European Medicines Agency
*Evaluation of Medicines for Human Use*

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**COMMITTEE FOR HERBAL MEDICINAL PRODUCTS**

**(HMPC)**

# 1st Draft Primula veris L., Primula elatior (L.) Hill, flos

**ASSESSMENT REPORT FOR THE DEVELOPMENT OF COMMUNITY MONOGRAPHS AND FOR INCLUSION OF HERBAL SUBSTANCE(S), PREPARATION(S) OR COMBINATIONS THEREOF IN THE LIST**

| | |
|---|---|
| **DISCUSSION IN HMPC MLWP** | March 2007 |
| **ADOPTION BY HMPC FOR RELEASE FOR CONSULTATION** | |
| **END OF CONSULTATION (DEADLINE FOR COMMENTS)** | |

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**FOURTH DRAFT ASSESSMENT REPORT**

**FOR HERBAL SUBSTANCE(S), HERBAL PREPARATION(S) OR COMBINATIONS THEREOF WITH TRADITIONAL USE**

**Primula veris L., Primula elatior (L.) Hill, flos**

**BASED ON ARTICLE 16D(1) AND ARTICLE 16F AND 16H OF DIRECTIVE 2001/83/EC AS AMENDED**

| | |
|---|---|
| Herbal substance(s) (binomial scientific name of the plant, including plant part) | **Primula veris L., Primula elatior (L.) Hill, flos** |
| Herbal preparation(s) | Tincture<br>Liquid extract (1:1, 25% ethanol, British Herbal Pharmacopoeia) |
| Pharmaceutical forms | Oral solutions |
| Rapporteur | Austria |
| Assessors | Heribert Pittner<br>Johann Krisper<br>Reinhard Länger |



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# 1 INTRODUCTION

## 1.1 Description of the traditional herbal substance(s), herbal preparation(s) or combinations thereof

**Herbal substance**[1][2]

Primula flower (Primulae flos)

Whole or cut, dried flowers including the calyx or without calyx of Primula veris L. and /or Primula elatior (L.) Hill for oral administration. The material complies with the German Deutscher Arzneimittel Codex (2006).

Some references restrict the plant source to the species Primula veris (British Herbal Pharmacopoeia (1983), Pharmacopée Francaise X$^{e}$ edition).

The haemolytical index (HI) has been used for biological standardisation of saponin containing herbal substances and herbal preparations. The HI cannot substitute chromatographic methods for quantification of saponins, however a comparison between the HI of a herbal drug and preparations thereof allows an estimation of the saponin content.

HI of Primulae flos: 35

Constitutents (Hänsel R et al (1994), Wichtl M (2004)):
Triterpene saponins (in the sepals up to 2%); structural details are missing.
Flavonoids (in the petals up to 3%): apigenine, rutoside (1,3% in P. elatior, 0,16% in P. veris), quercetagenin-3-gentiobioside, 3',4',5' – trimethoxyflavone; kaempferol-3-rutinosid and isorhamnetin-3-glucoside present in flowers of P. elatior only.
Carotenoids, traces of essential oil, rosmarinic acid, D- volemitol and other sugar alcohols.

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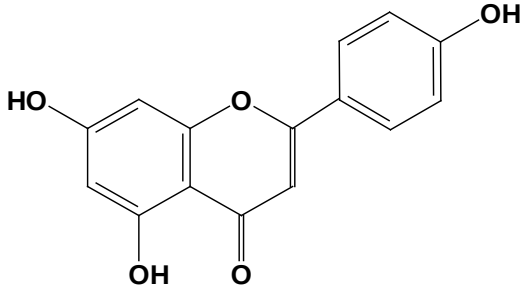
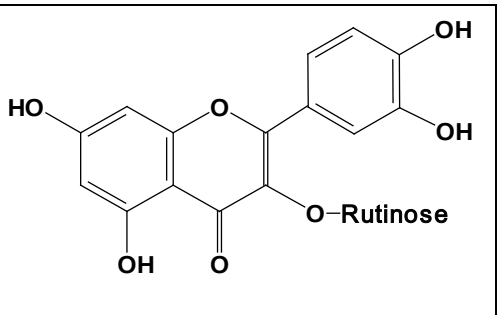
|  |  |
| Apigenin | Rutoside |

The aerial parts may contain primin and other quinoid compunds, which are responsible for contact allergenic properties of species of the genus Primula (Hausen BM (1978)).

