Herbals for cough

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MeSH terms

Phytotherapy; Cough; Risk Assessment.

Keywords

Cough, Phytotherapy, European Regulations, monography, eucalyptus, thyme, ivy, primula, ribwort plantain, marshmallow, hedge mustard.

Abbreviations

BSS: Bronchitis Severity Score
EBM: Evidence Based Medicine
EMA: European Medicines Agency
HMPC: Herbal Medicinal Product Committee
ICD: International Code of Diseases
MLWP: Monography List Working Party
OTC: Over-The-Counter
PSURs: Periodic Safety Update Reports
PS: Public Statement
TU: Traditional Use
VAS: Visual analogue scales
WEU: Well established use

Abstract

Belgium follows the European regulations for registration of herbal medicines. European monographs on medicinal plants are an important source of inspiration. This certainly applies to herbals used for coughing. Meta-analysis do mostly not take herbals into account. Nevertheless, patients should be informed on a transparent way about herbals used in case of cough.

Eucalyptus, ivy, primula, thyme, ribwort plantain, marshmallow and hedge mustard were selected for review. Therapeutic activity is most evident for extracts of ivy leaves. The way to evaluate effectiveness is discussed. With regard to Eucalyptus, it should be taken into account that most clinical studies, were conducted with eucalyptol. The use of the other plant species is mainly based on European tradition. The European Medicines Agency (EMA) narrows the use of herbals to well-defined preparations, like infusions, extracts (mostly made with water or ethanol), Macerates and tinctures, with clearly defined posology's. When evaluating herbals, one should not only focus on clinical efficacy, but also on identity and quality of herbal substances, guaranteed by a close cooperation with the European Pharmacopoeia. Safe use by the patient is a third issue. This article deals with opportunities and limits. The pharmacist should be able to make a risk-benefit approach and by this confirming his status as an expert.

1. Pharmaceutical Sciences KULeuven

1. Introduction

The symptoms of the common cold are based on the ICD-10 classification[1]. They are so well known that almost everyone is able to make a diagnosis. Transient cough is one of the characteristic symptoms. Knowing that the worst thing for coughs and colds belongs to the past after one week, there is some discussion about the usefulness of medication and common remedies.

1.1. What are the possible remedies for coughing and how are these remedies expected to work?

The application of self-care medicines or *Over-The-Counter* drugs (OTC) for cough is based on different working hypotheses.

- Centrally acting opioids or peripheral cough medicines are expected to suppress cough reflex and reduce the intensity of coughing [1]. Dextromethorphan is put forward by some authors as an option for non-productive cough [2]. Other authors point out the imperfections of clinical trials and argue that it remains difficult to formulate convincing arguments pro or contra certain OTC medications [3].

- Expectorants are supposed to dilute the bronchial secretions, making it easier for them to disappear from the air via ciliary transport. The secretions must be coughed up in this case [4]

- A similar effect is expected from mucolytics. These should reduce the viscosity of bronchial secretions. Again, coughing is necessary to remove these secretions from the respiratory tract [5].

- Antihistamines (in particular anti-H1 antihistamines) can intervene at the respiratory center to suppress the cough reflex. They have largely fallen into disuse, especially with children. A relationship was established between the use of antihistamines and cot death in young children [6]. By blocking H1-receptors, antihistamines may have an additional value on coughing with an allergenic component [7-9].

- The purpose of adding decongestants is to promote free breathing through the nose by stimulating the alpha receptors in the capillaries [10].

- According to a Cochrane study, honey tempers cough in children, more than when no treatment is given. Honey may work better than placebo and salbutamol. The effect would be similar to dextromethorphan. Most children received only one dose [11]. Possible contamination of honey by pyrrolizidine alkaloids impairs the application on a regular basis [12].

Herbal cough medicines is usually not discussed in classical literature.

1.2. Which basic principles apply to medicines and herbal products?

Quality must be proven by means of an analytical file. Identity, cultivation of plants, harvesting, storage as raw material, contamination (pesticides, microorganisms, heavy metals, environmental pollution), extraction, conditioning and shelf-life play a role. Safety can be demonstrated by clinical studies, but also by the so-called *Periodic Safety Update Reports* (PSURs) that companies must be able to submit at all times at the request of the pharmaceutical inspection. Thirdly, there is the therapeutic effectiveness and the way in which it was determined.

