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Suitability of Ivy Extract for the Treatment of Paediatric Cough

M. Schmidt,[1]* M. Thomsen[2] and U. Schmidt[3†]

[1]Herbresearch Germany, Wartbergweg 15, D-86874 Mattsies, Germany
[2]Herbresearch Pty Ltd, 29 Macfarlane Street, South Hobart, TAS 7004, Australia
[3]Arbeitsgemeinschaft für Arzneimittelsicherheit, Köln, Germany

Two galenical formulations of an ivy herbal extract, syrup and cough drops, were tested for their efficacy and safety in the paediatric treatment of cough and bronchitis in two independent open, non-interventional studies with identical design. Two-hundred and sixty-eight children aged 0–12 yr were treated with one of the two preparations for up to 14 days. The effects on cough-related symptoms were addressed on a verbal rating scale. At the end of the study the major symptoms rhinitis, cough and viscous mucus, were found to be only mildly expressed or absent in 93, 94.2 and 97.7% of cases. The global effect was rated as 'good' or 'very good' in 96.5% of cases. Tolerability and compliance were found 'good' to 'very good' in 99% (syrup) and 100% (drops) of patients on completion of the study. A subgroup analysis according to four different age and dosing groups did not reveal differences in treatment response. Safety was confirmed and corresponded to literature findings. Five adverse events classified as mild and non-serious were reported (1.9%). In conclusion, ivy leaf extract in the form of syrup and of cough drops was confirmed as an effective and safe treatment of cough in children.

Keywords: ivy; *Hedera helix*; cough; bronchitis; safety; adverse events.

INTRODUCTION

Preparations from ivy leaves (*Hedera helix* L., Araliaceae) are used in paediatric therapy as herbal medicinal products with expectorant activity for the treatment of cough associated with cold. The use of various types of ivy leaf extract for this indication has been accepted officially by the Herbal Medicinal Product Committee of the European Medicines Agency (HMPC, 2011).

Depending on the type of extract, the HMPC monograph specifically refers to the treatment of children above 4 yr of age (HMPC, 2011). In contrast, the monograph on ivy leaves by the European Scientific Cooperative on Phytotherapy recommends the application of specified doses in children of all age groups, including younger children (Anon, 2003). Whereas there is ample published experience with the administration of ivy extract preparations as referenced in the assessment report of the European Medicines Agency's (EMA) monograph, specific published data on the safety of use in paediatrics is not available for all kinds of extracts used in herbal medicinal products. This situation was the original motivation for the examination of the administration of two different galenical forms of a special ivy extract preparation in paediatrics. Although the studies were previously performed in 2001, the issue of safety in paediatric use has recently received increasing attention. We therefore decided to publish the clinical paediatric experience with the administration of two galenical formulations of a specific ivy leaf extract.

* Correspondence to: M. Schmidt, Herbresearch Germany, Wartbergweg 15, D-86874 Mattsies, Germany.
E-mail: Schmidt@herbresearch.de
†Deceased.

MATERIALS AND METHODS

Trial design. Two independent non-interventional studies with an identical design were conducted in paediatric medical practices to test the tolerability and efficacy of two different galenical formulations of the same ivy leaf extract preparation (syrup and drops) in children aged 0 to 12 yr suffering from acute respiratory catarrh and/or chronic recidivating inflammatory bronchial disease. The studies described herein were performed in accordance with the regulations of the German Federal Institute for Drugs and Medical Devices (BfArM) dated 4 December 1998. The regulatory authorities were duly notified according to §67 of the German Drug Law. Due to the study being characterized as a non-interventional trial, neither registration nor approval of an ethics committee was required.

Treatment duration averaged 10 days, with an interim visit on days 4–7 and a final visit on days 8–14. Inclusion criteria were diagnosis of catarrhal disease of the respiratory tract and/or symptoms of chronic inflammatory recidivating bronchitis, a body temperature $< 38.5\,^{\circ}C$ at screening and no concomitant treatment with antipyretic or antiinflammatory agents.