[1] According to "Note for guidance on Quality of herbal medicinal products" (CPMP/QWP/2819/00)
[2] According to "Note for guidance on Specifications: Test procedures and acceptance criteria for herbal drugs, herbal preparations and herbal medicinal products" (CHMP/QWP/2820/00)



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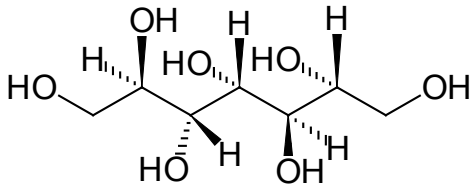
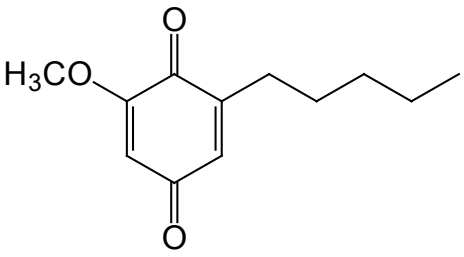
|  |  |
| Volemitol | Primin |

**Herbal preparation(s)**[1] [2]

Plant preparation to be specified for the individual finished product:
Tincture
Liquid extract (1:1, 25% ethanol, British Herbal Pharmacopoeia)

Assessors comment: no details could be found to the tincture which is cited in the publications of the commission E

**Combinations of herbal substance(s) and/or herbal preparation(s)**[3]

Primula flowers extracts are used in combinations with many other herbal substances / herbal preparations. This monograph refers exclusively to Primula flowers.

**Vitamin(s)**[4]

Not applicable

**Mineral(s)**[3]

Not applicable

## 2 TRADITIONAL MEDICINAL USE

### 2.1 Information on period of medicinal use in the Community regarding the specified indication

Data concerning the medicinal use of Primula flowers in Europe go back to the beginning of the 20th century (Zörnig H (1911), Dinand P (1921)). The herbal substance and preparations are also mentioned in Hager's Handbuch (List PH et al (1977)). Therefore it can be stated that the crude drug is continuously in medical use since about 100 years.

Therefore for Primula flowers a period of at least 30 years in medical use as requested by Directive 2004/24 EC for qualification as a traditional herbal medicinal product is easily fulfilled.

### 2.2 Type of tradition, where relevant

European tradition

[3] According to the Guideline on the clinical assessment of fixed combinations of herbal substances/herbal preparations (EMEA/HMPC/166326/2005)
[4] Only applicable to Community monographs



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## 2.3 Bibliographic/expert evidence on the medicinal use

### 2.3.1 Evidence regarding the indication/traditional use

The following indications have been reported for Primula flowers:

Ailments of the airways:

| | |
|---|---|
| Cough | List PH et al (1977), |
| Catarrhs of respiratory tract | Hänsel et al. (1994); German Commission E (1990), Wichtl M (2004), DAC (2006) |
| Expectorant for coughs and bronchitis | Wichtl M (2004), Zörnig H (1911) |

Further indications:

| | |
|---|---|
| Nervousness | List PH et al (1977), Wichtl M (2004), Fournier P (1948), Zörnig H (1911), Hänsel et al. (1994), British Herbal Pharmacopoeia (1983) |
| Headache | Wichtl M (2004), Flamm S et al (1940), Zörnig H (1911), Hänsel et al. (1994) |
| As a diaphoretic | Dinand P (1921), List PH et al (1977) |
| Rheumatism | List PH et al (1977), Zörnig H (1911) |
| Gout | List PH et al (1977), Zörnig H (1911) |
| As a diuretic | Zörnig H (1911), Auster F et al (1961) |

Plausibility of actions: saponins are only present in the sepals; therefore for the indication ‘cough’ the complete flowers must be used.
Further constituents do not support other traditional indications.

Based on the available literature and the known actions of saponins, the following text on the indication is recommended:
“Traditional herbal medicinal product used as an expectorant in cough associated with cold. The product is a traditional herbal medicinal product for use in specified indication exclusively based upon long-standing use.”

### 2.3.2 Evidence regarding the specified strength

Primula flowers are usually used in combination with other herbal substances. The primula content in these preparations varies in herbal teas from 10% to 30%, in liquid preparations it is about 1% and in solid dosage forms about 8%.

