

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/7380889>

Open Trial to Assess Aspects of Safety and Efficacy of a Combined Herbal Cough Syrup with Ivy and Thyme

Article in *Forschende Komplementärmedizin und Klassische Naturheilkunde / Research in Complementary and Classical Natural Medicine* · January 2006

DOI: 10.1159/000088934 · Source: PubMed

CITATIONS

69

READS

1,863

5 authors, including:



Mac Ramos

Servier

16 PUBLICATIONS 210 CITATIONS

[SEE PROFILE](#)



Jörg Melzer

Lou Andreas-Salomé Institute for Psychoanalysis and Psychotherapy

110 PUBLICATIONS 1,582 CITATIONS

[SEE PROFILE](#)

Open Trial to Assess Aspects of Safety and Efficacy of a Combined Herbal Cough Syrup with Ivy and Thyme

Samuel Büechi^a Roger Vögelin^b Mónica Mennet-von Eiff^c Mac Ramos^c Jörg Melzer^d

^aPhytocon GmbH, Trogen,

^bTeufen,

^cWeleda AG, Arlesheim,

^dUniversity Hospital, Department of Internal Medicine, Complementary Medicine, Zurich, Switzerland

Key Words

Dry ivy leaf extract · Thyme decoction · Cough ·
Open clinical trial · 'Anwendungsbeleg'

Summary

Background and Objectives: Changes in the symptoms of cough after treatment with a combined herbal preparation containing dry ivy leaf extract as main active ingredient, decoction of thyme and aniseed, and mucilage of marshmallow root (Weleda Hustenelixier, new formulation) and its tolerability were investigated in an open clinical trial ('Anwendungsbeleg'). **Patients and Methods:** Between January and March 2004, 13 general practitioners recruited and treated 62 patients with a mean age of 50 years (range 16–89). The patients had irritating cough in consequence of common cold (n = 29), bronchitis (n = 20) or respiratory tract diseases with formation of viscous mucus (n = 15). The mean daily intake was 10 ml (range 7.5–15) of syrup, and the mean duration of treatment was 12 days (range 3–23 days). Treatment results were assessed on the basis of changes in the symptom scores for cough and expectoration. Safety was evaluated by means of an analysis of adverse events. In addition, efficacy and tolerability were analyzed from the judgments of the doctors and patients. **Results:** At the final visit, all symptom scores showed an improvement as compared to baseline. Doctors and patients assessed efficacy as good or very good in 86% and 90% of the cases, respectively. Tolerability was assessed as good or very good by 97% of the doctors and patients. Only one adverse event was reported. However, a relation to the medication was classified to be unlikely. **Conclusion:** Considering the traditional use of ivy leaves, thyme herb, aniseed and marshmallow root in preparations for cough, the reduction in the symptom score as well as the good tolerability the investigated combined herbal cough syrup seems to alleviate cough in consequence of common cold, bronchitis or respiratory tract diseases with formation of mucus.

Schlüsselwörter

Efeublätter-Trockenextrakt · Thymian-Dekokt · Husten ·
Offener klinischer Versuch · Anwendungsbeleg