Interventions. Two galenical forms of the herbal medicinal product Hedelix® (Krewel-Meuselbach, Eitorf, Germany) were tested: one goup receiving the cough preparation as syrup, the other as cough drops. The active constituent of both preparations was ivy leaf (*Hederae helicis* folium) extract (drug:extract ratio 2.2–2.9:1, the extraction solvent was a mixture of 98 parts of ethanol 50% (v/v) and two parts of propylene glycol). The dosage was adapted to age and/or body weight of the individuals (Table 1).

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Table 1. Dose scheme and subgroups of ivy leaf extract

Group	Age (yr)	Body weight (kg)	Dosing scheme	Daily extract dose (mg)
I	0–1	3.5–11	1 × 2.5 ml syrup or 3 × 5 drops	50
II	1–4	>11–17	3 × 2.5 ml syrup or 3 × 16 drops	150
III	4–10	>17–32.5	4 × 2.5 ml syrup or 3 × 21 drops	200
IV	10–12	>32.5–61	3 × 5 ml syrup or 3 × 31 drops	300

Participants. The studies were performed in 2001. Participants were recruited in eight (cough syrup) and six (cough drops) treatment centres. The aim of the study was to include a total of at least 120 patients per galenical formulation, with approximately 30 patients per age/dose subgroup and formulation. The allocation to subgroups was based on age and body weight. In cases of doubt, body weight was the decisive factor as the drug products were to be dosed differentially according to body weight.

Outcome measures. The parameters of assessment were clinical effects and tolerance as well as safety. The severity of clinical symptoms (rhinitis, cough, pain on coughing, pain on breathing, production of viscous mucus, hoarseness, malaise, sweating and chills) was assessed for each individual upon study entry and at both visits on a four-step verbal rating scale (0 = not present, 1 = mild, 2 = moderate, 3 = severe). Well-being and sleep quality were rated on a five-step verbal rating scale (0 = excellent, 1 = good, 2 = moderate, 3 = poor, 4 = very poor). Physicians and patients or their caretakers rated the global effect and tolerance on the same five-step verbal rating scale. Body temperature was documented at each visit. Finally, dose and compliance in addition to the impression of taste and ease of application were addressed at the interim and final visit. Concomitant diseases and co-medication were documented. Adverse events were explicitly investigated and rated for their potential causality with the study medication.

Sample size. No sample size calculation was made due to the open, non-interventional design of the study. The number of patients was chosen to exclude any individual severe adverse event in 100 treated patients.

Statistical methods. The study results were descriptively analysed by subgroups according to age. Explorative group comparisons of ordinal or metric data were carried out using the Kruskal-Wallis Test (pairwise with the Mann–Whitney U-test), for nominal data the chi-square test was applied. In cases of early termination the missing data werc to be replaced by the 'last value carried over' method.

RESULTS

Participant flow and recruitment

The patient flow is indicated in Fig. 1, with the demographic data displayed in Table 2. Due to the open, non-interventional nature of the trial there was a difference in the number of patients in the safety group and in the effect group. All patients exposed to the study preparation were included into the safety group. There was no statistically significant difference for the age distribution between subgroups (chi square test).

Deviations from the allocation to subgroups were justified by body weight, in accordance with the study protocol. In the syrup-treated population one child (age 9.25 yr) was attributed to group IV because the body weight exceeded the threshold for the next age group. Similarly, two children with an age of 4.6 yr were attributed to cough drop group II instead of group III because of their low body weight. One patient from each group (both formulations) was 13 yr old, but inclusion was again justified by the low body weight.

Protocol violations

In one case (drops) the inclusion criterion of a body temperature $\leq 38.5\,^{\circ}C$ was violated. The patient was regularly treated as part of the safety and effect group. Seven patients from the syrup group and three patients from the cough drop group could not be evaluated for effects, as retrospectively, a concomitant intake of antibiotics, codeine or other herbal anticough formulations was found. In one case (drops) no data were recorded, resulting in a total of 11 exclusions from the effect population.

