EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Grindelia robusta* Nutt., *Grindelia squarrosa* (Pursh) Dunal, *Grindelia humilis* Hook. et Arn., *Grindelia camporum* Greene, herba

Based on Article 16d(1), Article 16f and Article 16h of Directive 2001/83/EC as amended (traditional use)

Final

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Grindelia robusta* Nutt., *Grindelia squarrosa* (Pursh) Dunal, *Grindelia humilis* Hook. et Arn., *Grindelia camporum* Greene, herba
Herbal preparation(s)	a) Comminuted herbal substance b) Liquid extract (DER 1:1), extraction solvent ethanol 22.5% V/V c) Tincture (ratio of herbal substance to extraction solvent 1:10), extraction solvent ethanol 60% V/V
Pharmaceutical forms	Comminuted herbal substance as herbal tea for oral use. Herbal preparations in liquid dosage forms for oral use.
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1. Introduction

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

- Herbal substance(s)

Grindeliae herba (gumweed herb) consists of the dried flowering tops of *Grindelia robusta* Nutt., *Grindelia squarrosa* Dunal, *Grindelia humilis* Hook. et Arn., *Grindelia camporum* Greene or a mixture of them (Pharmacopée Française 1998; ESCOP 2009).

In textbooks, the herbal substance is defined as follows:
- the dried aerial parts of *Grindelia camporum* Green and other species of *Grindelia* gathered before the flower heads expand (BHP 1976; Blaschek *et al.* 2006)
- the dried tops and leaves of *Grindelia robusta* Nutt., and/or *G. squarrosa* (Pursh) Dunal, gathered during flowering season (Blumenthal *et al.* 1998)
- the medicinal parts are the flowering branches and the dried leaves; the herbal substance consists of the dried tops and leaves of *Grindelia robusta* and/or *Grindelia squarrosa*, which are gathered during flowering season (Gruenwald *et al.* 2007).

The plants are native to Western North America and Mexico, herbs which secrete sticky resin, especially from the yellow composite flowers (Goetz 2005; BHP 1976).

Description of the plant

The plant is an erect biennial or perennial herb or small bush that grows up to 1 m high, often branched above (Gruenwald *et al.* 2007).

Macroscopical description of the cut herb: Leaf fragments rigid and brittle, minutely reticulately pitted, some pieces showing a serrated margin, pale green or rose-brown. Some separate yellow ray florets about 10 mm long. Groups of yellow disc florets, about 5 mm long with bristly pappus hairs. Loose pappus hairs. Portions of flat, circular, pale green receptacles, pitted with floret scars on the upper surface, with a margin of curved, stiff, resin covered, lanceolate bracts. Many stem pieces, perhaps split, pithy, faintly longitudinally striated, smooth, very pale green. Slight balsamic odour (BHP 1976).The leaves break off easily when dry (Gruenwald *et al.* 2007).

Microscopical description of the cut herb: Covering trichomes of the leaf uniseriate, of about 4 to 7 short cells with a longer, narrow terminal cell. Glandular trichomes, few on the leaf and situated on the edges of the reticulations, many on the bracts around the receptacles, broadly ovoid masses, multicellular, sessile, about 35 to 85 µm long, containing minute rosettes of calcium oxalate about 4 µm in diameter. Leaf epidermis with polygonal, beaded anticlinal walls, containing scattered birefringent crystals in small rosettes and needles. Stomata anomocytic raised above the surface. Ray florets, terminating in an acute apex. Disc florets tubular with a five-lobed corolla and five protruding stamen filaments the ends of which are intensely birefringent. All florets containing many small birefringent crystals on the lower half; rosettes just above the ovary and prisms further up the corolla and around the ovary. Pappus hairs loose each about half the length of the disc florets and about 90-110 µm wide, with the marginal cells overlapping outwards. Pollen grains compositous, spherical, with spiny exine and 3 pores, about 30 µm in diameter (BHP 1976).

Acid-insoluble ash: Not more than 2% of the ash is insoluble in diluted hydrochloric acid.