### 2.3.3 Evidence regarding the specified posology

Posology in adults:

Herbal substance

| | single dose | daily dose |
|---|---|---|
| British Herbal Pharm. (1938) | 1-2 g as infusion, 3 x daily | |
| Wichtl M (2004) | 1 teaspoon = 1,3 g | 2-4 g |
| Ergänzungsbuch 6 (1941) | 1 g | |
| DAC (2006) | 1 teaspoon = 1,3 g | 2,6-3,9 g |
| Hager (1977) | single dose 1 g | |
| Hänsel R (1994) | single dose 1 g | 3 g |
| Auster F (1961) | 1 g | |
| Commission E | | 2-4 g |



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1 Teaspoon = approx. 1,3 g.

**Preparations**

| **Tincture** | | **daily dose** |
|---|---|---|
| Commission E (1990) | | 2,5-7,5 g |
| | | |
| **Liquid extract** | | |
| British Herbal Pharm. (1983) | 1-2 ml, 3 x daily | 3-6 ml |

**Proposed posology for adolescent (>12) and adults:**
*Adolescents over 12 years of age, adults, elderly*

| | single dose | recommended mean daily dose |
|---|---|---|
| Herbal substance | 1 g | 2-4 g |
| Herbal preparations | | |
| Tincture | 0,8-2,5 g | 2,5-7,5 g |
| Liquid extract | 1-3 ml | 3-6 ml |

Dosage frequency: May be taken 3 x daily

Posology in children:
No data for a posology in children from clinical trials are available. The posology presented in Dorsch W et al (2002) is calculated.

The authors propose for the herbal substance as mean daily dose:

| | herbal substance, mean daily dose |
|---|---|
| 0-1 year | 0,5-1 g |
| >1-4 years | 1-2 g |
| >4-10 years | 2-3 g |
| >10-16 years | 2-4 g |

Therefore Primula flowers should not be used from children up to 12 years. Since data to Primula root suggest a use for children up from 1 year a use of Primula flowers up from 12 years could be justified.

### 2.3.4 Evidence regarding the route of administration

The oral administration is the only route of administration for Primula flower preparations in the recommended traditional indication.

### 2.3.5 Evidence regarding the duration of use

No restriction on the duration of use has been reported for Primula flowers.

*Adolescents over 12 years of age, adults, elderly*
Medical attention should be sought if after 1 week of treatment the symptoms do not improve.

If the symptoms persist during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.

## 2.4. Assessor's overall conclusion on the traditional medicinal use



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Preparations from Primula flowers have been used for the relief of symptoms of the upper respiratory tract in coughs associated with cold for many decades. Since the clinical documentation is poor and no controlled clinical studies are available, the use of Primula flower preparations has to be regarded as traditional.

## 2.5 Bibliographic review of safety data of the traditional herbal medicinal substances

### 2.5.1 Patient exposure

No exact data on patient exposure are available.

### 2.5.2 Adverse events

All references (e.g. Hänsel R et al (1994), Commission E, Hänsel R (2007)) agree that in single cases gastric disorders and nausea may occur.

Contact allergic properties have been described for primin and other quinoid compounds obtained from Primula elatior and Primula veris (Hausen BM (1978)). Primin and other quinoid compounds occur in the aerial parts only (Hausen BM (1978)). Hypersensitivity against primin could be of clinical relevance.

The search in the database of the Austrian medicines and medical devices agency AGES PharmMed (date: 06-12-12) contains only 3 reports of adverse effects referring to preparations containing Primula. All reports belong to the product Sinupret, which is a combination of a liquid extract of Primulae flos and four other herbal preparations (Gentianae radix, Rumicis herba, Sambuci flos, Verbenae herba). The adverse effects cannot be exclusively assigned to Primula flowers, the contribution of the combination partners is not known. In 2 cases the application of Sinupret caused allergic reactions (rash, face oedema), in the third case the combination of Sinupret, Novalgin, Parkemed and Tricef caused an anaphylactic shock.

In the WHO database one report of allergic reaction after ingestion of Primula flower is listed, the type of preparation is not mentioned.

Proposed wording:

Special warnings:

> Caution is recommended in patients with gastritis or gastric ulcer.
> When dyspnoea, fever or purulent sputum occur, or when the symptoms persist during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.
>
> For tinctures and extracts, the appropriate labelling for ethanol, taken from the ‘Guideline on excipients in the label and package leaflet of medicinal products for human use’, must be included.