Effects

Data of 257 patients ranging in age from 1 month to 13 yr were available for the assessment of effects of the ivy leaf extract preparation in the form of a syrup or as cough drops. The studies were analysed independently (data not shown). There were no clinically relevant differences in improvement of the various symptoms evaluated according to galenical form when comparing the results of both studies: in most cases the observed frequency of the individual symptoms in the subgroups was in the range of ±10% of the combined database. The results on effects are therefore presented for the combined study population. In both studies independent subgroup analyses of reduction of the symptom index did not show statistically significant differences between groups (Kruskal-Wallis test), which means that all age groups profited from similar effect size.

As the assessment of symptoms was obtained from the patients or their caretakers, some more subjective symptoms such as pain on breathing or pain on coughing could not always be evaluated precisely in the children of groups I and II. The population for the assessment of the single symptoms therefore varied between 199 and 257 patients. Details on the percentage of patients

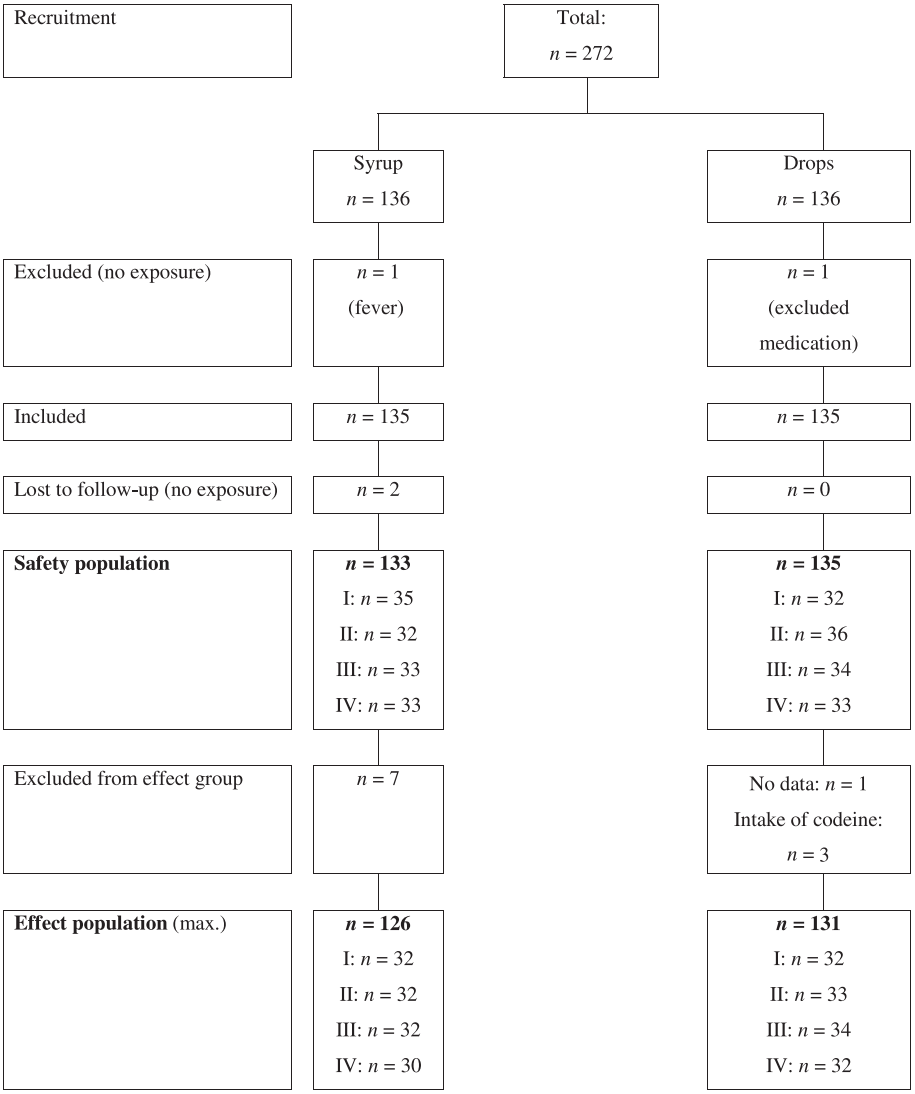

Figure 1. Patient flow.