Extractive: Not less than 20% is yielded to 90%.

The material complies with the monograph of the 'Pharmacopée Française' (1998).

Other names: August flower, California gum plant, Resin-weed, Scaly *Grindelia*, Tar weed, in Indian tribes: in Lakotas pte ichi yuha, in Poncas Omaha pezhe wasek (Goetz 2005).

In Germany, the use of gumweed herb was approved by the Commission E (Blumenthal *et al.* 1998).

Chemical constituents according to existing references (Paris & Moyse 1971; BHP 1976; Madaus 1979; Duke 1985, Goetz 2005; Gruenwald *et al.* 2007; ESCOP 2009)

- resin (5-20% depending on the species) consisting mainly of diterpenic acids such as grindelic acid, 7-8-epoxygrindelic acid and 17-acetoxygrindelic acid; acetylenic compounds such as matricarianol and marticarianol acetate (Timmermann *et al.* 1987; Didry *et al.* 1982, Blaschek *et al.* 2006)
- flavonoids such as kaempferol-3-methylether and kaempferol-3,7-dimethylether and various quercetin-methylethers (Pinkas *et al.* 1978; Didry *et al.* 1982; Pharmacopée Française 1998; Krenn *et al.* 2009)] and main compounds quercetin-3-methyl-ether and 6-OH-kaempferol-3,6-dimethylether
- triterpenoid saponins with grindelia sapogenin D, bayogenin and oleanolic acid as the sapogenins (Paris & Moyse 1971; Kreutzer *et al.* 1990; Pharmacopée Française 1998)
- phenolic acids such as chlorogenic, *p*-hydrobenzoic and *p*-coumaric acids (Pinkas *et al.* 1978; Didry *et al.* 1982)
- approximately 5% of tannins (Paris & Moyse 1971; Blaschek *et al.* 2006)] and
- approximately 0.2% of essential oil consisting mainly of mono- and sesquiterpenes, and especially for *G. robusta* - borneol (15.2%) (Paris & Moyse 1971), alpha-pinene (10.3%), trans-pinocarveol (7%), bornyl acetate (4.5%), limonene (4.3%) (Blaschek *et al.* 2006; El-Shamy *et al.* 2000; Schäfer & Schimmer 2000; Fraternale *et al.* 2007)

- Herbal preparation(s)

See section 2.2

- Combinations of herbal substance(s) and/or herbal preparation(s) including a description of vitamin(s) and/or mineral(s) as ingredients of traditional combination herbal medicinal products assessed, where applicable.

There are some combinations registered/marketed in the European Union (EU).

The Community herbal monograph refers only to Grindeliae herba.

1.2. Information about products on the market in the Member States

Regulatory status overview

Member State	Regulatory Status				Comments
Austria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No marketed products
Belgium	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Bulgaria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No marketed products
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No marketed products
Czech Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No marketed products
Denmark	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No marketed products
Estonia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No marketed products
Finland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No marketed products
France	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	Only combinations with *Erysimum*
Germany	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No marketed products
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No marketed products
Hungary	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Ireland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Latvia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Liechtenstein	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Lithuania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Luxemburg	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Malta	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
The Netherlands	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No marketed products
Norway	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No marketed products
Poland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Portugal	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No marketed products
Romania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not known
Slovak Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No marketed products
Slovenia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No marketed products
Spain	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	One combination product (syrup) - formulation of 12 ingredients, containing *Grindelia* tincture.
Sweden	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No marketed products
United Kingdom	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No marketed products

MA: Marketing Authorisation
TRAD: Traditional Use Registration
Other TRAD: Other national Traditional systems of registration
Other: If known, it should be specified or otherwise add 'Not Known'
This regulatory overview is not legally binding and does not necessarily reflect the legal status of the products in the MSs concerned.

1.3. Search and assessment methodology

Search terms: *Grindelia robusta* Nutt., *Grindelia squarrosa* (Pursh) Dunal, *Grindelia humilis* Hook. *et* Arn., *Grindelia camporum* Greene herb, Gumweed herb, Grindeliae herba.