Undesirable effects:

> Gastric disorders, nausea and allergic reactions may occur. The frequency is not known.
>
> If other adverse reactions not mentioned above occur, a doctor or a qualified health care practitioner should be consulted.

### 2.5.3 Serious events and deaths

The anaphylactic shock observed after the concomitant application of Sinupret, Novalgin, Parkemed and Tricef cannot be causally assigned to Primulae flos present in Sinupret.

Therefore the assessors propose:



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None known for Primula flower preparations for oral administration.

### 2.5.4.1 Intrinsic (including elderly and children)/extrinsic factors

None known

### 2.5.4.2 Drug-drug interactions and other interactions

In general saponins are said to enhance the absorption of other substances in the gastro-intestinal tract (Hänsel R (2007)). It is assumed that saponins reduce the particle size of drugs which are only poorly soluble in water. In addition the irritation of the mucous layer may make the diffusion of substances easier. It is postulated that these effects may be of relevance for flavones, phytosterols and silicic acid. Systematic investigations are lacking, no data are available for saponins of Primula species. Walthelm U et al (2001) studied the effect of saponins on the water solubility of model compounds. The Primula saponins showed no clear dose-dependent effect. The authors conclude that saponins generally should not be regarded as solubilizers.
The dietary intake of saponins has been estimated as 15 mg per person per day in an average UK family; for vegetarians the figure is substantially higher, sometimes over 200 mg per person per day (Hostettman K et al (1995)). Saponins administered with preparations of Primulae flowers (4 g with 2% saponins in the sepals only) exceed slightly the one of typical dietary intake. It is not known whether this increase affects the absorption of other drugs.
No interactions have been reported.

### 2.5.4.3 Use in pregnancy and lactation

Safety during pregnancy and lactation has not been established definitely. No adverse effects have been reported from the use of Primula flower as a medicinal product during pregnancy and lactation.

In the absence of sufficient data, the use during pregnancy and lactation is not recommended.

### 2.5.4.4 Overdose

Overdose may lead to stomach upset, vomiting or diarrhoea.

### 2.5.4.5 Drug abuse

None known

### 2.5.4.6 Withdrawal and rebound

None known

### 2.5.4.7 Effects on ability to drive or operate machinery

No studies on the effect on the ability to drive and use machines have been performed.

### 2.5.4.8 Contra indications (hypersensitivity and allergic potential to be both covered)

Hypersensitivity to the active substance or to other Primula species.
Hypersensitivity to primin and other quinoid substances.
Children with a history of acute stenosing laryngo-tracheitis.

Asthma.

## 2.5.5 Non-clinical safety data

### 2.5.5.1 Overview of available data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

(e.g. single/repeat dose toxicity, genotoxicity, carcinogenicity and reproductive and developmental toxicity, local tolerance, other special studies)



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Oral toxicity

There are no Primula-specific toxicity data available.

In the United States flowers of Primula veris and P. elatior are classified as Class 1, this means that herbs can be safely consumed when used appropriately (McGuffin M et al (1997)).

Data on saponins in general:

> After oral administration of saponins no signs of absorption of toxic doses have been found. In vivo studies in rats with higher oral doses of saponins resulted in observations of damages in liver metabolism and fatty degeneration of kidney cells (Vogel G et al (1963)).

> The oral toxicity of saponins in mammals is relatively low, with LD50 values in the range of 50 (which is not very low when the figures are correct) and 1000 mg/kg, due to their poor absorption (Hostettman K et al (1995); Oakenfull D (1981)).

> The dietary intake of saponins has been estimated as 10 mg per person per day in an average UK family; for vegetarians the figure is substantially higher, sometimes over 200 mg per person per day. With a few exceptions (such as liquorice), no negative effects are apparent from prolonged intake of edible plants containing saponins. Primula saponins are considered to have a favourable risk-benefit ratio (Hostettman K et al (1995)).
>
> Chibanguza G et al (1984) have performed in vivo studies on rabbits which contain some information concerning toxicological considerations. Except for the red blood count, none of the parameters tested (rate of breathing, pulse rate, Quick-%-value, electrolyte concentrations of calcium, potassium, sodium) was influenced by the intragastral application of the extract from Primulae flos in the 50fold therapeutic concentration.

