Flos Arnicae

Definition
Flos Arnicae consists of the dried flower heads (capitula) of *Arnica montana* L. (Asteraceae) (*1–3*).

Synonyms
Doronicum arnica Desf., *D. montanum* Lam. (*4*). Asteraceae are also known as Compositae.

Selected vernacular names
Arnica, arnika, arnique, bétoine des montagnes, betouana, Bergwohlverleih, celtic bane, dokhanolfouh, Echtes Wolferlei, estourniga, estrunica, Fallkraut, Kraftwurz, leopard's bane, mountain arnica, mountain tobacco, St Luzianskraut, Stichwurzel, strunica, Verfangkraut, Wohlverleih, wolf's bane, Wundkraut (*4–9*).

Geographical distribution
Indigenous to central Europe. Widely cultivated around the world (*1, 4, 7*).

Description
A perennial herb, 20–50 cm high. Aerial portion consists of a basal rosette of entire oblanceolate leaves up to 17 cm long, five to seven veins, from the centre of which projects an erect, simple, glandular hairy stem up to 0.6 m high. Stem bears two to four pairs of cauline leaves, ovate, elliptic-oblong, lanceolate or oblanceolate, with rounded or rounded-toothed apex and clothed with numerous nonglandular and glandular hairs, up to 16 cm long and 5 cm wide. Peduncles, one to three, bearing alternate bracteoles, extending from the uppermost pair of cauline leaves; glandular–puberulent, each terminating in a hemispherical or turbinate capitulum bearing orange-yellow flowers, which are tubular. Fruits, black to brown, five-ribbed, with a bristle tuft of hairs (*5, 8*).

Plant material of interest: dried flower heads

General appearance

Capitulum about 20 mm in diameter and 15 mm deep, with a peduncle 2–3 cm long. Involucre with 18–24 elongated lanceolate bracts, 8–10 mm long with acute apices, arranged in one or two rows, green with yellowish-green external hairs visible under a lens. Receptacle, about 6 mm in diameter, convex, alveolate and covered with hairs; periphery bears about 20 ligulate florets 20–30 mm long; disc bears a greater number of tubular florets about 15 mm long. Ovary, 4–8 mm long, crowned by a pappus of whitish bristles 4–8 mm long. Some brown achenes, crowned or not by a pappus, may be present (*3*).

Organoleptic properties

Odour: characteristic aromatic (*1, 3, 5*); taste: bitter and acrid (*1, 5*).

Microscopic characteristics

Epidermis of corolla papillose, containing yellow-orange globular masses, some cells also containing dark brown–black patches of phytomelan; base of corolla tube of ligulate florets with uniseriate covering trichomes of four to six cells, up to 1 mm in length; bristles of pappus four to six cells in diameter and barbed by exertion of the pointed cell apices. Cells of ovary or fruit walls contain abundant black patches of phytomelan. Corolla and ovary wall with numerous composite glandular trichomes; ovary wall with numerous appressed twin hairs each composed of two narrow parallel cells diverging at the tips. Pollen grains spiky, spherical 35–52 µm in diameter, with finely granular exine, spines up to 8 µm long, three pores and furrows (*1*).

Powdered plant material

Light yellowish-brown to light olive-brown. Epidermis of the involucre bracts with stomata and trichomes, which are more abundant on the outer surface. Trichomes include: uniseriate multicellular covering trichomes, 50–500 µm long, particularly abundant on the margins; secretory trichomes about 300.0 µm long with uni- or biseriate multicellular stalks and with multicellullar, globular heads, abundant on the outer surface; similar trichomes, 80.0 µm long, abundant on the inner surface of the bract. Epidermis of the ligulate corolla consists of lobed or elongated cells, a few stomata and trichomes of different types: covering trichomes, with very sharp ends, whose length may exceed 500 µm; secondary trichomes with multicellular stalks and multicellular globular heads. Ligule ends in rounded papillose cells. Epidermis of the ovary covered with trichomes: secondary trichomes with short stalks and multicellular globular

heads; twinned covering trichomes usually consisting of two longitudinally united cells, with common punctuated walls, their ends sharp and sometimes bifid. Epidermis of the calyx consists of elongated cells bearing short, unicellular, covering trichomes pointing towards the upper end of the bristle. Pollen grains, about 30 µm in diameter, rounded, with spiny exine, and three germinal pores (*3*).

