Calendula

Species (Family)

Calendula officinalis L. (Compositae)

Synonym(s)

Gold-bloom, Marigold, Marybud, Pot Marigold

Part(s) Used

Flower

Pharmacopoeial and Other Monographs

BHP 1996[G9]
BP 2001[G15]
Complete German Commission E[G3]
ESCOP 1996[G52]
Martindale 32nd edition[G43]
Mills and Bone[G50]
PDR for Herbal Medicines 2nd edition[G36]
Ph Eur 2002[G28]
WHO volume 1 1999[G63]

Legal Category (Licensed Products)

GSL (external use only)[G37]

Constituents[G2,G48,G52,G53,G62,G64]

Flavonoids Pharmacopoeial standard not less than 0.4% flavonoids.[G15,G28] Flavonol (isorhamnetin, quercetin) glycosides including isoquercitrin, narcissin, neohesperidoside, and rutin.[1]

Polysaccharides Three polysaccharides PS-I, -II and -III have a (1→3)-β-D-galactan backbone with short side chains at C-6, comprising α-araban-(1→3)-araban, α-L-rhamnan-(1→3)-araban or simple α-L-rhamnan moieties.[2]

Terpenoids Many components, including α- and β-amyrin, lupeol, longispinogenin, oleanolic acid, arnidiol, brein, calenduladiol, erythrodiol, faradiol, faradiol-3-myristic acid ester, faradiol-3-palmitic acid ester,[3] helantriols A1, B0, B1 and B2, lupeol, maniladiol, urs-12-en-3,16,21-triol, ursadiol; oleanolic acid saponins including calendulosides C–H;[4] campesterol, cholesterol, sitosterol, stigmasterol and taraxasterol (sterols).[5]

Volatile oils Terpenoid components include menthone, isomenthone, caryophyllene and an epoxide and ketone derivative, pedunculatine, α- and β-ionone, a β-ionone epoxide derivative, dihydroactinidiolide.[6]

Other constituents Bitter (loliolide),[7] arvoside A (sesquiterpene glycoside),[8] carotenoid pigments[9] and calendulin (gum).[9]

Food Use

Calendula is not used in foods. In the USA, calendula is listed as GRAS (Generally Recognised As Safe).[G65]

Herbal Use[G2,G4,G7,G32,G43,G52,G54,G56,G64]

Calendula is stated to possess antispasmodic, mild diaphoretic, anti-inflammatory, anti-haemorrhagic, emmenagogue, vulnerary, styptic and antiseptic properties. Traditionally, it has been used to treat gastric and duodenal ulcers, amenorrhoea, dysmenorrhoea and epistaxis; crural ulcers, varicose veins, haemorrhoids, anal eczema, proctitis, lymphadenoma, inflamed cutaneous lesions (topically) and conjunctivitis (as an eye lotion). The German Commission E approved internal and external use for inflammation of oral and pharyngeal mucosa and external use in treatment of poorly healing sores.[G3]

Dosage

Dried florets 1–4 g or by infusion three times daily.[G7]

Liquid extract 0.5–1.0 mL (1 : 1 in 40% alcohol) three times daily.[G7]

Calendula Tincture (BPC 1934) 0.3–1.2 mL (1 : 5 in 90% alcohol) three times daily.[G7]

External use Tincture–liquid extract (1 : 1) in 40% alcohol or tincture 1 : 5 in 90% alcohol. Apply to wounds as such and dilute 1 : 3 with water for compresses. Ointment 2.5%.[G52]

Pharmacological Actions

In vitro and animal studies

Anti-inflammatory, antibacterial and antiviral activities have been reported for calendula.[10] Weak anti-inflammatory activity in rats (carrageenan-induced oedema) has been reported.[11,12] An aqueous ethanolic extract had mild dose-dependent action in the mouse croton oil test with 20% inhibition being reached at a dose of 1200 µg/ear, whereas a carbon dioxide extract exhibited 70% inhibition at the same concentration.[5,13] The activity was shown to be due to the triterpenoids, the most active being a monoester of faradiol. Further separation of the triterpenoids has shown that the three most active compounds in the croton oil mouse test are faradiol-3-myristic acid ester, faradiol-3-palmitic acid ester and 4-taraxosterol.[3]

A polysaccharide enriched extract showed strong concentration-dependent adhesive properties on porcine buccal membranes *ex vivo*.[14] Fluorescent labelled rhamnogalacturan indicated the presence of polysaccharide layers on buccal membranes, leading to the suggestion that irritated buccal membranes may be smoothed by mucilage.

The formation of new blood vessels is an essential part of the wound-healing process. Angiogenic activity has been shown for a freeze-dried aqueous extract of calendula utilising the chick chorioallantoic membrane (CAM) assay.[15] The number of microvessels in calendula-treated CAMs was significantly higher than in the control ($p < 0.0001$). Furthermore, calendula-treated CAMs were positive for the glycosaminoglycan hyaluronan (HA) associated with neovascularisation. The presence of HA was not demonstrated in control CAMs.