Evidence Based Medicine (EBM) often focuses on therapeutic efficacy. Randomized controlled double-blind studies (RCTs) are considered the highest standard in this respect. However, decisions taken in these studies should be treated with caution.

Krauss (2018) [13] analyzed the 10 most cited clinical trials (selection until June 2016). He points out a number of weaknesses, including differences between patients, carelessness in the case of evaluating the outcomes and inadequate blinding. In addition, the fact that results are often given as averages, an outcome that does not permit to extrapolate to the individual patient in daily practice.

1.3. How are medicinal products and herbal products registered in the European Union?

The European Medicines Agency (EMA) was established in 1994. Shortly afterwards, EMA discussed a pan-European approach to the registration of phytotherapeutics. For this, an *ad hoc working party* was founded, with representatives of the National Agencies in the Member States. This working group made a substantial contribution to the creation of the European Directive 2001/83/EC[2]. This directive defines the regulatory context for registration of herbal medicinal products [14].

The *ad hoc working party* was transformed into the *Herbal Medicinal Product Committee* (HMPC) in 2004. In this, each country of the European Union is represented as well as a

1. ICD (Inte rnational Code of Diseasesl https,//www. icd 1 Odata .com/I CD 1 OC M/Codes/ J 00-J99/ JOO-J06/JOO: consulted on 11 June 2018.
2. Directive 2004/24/EC of the European Parliament and the Council of 3 1 March 2004 amending, as regards traditional herb a l me di cina l products. Direc tive 2001/83/EC on the **Community code relat ing to medicinal products for human** use. Official Journal L - 136, 30/04/2004, p. 85 - 90.

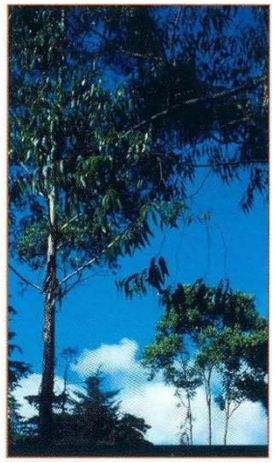
number of co-opted experts. A *Monography List Working Party* (MLWP) was also established. The task of this working group was to carry out studies of medicinal plants. These studies or evaluation reports are available for the pharmaceutical industry, to facilitate the registration of herbal medicines. To date, more than 180 reports have been produced on medicinal plants. Depending on the case, a plant is labeled *Traditional Use (TU) or Well Established Use (WEU).*

Traditional use can only be awarded to preparations of plants that have been used for at least 30 years in a Western tradition, with at least 15 years known to have been used in countries in the European Union. When sufficient robust clinical studies are available, a preparation of a plant can get the status *Well Established use*. In addition, the preparation must have been marketed in one or more countries of the European Union for at least 10 years. Plants that do not meet the conditions fur TU or WEU, may be the subject of a *Public Statement* (PS). This concerns, for example, Chinese herbs that have recently been registered in some member state. With a Public Statement, HMPC and EMA can also indicate that there are problems of toxicity to a plant. *Chelidonium majus* or stinking gold is an example of such a plant. Since the publication of the first monographs in 2007, more than 3,500 applications for registration (TU or WEU) were submitted in the 28 countries of the European Union. Of these, more than 2300 were approved.

2. What is known about plants used in coughing?

The following plants are treated: eucalyptus, ivy, primula, thyme, ribwort plantain, marshmallow and hedge mustard. With the exception of Eucalyptus, it is about plants that grow in our own environment and are therefore well known. Information is mainly based on the monographs of the EMA.

2.1. Eucalyptus globulus Labill.



Eucalyptol of 1, 8 cineol

In the pharmacy [15, 16]

There is a European monograph on the volatile oil of eucalyptus species. More specifically, about *Eucalyptus globulus Labill, Eucalyptus polybractea* R.T. Baker and *Eucalyptus smithii* R.T. Baker. The oil is obtained by steam distillation from the leaves.

Eucalyptus Oil is available as such in pharmacies or as an ingredient in medicines for nasal inhalation.