General identity tests

Macroscopic and microscopic examinations (*1*, *3–5*), and thin-layer chromatography for phenolic compounds (*3*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*10*).

Foreign organic matter

Not more than 5.0% (*3*).

Total ash

Not more than 10% (*3*).

Acid-insoluble ash

Not more than 1.2% (*11*).

Sulfated ash

Not more than 13% (*2*).

Water-soluble extractive

Not less than 17% (*2*).

Alcohol-soluble extractive

Not less than 15% using 45% ethanol (*1*).

Loss on drying

Not more than 10% (*3*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*12*). For other pesticides, see the *European Pharmacopoeia*

(*12*) and the WHO guidelines on quality control methods for medicinal plants (*10*) and pesticide residues (*13*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*10*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*10*) for the analysis of radioactive isotopes.

Other purity tests

Chemical tests to be established in accordance with national requirements.

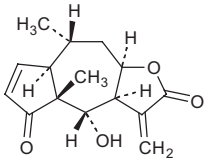
Chemical assays

Contains not less than 0.40% of total sesquiterpene lactones calculated as helenalin tiglate, determined by high-performance liquid chromatography (*3*).

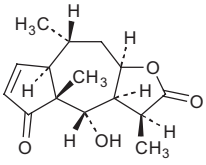
Major chemical constituents

The major constituents include the essential oil (0.5%), fatty acids (content not specified), thymol (content not specified), pseudoguaianolide sesquiterpene lactones (0.2–0.8%) and flavonoid glycosides (0.2–0.6%) (*4, 9, 14*). The primary sesquiterpene lactones are helenalin, 11α,13-dihydrohelenalin and their fatty acid esters. Flavonoids include glycosides and/or glucuronides of spinacetin, hispidulin, patuletin and isorhamnetin, among others (*4, 7, 9, 14–16*). The structures of helenalin and 11α,13-dihydrohelenalin are presented below.

helenalin



11α,13-dihydrohelenalin



Medicinal uses

Uses supported by clinical data

None.

Uses described in pharmacopoeias and well established documents

As a topical counterirritant for treatment of pain and inflammation resulting from minor injuries and accidents, including bruises, ecchymoses,

haematomas and petechiae (*1, 17*). Treatment of inflammation of the oral mucous membranes, insect bites and superficial phlebitis (*17*).

Uses described in traditional medicine

Treatment of indigestion, cardiovascular disease, and rheumatism. As an emmenagogue (*9*).

Pharmacology

Experimental pharmacology

Analgesic and anti-inflammatory activity

In vitro, helenalin, 5.0 µmol/l, significantly ($P < 0.01$) suppressed the activity of prostaglandin synthetase in mouse and rat homogenates, and human polymorphonuclear neutrophils, indicating an anti-inflammatory effect (*18*). Human polymorphonuclear neutrophil chemotaxis was inhibited by helenalin, 5.0 µmol/l, in vitro. It was concluded that the α-methylene-γ-lactone moiety played a role in the anti-inflammatory activity of this compound (*18*). Helenalin, 4.0 µmol/l, selectively inhibited the transcription factor nuclear factor (NF)-κβ (*19*).

Intragastric administration of 100.0 mg/kg body weight (bw) of an 80% ethanol extract of Flos Arnicae reduced carrageenan-induced hind paw oedema by up to 29% in rats (*20*). Intraperitoneal administration of 2.5–5.0 mg/kg bw of helenalin significantly ($P < 0.001$) inhibited carrageenan-induced hind paw oedema in rats by 77% after 72 hours (*21*). Intraperitoneal administration of 20.0 mg/kg bw of helenalin strongly inhibited acetic acid-induced writhing by 93% in mice but did not have analgesic effects in mice in the hot-plate test. Intraperitoneal administration of 2.5 mg/kg bw of helenalin to rats inhibited arthritis induced by *Mycobacterium butyricum* by 87% (*21*).

