groß J, Mutschler E, Nahrstedt A. In vitro spasmolytic principle of commercial dry extract from *Hedera helix* L. In: Abstracts of 2nd International Congress on Phytomedicine. Munich, 11-14 September 1996. Published as: Phytomedicine 1996;3(Suppl 1):248 (Abstract P-73).
22. Trute A, Gross J, Mutschler E, Nahrstedt A. In vitro antispasmodic compounds of the dry extract obtained from *Hedera helix*. Planta Med 1997;63:125-9.
23. Cioacă C, Margineanu C, Cucu V. The saponins of *Hedera helix* with antibacterial activity. Pharmazie 1978;33:609-10.
24. Ieven M, Vanden Berghe DA, Mertens F, Vlietinck A, Lammens E. Screening of higher plants for biological activities. I. Antimicrobial activity. Planta Med 1979;36:311-21.
25. Timon-David P, Julien J, Gasquet M, Balansard G, Bernard P. Recherche d'une activité antifongique de plusieurs principes actifs. Extraits du lierre grim pant: *Hedera helix* L. Ann Pharm Fr 1980;38:545-52.
26. Moulin-Traffort J, Favel A, Elias R, Regli P. Study of the action of  $\alpha$ -hederin on ultrastructure of *Candida albicans*. Mycoses 1998;41:411-6.
27. Rao GS, Sinsheimer JE, Cochran KW. Antiviral activity of triterpenoid saponins containing acylated  $\beta$ -amyryn aglycones. J Pharm Sci 1974;63:471-3.
28. Maffei Facino R, Carini M, Stefani R, Aldini G, Saibene L. Anti-elastase and anti-hyaluronidase activities of saponins and sapogenins from *Hedera helix*, *Aesculus hippocastanum* and *Ruscus aculeatus*: Factors contributing to their efficacy in the treatment of venous insufficiency. Arch Pharm (Weinheim) 1995;328:720-4.
29. Julien J, Gasquet M, Maillard C, Balansard G, Timon-David P. Extracts of the ivy plant, *Hedera helix*, and their anthelmintic activity on liver flukes. Planta Med 1985;51:205-8.
30. Majester-Savornin B, Elias R, Diaz-Lanza AM, Balansard G, Gasquet M, Delmas F. Saponins of the ivy plant, *Hedera helix*, and their leishmanicidal activity. Planta Med 1991;57:260-2.
31. Delmas F, Di Giorgio C, Elias R, Gasquet M, Azas N, Mshvildadze V et al. Antileishmanial activity of three saponins isolated from ivy,  $\alpha$ -hederin,  $\beta$ -hederin and hederacolchiside A<sub>1</sub>, as compared to their action on mammalian cells cultured *in vitro*. Planta Med 2000;66:343-7.
32. Ridoux O, Di Giorgio C, Delmas F, Elias R, Mshvildadze V, Dekanosidze G et al. *In vitro* antileishmanial activity of three saponins isolated from ivy,  $\alpha$ -hederin,  $\beta$ -hederin and hederacolchiside A<sub>1</sub>, in association with pentamidine and amphotericin B. Phytother Res 2001;15:298-301.
33. Tedlaouti F, Gasquet M, Delmas F, Timon-David P, Elias R, Vidal-Ollivier E et al. Antitrypanosomal activity of some saponins from *Calendula arvensis*, *Hedera helix* and *Sapindus mukurossi*. Planta Med 1991;57(Suppl 2):A78.
34. Haen E. Pharmacological activities of *Thymus vulgaris* and *Hedera helix*. In: Abstracts of 2nd International Congress on Phytomedicine. Munich, 11-14 September 1996. Published as: Phytomedicine 1996;3(Suppl 1):144 (Abstract SL-115).
35. Vogel G, Marek M-L. Zur Pharmakologie einiger Saponine. Arzneim-Forsch 1962;12:815-25.
36. Liu J, Choudhuri S, Liu Y, Kreppel H, Andrews GK, Klaassen CD. Induction of metallothionein by  $\alpha$ -hederin. Toxicol Appl Pharmacol 1993;121:144-51.