The volatile oil is also replaced with pure eucalyptol, what may not be considered as a volatile oil.

NOTE: In food supplements, the leaves of Eucalyptus species may be used without restriction. Compounds containing volatile oil, are the subject of a separate investigation.

Restrictions [15]

- Contra-indicated by children with a history of (fever) convulsions.
- Laryngospasm may occur in children under 30 months after inhalation.
- Medical examination is necessary if dyspnea, fever or purulent sputum occur
- Not recommended during pregnancy and lactation.

Therapeutic indication (TUI) [15]

Traditional herbal medicinal product used for coughing during colds.

Secondary metabolites

The discussed species of the genus Eucalyptus have a different content of eucalyptol or 1,8-cineol, a monoterpene alcohol. At least 70% of the essential oil exists of eucalyptol.

Preclinical pharmacology [15]

- Increased production of bronchial secretion in guinea pigs after administration by a stomach probe.
- In supra-therapeutic concentrations: light increase of the ciliary activity in nasal epithelia.
- Anti-inflammatory in the 'rat paw oedema' model.
- Stimulation of immunity: cf. increase of circulating mononuclear cells (in vivo] and exemption of inter leukines *(in vitro].*
- Pain relieving effect in mice after intraperotonic (IP) administration (writhing-test).

Clinical studies [17-24]

Patients

- Mostly adult patients.
- Acute rhinosinusitis, COPD, acute bronchitis, asthma.
- Number: more than 450 patients.

Intervention

- In Clinical studies, almost exclusively eucalyptol is used: 100 to 200mg up to 4x daily in gastro-resistant capsules.
- Both double-blind and open (comparative) studies. Compared with herbal mixtures or ambroxol.
- Depending on the pathology of the patients, the studies lasted from a few days to 6 months.

Results

Eucalyptol scores significant better (compared to placebo or mixture) for the following symptoms: headache when bending the head, pressure pain on the trigeminal nerve, amount and viscosity of the nasal mucus, nasal congestion, redness of the mucosa. No significant differences for tracheitis, laryngitis, conjunctivitis and bronchitis.

In lung diseases, respiratory parameters are scored (vital capacity, peak current), and the dose of prednisolone is reduced.

Undesirable effects [15]

-> Gastric irritation and exanthema [> 1%).

Discussion

To what extent do the patients studied correspond to those in the pharmacy?

The studies described include patients with various respiratory pathologies. The indication is limited to coughing with colds. In pathologies such as asthma and COPD, eucalyptol as an adjuvant therapy was studied.

What about the safe use of eucalyptus preparations?

The three species of eucalyptus treated are the subject of a monograph of the European Pharmacopeia. The identity and characteristics of the raw material are described in detail.

Direct inhalation of eucalyptus oil or eucalyptol is contraindicated in children younger than 2.5 years of age. (Cf. glottis spasms).The volatile oil lowers the convulsion threshold and is contraindicated in a history of fever.

In children from 4 years of age, the oil can be inhaled indirectly (e.g. via spraying in a room like the bedroom or adding it to bath oil).

Animal experimental data indicate the passage of volatile oil components through the placenta, but not through the blood-milk barrier. No teratogenicity was reported (doses up to 500 times the therapeutic). Due to insufficient data, the use during pregnancy and lactation is not recommended. This recommendation is based on an older publication [25].

What about the therapeutic efficacy?

The volatile oil was given the status of traditional use, because the studies were carried out with eucalyptol and not with the volatile oil. The use of the volatile oil (by inhalation or orally) in diseases of the respiratory tract is based on tradition.

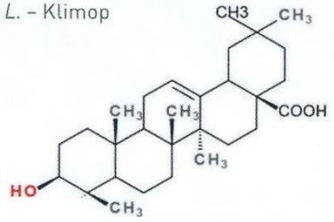
Eucalyptus oil makes the cold receptors more sensitive to passing air, which can lead to a feeling of comfort [24].

With oral ingestion of eucalyptol, a Tmax follows within approximately one hour (chewed tablet) or within 2,5 hours (unchewed) (human). Through inhalation of the eucalyptus oil, a Tmax was reach in 20 minutes. This is followed by a distribution phase ($T_{1/2}$ = 2 to 13 minutes) and a elimination phase ($T_{1/2}$ = 30 to 280 minutes). When inhalation is stopped, plasma levels immediately drop. After 40 minutes, they amount to only 10% of the maximum (human data).