Antioxidant activity

The effect of a tincture of Flos Arnicae on lipid peroxidation and glutathione metabolism in rat liver was assessed following induction of hepatitis by the administration of carbon tetrachloride. Intragastric administration of 0.2 ml/g bw of the tincture to rats decreased the rate of lipid oxidation and increased the activities of the enzymes involved in glutathione metabolism (*22*). Intragastric administration of 0.2 ml/g bw of the tincture per day for 14 days to rats with hepatitis induced by carbon tetrachloride led to a normalization of the hydrolytic enzymes (*23*).

Antitumour activity

Helenalin is cytotoxic to a wide variety of cancer cell lines in vitro, with a median effective dose (ED_{50}) range of 0.03–1.0 µg/ml (*24–27*). Intraperi-

toneal administration of 1.5–33.3 mg/kg bw of helenalin to mice and rats had antitumour activity against a variety of chemically induced tumours (*28–30*).

Cardiovascular effects

Flos Arnicae and extracts of the flower heads have cardiotonic and hypotensive effects in various animal models. Intravenous administration of a single dose of 1.0 ml of a tincture of the flower heads to rabbits had negative chronotropic effects and reduced blood pressure (*31*). Intravenous administration of 1.0 ml of an aqueous or 95% ethanol extract of the flower heads had cardiotonic effects in frogs, and a tincture demonstrated hypotensive activity in rabbits after intravenous administration of 1.0 ml (*32, 33*). A 30% ethanol extract of the flower heads, 0.1–0.3% in the bath medium, had positive inotropic effects in isolated guinea-pig hearts (*33*). Intravenous administration of 5.0 g/kg bw of a fluid extract or tincture of the flower heads increased the blood pressure of cats and guinea-pigs (*34*).

Helenalin, 50.0 µg/ml, decreased intracellular calcium levels in cultured fibroblasts, and potentiated the responses induced by vasopressin and bradykinin (*35*). Intravenous administration of helenalin had cardiotoxic effects in mice (25.0 mg/kg bw) and dogs (90.0 mg/kg bw) (*36*).

Choleretic activity

Intravenous administration of 1.0 ml of a 95% ethanol extract of the flower heads to dogs increased bile secretion by 25–120% (*37*). Intragastric administration of a hot aqueous extract of the flower heads had choleretic effects in rats (dose not specified) (*38*) and dogs (50.0 ml/animal) (*39*).

Toxicology

The oral median lethal dose (LD_{50}) of a 30% ethanol extract of the flower heads was 37.0 ml/kg in mice (*33*). The intragastric LD_{50} for helenalin has been established for numerous species: mice 150.0 mg/kg bw, rats 125.0 mg/kg bw, rabbits 90.0 mg/kg bw, hamsters 85.0 mg/kg bw and ewes 125.0 mg/kg bw (*40*).

Uterine stimulant effects

Intragastric administration of a tincture of the flower heads (dose not specified) had uterine stimulant effects in guinea-pigs (*41*). Intragastric administration of a hot aqueous extract of the flower heads (dose not specified) stimulated uterine contractions in rats (*38*).

Clinical pharmacology

No information available. Clinical trials of homeopathic preparations were not assessed.

Adverse reactions

Numerous cases of dermatitis of toxic or allergic origin have been reported (*42*), usually following prolonged, external application of a tincture of Flos Arnicae. The compounds responsible for the hypersensitivity reaction are the sesquiterpene lactones helenalin and helenalin acetate (*43*). Cross-reactivity to other Asteraceae flowers has been reported (*44–47*).

The flower heads are irritant to the mucous membranes and ingestion may result in gastroenteritis, muscle paralysis (voluntary and cardiac), an increase or decrease in pulse rate, heart palpitations, shortness of breath and death. A fatal case of poisoning following the ingestion of 70.0 g of a tincture of the flower heads has been reported (*48*).

A case of severe mucosal injuries following the misuse of an undiluted mouth rinse with a 70% alcohol content, which also contained oil of peppermint and Flos Arnicae, has been reported (*49*).