A combination of allantoin and calendula extract applied to surgically induced skin wounds in rats has been reported to stimulate physiological regeneration and epithelisation.[16] This effect was attributed to a more intensive metabolism of glycoproteins, nucleoproteins and collagen proteins during the regenerative period in the tissues.[16] Allantoin applied on its own was found to exert a much weaker action.[16]

A proprietary cream containing a combination of plant extracts, including calendula, has been reported to be effective in dextran and burn oedemas and in acute lymphoedema in rats. Activity against lymphoedema was primarily attributed to an enhancement of macrophage proteolytic activity.[17] Slight increases in foot oedema were attributed to a vasodilatory action.

The trichomonacidal activity of calendula has been associated with the essential oil terpenoid fraction.[6]

An *in vitro* uterotonic effect has been described for calendula extract on rabbit and guinea-pig preparations.[18]

Immunostimulant activity, assayed using granulocyte and carbon clearance tests, of calendula extracts has been attributed to polysaccharide fractions of high molecular weight.[19] Polysaccharides PS-I, -II and -III have immunostimulant activity at concentrations of 10^{-5} to 10^{-6} mg/mL, stimulating phagocytosis of human granulocytes *in vitro*.[2] A dry 70% ethanolic extract was not directly mitogenic, and was inhibitory in the mitogen-induced lymphocyte assay, causing stimulation at concentrations of 0.1–10 µg/mL, and inhibition at higher concentrations.[20]

A 70% methanolic extract of calendula was successively extracted with ether, chloroform, ethyl acetate and *n*-butanol, leaving a residual aqueous extract. Each of the five extracts were concentrated and dissolved in 50% ethanol to produce 6% (w/v) solutions which were assessed for activity on liposomal lipid peroxidation induced by Fe^{2+} and ascorbic acid. The ether, butanol and water extracts showed antioxidant activity.[21]

The triterpenoid constituents of calendula are reported to be effective as spermicides and as antiblastocyst and abortion agents.[G53]

In vitro cytotoxic activity and *in vivo* antitumour activity (against mouse Ehrlich carcinoma) have been documented for calendula extracts.[7] The most active fraction *in vivo* (saponin-rich) was not the most active *in vitro*.[10]

A 70% aqueous ethanolic extract had marked antiviral activity against influenza virus and herpes simplex virus.[G52] A dichloromethane–methanol (1:1) extract exhibited potent anti-HIV activity in an *in vitro* MTT/tetrazolium-based assay.[22] Uninfected Molt-4 cells were completely protected for up to 24 hours from fusion and subsequent death caused by co-cultivation with persistently infected U-937/HIV-1 cells. The organic extract caused a significant concentration- and time-dependent reduction of HIV-1 reverse transcriptase.[22]

In a study in mice fed for three weeks with a diet containing either 0.1% or 0.4% of a calendula extract (containing 37% of esters of the carotenoid lutein), mammary tumour cells were infused into the mammary glands. Tumour latency increased, and tumour growth was inhibited in a dose-dependent manner by dietary lutein. In addition, dietary lutein was reported to enhance lymphocyte proliferation.[23]

Clinical studies

A proprietary cream preparation containing several plant extracts, including calendula, has been reported

to reduce pain associated with postmastectomy lymphoedema, although there was no significant clinical difference in the reduction of oedema between controls and experimental groups.[17] Calendula tincture 20% has been reported to be useful in the treatment of chronic suppurative otitis.[24] Calendula extracts are used to accelerate healing and to reduce inflammation.[9] Thirty patients with burns or scalds were treated three times daily with a hydrogel containing 10% aqueous ethanolic extract of calendula for 14 days in an open, uncontrolled, pilot study.[25] Improvement was noted for reddening, swelling, blistering, pain, soreness and heat sensitivity.

Side-effects, Toxicity

An aqueous extract of calendula had an LD_{50} of 375 mg/kg (intravenous administration) and an LD_{100} of 580 mg/kg (intraperitoneal administration) in mice.[G52] Aqueous ethanolic extracts (drug/extract ratio 1 : 1 and 0.5 : 1, 30% ethanol) had LD_{50} values of 45 mg/mouse (subcutaneous administration) and 526 mg/100 g in rat (intravenous administration). An aqueous extract was not toxic following chronic administration to mice. Six saponins at doses of 400 µg were non-mutagenic in the Ames test using *Salmonella typhimurium* TA98 with and without S9 activation mixture.[G52] *In vitro* cytotoxicity has been reported for calendula extracts.[10] Extracts have been reported to be non-carcinogenic in rats and hamsters.[G52]

Contra-indications, Warnings

Calendula may cause an allergic reaction in sensitive individuals, especially those with an existing hypersensitivity to other members of the Asteraceae/Compositae.

Pregnancy and lactation Calendula is traditionally reputed to affect the menstrual cycle. An uterotonic effect (*in vitro*) has been reported, and the triterpenoid constituents are reported to be effective as spermatocides and as antiblastocyst and abortion agents. In view of the lack of toxicity data, the use of calendula is best avoided during pregnancy and lactation.