Eucalyptol is mainly hydroxylated to hydroxycinols (phase I) and then glucorunated (phase II) allowing it to be excreted through the urine. The hydroxylated forms peaked after about 1 hour in the plasma (rabbit). The metabolites could be detected in animal experimental research (rats) [27-29].

2.2. Hedera helix L.

Hedera helix L. – Klimop



Hederagenin = triterpene saponin

In the pharmacy [30]

A European monograph and evaluation report exists on the leaf of ivy. These contain practical information on registered medicines that are available in the European Union. Most of these are ethanolic extracts.

Depending on the clinical studies carried out with the extract, a *well-established use* or *traditional use* is assumed.

NOTE: Syrup based on ivy extract may be used from the age of 2 years.

Restrictions [30]

- Do not use for more than one week.
- Do not use in patients with a history of gastrointestinal ulcers.
- Not recommended during pregnancy or lactation.

NOTE [16] For food supplements based on ivy, restrictions in terms of age and maximum dose apply.

Therapeutic indication (WEU) [30]

Herbal medicine used as expectorants in a productive cough.

Secondary metabolites

Hederagenin = triterpene saponin [containing 30 C-atoms and saponifying properties].

Preclinical pharmacology [31-37]

- Spasmolytic and bronchodilateral: on in vitro model of the guinea pig ileum.
- Inhibition of the internalization of the beta receptors in alveolar epithelial cells.
- Inhibition of allergen-induced bronchoconstriction (Ovalbumin in sensitized guinea pigs].
- Secretolytic: possible vagal stimulation and stimulation by activation beta receptors.

Clinical studies [31-37]

Patients

- From the age of 2 year.
- Pertussis, acute bronchitis, cough due to malignant diseases, COPD, asthma, and pneumonia
- More than 800 patients in controlled, randomized, double-blind studies, including more than 400 children.
- More than 60,000 patients in open observational studies, including more than 30,000 children.

Intervention

Open study versus standard therapy (= Classic coughing medicines). Double-blind placebo-controlled, crossover, comparative studies (Acetylcysteine, ambroxoll).

Results

Bronchitis severity score (BSS), spirometry, visual analogue scale (VAS) for expectoration and cough, frequency and intensity of cough.

Undesirable effects [30]

-> Especially gastrointestinal symptoms (nausea, vomiting and diarrhoea]. Frequency: 1% - 10%.

Discussion

To what extent do the patients studied correspond to those in the pharmacy?

Patients included in clinical studies show a wide variety of pathologies. This led to a broad therapeutic indication, aimed at productive coughing.

What about the safe use of ivy?

The raw material is the subject of a monograph in the European Pharmacopeia. Macroscopic, microscopic and chemical identification gives certainty about the identity.

There is sufficient experience with medicinal products and on the basis of ivy in various countries of Europe, especially in German-speaking Europe and the former Eastern bloc countries. The doses of these drugs are well known and in compliance with the *'dose finding studies'* such as those of Gulyas et al. (1997) [32]. Gastro-intestinal side-effects may occur (Cf. saponines). It's best to take it in after a meal. Some cases have been reported in which respiratory symptoms worsened during the use of ivy extracts. Therefore, use in children younger than 2 years is not recommended. Extracts with a high ethanol content (70% V/V) are not recommended for children. Due to a lack of experience, ivy extracts do not qualify for use during pregnancy and lactation.

Open studies with more than 60,000 patients play an important role in the structured reporting of side effects. When using ivy, registered medicines are preferable, because only in a medical-pharmaceutical environment structural pharmacovigilance can be done.

What about the therapeutic efficacy?

The numbers of patients studied is high, of which more than half the children.

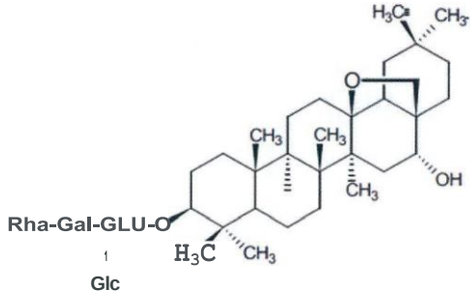
Ethanolic extracts of ivy are among the most intensively studied medicines for a cough of various origins, especially in children.