Databases: PubMed, Medline, HealLink, Scopus.

Libraries: University of Athens, Laboratory of Pharmacognosy and Chemistry of Natural Products of the University of Athens.

2. Historical data on medicinal use

2.1. Information on period of medicinal use in the Community

The genus name *Grindelia* derives from the name of the German botanist David Grindel (1766-1836) [Madaus 1979] and it has been utilised by Native Americans to treat bronchial problems as well as skin afflictions of all kinds, including allergic reactions to the poison ivy plant. The medicinal value of this plant was not recognised by the orthodox practitioners of medicine in the United States (US) till the middle of the 19th century - after which it came into prominence as a major medicinal plant. Official recognition of *Grindelia* came with the introduction of the herb in the Pharmacopoeia of the United States from 1882 to about 1926 and in the U.S. National Formulary till 1960 (Goetz 2005). Modern herbalists still prescribe the herb for the treatment of some types of disorders. *Grindelia* has also been used for a long time as a remedy for dermatitis caused by poison oak or poison ivy. The latter belongs to the genus *of Toxicodendron* and contains a sap called urushiol, which causes severe allergic reactions in case of contact with skin. *Grindelia* was used to provide relief in urushiol-induced contact dermatitis by the Native Americans and also in pharmaceutical medications in the early 1900's. *Grindelia* was also used in combination herbal products of asthmatic conditions (such as *Lobelia* and the pill-bearing spurge - *Euphorbia hirta* syn. *E. pilulifera*). This combination remedy was claimed to be effective in dealing with asthmatic conditions (BHP 1976).

Herbal Use

The Commission E approved gumweed herb for catarrhs of the upper respiratory tract (Blumenthal *et al.* 1998). Grindeliae herba traditionally has been indicated for the treatment of upper respiratory catarrh, common cold, asthma, bronchitis, whooping cough, cystitis, and used for its action as antispasmodic, expectorant and cardiac depressant (BHP 1976; Duke 1985; ESCOP 2009).

It has been also used externally in lotion form in poison-ivy dermatitis, while it was used traditionally in combinations with *Lobelia inflata* and *Glycyrrhiza glabra* in asthma and bronchitis (BHP 1976) as well as with *Gelsemium* and *Erysimum* (information concerning the French market).

2.2. Information on traditional/current indications and specified substances/preparations

According to the data on the European market, there are no herbal medicinal products containing neither the herbal substance Grindeliae herba nor Grindeliae herba preparations as single active substance in Europe. The herbal preparations (**a**), (**b**) and (**c**) were found in literature references, and the period of their medicinal use dates back to more than 30 years (Belgische Pharmacopee 5th Edition 1969; Paris & Moyse 1971; BHP 1976).

Therefore, for Grindeliae herba, the requirement for a period of at least 30 years in medicinal use set out in Directive 2004/24/EC for qualification as a traditional herbal medicinal product is fulfilled. The evidence on traditional medicinal use is confirmed by a number of publications providing supporting information.

From the literature (BHP 1976; Blumenthal *et al.* 1998; Blaschek *et al.* 2006; Gruenwald *et al.* 2007, ESCOP 2009), the following herbal preparations have been identified:

a) Comminuted herbal substance (Belgische Pharmacopee 5th Edition 1969; Paris & Moyse 1971; BHP 1976)

b) Liquid extract (DER 1:1), extraction solvent ethanol 22.5% V/V (Belgische Pharmacopee 5th Edition 1969; Paris & Moyse 1971; BHP 1976)

c) Tincture (ratio of herbal substance to extraction solvent 1:10), extraction solvent ethanol 60% V/V (Belgische Pharmacopee 5th Edition 1969; Paris & Moyse 1971; BHP 1976)

Upon assessment of data on traditional and current indications (see section 2.1), the indication proposed for the Community herbal monograph is:

'Traditional herbal medicinal product for relief of cough associated with cold'.