Parenteral toxicity, toxicity of topical application

> Hänsel R et al (1994) give toxicological data on Primula root: There are only LD values for the saponin fraction from P. veris ($LD_{50}$ mouse, i.p. 24.5 mg $kg^{-1}$ b.w.) or for primula acid ($LD_{50}$ rat, i.v. 1.2 mg $kg^{-1}$ b.w.) available, which have no relevance for the oral administration of Primula flower preparations. Saponins damage the cell membranes, this results in local irritation and in higher doses in cytotoxicity. After parenteral administration, haemolysis with liver and kidney lesions, cardiac dilatation and circulatory failure may occur. Local irritating effects have been observed on the rabbit cornea.
>
> Vogel G et al (1963) has pointed out that according to his in vivo studies with rats, parenteral toxicity is not correlated with the haemolytic index of the saponins.

There are no data on genotoxicity, carcinogenicity, reproductive and developmental toxicity published.

### 2.5.6 Assessor's overall conclusions on safe use

The oral administration of Primula flower preparations can be regarded as safe, especially at therapeutic doses; the contact allergic properties of different Primula species can cause rarely allergic reactions. The data available from pharmacovigilance data bases do not show a serious risk for the use of Primula flowers.



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## 2 PHARMACOLOGICAL PROPERTIES[5]

### 3.1 Overview of pharmacological effects of herbal substance(s), herbal preparation(s) and relevant constituents thereof on the basis of long-standing use and experience

The mode of the expectorant action of Primula saponins is not yet satisfactorily clarified. In literature there is a general agreement that saponins irritate locally the gastric mucosa, which provokes a reflex increase in bronchial secretion, which dilutes the mucus and reduces its viscosity (Hänsel R et al (1994), Boyd EM (1954), Hänsel R et al (2007), ESCOP monographs (2003)). Irritation of mucous membranes in the throat and respiratory tract by saponins may also cause an increase in bronchial secretion, and the surface-tension lowering action of saponins might help to reduce the viscosity of sputum, making it easier to eject (Hostettman K et al. (1995).

Recently a very specific influence on the $\beta_2$-adrenergic receptors of alveolar cells has been reported for the saponins of Hedera helix, which is used for the same indications like Primula root (Häberlein H et al (2005)). At present it is not known whether these effects are restricted to saponins of Hedera.

**IN VITRO EXPERIMENTS**

Most of the published in vitro experiments deal with the antiviral, antimycotic and antibacterial activity, which are common properties of saponins independent of their plant source.

Wolters B (1966) has compared the antifungal and antibacterial effects of 30 herbal drugs containing saponins. Among these drugs, Primula root extracts belong to the group of extracts with the most pronounced fungistatic or fungicide effects, while the antibacterial effect of Primula root extract is much less. The author regards saponins as possibly important resistance factors of the plants.

Tschesche R et al (1965) describe both antifungal and antibacterial (Staphylococcus aureus, Escherichia coli) effects of Primula saponin (Primula elatior).

Against various strains of Candida albicans the total saponins isolated from Primula acaulis (= P. vulgaris Huds.) were effective at concentrations of 80 – 97 µg/ml, comparable to nystatin at concentrations of 2-45 µg/ml (Margineanu C et al (1976). The antimycotic effect of these saponins is quantitatively less than that of the typical antimycotics nystatine and stamicine. The aglycones of the saponins of P. vulgaris root are identical with those found in the roots of P. elatior.

An unspecified saponin mixture from Primula veris exhibited activity against influenza($A_2$/Japan 305) virus, producing 89 % inhibition at a concentration of 6,2 µg/ml (Rao GS et al (1974); Büechi S (1996)).

Further in vitro experiments:

A hexane extract (50 µg/ml) of Primula veris root inhibited COX (cyclooxygenase)-1 and COX-2 by 54 % and 66 % respectively (Lohmann K et al (2000)). Since this finding has only been published as a poster and clinical studies on a possible analgesic effect of Primula root extracts are lacking, this finding is of no clinical relevance with regard to the traditional use of Primula root.

Oswiecimska M et al (1975) have described antimitotic activity of saponin fractions and extracts from Primulae radix and other herbal substances by means of the allium test.