Zusammenfassung

Hintergrund und Fragestellung: Im Rahmen einer offenen Studie (Anwendungsbeleg) wurden die Veränderung der Hustensymptomatik sowie die Verträglichkeit einer Therapie mit einem pflanzlichen Kombinationspräparat aus Efeublätter-Trockenextrakt als Hauptwirkstoff sowie Thymian-Anis-Dekokt und Eibischwurzelschleim untersucht (Weleda Hustenelixier, neue Formulierung). **Patienten und Methoden:** Zwischen Januar und März 2004 wurden von 13 Allgemeinärzten 62 Patienten mit einem durchschnittlichen Alter von 50 Jahren (Range 16–89) rekrutiert und behandelt. Die Patienten hatten Husten infolge von Erkältungen (n = 29), Bronchitiden (n = 20) oder Atemwegserkrankungen mit Bildung von zähem Schleim (n = 15). Sie nahmen täglich durchschnittlich 10 ml (Range 7,5–15) Sirup ein. Die mittlere Therapiedauer betrug 12 Tage (Range 3–23). Der Erfolg der Behandlung wurde anhand der Veränderung der Symptome Husten und Expektoration beurteilt (Symptomscore). Die Sicherheit der Behandlung wurde anhand unerwünschter Wirkungen bewertet. Zusätzlich wurden Wirksamkeit und Verträglichkeit mittels des Urteils der Ärzte und Patienten erfasst. **Ergebnisse:** Im Vergleich zur Anfangsuntersuchung zeigte sich bei der Schlussuntersuchung bei den Symptomscores für Husten und Auswurf eine deutliche Besserung. Die Ärzte und Patienten beurteilten die Wirkung zu 86% resp. 90% als gut oder sehr gut. Die Verträglichkeit wurde von 97% der Ärzte und Patienten als gut oder sehr gut beurteilt. Nur ein unerwünschtes Ereignis trat auf. Ein Zusammenhang mit der Medikation wurde jedoch als unwahrscheinlich beurteilt. **Schlussfolgerung:** In Anbetracht der traditionellen Anwendung von Efeublättern, Thymiankraut, Anisfrüchten und Eibischwurzel für Hustenpräparate sowie der Reduktion der Symptomscores und der guten Verträglichkeit scheint der untersuchte Sirup zur Linderung von Husten infolge Erkältung, Bronchitiden oder Atemwegserkrankungen mit Schleimbildung geeignet.

Introduction

Herbal drugs are used to treat symptoms of common cold [1], and among these drugs mucolytic agents are frequently used in cases of irritating cough in consequence of common cold and other respiratory tract diseases with formation of viscous mucus like bronchitis. Besides synthetic agents such as acetylcysteine, carbocysteine, ambroxol and bromhexine, herbal medicines containing saponins, i.e. ivy leaves preparations, are widely used in these indications. Not only ivy but also thyme herb, aniseed, marshmallow root or iceland moss [2] are herbal drugs that are traditionally used for drops, syrups or infusions administered to treat cough. The present clinical trial has been carried out due to the legislation in Switzerland ('Phyto-Anleitung' [3]) which enables registration of preparations of traditional herbal medicine provided there is evidence on efficacy and safety from a so-called 'Anwendungsbeleg'. For this kind of open trial, the authorities expect the data of at least 50 patients from at least 2 doctors.

Ivy extracts seem likely to be efficacious and safe in the following indications specified by the European Scientific Cooperative on Phytotherapy (ESCOP): coughs, particularly when associated with hypersecretion of viscous mucus; as adjuvant treatment of inflammatory bronchial diseases [4]. Additionally, this indication is given in the monographs of the 'Kommission E' [5] and the PDR (Physicians' Desk Reference) [6]. Furthermore, a randomized, double-blind comparative trial showed the effect of ivy on bronchitis in 99 patients who received an oral liquid containing dry ivy leaf extract (drug extract ratio, DER: 5–7.5 : 1, ethanol 30% m/m), or ambroxol tablets. Improvements in spirometric and auscultation parameters were observed in both groups with no significant differences between the groups. The patients' diaries indicated a tendency towards greater decreases in the frequency of coughing, sputum production and dyspnoea in the verum group [7]. With respect to respiratory tract infections an open clinical trial on 372 children was performed with an ethanol-free oral liquid with a dry ivy leaf extract (DER: 6–7 : 1, ethanol 40% m/m). As compared to baseline, substantial improvements were observed in lung function and cough symptoms [8]. Regarding the indication of dry ivy leaf extract in the treatment of chronic airway obstruction in children suffering from bronchial asthma a systematic review is available [9]. The trials included in that review indicate that ivy leaf extract preparations do have effects in terms of an improvement of respiratory functions in children with chronic bronchial asthma, but more far-reaching conclusions can hardly be drawn because of the meager database.

Patients and Methods

The present study was conducted in Switzerland in co-operation with 13 general practitioners from the Cantons of St. Gallen and Appenzell

Table 1. Baseline data of the patients (n = 62)

Sex	
– Female, n	37
– Male, n	25
Mean age, years (range)	50 (16–89)
Mean weight, kg (range)	68 (46–104)
Indications (multiple referencing possible*), n	
– Irritating cough in consequence of common cold	29
– Acute or chronic bronchitis	20
– Respiratory tract diseases with intense formation of viscous mucus	15

*Out of 2 patients with cough, 1 additionally had bronchitis and 1 had respiratory disease. Therefore, the total is 64 instead of 62.