Pharmaceutical Comment

Phytochemical studies have reported four main groups of constituents, for calendula, namely flavonoids, polysaccharides, volatile oil and triterpenes. The latter seems to represent the principal group, with many compounds isolated including pentacyclic alcohols, glycosides (saponins) and sterols. Animal studies have reported wound-healing and anti-inflammatory effects, supporting the traditional uses of calendula in various dermatological conditions. The anti-inflammatory effect is due to the triterpenoid constituents although flavonoids may contribute to the activity. The reputed antispasmodic effect may be attributable to the volatile oil fraction. In addition, immunostimulant activity has been reported for high molecular weight polysaccharide components. Despite the popularity of calendula in herbal preparations there is little substantial clinical evidence to support its use.

References

See also General References G2, G3, G5, G9, G10, G15, G28, G31, G32, G36, G37, G43, G48, G52, G53, G54, G56, G62 and G64.

1 Vidal-Ollivier E *et al.* Flavonol glycosides from *Calendula officinalis* flowers. *Planta Med* 1989; 55: 73.
2 Varljen J *et al.* Structural analysis of a rhamnoarabinogalactan and arabinogalactans with immunostimulating activity from *Calendula officinalis*. *Phytochemistry* 1989; 28: 2379–2383.
3 Zitterl-Eglseer K *et al.* Anti-oedematous activities of the main triterpendiol esters of marigold (*Calendula officinalis* L.). *J Ethnopharmacol* 1997; 57: 139–144.
4 Pizza C *et al.* Plant metabolites. Triterpenoid saponins from *Calendula arvensis*. *J Nat Prod* 1987; 50: 927–931.
5 Della Loggia R *et al.* The role of triterpenoids in the topical anti-inflammatory activity of *Calendula officinalis* flowers. *Planta Med* 1994; 60: 516–520.
6 Gracza L. Oxygen-containing terpene derivatives from *Calendula officinalis*. *Planta Med* 1987; 53: 227.
7 Willuhn G, Westhaus R-G. Loliolide (Calendin) from *Calendula officinalis*. *Planta Med* 1987; 53: 304.
8 Pizza C, de Tommasi N. Plants metabolites. A new sesquiterpene glycoside from *Calendula arvensis*. *J Nat Prod* 1987; 50: 784–789.
9 Fleischner AM. Plant extracts: To accelerate healing and reduce inflammation. *Cosmet Toilet* 1985; 100: 45.
10 Boucard-Maitre Y *et al.* Cytotoxic and antitumoral activity of *Calendula officinalis* extracts. *Pharmazie* 1988; 43: 220.
11 Peyroux J *et al.* Propriétés anti-oedémateuses et anti-hyperhémiantes du *Calendula officinalis* L. *Plant Méd Phytothér* 1981; 15: 210–216.
12 Mascolo N *et al.* Biological screening of Italian

medicinal plants for anti-inflammatory activity. *Phytother Res* 1987; 1: 28–31.
13 Della Loggia R *et al.* Topical anti-inflammatory activity of *Calendula officinalis* extracts. *Planta Med* 1990; 56: 658.
14 Schmidgall J *et al.* Evidence for bioadhesive effects of polysaccharides and polysaccharide-containing herbs in a *ex vivo* bioadhesion assay on buccal membranes. *Planta Med* 2000; 66: 48–53.
15 Patrick KFM *et al.* Induction of vascularisation by an aqueous extract of the flowers of *Calendula officinalis* L. the European marigold. *Phytomedicine* 1996; 3: 11–18.
16 Kioucek-Popova E *et al.* Influence of the physiological regeneration and epithelization using fractions isolated from *Calendula officinalis. Acta Physiol Pharmacol Bulg* 1982; 8: 63–67.
17 Casley-Smith JR, Casley-Smith JR. The effect of 'Unguentum lymphaticum' on acute experimental lymphedema and other high-protein edemas. *Lymphology* 1983; 16: 150–156.
18 Shipochliev T. Extracts from a group of medicinal plants enhancing the uterine tonus. *Vet Med Nauki* 1981; 4: 94–98.
19 Wagner H *et al.* Immunostimulating polysaccharides (heteroglycans) of higher plants. *Arzneimittelforschung* 1985; 35: 1069.
20 Amirghofran Z *et al.* Evaluation of the immunomodulatory effects of five herbal plants. *J Ethnopharmacol* 2000; 72: 167–712.
21 Popović M *et al.* Combined effects of plant extracts and xenobiotics on liposomal lipid peroxidation. Part 1. Marigold extract-ciprofloxacin/pyralene. *Oxidation Commun* 1999; 22: 487–494.
22 Kalvatchev Z *et al.* Anti-HIV activity of extracts from *Calendula officinalis* flowers. *Biomed Pharmacother* 1997; 51: 176–180.
23 Chew BP *et al.* Effects of lutein from marigold extract on immunity and growth of mammary tumors in mice. *Anticancer Res* 1996; 16: 3689–3694.
24 Shaparenko BA. On use of medicinal plants for treatment of patients with chronic suppurative otitis. *Zh Ushn Gorl Bolezn* 1979; 39: 48–51.
25 Baranov von AP. Calendula – wie ist die wirksamkeit bei verbrennungen und verbrühungen?. *Dtsch Apotheker Zeitung* 1999; 139: 2135–2138.