[5] Not required as per Article 16c(1)(a)(ii) of Directive 2001/83/EC as amended



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Herre E (1937) has given some data in rats concerning diuretic properties of Primula officinalis (= Primula veris), but there are no more recent investigations which endorse these findings.

**IN VIVO EXPERIMENTS**

Experiments relevant for the proposed indications:

In vivo studies (rabbit) on pharmacological / toxicological effects of extracts from Primula flower showed a significant increase in the production of bronchial secretion at the concentrations tested (Chibanzuga G et al. (1984)). The observed effect was in the range of the reference substances bromhexin and acetylcysteine which had been tested simultaneously. Even though these studies had been carried out with extracts from Primula flower, they might be of some interest: The German Commission E has given the same indications to both Primula flowers and Primula root; Primula flowers also contain saponins.

An undefined mixture of saponins from Primula root, at a concentration of 1:10,000, increased the ciliary activity of throat epithelium of curarized frog. This effect was assumed to be due to a decrease in surface tension of the mucus. The ciliary activity was less at a concentration of 1:6,000 and ceased at 1:3,000 due to toxic effects (Vogel G (1963)).

Further in vivo experiments:

An unspecified saponin of Primula root, administered parenterally, inhibited the growth of Walker carcinoma in rats with an ED50 of 40 mg/kg, although this dose was too toxic in relation to the LD50 of 70 mg/kg to be of practical significance (Tschesche R et al (1973)).

Sufka KJ et al (2001) tested herbal extracts for their anxiolytic properties in the chick social separation-stress procedure. For Primula veris (plant part not mentioned) no sedative effects were observed, in addition no alteration of stress responses could be detected.

**CLINICAL STUDIES**

Clinical studies with preparations containing solely Primula flowers do not exist.
The data generated in clinical trials with the special preparation ‘Sinupret’ cannot be included, because the contribution of the Primula flower extract to the overall-activity cannot be estimated.

**PHARMACOKINETIC PROPERTIES**

No specific data are available on the pharmacokinetics of Primula flower saponins. In general, saponins are poorly absorbed by the body (Hostettman K et al (1995)). Usually glycosidic bonds are easily cleaved by enzymes of the gastrointestinal tract. The amount of absorption depends on the galenic form of the preparation (Hänsel R et al (2007)).

## 3 LITERATURE REFERENCES

Search entries: Primula elatior, Primula veris, Primula officinalis
Search using Pubmed and SciFinder, Data bases: CAPLUS, MEDLINE, REGISTRY, CASREACT, CHEMLIST, and CHEMCATS
Library search: specialized library for Pharmacy and Nutritional Sciences, Univ. Vienna