Ausserrhoden. Patient recruitment started in January 2004. The following inclusion and exclusion criteria were used to recruit patients for this study: *Inclusion criteria:* (1) cases of irritating cough in consequence of common cold, (2) bronchitis (acute or chronic), (3) respiratory tract diseases with intense formation of viscous mucus, (4) information about the aim of the study and written consent, (5) age: at least 6 years. The indications chosen were those that can be obtained from authorities (Swissmedic) for OTC (over the counter) preparations containing ivy. The indication of respiratory tract diseases can be defined as inflammatory airway diseases (without pneumonia). *Exclusion criteria:* (1) concomitant use of other expectorants, (2) pneumonia, pregnancy and lactation, (3) known drug allergy or hypersensitivity to one of the ingredients of the combined herbal cough syrup. As a convenience sample 62 patients took part in the trial.

The study was conducted according to study protocol DC-ELX-1, version 2, valid from 10th October, 2003. The Declaration of Helsinki in its revised version of 1975 and its amendments of 1983, 1989, and 1996 and GCP (Good Clinical Practice) standards were fulfilled during organization and performance of the study. The approvals of the Medical Ethics Committees of the Cantons of St. Gallen and Appenzell Ausserrhoden were obtained.

At the initial visit of the patients, inclusion and exclusion criteria were checked by the doctors. A duration of treatment of up to 2 weeks per patient was recommended. The final visit took place after the end of each individual treatment. In March 2004, treatment of the last patient was completed.

The combined herbal cough syrup is a remedy prepared on the basis of dry extract of ivy leaf (*Hederae helix* folium), a decoction (boiling water extract) of thyme (*Thymi herba*), and adjuvant herbal preparations (decoction of aniseed (*Anisi fructus*) and mucilage (water macerate) of marshmallow root (*Althaeae radix*). All herbal drugs are known according to the 'Stoffliste' of Swissmedic [10]. 5 ml (6.7 g) syrup contains 0.07 g of dry ivy leaf extract (DER: 4–8 : 1, ethanol 30% m/m) and 1.7 g of decoction of thyme and aniseed corresponding to a DER of 1 : 3.5–4.0 in relation to thyme. Aniseed is just an enhancement for the flavor. The following additional pharmaceutical aids are used: mucilage of marshmallow root as a thickener, malt extract, and sugar. Besides sugar no other preservatives are used. Extracts of thyme, aniseed and marshmallow can be regarded as additional active ingredient (secretolytic and mucilaginous agents) or as excipients (aromatics and thickening agents). The following dosage was recommended: Adults: 1–2 × 5 ml per day. Children from 6 to 12 years: 1–3 × 2.5 ml per day. Each patient received a 200 ml bottle of the syrup, sufficient for 20 days at a dosage of 5 ml twice per day.

The main criteria observed were changes in the strength of the stimulus to cough and in expectoration (amount, consistency, ease, color) between initial and final visit. At both visits, the doctors asked the patients on their symptoms using a 4-level symptom score to assess changes: none or little = 1, medium = 2, strong = 3, very strong = 4.

Table 2. Data of the 4-level symptom score of the subgroups

	Irritating cough due to common cold (n = 29)*						Bronchitis (acute or chronic) (n = 20)						Respiratory tract diseases with formation of mucus (n = 15)					
	1	2	3	4	Md	M	1	2	3	4	Md	M	1	2	3	4	Md	M
Strength of stimulus to cough																		
– Initial	3	6	10	10	3	2.9	0	6	10	4	3	2.9	1	3	8	3	3	2.9
– Final	22	7	0	0	1	1.2	12	8	0	0	1	1.4	12	3	0	0	1	1.2
Amount of expectoration																		
– Initial	14	11	3	1	2	1.7	3	7	8	2	3	2.5	3	4	6	2	3	2.5
– final	25	2	2	0	1	1.2	16	2	2	0	1	1.3	10	4	0	1	1	1.5
Consistency of the expectoration																		
– Initial	4	5	16	4	3	2.7	0	8	9	3	3	2.8	0	3	8	4	3	3.1
– Final	14	11	4	0	2	1.7	14	6	0	0	1	1.3	7	6	2	0	2	1.7
Ease of expectoration																		
– Initial	5	10	9	5	2	2.5	2	9	8	1	2	2.4	0	5	8	2	3	2.8
– Final	20	7	2	0	1	1.4	17	3	0	0	1	1.2	14	1	0	0	1	1.1

Rating: 1 = none or little, 2 = medium, 3 = strong, 4 = very strong. MD = median; M = mean.