The HMPC accepted the *Bronchitis Severity Score* to evaluate the therapeutic efficacy of ivy extracts. The BSS was constructed on the basis of typical symptoms of bronchitis. After observation the following symptoms were scored: coughing, mucus, squeaking sound at auscultation, chest pain at coughing and dyspnea. The choice of symptoms is based on clinical studies. They are scored on a 5-point scale. Adding up the scores gives a total value. Factor analysis indicates the weight of individual symptoms on the totality of the score [38-39]. This is a well-known procedure for validation of evaluation instruments. Cough is the main BSS component.

The evaluation of EMA mentions 8 clinical double-blind, randomized studies with ethanolic ivy extracts. The number of patients per study was minimal 25 and up to 590. Evaluation of the therapeutic effect occurred in more than half of the patients with the BSS. Depending on the pathology, respiratory parameters or individual components of the BSS were also used. Ivy extracts scored significantly better than placebo; better than Acetylcysteine and similar to ambroxol. For this reason, the HMPC labeled ethanolic ivy extracts as well established use with a therapeutic indication of a productive cough.

2.3. Primula veris L. and Primula elatior (L.) Hill.

Primula veris L. and Primula elatior } {L. Hili. - respectively guilder cowslip and primrose slim



In the pharmacy [16; 40]

There is a European monograph and evaluation report on the root of both Primula species. Most of these are about ethanolic and aqueous extracts.

NOTE: No restrictions apply to root-based food supplements of both primula species.

Restrictions [40]

- Not recommended for patients with history of gastrointestinal ulcers.
- Not during pregnancy.
- The monograph gives posology's from the age of 4 years.

Therapeutic indication [40]

Traditional medicine used as an expectorant in case cough common cold.

Secondary metabolites [4

The effect is attributed to the primula saponins.

Preclinical pharmacology [40]

Expectation would be distinguished corpse relying on the stomach reflex. *In vivo* (rabbits), an increased amount of secretion was seen in the bronchial tract.

Clinical studies [40]

- Only Open studies with the combination Primula-Thymus.
- Patients are usually children from an age < 1 year. More than 2000 patients with colds and acute bronchitis.
- Cough is considered to be the therapeutic endpoint.

Undesirable effects [40]

-> None reported.

discussion

To what extent do the patients studied correspond to those in the pharmacy?

Extracts of primula along with thyme were studied in children with coughs and colds. The children had a young age (6 months). However, in the monograph, the lower age limit shall be 4 years.

What about the safe use of primula?

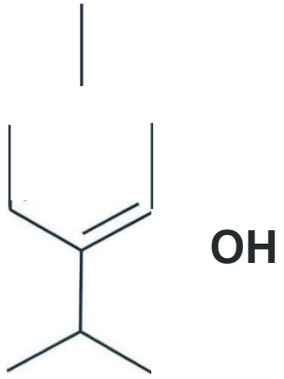
The roots of the Primula species discussed here are described in a monograph of the European Pharmacopoeia. This facilitates the identification and research of the quality of raw material.
There are no side effects reported. Due to possible gastric irritation by saponins, extracts of Primula are contraindicated in patients with a history of gastrointestinal or intestinal ulcers. The samples should preferably be taken after the meal.

What about the therapeutic efficacy?

There are no clinical trials with Primula root as a mono preparation. Use belongs to the tradition. There is also a European tradition of combining Primula with thyme, for which a separate monograph was prepared.

2.4. Thymus vulgaris L.

Thymus vulgaris L. - Thyme



In the pharmacy [16; 41]

There is a European monograph and evaluation report on thyme grass. The medicines registered in Belgium contain ethanolic extracts of *Thymus vulgaris*. It's about traditional use.

NOTE: There are no restrictions on the use of thyme-based preparations in food supplements.

Restrictions [41]

Medical advice is needed for complaints that last longer than one week at dyspnea, purulent sputum and fever.

The presence of phenols brings with it a theoretical risk with pregnancy and lactation.