2.3. Specified strength/posology/route of administration/duration of use for relevant preparations and indications

Based on literature data and information from the Member States (France), the following posology and duration of use is proposed for the different herbal preparations (Belgische Pharmacopee 5th Edition 1969; Paris & Moyse 1971; BHP 1976):

Posology

Adults and elderly

a) Comminuted herbal substance

Single dose

Herbal tea: 2-3 g of the comminuted herbal substance in 150 ml of boiling water as a herbal infusion up to 3 times daily

b) Liquid extract: 1.8-3.6 ml daily

c) Tincture: 1.5-3 ml daily

The use in children and adolescents under 18 years of age is not recommended (see section 5.5.).

Duration of use

If the symptoms persist longer than 1 week during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted (this information is in accordance with previous relevant monographs).

3. Non-Clinical Data

3.1. Overview of available pharmacological data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

In vitro experiments

Antibacterial ability

Ethanolic extracts and resin fractions (Blaschek *et al.* 2006; Pinkas *et al.* 1978), as well as a polyphenolic fraction and phenolic acids from *Grindelia* inhibited the growth of several bacterial strains, including *Staphylococcus aureus* and *Bacillus subtilis*. In all cases, not further details on the species used were given. No antibacterial ability was exhibited by isolated flavonoids or a saponin fraction (ESCOP 2009; Kreutzer *et al.* 1990).

Fungistatic activity

In the plate diffusion test concentrations of up to 10 mg/plate of a mixture of bisdesmosidic *Grindelia* saponins dose-dependently inhibited the growth of the fungi *Candida tropicalis*, *Mucor mucedo*, *Trichoderma viride* and *Botrytis cinerea*. In another experiment, the same mixture inhibited the growth of three of these fungi species with MIC values between 0.31 and 5 mg/plate (comparable to aescin) compared to 0.6 µg per plate for clotrimazole (ESCOP 2009).

The essential oil of *Grindelia* was also tested and it showed an inhibition of the growth of *Penicillium expansum, Aspergillus flavus, Trichoderma viride, Phomopsis* spp., *Monilia fructigena* and *Fusarium culmorum* by 9-83% in comparison with the control (econazole, 100%) when applied for 6 days at 2 µl per plate and showed an inhibition by 71-83% at 30 µl per plate (ESCOP 2009).

Recently, the methanolic extract from *Grindelia camporum* showed significant activity against all target fungal species. The growth inhibitory effect was tested against six significant pathogenic and toxinogenic fungal species: *Fusarium oxysporum, F. verticillioides, Penicillium expansum, P. brevicompactum, Aspergillus flavus* and *A. fumigatus*. The most sensitive target fungus was the toxinogenic and human pathogenic species *A. fumigatus*. No further details on the concentrations were given (Zabka *et al.* 2011).

Antispasmodic activity

A fluid extract (1:1, ethanol 75%) and a polyphenolic fraction from *Grindelia* exhibited mild antispasmodic activity on contractions of isolated guinea pig ileum. ED_{50} values for acetylcholine-, histamine-, serotonin- and bradykinin-induced contractions were respectively 150-200 µg/ml, 40 µg/ml, 10-50 µg/ml and 10-40 µg/ml for the fluid extract, and 150-200 µg/ml, 10-20 µg/ml, 10 µg/ml and 10 µg/ml for the polyphenolic fraction. However, the effect could not be confirmed in later research using a 50% V/V methanolic extract of *Grindelia*; no antispasmodic activity was observed on spontaneous or acetylcholine- or barium chloride-induced contractions of isolated guinea pig ileum at concentrations up to 800 µg/ml (ESCOP 2009; Izzo *et al.* 1996).

Antioxidant activity

The antioxidant activity of the essential oil obtained from *Grindelia robusta* aerial parts from central Italy was evaluated using the DPPH and 5-lipoxygenase tests showing IC_{50} 358±28.6 and 16.75±1.83 µg/ml respectively a moderate activity in comparison with Trolox® and ascorbic acid (Fraternale *et al.* 2007).