*Out of 2 patients with cough, 1 additionally had bronchitis and 1 had respiratory disease. Therefore the total is 64 instead of 62.

Secondary criteria were the patients' and doctors' answers to the following questions: (1) How do you judge efficacy? (2) How do you judge safety? (3) Would you recommend the medicine? (4) Would you use the medicine again? (5) How do you judge the taste? Patients were asked to answer questions 1, 2, 4, 5, and doctors questions 1, 2, 3, respectively. The questions had to be answered at the final visit according to a 4-level rating system: Depending on the questions, answers could either be 'very good, good, satisfactory, and unsatisfactory', or 'yes, maybe, maybe not, and surely not'. The symptom score was developed for this trial and has not been validated.

Results

The baseline data of the 62 patients enrolled and evaluated in our study is shown in table 1. During the clinical trial, the following daily dosages were prescribed: 2 × 5 ml (n = 48), 3 × 2.5 ml (n = 9), 3 × 5 ml (n = 3), 5 × 2.5 ml (n = 1). In one case, the doctor prescribed an initial dosage of 3 × 5 ml per day, which was then reduced to 2 × 5 ml. The single dose ranged from 2.5 (n = 10) to 5 ml (n = 52). The mean daily intake was 10 ml (7.5–15 ml). The duration of treatment – defined as the time between initial and final visit – was 3–23 days (mean M: 12 days, median Md: 13 days).

Regarding the main criteria the median of the symptom scores changed as follows (table 2): strength of the stimulus to cough: 3 to 1 (M: 2.9 to 1.3), amount of expectoration: 2 to 1 (M: 2.1 to 1.3), consistency of expectoration: 3 to 1 (M: 2.8 to 1.5), ease of expectoration 3 to 1 (M: 2.5 to 1.2). The color of the expectoration changed from 24 clear or white and 35 colored expectorations (green, gray, or yellow) at the initial visit to 43 clear or white and 8 colored expectorations at the final visit (data not shown).

Regarding the secondary criteria, efficacy (question 1) was assessed by doctors and patients as good or very good in 86% and 90% of the cases, respectively (table 3). As to tolerability (question 2) doctors and patients assessed it as good or very good in 97% (table 3). Questions 3–5 were answered as follows (data not shown): 49 (79%) of the doctors answered 'yes' to the question 'Would you recommend the medicine?' (n = 62). To the question 'Would you use the medicine again?' 54 (89%) patients answered 'yes' (n = 61). The question 'How do you judge the taste?' was answered with 'very good/good' by 52 (84%) of the patients (n = 62).

Concomitant use of expectorants in addition to the medication was not allowed and did not occur. In 24 cases, other medicines were used. In three cases, the use of antitussive agents (dextromethorphan) was reported.

The doctors asked their patients about adverse reactions. One adverse event (vomiting while eating) was reported. This happened once one day before the start of the treatment, and once during treatment in a patient (female, aged 82) with a hiatal hernia. Sporadic incidents of reflux as well as nausea in conjunction with irritating cough are known. Treatment was not interrupted. No further vomiting occurred. A relation to the medication seems rather unlikely.

Discussion

Dry ivy leaf extract is the main active ingredient of the combined herbal preparation examined in this study. In terms of DER and extractant, quality and dosage of this extract are similar to that used in Prospan® (Engelhard, Niederdor-

Table 3. Rating of efficacy and tolerability according to a 4-level rating system (n = 62)

	Efficacy n (%)	Tolerability n (%)
<i>Doctors</i>		
1 very good	29 (46.8)	49 (79.0)
2 good	24 (38.7)	11 (17.7)
3 moderate	7 (11.3)	2 (3.2)
4 insufficient	2 (3.2)	0 (0)
<i>Patients</i>		
1 very good	32 (51.6)	52 (83.8)
2 good	24 (38.7)	8 (12.9)
3 moderate	5 (8.1)	2 (3.2)
4 insufficient	1 (1.6)	0 (0)

felden, Germany). The combined herbal cough syrup examined is a newly developed product in the tradition of European phytotherapeutics.