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|---|---|
| Auster F, Schäfer J | Primula veris: in Arzneipflanzen, Verlag Georg Thieme, Leipzig 1961 |
| Boyd EM (1954) | Expectorants and respiratory tract fluid. J Pharm Pharmcol 1954;6: 521-542 |
| Büechi S. (1996) | Antivirale Saponine. Pharmakologische und klinische Untersuchungen. Dtsch Apoth Ztg 1996; 136: 89-98 |
| Chibazunga G, Maerz R, Sterner W (1984) | Zur Wirksamkeit und Toxizität eines pflanzlichen Sekretolytikums und seiner Einzeldrogen. Drug Res. 1984; 34, 32-36 |
| Commission E monographs (1998) | The complete german commission E monographs. Translation by Blumenthal M et al, American Botanical Council, Austin 1998 |
| Dinand P (1921) | Handbuch der Pflanzenkunde, Schreiber, Esslingen, 1921 |
| Dorsch W, Loew D, Meyer-Buchtela E, Schilcher H. (2002) | Primulae radix. Kinderdosierungen von Phytopharmaka. Bonn: Kooperation Phytopharmaka, 2002. |
| ESCOP Monograph (2003) | PRIMULAE RADIX (Primula Root). ESCOP Mongographs Second edition (ESCOP 2003) |
| Flamm S, Kroeber L, Seel H (1940) | Pharmakodynamik deutscher Heilpflanzen. Hippokrates, Stuttgart, 1940 |
| Fournier P (1948) | Le Livre des Plantes médicinales et vénéneuses de France. Lechevalier, Paris, 1948 |
| Häberlein H, Prenner L | Ein Meilenstein in der Efeu-Forschung: ein biophysikalischer und zellbiologischer Beitrag zum Wirkungsmechanismus. Kongressband Phytopharmaka Phytotherapie 2005: S9 |
| Hänsel R, Keller K, Rimpler H, Schneider G, editors (1994) | Primula. In: Hagers Handbuch der Pharmazeutischen Praxis, 5th ed. Band 6, Drogen P-Z. Berlin. Springer-Verlag, 1994: 269-287 |
| Hänsel R, Sticher O (2007) | Pharmakognosie – Phytopharmazie. Springer, Heidelberg, 2007 |
| Hausen BM (1978) | On the occurrence of the contact allergen Primin and other quinoid compounds in species of the family of primulaceae. Arch Derm Res 1978; 261, 311 - 321 |
| Herre E (1937) | Die diuretische Wirkung der in Naturheilkunde und Volksmedizin angewandten harntreibenden Mittel. *Naunyn Schmiedeberg´s Arch. Pharmacol*. 1937; 184, 710-715 |
| Hostettman K, Marston A: (1995) | Saponins: Cambridge: Cambridge University Press, 1995. |
| List PH, Hörhammer L | Primula. In: Hagers Handbuch der Pharmazeutischen Praxis, 4th ed. Berlin. Springer-Verlag, 1977: 873-883. |
| Lohmann K, Reiniger E, Bauer R | Screening of european anti-inflammatory herbal drugs for inhibition of cyclooxygenase-1 and -2. Phytomedicine Suppl. II 2000, 7: 99 |
| Margineanu C, Cucu V, Grecu L, Parvu C. (1976) | Die Anticandida Wirkung der Primula Saponine. Planta Med 1976; 30: 35-38 |
| McGuffin M, Hobs Ch, Upton R, Goldberg A (1997 | Botanical safety handbook. CRC Press, Boca Raton, 1997 |
| Oakenfull D. (1981) | Saponins in food – a review. Food Chemistry 1981; 7: 19 - 40 |
| Oswiecimska M , Sendra J, Janeczko Z (1975) | Antimitotic activity of saponin fractions amd extracts from rx primulae, rx saponariae and sem hippocastani. Pol J Pharmacol Pharm 1975; 27, 349 - 354 |
| Rao GS, Sinsheimer JE, Cochran KW. (1974) | Antiviral activity of triterpenoid saponins containing acylated ß-amyrim aglycones. J Pharm Sci 1974;63: 471-473 |
| Sufka KJ, Roach T, Chambliss WG, Broom SL, Feltenstein MW, Wyandt CM, Zeng L (2001) | Anxiolytic properties of botanical extracts in the chick social separation-stress procedure. Psychopharmacology 153: 219-224, 2001 |
| Tschesche R, Wulff G. (1965) | Über die antimikrobielle Wirksamkeit von Saponinen. Z Naturforsch 1965; 20b, 543 – 546 |




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| | |
|---|---|
| Tschesche R, Wulff G. (1973) | Chemie und Biologie der Saponine. In: Herz W, Grisebach H, Kirby GW, editors. Fortschritte der Chemie organischer Naturstoffe / Progress in the Chemistry of Organic Natural Products, Volume 30. Vienna-New York: Springer-Verlag, 1973: 461-606. |
| Vogel G. (1963) | Zur Pharmakologie von Saponinen. Planta Med 1963;11, 362 – 376 |
| Walthelm U, Ditrich K, Gelbrich G, Schöpke Th (2001) | Effects of saponins on the water solubility of differnt model compounds. Plante Med 67: 49-54, 2001 |
| Wichtl M. (2004) | Primulae radix. In: Wichtl M, editor: Herbal drugs and Phytopharmaceuticals. Stuttgart: medpharm Scientific Publishers, 2004: 472-474 |
| Wolters B (1966) | Die Verbreitung antibiotischer Eigenschaften bei Saponindrogen. Dtsch Apoth Ztg 1966;106: 1729-1733 |
| Zörnig H | Arzneidrogen. Verlag Werner Klinkhardt, Leipzig, 1911 |


## 4 USE IN MEMBER STATES

AT: authorized products: only combinations with other herbal substances

## 5 ASSESSOR'S OVERALL CONCLUSIONS

The expectorant effects of Primula flower preparations have long been recognised empirically; the uses are made plausible by pharmacological data (level of evidence 4). Controlled clinical studies are lacking.
In conclusion, Primula flower preparations can be regarded as traditional herbal medicinal products.



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