Table 2. Demographic data of the study populations (syrup: $n = 133$; drops: $n = 135$). In both cases there was no statistically significant difference between the two preparations. Within groups, the only noteworthy difference was the time from first occurrence of symptoms to presentation for the baseline visit, with a statistically significant longer delay with increasing age (Kruskal-Wallis test; $p = 0.006$ for syrup and $p = 0.025$ for drops)

Variables	Preparation	Group I	Group II	Group III	Group IV
Male	Syrup	21 (60.0%)	15 (46.9%)	3 (39.4%)	17 (51.5%)
	Drops	12 (37.5%)	20 (55.6%)	20 (58.8%)	14 (42.4%)
Female	Syrup	14 (40.0%)	17 (53.1%)	20 (60.6%)	16 (48.5%)
	Drops	20 (62.5%)	16 (44.4%)	14 (41.2%)	19 (57.6%)
Age (months)	Syrup	6.7 ± 2.5 (1–12)	33.0 ± 11.3 (12–49)	70.6 ± 19.5 (49–119)	139.9 ± 10.8 (112–156)
	Drops	8.0 ± 2.8 (3–13)	33.8 ± 12.0 (12–56)	79.5 ± 23.9 (49–121)	138.8 ± 9.5 (121–151)
Size (cm)	Syrup	67.8 ± 5.7 (53–78)	92.9 ± 9.0 (75–109)	114.2 ± 10.8 (99–138)	148.3 ± 7.0 (136–164)
	Drops	70.2 ± 4.8 (60–78)	91.9 ± 8.8 (72–104)	119.0 ± 13.9 (100–147)	138.8 ± 9.5 (121–151)
Body weight (kg)	Syrup	7.6 ± 1.5 (3–11)	13.6 ± 2.3 (9–18)	20.1 ± 4.8 (14–33)	39.8 ± 8.2 (18–60)
	Drops	8.6 ± 1.5 (6–12)	14.0 ± 2.2 (10–18)	24.2 ± 7.5 (16–52)	40.3 ± 6.8 (32–59)
Duration of complaints until V0 (days)	Syrup	2.7 ± 1.4 (1–7)	3.1 ± 1.5 (1–7)	3.7 ± 3.7 (1–21)	4.4 ± 2.9 (1–14)
	Drops	2.8 ± 0.99 (2–5)	3.5 ± 2.5 (1–14)	3.9 ± 1.8 (2–8)	4.3 ± 3.5 (1–21)

reporting the severity of the individual symptoms are given in Table 3: as expected for ivy as an antitussive preparation, the typical cough symptoms subsided markedly under treatment.

Well-being and sleep quality were similarly improved under treatment with the two galenical forms of ivy leaf extract, with no statistically significant difference between subgroups (Kruskal-Wallis test). At screening,

Table 3. Development of symptoms during the study

Symptom	Visit	Not present (%)	Mild (%)	Moderate (%)	Strong (%)
Rhinitis (n = 257)	Screening	3.5	17.5	33.1	45.9
	Days 4–7	7.4	37.7	49.0	5.8
	Days 8–14	35.0	58.0	5.4	1.6
Cough (n = 257)	Screening	0	7.0	41.6	51.4
	Days 4–7	4.7	41.6	48.2	5.4
	Days 8–14	46.3	47.9	3.9	1.9
Pain on coughing (n = 201)	Screening	37.3	26.9	21.4	14.4
	Days 4–7	72.6	19.4	7.5	0.5
	Days 8–14	98.5	0.5	0.5	0.5
Pain on breathing (n = 199)	Screening	66.3	18.6	11.1	4.0
	Days 4–7	94.0	4.5	1.5	0
	Days 8–14	99.5	0	0.5	0
Vicous mucus (n = 252)	Screening	28.6	17.5	33.3	20.6
	Days 4–7	35.7	41.7	22.2	0.4
	Days 8–14	80.6	17.1	2.4	0
Hoarseness (n = 255)	Screening	27.1	30.6	25.1	17.3
	Days 4–7	61.2	35.3	3.5	0
	Days 8–14	93.3	5.1	1.6	0
Malaise (n = 233)	Screening	19.3	23.2	28.8	28.8
	Days 4–7	46.8	27.0	25.3	0.9
	Days 8–14	73.8	22.3	3.0	0.9
Sweating (n = 248)	Screening	37.5	11.7	23.4	27.4
	Days 4–7	61.7	26.6	11.7	0
	Days 8–14	92.7	5.6	1.6	0
Chills (n = 242)	Screening	56.6	10.3	12.8	20.2
	Days 4–7	81.4	14.0	4.5	0
	Days 8–14	96.7	2.1	1.2	0