Anti-inflammatory activity

Grindelia extracts of varying polarity have been tested in a neutrophil elastase assay. As observed earlier with various phenolic compounds, the extracts had a remarkable inhibitory effect (greater than 50%) at a concentration of 1 mg dried extract/0.5 ml, indicating anti-inflammatory potential. In the thrombin activity test, the IC_{50} values of an acetone extract and a carbon dioxide extract were 330 and 500 µg/ml respectively (ESCOP 2009).

Plant extracts and/or secondary metabolites receive considerable attention as therapeutic agents for treating inflammatory diseases such as periodontitis, which affects the tooth supporting tissues. In a recent study, the effect of a *Grindelia robusta* extract enriched in saponins and polyphenols was investigated on *Aggregatibacter actinomycetemcomitans* lipopolysaccharide (LPS)-induced inflammatory mediator (IL-6, TNF-α, RANTES, MCP-1, PGE(2)) and matrix metalloproteinase (MMP-1, -3, -7, -8, -9, -13) secretion of macrophages. LPS induced a marked increase in the secretion of all inflammatory mediators and MMPs tested by macrophages, as determined by enzyme-linked immunosorbent assays. At non-cytotoxic concentrations (200 µg/ml of the extract), the *G. robusta* extract inhibited dose-dependently the secretion of IL-6, RANTES, MCP-1 and, to a lesser extent, PGE(2) and TNF-α. Such inhibition was also observed for MMP-1, -3, -7, -8, -9 and -13 secretion. This ability of *G. robusta* extract to reduce the LPS-induced secretion of inflammatory mediators and MMPs was associated with a reduction of nuclear factor-kappa B (NF-kB) p65 activation. The results suggest that *G. robusta* extract possesses an anti-inflammatory therapeutic potential through its capacity to reduce the accumulation of inflammatory mediators and MMPs (La *et al.* 2010).

Methanolic extract of *Grindelia robusta* was evaluated for its anti-inflammatory activity, showing up to 4.5-fold inhibition of nitric oxide (NO) production in the J774 murine macrophage cells challenged with LPS without cytotoxicity. The extract at concentration of 100 µg/ml significantly reduced the protein levels of inducible NO synthase (iNOS) and the cyclooxygenase-2 (COX-2) as observed by Western blot analysis. *G. robusta* extract significantly inhibited (by 50%) IL-1β and IL-12 secretions. Furthermore, the plant extract was shown to prevent the LPS-mediated nuclear translocation of NF-kB. All the above observations indicate the anti-inflammatory potential of the plant (Verma *et al.* 2010).

In vivo experiments

Anti-inflammatory activity

A *Grindelia robusta* dry extract (80% ethanol) orally administrated at 100 and 200 mg/kg body weight dose-dependently inhibited carrageenan-induced rat paw oedema by 41% ($p<0.01$) and 63% ($p<0.001$) respectively, compared to 45% inhibition by indomethacin at 5 mg/kg (Goetz 2005).

The anti-inflammatory activity of a *Grindelia* fluid extract (1:1, ethanol 75%) was demonstrated in similar experiments. When administrated intraperitoneally at 65 mg/kg 30 minutes before carrageenan injection, the extract inhibited rat paw oedema by 53% compared to 24% by lysine acetylsalicylate at 100 mg/kg and 30% by rutin at 100 mg/kg (ESCOP 2009).

Expectorant activity

In an old study by Boyd *et al*. in 1946 (ESCOP 2009) on urethanized cats, rabbits and guinea pigs, respiratory tract fluid (RTF) was collected from the trachea 3 hours before and 4 hours after gastric administration of a *Grindelia* fluid extract (conforming to 'Normes Françaises NF 7' 1942) at doses from 0.1 to 10 ml/kg body weight. The RTF output 2 hours after administration increased by 79% in cats while no effects was observed in rabbits or guinea pigs. Controls showed increases or decreases in RTF output of up to 30% over 4 hours.