The study results show that symptom scores between initial and final visit reduced most markedly for the symptoms of cough in the majority of the patients, followed by expectoration. These changes might be assigned to a mucolytic action and/or an improvement of mucociliary transportation. A comparable effect was shown in another open clinical trial with the same indications and a similar design investigating a different preparation (pastilles) of the same ivy extract [11]. In that study, 56 patients took 2–6 pastilles per day for an average of about 7 days. One pastille contains 26 mg of the same dry ivy leaf extract (DER: 4–8 : 1, ethanol 30% m/m).

Nevertheless, the present trial has several limitations: Although the open design of the study ('Anwendungsbeleg') facilitates research within the setting of practices of general practitioners and is approved by Swiss regulation authorities to give a hint concerning safety and efficacy of traditionally used herbal medicine, it only provides evidence at a low level of the hierarchy of evidence-based medicine as compared to randomized controlled trials. Additionally, the self-limiting character of coughs in consequence of common cold is difficult to differentiate from the effect of the herbal preparation, especially in those patients who used the syrup over a period of more than 2 weeks (n = 20). Therefore, an effect on the duration of the symptoms can hardly be assessed. Yet, regarding the severity of symptoms a reduction from very strong/strong

to little/none was found in most of the patients (data not shown). Finally, the explanatory power of the symptom score used for measuring changes in symptoms is limited.

In the present study no serious adverse events occurred, and the only adverse event was classified to be unlikely attributable to the drug. However, due to the limited number of patients included in the study, only very common adverse events were likely to be observed. In general, decoctions of thyme herb or aniseed and mucilages of marshmallow root are considered to be very well tolerated. In fact, the essential oil of thyme and aniseed are of toxicological relevance, but due to the poor water-solubility of essential oils, extracts like decoctions contain only traces of essential oils. Allergic and irritant contact dermatitis caused by contact with ivy plants may occur. Polyacetylenes (falcariinol and didehydrofalcariinol) were identified as allergenic substances [12]. However, there are some theoretical concerns with regard to ivy leaves because of their saponin content. Saponin containing drugs are said to cause vomiting in cases of intoxication. The dosages to reach this effect are much higher than the dosage used in this trial. In a fairly large-scale post-marketing surveillance study of an ivy extract preparation (DER: 5–7.5 : 1, ethanol 30% m/m), only 3 out of 1,350 patients showed effects where an involvement of the medicine could not be ruled out (2 cases of eructation, 1 case of nausea) [13]. A similar picture emerged from a retrospective survey into the tolerance of dry ivy leaf extract in children [14]. The Swiss authorities (Swissmedic) have no records of adverse reactions to ivy leaf or ivy leaf preparations [15].

Considering the traditional use of ivy leaves, thyme, aniseed and marshmallow root in preparations for cough, the reduction of symptom scores as well as the good tolerability the combined herbal cough syrup investigated here seems to alleviate symptoms of cough in consequence of common cold, bronchitis or respiratory tract diseases with formation of mucus.

Acknowledgements

The principal investigator was Dr. med. Roger Voegelin, Teufen. The trial was monitored and organized by Dr. phil. II Samuel Büechi, Phytocon GmbH, Trogen. The sponsor of the trial was Weleda AG, Arlesheim, Project Manager Stephanie von Burg. The Head of Clinical Research responsible for the study was Dr. med. Mac H. Ramos F.