well-being and sleep quality were found to be 'poor' or 'very poor' by 40.0% and 56.8% of patients respectively, and considered 'good' or 'very good' by 16.0 and 8.6% (n = 257). At the end of the study this percentage was modified to 1.6 and 2.3% of assessments as 'poor' or 'very poor', and to 93.4 and 80.9% ratings as 'good' or 'very good'.

The global assessment of effects by the physician already described 96.5% as 'good' or 'very good', with an almost identical rating at the time of the interim visit after 4–7 days. The patients themselves or their caretakers came to a similar result, with 93.6% of ratings as 'good' or 'very good' at the conclusion of the study.

The global assessment of effects by the physician was not significantly different for the various age groups, with the exception of the rating for group III at the interim visit at days 4–7 (Kruskal-Wallis test: $p = 0.017$ with syrup and $p = 0.007$ with drops): Here the result was found to be better in comparison with the other groups. At the end of the study there was no further difference between age groups.

Tolerability

As for the clinical symptoms, the tolerability of the two study preparations was analysed individually (data not presented), but upon comparison of the outcomes of the two studies no clinically relevant differences were found. The results are therefore presented as a combined analysis of both studies.

The global assessment of tolerability by the physician is displayed in Fig. 2. For patients administered the syrup preparation, the global assessment of tolerability by the physician yielded 'good' to 'very good' results in 129/131 cases (98.4%) at the interim visit on days 4–7, and in 118/119 cases (99.2%) at the final visit. 'Good' to 'very good' results were achieved with the drops by 133/134 cases (99.2%) at the interim visit, and in 124/124

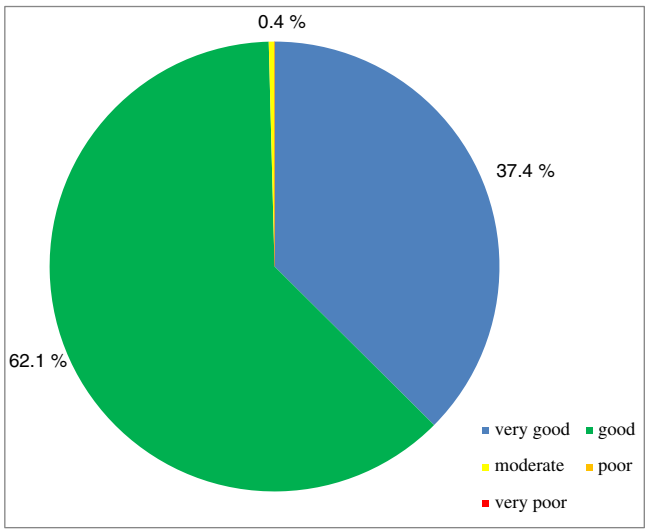

Figure 2. Global assessment of tolerability by the physician on days 8–14 (n = 243). This figure is available in colour online at wileyonlinelibrary.com/journal/ptr.

Table 4. Adverse events.