Contraindications

Flos Arnicae is used in traditional systems of medicine as an emmenagogue (*9*), and its safety during pregnancy and nursing has not been established. Therefore, in accordance with standard medical practice, the flower heads should not be administered to pregnant or nursing women. Flos Arnicae is also contraindicated in cases of known allergy to *Arnica* or other members of the Asteraceae (Compositae) (*37, 42, 50, 51*).

Warnings

A fatal case of poisoning following the ingestion of 70.0 g of a tincture of Flos Arnicae has been reported (*48*). Internal use of Flos Arnicae or extracts of the flower heads is not recommended. For external use only. Do not apply to open or broken skin. Keep out of the reach of children (*17*).

Precautions

General

Avoid excessive use. Chronic, frequent external applications may induce allergy-related skin rashes with itching, blister formation, ulcers and superficial necrosis. Prolonged treatment of damaged or injured skin or indolent leg ulcers may induce the formation of oedematous dermatitis with the formation of pustules (*17*).

Carcinogenesis, mutagenesis, impairment of fertility

Helenalin has cytotoxic effects in vitro (see Experimental pharmacology). However, in the *Salmonella*/microsome assay, helenalin was not muta-

genic in *S. typhimurium strains* TA102, TA98 or TA100 at concentrations of up to 30 µg/ml (*52, 53*).

Pregnancy: teratogenic effects
Intraperitoneal administration of 6.0–20.0 mg/kg bw of helenalin was not teratogenic in mice (*21*).

Pregnancy: non-teratogenic effects
See Contraindications.

Nursing mothers
See Contraindications.

Paediatric use
See Warnings. For external use only. Do not apply to abraded or broken skin.

Other precautions
No information available on precautions concerning drug interactions; or drug and laboratory test interactions.

Dosage forms
Dried flower heads and other galenical preparations. Store protected from light and moisture (*7*).

Posology
(Unless otherwise indicated)
For external applications only, apply undiluted externally on the affected area two or three times daily: infusion for compresses, 2 g of Flos Arnicae per 100 ml water; tincture for compresses, one part Flos Arnicae to 10 parts 70% ethanol; mouth rinse, 10-fold dilution of tincture, do not swallow; ointment, 20–25% tincture of Flos Arnicae or not more than 15% essential oil (vehicle not specified) (*17*).

References
1. *British herbal pharmacopoeia.* Exeter, British Herbal Medicine Association, 1996.
2. *Pharmacopoeia helvetica*, 8th ed. Berne, Federal Department of the Interior, 1997.
3. *European pharmacopoeia*, 3rd ed. Suppl. 2001. Strasbourg, Council of Europe, 2000.