References

- Härtel U, Volger E: Inanspruchnahme und Akzeptanz klassischer Naturheilverfahren und alternativer Heilmethoden in Deutschland – Ergebnisse einer repräsentativen Bevölkerungsstudie. *Forsch Komplementärmed Klass Naturheilkd* 2004;11: 327–334.
- Hecker M, Völz A: Verträglichkeit von Isländisch-Moos-Pastillen bei Erkrankungen der oberen Atemwege – multizentrische Anwendungsbeobachtung mit 3143 Kindern. *Forsch Komplementärmed Klass Naturheilkd* 2004;11:76–82.
- Swissmedic (Hrsg): Anleitung zum Einreichen von Zulassungsgesuchen für pflanzliche Arzneimittel der Humanmedizin (Phyto-Anleitung). *Swissmedic J* 2004;9:843–860.
- European Scientific Cooperative on Phytotherapy (ed): *ESCOP Monographs*, ed 2. Stuttgart, Thieme, 2003.
- Eberwein E, Vogel G: *Arzneipflanzen in der Phytotherapie. Einzelstoffmonographien und Stoffcharakteristiken*, Bd 1. Bonn, Kooperation Phytopharmaka, 1990–1995.
- Grünwald J, Brendler T, Jänicke C (eds): *Physicians' Desk Reference (PDR) for Herbal Medicines*, ed 3. Montvale, Thompson, 2004.
- Meyer-Wegener J, Liebscher K, Hettich M, Kastner H-G: Efeu versus Ambroxol bei chronischer Bronchitis. *Z Allgemeinmed* 1993;69:61–66.
- Jahn E, Müller B: Efeublättertrockenextrakt. Pädiatrische Therapiestudie zur Wirksamkeit. *Dtsch Apotheker Z* 2000;12:135–138.

- 9 Hofmann D, Hecker M, Völz A: Efficacy of dry extract of ivy leaves in children with bronchial asthma – a review of randomized controlled trials. *Phytomedicine* 2003;10:213–220.
- 10 Swissmedic Schweizerisches Heilmittelinstitut: <http://www.swissmedic.ch/files/pdf/Stoffliste.pdf>. [updated 2005 Feb 10; cited 2005 Feb 14].
- 11 Büechi S, Kähler D: Efeu (*Hedera helix*) bei Atemwegserkrankungen. Eine offene klinische Studie mit Efeu Pastillen. *Schweizerische Z Ganzheitsmedizin* 2003;15:124–128.
- 12 Hausen BM, Bröhan J, König WA, Faasch H, Hahn H, Bruhn G: Allergic and irritant contact dermatitis from falcariol and didehydrofalcariol in common ivy (*Hedera helix* L.). *Contact Dermatitis* 1987;17:1–9.
- 13 Hecker M, Runkel F, Völz A: Behandlung chronischer Bronchitis mit einem Spezialextrakt aus Efeublättern – multizentrische Anwendungsbeobachtung mit 1350 Patienten. *Forsch Komplementärmed Klass Naturheilkd* 2002;9:77–84.
- 14 Kraft K: Verträglichkeit von Efeublättertrockenextrakt im Kindesalter. *Z Phytotherapie* 2004;25: 179–181.
- 15 Swissmedic: E-mail from Dr. med. Julia Djonowa, Swissmedic, dated 20.10.2004.

New Open Learning Masters in Complementary & Integrated Health Sciences



The **topics** included in the EU Master's programme in Complementary Health Sciences are:

- health promotion (WHO), individual and community promotion of health: health-related knowledge or fundamentals of salutogenesis
- deepening of psychosocial skills (fundamentals of depth psychology)
- competency in communication in therapeutic relationships and in public work
- understanding paradigms and outlines of complementary approaches – including regulatory biology
- the state of research in complementary medicine
- participation in research studies, designing and performing these studies, and writing a scientific thesis.

The project is co-ordinated by the Interuniversity College for Health and Development Graz/Castle of Seggau (www.inter-uni.net). At present, this is the only supported *distance-learning* course that leads to an EU Master's in Complementary Health Sciences. A pioneering spirit is prerequisite for enrolling on the course as it includes individual, personal growth in addition to fulfilling methodical-technical and intellectual training.

The MSc takes three years part-time. Students gather for two-four day seminars each year at their local campuses, for the English speaking course this will be at Schengen castle in Luxemburg on the border of three countries. There will be lectures, psychosocial and Balint-groups and supported mutual exchange.

If you are interested in this course and would like **further information**, please see www.inter-uni.net or email college@inter-uni.net or Phone Pam Schickler on +44 207 435 6316 or pam@schickler.freeseve.co.uk