Adverse event	Sex	Age	Preparation	Dose	Duration	Severity	Outcome	Causality assessment
Diarrhoea	F	8 months	Syrup	1 × 2.5 mL	4 days	Moderate	Symptoms persisted three days post discontinuation	Unrelated
Nausea*	F	10 yr	Syrup	3 × 5 mL	10 days	Moderate	Symptoms resolved with dose reduction to 3 × 2.5 mL	Possible
Vomiting	M	4 yr	Drops	16 drops	1st dose	Mild	Mild, transient	Possible
	F	9 months	Drops	3 × 5 drops	4 days	Mild	Mild, drop-out	Probable
Angular cheilitis and diaper dermatitis	F	4 months	Drops	3 × 5 drops	10 days	Moderate	Resolved with specific topical therapy	Possible

*Co-medication: tablets with plant powders of vervain herb, gentian root, common sorrel herb, elderberry flower and primrose flowers.

cases (100%) at the final visit. The difference in absolute numbers of the safety group was caused by early study termination and correspondingly missing values. Of note: tolerability was rated significantly better in subgroup III (4–10 yr) using syrup, but not drops, in comparison with the other subgroups (Mann–Whitney U-test: days 4–7 $p = 0.003$ for III vs. I; not significant for III vs. II and for III vs. IV; final visit $p = 0.017$ for III vs. I; $p = 0.006$ for III vs. II; $p = 0.047$ for III vs. IV). The reason for this effect is as yet unexplained. The children themselves ($n = 57$ and 68 with syrup and drops on days 4–7; $n = 55$ and 65 at the final visit) indicated a good or very good tolerability in 98.2 and 94.1% of cases with syrup and drops, respectively on days 4–7, and in 98.2 and 96.9% of cases at the final visit.

Compliance was in most cases excellent. Unpleasant taste was indicated for the syrup in seven cases at the first control visit (two drop-outs), and in five cases at the final visit. Four of the patients indicating unpleasant taste at the end of the study had also expressed this at the control visit. However, compliance was negatively affected by taste in only one of the patients stating a 'bad taste' at the interim visit, and did not influence compliance in all other cases. Unpleasant taste led to early study termination in 10 cases in the study population taking the drops. The taste was, however, rated as good to excellent in 88.9% of cases, and the examination of compliance did not note specific problems.

Correspondingly, the administration of the syrup was rated as easy by 98.2% of the children, whereas drop-counting for the alternative formulation was found burdensome in some cases, resulting in an assessment of easy administration in only 90.8% of children.

Adverse events

A total of five adverse events were reported, none of them serious (Table 4). Four of the five reports related to gastrointestinal complaints. Symptoms such as nausea, vomiting or diarrhoea are listed as potential adverse effects occurring 1 to 10 out of 1000 patients ('occasionally'). Even with the assumption of causality by ivy extract in all cases the observed frequency of adverse events would still correspond to this classification. In addition, safety is validated by the lack of severe adverse reactions.

DISCUSSION

These two non-intervention studies evaluated safety and to a lesser extent efficacy in children as an important target patient group for ivy preparations. Due to the lack of a placebo or reference control, non-intervention studies have only limited value with respect to efficacy. Correspondingly, the development of symptoms has been analysed descriptively. The observations with respect to the reduction of clinical symptoms do, however, correspond to the experience with ivy preparations in controlled clinical trials (Meyer-Wegener *et al*., 1993; Gulyas *et al*., 1997; Unkauf and Friedrich, 2002; Maidannik *et al*., 2003) and in non-controlled studies (Lässig *et al*., 1996; Hecker, 1997; Roth, 2000; Hecker *et al*., 2002; Jahn and Müller, 2000; Buechi and Kähler, 2003; Kraft, 2004; Fazio *et al*., 2009). The study presented here is the first report on the safety and ease of administration of the ivy leaf extract in the galenical formulations as syrup and as drops in children of all age groups up to the age of 0–12 yr. The results are supported by the findings of a recently published clinical double-blind trial, where the same medication (Hedelix drops) was tested against another well-established ivy leaf extract preparation in 590 mostly paediatric patients (Cwientzek *et al*., 2011).

Our observations specifically confirm the ease of administration and safety of ivy leaf extract in children – a paediatric treatment option for which the use has officially been declared 'well-established' by the Herbal Medicinal Product Committee of the European Medicines Agency.