NOTE: The FAMHP Herbal Medicines Commission authorizes the use of syrups based on thyme extract from 2 years, by analogy with acetylcysteine, bromhexine and carbocysteine.

Therapeutic indication [41]

Traditional herbal medicinal product used in productive cough in case of colds.

Secondary metabolites

There are at least 6 chemotypes of *Thymus vulgaris*, with different compositions. Only thyme of the 'thymol' type, with predominantly thymol as a phenolic component, corresponds to the type described in the European Pharmacopoeia. The dried herb contains about 2.5% of volatile oil.
There are also chemotypes low in phenols, where flavonoids characterize the composition.

Preclinical pharmacology [41]

- Spasmolytic action *in vitro* on the trachea (rat, guinea pig) and ileum (guinea pig).
- Antibacterial and antimycotic action in vitro.
- Experiments were usually performed with volatile thyme oil in supra-therapeutic concentrations.

Clinical studies [42-43]

Patients

Children (2 years and older) (n=153) with acute bronchitis and adults with cough (n=60).

Intervention
Open (children) or comparing with ambroxol (adults).

Results
Subjective improvement of cough as the most important parameter.

NOTE: The combination Primula - Thymus has been studied more clinically.

Undesirable effects [41]

-> Gastrointestinal burden can occur.

Discussion

To what extent do the patients studied correspond to those in the pharmacy?

Time-extracts such as mono-preparations were limited clinically studied in both children and adults. The therapeutic indication is based on traditional use in respiratory tract infections.

What about the safe use of thyme?

Thymus vulgaris herba is described in a monograph of the European Pharmacopoeia. This facilitates the identification and research of the quality of raw materials.

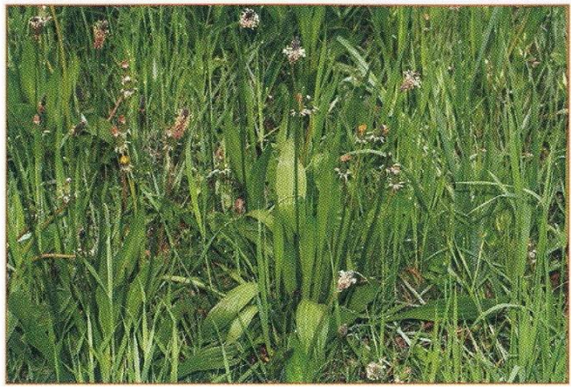
Centuries of use of thyme has not brought to light any major problems of safety.

What about the therapeutic efficacy?

Application of thyme is based on tradition. Pre-clinical and clinical research contributes to the plausibility of the indication.

After oral administration of a single dose of thyme extract (equivalent to approximately 1 mg of thymol), only thymol sulphate could be detected in human plasma, not free thymol or glucuronide. The sulphate was detected after 20 minutes, with a T_{max} of approximately 2 hours. Thymol was detectable in plasma for over 38 hours. Renal elimination was complete after 24 hours. An elimination half-life of about 10 hours was calculated [44],

2.5. Plantago lanceolata L.



Plantago lanceolata L. Ribwort plantain

In the pharmacy [16; 45]

There is a European monograph and evaluation report on the leaf of plantain. Both ethanolic and aqueous extracts are described for traditional use.

NOTE: Above ground parts of ribwort plantain may be used without restriction as a food supplement.

Restrictions [45]

- In the EMA monograph the lower age limit is set at 3 years.
- In case of dyspnea or purulent sputum, medical advice is necessary.
- Treatment is limited to one week.
- Insufficient data on the safe use during pregnancy and lactation.

Therapeutic indication [45]

Traditionally used as a softening agent for symptomatic treatment of mouth and throat irritation associated with coughing.

Secondary metabolites [45]

Iridoid glycosides (aucubine and catalpol) mainly in freshly harvested leaves (up to 9%) and tannins (about 6.5%).

The soothing properties are mainly attributed to the mucilages (2 to 6.5%) that can be enriched in extracts. It's mainly about arabinogalactan, glucomannan, rhamnogalacturonan with an arabinogalactan side chain and rhamnoarabinogalactan and a linear (1-6)-alpha-D glucan structure.