Antispasmodic activity

A *Grindelia* fluid extract (1:1, ethanol 75%) and a polyphenol fraction showed no antispasmodic activity against histamine- or serotonin-induced bronchospasms at higher doses (close to the toxic dose) (Pinkas *et al.* 1978; ESCOP 2009).

Bioactivities of secondary metabolites from gumweed

Anti-inflammatory activity

The contribution of methylated exudate flavonoids (main compounds quercetin-3-methylether and 6-OH-kaempferol-3,6-dimethylether) to the anti-inflammatory activity of *Grindelia robusta*, was tested through an assay for their activity to inhibit neutrophil elastase. Quercetin-3-methylether was shown to be most active with an IC_{50} of 19 µM, thus obviously contributing to the anti-inflammatory activity of this herbal drug (Krenn *et al.* 2009).

All these observations of such bioactivities help to account for some of the existing medical effects.

3.2. Overview of available pharmacokinetic data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

No data on gumweed herb preparations/extracts have been found or reported.

3.3. Overview of available toxicological data regarding the herbal substance(s)/herbal preparation(s) and constituents thereof

Single-dose and repeated-dose toxicity studies

No mortality occurred and no toxic effects were apparent in rats after a single oral dose of a *Grindelia robusta* dry extract (80% ethanol) at 2.5 g/kg body weight (Goetz 2005; ESCOP 2009).

Intraperitoneal LD_{50} values in mice for a fluid extract and a polyphenolic fraction from *Grindelia* species were determined as 250 mg/kg and > 500 mg/kg body weight, respectively (Pinkas *et al.* 1978; ESCOP 2009).

Genotoxicity studies

No genotoxicity studies carried out on gumweed herb can be found in the scientific literature.

Carcinogenicity studies

No carcinogenicity studies carried out on gumweed herb are available in the scientific literature.

Reproductive and developmental toxicity studies

No reproductive and developmental toxicity studies carried out on gumweed herb are available in the scientific literature.

The safety of gumweed herb during pregnancy and lactation has not been established. In accordance with general medical practice, the herbal medicinal products (herbal teas or finished products) should not be used during pregnancy and lactation.

3.4. Overall conclusions on non-clinical data

Grindeliae herba has officially been recognised at least since 1969 in the Belgische Pharmacopee 5th edition, by Paris & Moyse in 1971 and in 1976 in the BHP; it is still in the current edition of the French Pharmacopoeia (monograph last amended in Pharmacopée Française 1998) as a herbal remedy traditionally used for the relief of catarrh of the upper respiratory tract. Gumweed herb is also approved by the German Commission E monograph (Blumenthal *et al.* 1998). It has been used as a traditional remedy without safety problems for more than 30 years.

The published data referring to the indications and preparations is limited, but existing data on the above-mentioned pharmacological activities (Belgische Pharmacopee 5th edition 1969; Paris & Moyse 1971; BHP 1976; Madaus 1979; Duke 1985; Gruenwald *et al.* 2007) support the traditional use, for relief of cough associated with cold, of preparations of *Grindelia robusta* Nutt., *Grindelia squarrosa* (Pursh) Dunal, *Grindelia humilis* Hook. et Arn., *Grindelia camporum* Greene, herba.

The lack of genotoxicity, carcinogenicity as well as reproductive and developmental toxicity studies do not allow the establishment of a Community list entry.

4. Clinical Data

4.1. Clinical Pharmacology

4.1.1. Overview of pharmacodynamic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents

No data available.

4.1.2. Overview of pharmacokinetic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents

No data available.

4.2. Clinical Efficacy

4.2.1. Dose response studies

No data available.

4.2.2. Clinical studies (case studies and clinical trials)

Poison oak and related hypersensitivity dermatitis are age-related problems that have historically been treated with herbal medicines before the availability of corticosteroids. Few of these historical therapies

have been rigorously investigated. *Grindelia* preparations were used in earlier times to treat exanthema caused by intoxication with *Rhus toxicodendron* (poison oak) (ESCOP 2009).