4. Hänsel R et al., eds. *Hagers Handbuch der pharmazeutischen Praxis. Bd 4, Drogen A–D*, 5th ed. [Hager's handbook of pharmaceutical practice. Vol. 4, Drugs A–D, 5th ed.] Berlin, Springer, 1992.
5. Youngken HW. *Textbook of pharmacognosy*, 6th ed. Philadelphia, PA, Blakiston, 1950.
6. Zahedi E. *Botanical dictionary. Scientific names of plants in English, French, German, Arabic and Persian languages*. Tehran, Tehran University Publications, 1959.
7. Bisset NG. *Herbal drugs and phytopharmaceuticals*. Boca Raton, FL, CRC Press, 1994.
8. *Physician's desk reference for herbal medicine*. Montvale, NJ, Medical Economics Co., 1998.
9. Farnsworth NR, ed. *NAPRALERT database.* Chicago, University of Illinois at Chicago, IL, 9 February, 2001 production (an online database available directly through the University of Illinois at Chicago or through the Scientific and Technical Network (STN) of Chemical Abstracts Services).
10. *Quality control methods for medicinal plant materials.* Geneva, World Health Organization, 1998.
11. Karnick CR, ed. *Pharmacopoeial standards of herbal plants*. Delhi, Sri Satguru Publications, 1994 (Indian Medical Science Series, No. 36).
12. *European pharmacopoeia*, 3rd ed. Strasbourg, Council of Europe, 1996.
13. *Guidelines for predicting dietary intake of pesticide residues*, 2nd rev. ed. Geneva, World Health Organization, 1997 (WHO/FSF/FOS/97.7; available from Food Safety, World Health Organization, 1211 Geneva 27, Switzerland).
14. Bruneton J. *Pharmacognosy, phytochemistry, medicinal plants*. Paris, Lavoisier Publishing, 1995.
15. Merfort I. Flavonol glycosides of Arnicae Flos DAB 9. 36th Annual Congress on Medicinal Plant Research, Hamburg, 22–27 September 1986. *Planta Medica*, 1986, Abstr. K24.
16. Merfort I, Wendisch D. *Flavonolglucuronide aus den Blüten von* Arnica montana. [Flavonoid glucuronides from the flowers of *Arnica montana*.] *Planta Medica*, 1988, 54:247–250.
17. Blumenthal M et al., eds. *The complete German Commission E monographs*. Austin, TX, American Botanical Council, 1998.
18. Hall IH et al. Mode of action of sesquiterpene lactones as anti-inflammatory agents. *Journal of Pharmaceutical Sciences*, 1980, 69:537–543.
19. Lyss G et al. Helenalin, an anti-inflammatory sesquiterpene lactone from *Arnica*, selectively inhibits transcription factor NF-κβ. *Biological Chemistry*, 1997, 378:951–961.
20. Mascolo N et al. Biological screening of Italian medicinal plants for anti-inflammatory activity. *Phytotherapy Research*, 1987, 1:28–31.
21. Hall IH et al. Anti-inflammatory activity of sesquiterpene lactones and related compounds. *Journal of Pharmaceutical Sciences*, 1979, 68:537–542.

22. Yaremy IM, Grygorieva NP, Meshchishen IF. [Effect of *Arnica montana* on the state of lipid peroxidation and protective glutathione system of rat liver in experimental toxic hepatitis.] *Ukrainskii Biokhimicheskii Zhurnal*, 1998, 70:78–82 [in Russian].
23. Yaremy IM, Grygorieva NP, Meshchishen IF. [Effect of *Arnica montana* tincture on some hydrolytic enzyme activities of rat liver in experimental toxic hepatitis.] *Ukrainskii Biokhimicheskii Zhurnal*, 1998, 70:88–91 [in Russian].
24. Lee KH et al. Cytotoxicity of sesquiterpene lactones. *Cancer Research*, 1971, 31:1649–1654.
25. Lee KH et al. Antitumor agents. 11. Synthesis and cytotoxic activity of epoxides of helenalin related derivatives. *Journal of Medicinal Chemistry*, 1975, 18:59–63.
26. Woerdenbag HJ et al. Cytotoxicity of flavonoids and sesquiterpene lactones from *Arnica* species. *Planta Medica*, 1993, 59(Suppl.):A681.
27. Beekman AC et al. Structure–cytotoxicity relationships of some helenanolide-type sesquiterpene lactones. *Journal of Natural Products*, 1997, 60:252–257.
28. Pettit GR, Cragg GM. Antineoplastic agents 32. The pseudoguaianolide helenalin. *Experientia*, 1973, 29:781.
29. Hall IH et al. Antitumor agents XXX. Evaluation of α-methylene-γ-lactone-containing agents for inhibition of tumor growth, respiration, and nucleic acid synthesis. *Journal of Pharmaceutical Sciences*, 1978, 67:1235–1239.
30. Hall IH et al. Antitumor agents XLII. Comparison of antileukemic activity of helenalin, brusatol and bruceantin, and their esters on different strains of P-388 lymphocytic leukemic cells. *Journal of Pharmaceutical Sciences*, 1981, 70:1147–1150.
31. Stimpson HS. *Arnica montana. Journal of the American Institute of Homeopathy*, 1926, 19:213–215.
32. Barz E. Action of different constituents of *Arnica montana* on the isolated frog heart. *Zeitschrift für die Gesamte experimentelle Medizin*, 1943, 111:690–700.
33. Leslie GB. A pharmacometric evaluation of nine Bio-Strath herbal remedies. *Medita*, 1978, 8:3–19.
34. Forst AW. *Zur Wirkung der* Arnica montana *aus den Kreislauf*. [The effect of *Arnica montana* on the circulation.] *Archives of Experimental Pathology and Pharmacology*, 1943, 201:243–260.
35. Narasimhan TR, Kim HL, Safe SH. Effects of sesquiterpene lactones on mitochondrial oxidative phosphorylation. *General Pharmacology*, 1989, 20:681–687.
36. Szabuniewicz M, Kim HL. Pharmacodynamic and toxic action of *Helenium microcephalum* extract and helenalin. *Southwest Veterinarian*, 1972, 25:305–311.