Preclinical pharmacology [45]

- Spasmolytic on the guinea pig's ileum.
- Antibacterial, antiviral activity and immunostimulatory properties are of a more qualitative nature.

Clinical studies [45]

Patients

Respiratory diseases.

Intervention

- Open post-marketing studies in more than 500 patients (1 to 88 years).
- The duration of treatment with plantain syrup was 3 to 14 days.

Results

Both patients and treating physicians gave a positive appreciation.

Undesirable effects [45]

-> The EU monograph do not mention any side effect.

Discussion

To what extent do the patients studied correspond to those in the pharmacy?

Patients in clinical trials have respiratory infections and show a strong variation in age. The clinical cohorts are representative, but limited in number.

What about the safety of ribwort plantain?

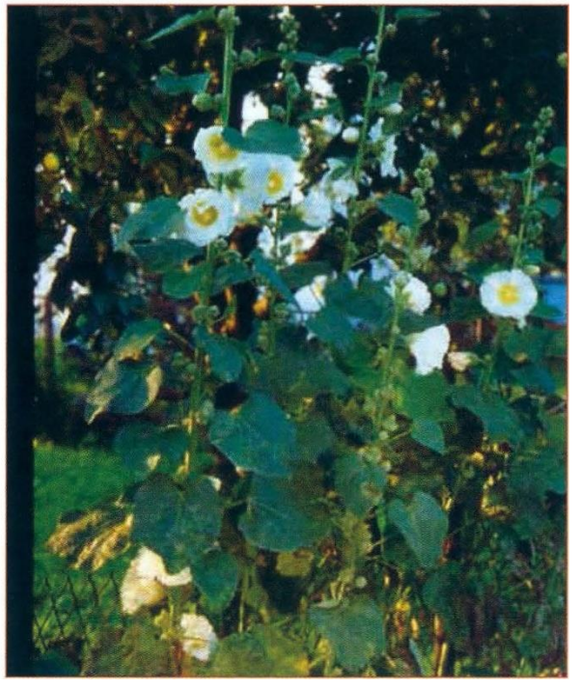
The characteristics of the leaves of Plantago lanceolata are described in the European Pharmacopoeia. This allows verification of the raw material.

The application is based on tradition. No serious side effects are reported.

What about the therapeutic efficacy?

There is insufficient controlled and randomized clinical trial to determine the effectiveness. The application is based on tradition.

2.6. Althaea officinalis L.



Althaea officinalis L. - Marshmallow

In the pharmacy [16; 46]

There is a European monograph and evaluation report on the root of marshmallow. Both aqueous and ethanolic extracts (25%) are described for traditional use.

NOTE: The whole plant may be used without restriction in food supplements.

Restrictions [46]

- In the EMA monograph, the lower age limit is set at 3 years.
- In case of dyspnea or purulent sputum, medical advice is necessary.
- Depending on the preparation, the treatment is limited to one or two weeks.
- A warning shall be given for delayed intake of concomitantly administered medicinal products. Compounds with haemorrhoids should not be taken 1/2 to 1 hour before taking any other medicines.

Therapeutic indication [46]

Traditionally used as a softening agent for symptomatic treatment of mouth and throat irritation accompanied by cough.

Ingredients [46]

The main components (5 to 12%) form a mucilago consisting of colloid water-soluble polysaccharides.

Preclinical pharmacology (polysaccharides) [46]

Bio-adhesive effects on membranes (in vitro research).
Suppressive effect on mechanical or citric acid-induced cough (respectively in cats and guinea pigs).

Clinical studies [46]

Patients

- Infants and children (from 0 years of age) with irritating cough.
- Adult patients with irritating cough due to ACE inhibitors.

Intervention

- Infants and children: open studies; n> 800.
- Adults: double-blind, placebo - controlled.

Results

Positive results on cough.

Undesirable effects [46]

-> The EU monograph does not mention any side effects.

Discussion

To what extent do the patients studied correspond to those in the pharmacy?

The pediatric population is strongly represented. Adult patients are not representative of the population with cough and cold.

What about the safety of marshmallow?