In a recent case study involving a woman suffering from poison oak dermatitis, application of a tincture (85% ethanol) from fresh flower buds of *Grindelia* spp. had an immediate effect, diminishing pruritus and decreasing transudation. The tincture mixed into a *calendula* cream base produced further relief (Canavan & Yarnell 2005).

There is a lack of clinical research, except the above-mentioned reference by Canavan & Yarnell 2005, assessing the effects of gumweed herb.

4.2.3. Clinical studies in special populations (e.g. elderly and children)

None reported.

4.3. Overall conclusions on clinical pharmacology and efficacy

Despite the absence of data from clinical studies, the data on traditional use from published literature and information on use of Grindeliae herba preparations in products marketed in the EU are considered sufficient (efficacy is plausible on basis of long-standing use and experience).

5. Clinical Safety/Pharmacovigilance

5.1. Overview of toxicological/safety data from clinical trials in humans

There is a lack of clinical safety and toxicity data for gumweed herb from clinical trials and further investigation of these aspects is required.

5.2. Patient exposure

No data available.

5.3. Adverse events and serious adverse events and deaths

In sensitive persons, irritation of the gastric mucosa might occur (ESCOP 2009) while side effects listed in older scientific literature include gastric irritation and diarrhoea (Gruenwald *et al.* 2007) as well as irritation of kidney and/or stomach at high doses (Duke 1985). There is no any published data and/or case reports reporting any kind of adverse events.

5.4. Laboratory findings

No data available.

5.5. Safety in special populations and situations

Special patient populations

No data on use in children and adolescents are available; therefore Grindeliae herba is intended only for use by adults and elderly.

Use in pregnancy and lactation

In the absence of data available and in accordance with general medical practice, it is recommended not to use herbal medicinal products containing gumweed herb and preparations thereof during pregnancy and lactation.

Overdose

No cases of overdose have been recovered in the scientific literature.

Drug abuse

No information in the literature.

Effects on ability to drive and use machines

No data in the literature.

5.6. Overall conclusions on clinical safety

Grindeliae herba is intended only for adults and elderly.

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

Some adverse effects in sensitive persons i.e. irritation of the gastric mucosa have been reported in the literature (ESCOP 2009) as well as adverse effects occurring at high doses i.e. diarrhoea and irritation of kidney and/or stomach (Gruenwald *et al.* 2007; Duke 1985). There are no recent published data and/or case reports reporting any kind of adverse events, pointing to the safety of Grindeliae herba in case of therapeutic application. However, the lack of mono-component products on the market queries the significance of this apparent lack of reports of adverse events.

As there are no available data on genotoxicity, carcinogenicity and reproductive and developmental toxicity of gumweed herb and preparations thereof, it is not possible to establish a Community list entry.

6. Overall conclusions

The positive effects of gumweed herb on the relief of symptoms of common cold have been recognised empirically. This application is plausible only on the basis of the traditional use of the plant and the existing *in vitro* and *in vivo* pharmacological data. There is a lack of controlled clinical studies with preparations containing Grindeliae herba.

In conclusion, Grindeliae herba preparations can be used in traditional herbal medicinal products in the following indication:

‘Traditional herbal medicinal product for relief of cough associated with cold’.

In the absence of adequate data in other populations, Grindeliae herba is intended only for adults and elderly.

In the absence of sufficient data and in accordance with general medical practice, it is recommended not to use herbal medicinal products containing gumweed herb and preparations thereof during pregnancy and lactation.

There is no any recent published data and/or case reports reporting any kind of adverse events, pointing to the safety of Grindeliae herba in case of therapeutic application; this supports a safe use in

the proposed traditional indication and according to the specified conditions of use described in the monograph.

As there are no available data on genotoxicity, carcinogenicity and reproductive and developmental toxicity on gumweed herb and preparations thereof, it is not possible to establish a Community list entry.

Annex

List of references