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Conflict of Interest

Krewel-Meuselbach provided the original study reports to the authors for the preparation of the manuscript, but did not contribute to the process of drafting of the manuscript. There was no conflict of interest.

REFERENCES

Anon. 2003. *Hederae helicis* folium. Ivy leaf. In *ESCOP Monographs. The Scientific Foundation for Herbal Medicinal Products*, 2nd edn, ESCOP (ed). Thieme: Stuttgart; 241–247.

Buechi S, Kähler D. 2003. Efeu (Hedera helix) bei Atemwegserkrankungen. *Schweiz Zschr Ganzheitsmed* **15**: 124–128.

Cwientzek U, Ottillinger B, Arenberger P. 2011. Acute bronchitis therapy with ivy leaves extracts in a two-arm study. A double-blind, randomised study vs. another ivy leaves extract. *Phytomedicine* **18**(13): 1105–1109.

Fazio S, Pouso J, Dolinsky D, *et al*. 2009. Tolerance, safety and efficacy of Hedera helix extract in inflammatory bronchial diseases under clinical practice conditions: a prospective, open, multicentre postmarketing study in 9657 patients. *Phytomedicine* **16**(1): 17–24.

Gulyas A, Repges R, Dethlefsen U. 1997. Konsequente Therapie chronisch-obstruktiver Atemwegserkrankungen bei Kindern. *Atemw -Lungenkrkh* **23**: 291–294.

Hecker M. 1997. Efeublättertrockenextrakt: Hustentropfen mit Ethanol - deutlich bessere Wirksamkeit. Verschiedene Zubereitungen von Efeublättertrockenextrakt: Dosisanpassung erforderlich. *Therapie Erfolg Pädiatrie* **10**: 648–650.

Hecker M, Runkel F, Völp A. 2002. Behandlung chronischer Brochitis mit einem Spezialextrakt aus Efeublättern – multizentrische Anwendungsbeobachtung mit 1350 Patienten. *Forsch Komplementarmed* **9**: 77–84.

HMPC. 2011. *Community Herbal Monograph on Hedera helix L., folium*. EMEA/HMPC/289430/2009. European Medicines Agency: London.

Jahn E, Müller B. 2000. Efeublättertrockenextrakt. Pädiatrische Therapiestudie zur Wirksamkeit und Verträglichkeit. *Dtsch Apoth Ztg* **140**: 1349–1352.

Kraft K. 2004. Verträglichkeit von Efeublättertrockenextrakt im Kindesalter. *Z Phytother* **25**: 179–181.

Lässig W, Generlich H, Heydolph F, Paditz E. 1996. Wirksamkeit und Verträglichkeit efeuhaltiger Hustenmittel. Prospan(R) Kindersaft bei rezidivierenden obstruktiven Atemwegserkrankungen. *TW Pädiatrie* **9**: 489–491.

Maidannik V, Duka E, Kachalova O, Efanova A, Svoykina S, Sosnofskaja T. 2003. Efficacy of Prospan application in children's diseases of respiratory tract. *Pediatrics, Toxicology and Gynecology* **4**: 1–7.

Meyer-Wegener J, Liebscher K, Hettich M, Kastner HG. 1993. Efeu versus Amboxol bei chronischer Bronchitis. Eine Doppelblindstudie zum Vergleich der klinischen Wirksamkeit und Verträglichkeit von Efeublättertrockenextrakt und Ambroxol. *Z Allg Med* **69**: 61–66.

Roth R. 2000. Anwendungsbeobachtung bestätigt Wirksamkeit der Behandlung mit Efeublätter-Trockenextrakt. Efeublätter wirken sekretolytisch und bronchospasmolytisch. *Pädiatr Nachrichten* **September** (Suppl. 1): 1–3.

Unkauf M, Friedrich M. 2002. Bronchitis bei Kindern: Klinische Studie mit Efeublätter-Trockenextrakt. *Der Bayerische Internist* **4**(Suppl. 29.6): 1–4.