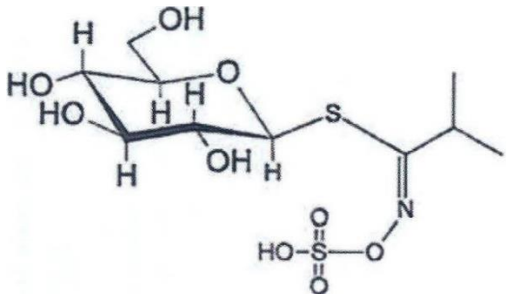
The characteristics of the root of Althaea officinalis are described in the European Pharmacopoeia. That allows a verification of the commodity.
The application is based on tradition. No serious side effects are reported.

What about the therapeutic efficacy?

There is insufficient control and randomization clinical trials to determine efficacy. A sufficient number of infants and children have been studied, but only in open studies.

2.7. Sisymbrium officinale (L.) Scop.

Sisymbrium officinale (L.} Scop. – hedge mustard



In the pharmacy [16; 47]

There is a European monograph and evaluation report on the above-ground parts of Sisymbrium officinale. Aqueous extracts are made from the herb.

NOTE: Use of above ground parts in food supplements is permitted.

Restrictions [16]

Lower age limit fixed at 3 years.

NOTE: For food supplements, the following restriction applies: analysis must demonstrate that the preparation does not contain detectable amounts of cardioactive steroid glycosides.

Therapeutic indication [47]

Traditional plant-based medicinal product used to treat symptoms indicating irritation of the throat, in particular hoarseness and dry cough.

Secondary metabolites

Glycosinolates (characteristic of species of the *Brassicaceae* family or crucifers), more specifically glucoputranjivine. They contribute to the characteristic taste (cf. leaves of the plant taste like radishes).

NOTE: Presence of polysaccharides (primary metabolites) gives some plausibility to the therapeutic indication.

Preclinical pharmacology [47]

No specific activity referring to the clinical application.

Clinical studies [47]

No clinical trials.

Undesirable effects [47]

None reported.

Discussion

Use of aqueous extracts of *Sisymbrium officinale* is based on more than 30 years of tradition according to the European Directive 2004/24/EC. In the absence of preclinical and clinical evidence, the possible mitigating effect can be attributed to the presence of polysaccharides.

In order to obtain sufficient enrichment of the slime-forming polysaccharides, aqueous extracts are preferable. Extraction with water is also a guarantee that no cardenolides will be extracted: a limit of 1 ppm is applied in the monograph (see also restrictions on food supplements).

The European monograph does not recommend use during pregnancy and lactation.

3. Decision

EBM and quality

Evaluating herbal medicinal products only on the basis of EBM-related clinical efficiency is scientifically incomplete. In addition to efficiency, there is also quality and safety.

Quality is an aspect that every pharmacist should be interested. We owe it to our unique fundamental formation. The pharmacist is the only provider of care who has been allowed to become more or less acquainted with the specificity of medicinal plants during his studies. The close cooperation between the European Pharmacopoeia and the European Agency for the Evaluation of Medicinal Products guarantees high quality raw materials. Preference is given to plants from our age-old European tradition.

Primum non nocere

EBM focused solely on therapeutic efficacy can lead to therapeutic nihilism in which patients are turning away from medical pharmaceutical care.

Evidence of absence is an important principle in the scientific evaluation of risks. When patients are looking for ways to alleviate the annoyance caused by coughing, it is desirable that they use safe products in a professional healthcare environment. As pharmacists we guide patients in an honest way. We will protect them from exaggerated expectations, without depriving them of safe drugs, always with the freedom of patients in mind and taking into account their use of other medications and risk factors.

EBM and clinical effectiveness

When both quality and safety are guaranteed, the score is already 2 out of 3. To reach the third point is not self-evident with coughing. It is a challenge to have a solid clinical to set up a study with cough as the primary endpoint. A good job has been done with ivy. It is the only plant that received the well-established use label from EMA.

All other plants fall under *traditional use.* For most of these plants there are clinical data, even with infants and young children. Hopefully data from this article will help in order to substantiate a responsible care practice in which we guard against over- and undervaluation.

Thank you

Photos of the discussed plants are partly taken from the KULAK plant guide: http://www.kuleuven-kulak.be/bioweb/ thanks to the KULeuven for use of the images.

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