37. Hausen BM. The sensitizing capacity of Compositae plants. III. Test results and cross-reactions in Compositae-sensitive patients. *Dermatologica*, 1979, 159:1–11.
38. Kreitmair H. Pharmakologische Versuche mit einigen einheimischen Pflanzen. [Pharmacological trials with some domestic plants.] *E Merck's Jahresbericht über Neuerungen auf den Gebieten der Pharmakotherapie und Pharmazie*, 1936, 50:102–110.
39. Pasechnik IK. [The possibility of using preparations of *Arnica montana* and *Matricaria chamomilla* for some affections of the liver, bile ducts, and gall bladder.] In: [Information on the Fifth Scientific and Practical Conference of Ternopol' Medical Institute], 1963, 61 [in Russian].
40. Witzel DA, Ivie W, Dollahite JW. Mammalian toxicity of helenalin the toxic principle of *Helenium microcephalum* (smallhead sneezeweed). *American Journal of Veterinary Research*, 1976, 37:859–861.
41. Brunzell A, Wester S. *Arnica chamissonis* and *Arnica montana* compared. *Svensk Farmacevtisk Tidskrift*, 1947, 51:645–651.
42. Hörmann HP, Korting HC. Allergic acute contact dermatitis due to *Arnica* tincture self-medication. *Phytomedicine*, 1995, 4:315–317.
43. Hermann HD, Willuhn G, Hausen B. Helenalin methacrylate, a new pseudoguaianolide from the flowers of *Arnica montana* L. and the sensitizing capacity of their sesquiterpene lactones. *Planta Medica*, 1978, 34:229–304.
44. Paschould JM. *Kontaktekzem durch Chrysanthemen-Gekreuzte Überempfindlichkeitsreaktion mit Arnicatinktur*. [Contact eczema due to chrysanthemum-Arnica tincture cross-reactive hypersensitivity.] *Hautarzt*, 1965, 16:229–231.
45. Hausen BM, Oestmann G. *Untersuchungen über die Häufigkeit berufsbedingter allergischer Hauterkrankungen auf einem Blumengrossmarkt.* [Studies on the incidence of occupationally induced allergic skin disease in flower market vendors.] *Dermatosen*, 1988, 36:117–124.
46. Pirker C et al. Cross-reactivity with *Tagetes* in *Arnica* contact eczema. *Contact Dermatitis*, 1992, 26:217–219.
47. Machet L et al. Allergic contact dermatitis from sunflower (*Helianthus annuus*) with cross-sensitivity to Arnica. *Contact Dermatitis*, 1993, 28:184–185.
48. Schulz V, Hänsel R, Tyler VE, eds. *Rational phytotherapy. A physicians' guide to herbal medicine*. Berlin, Springer, 1998.
49. Moghadam BK, Gier R, Thurlow T. Extensive oral mucosal ulcerations caused by misuse of a commercial mouthwash. *Cutis*, 1999, 64:131–134.
50. Rudzki E, Grzywa Z. Dermatitis from *Arnica montana. Contact Dermatitis*, 1977, 3:281–282.
51. Ippen H. Grundfragen zur "Arnika-Allergie". [Rationale for "*Arnica* allergy".] *Dermatosen*, 1994, 42:250–252.
52. MacGregor JT. Mutagenic activity of hymenovin, a sesquiterpene lactone from western bitterweed. *Food and Cosmetics Toxicology*, 1977, 15:225.
53. Stuppner H, Stuppner H, Rodriguez E. A novel enol-pseudoguaianolide from *Psilostrophe cooperi. Phytochemistry*, 1988, 27:2681–2684.