37. Liu J, Liu Y, Bullock P, Klaassen CD. Suppression of liver cytochrome P450 by  $\alpha$ -hederin: relevance to hepatoprotection. Toxicol Appl Pharmacol 1995;134:124-31.
38. Stöcklin P. Klinische Erfahrungen mit dem Hustenmittel "Prospan". Schweiz Rundschau Med (Praxis) 1959;48:934-8.
39. Rath F. Klinische Prüfung der Wirksamkeit des Hustenmittels Prospan. Fortschr Med 1968;86:1015-6.
40. Arch F. Erfahrungsbericht über die Aerosol-Behandlung der Bronchitis mit Prospan®. Notabene Medici 1974;4(6):2-8.
41. Düchtel-Brühl A. Ergebnisse der Behandlung spastischer Bronchitiden im Kindesalter mit Prospan. Med Welt 1976;27:481.
42. Böhlau V. Therapeutische Erfahrungen mit Prospan® bei chronisch-obstruktiven Atemwegserkrankungen. Notabene Medici 1977;7(11):26-9.
43. Rudkowski Z, Latos T. Inhalationsbehandlung chronischer Bronchitiden im Kindesalter mit Prospan®. Ärztliche Praxis 1979;31:342-6.
44. Leskow P. Behandlung bronchialer Erkrankungen mit dem Phytotherapeutikum Prospan®. Z Phytotherapie 1985;6:61-4.
45. Bucher K. Pharmakologische und toxikologische Untersuchungen mit Extrakten aus *Hedera helix*. Internal report for Karl Engelhard Fabrik, Frankfurt, October 1969.
46. Lanza JP, Steinmetz MD, Pellegrin E, Mourgue M. Actions toxique et pharmacodynamique sur le rat d'extraits de lierre grim pant (*Hedera helix* L.). Plantas Méd Phytothér 1980;14:221-9.
47. Kramer H. Untersuchungen zur chronischen Toxizität eines Efeu-Trockenextraktes an Ratten. Battelle-Institut, Frankfurt: Internal report for Hausheer AG, Wettingen, Switzerland, April 1968.
48. Elias R, De Méo M, Vidal-Ollivier E, Laget M, Balansard G, Duménil G. Antimutagenic activity of some saponins

## HEDERAE HELICIS FOLIUM

- isolated from *Calendula officinalis* L., *C. arvensis* L. and *Hedera helix* L. *Mutagenesis* 1990; 5:327-31.
49. Amara-Mokrane YA, Lehucher-Michel MP, Balansard C, Duménil G, Botta A. Protective effects of  $\alpha$ -hederin, chlorophyllin and ascorbic acid towards the induction of micronuclei by doxorubicin in cultured human lymphocytes. *Mutagenesis* 1996; 11:161-7.
  50. Quetin-Leclercq J, Elias R, Balansard G, Bassleer R, Angenot L. Cytotoxic activity of some triterpenoid saponins. *Planta Med* 1992;58:279-81.
  51. Danloy S, Quetin-Leclercq J, Coucke P, De Pauw Gillet M-C, Elias R, Balansard G et al. Effects of  $\alpha$ -hederin, a saponin extracted from *Hedera helix*, on cells cultured *in vitro*. *Planta Med* 1994;60:45-9.
  52. Daston GP, Overmann GJ, Baines D, Taubeneck MW, Lehmann-McKeeman LD, Rogers JM, Keen CL. Altered Zn status by  $\alpha$ -hederin in the pregnant rat and its relationship to adverse development outcome. *Reproductive Toxicol* 1994;8:15-24.
  53. Duffy JY, Baines D, Overmann GJ, Keen CL, Daston GP. Repeated administration of  $\alpha$ -hederin results in alterations in maternal zinc status and adverse developmental outcome in the rat. *Teratology* 1997;56:327-34.