A review on phytochemistry and ethnopharmacological aspects of genus *Calendula*

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ABSTRACT

This review includes 84 references on the genus *Calendula* (*Asteraceae*) and comprises ethnopharmacology, morphology and microscopy, phytoconstituents, pharmacological reports, clinical studies and toxicology of the prominent species of *Calendula*. Triterpene alcohols, triterpene saponins, flavonoids, carotenoids and polysaccharides constitute major classes of phytoconstituents of the genus. A few species of this genus have medicinal value, among these *Calendula officinalis* Linn., has been traditionally used in the treatment of various skin tumors, dermatological lesions, ulcers, swellings and nervous disorders as well as almost 200 cosmetic formulations, i.e., creams, lotions, shampoos. Despite a long tradition of use of some species, the genus has not been explored properly. In the concluding part, the future scope of *Calendula* species has been emphasized with a view to establish their multifarious biological activities and mode of action.

Key words: *Calendula*, carotenoids, flavonoids, triterpene alcohols

INTRODUCTION

This review emphasizes the traditional uses and clinical potential of *Calendula* species. The review is intended to attract the attention of natural product researchers throughout the world to focus on the unexplored potential of the *Calendula* species. This genus needs to be investigated systematically so that potential species can be exploited as therapeutic agents.

The review has been compiled using references from major databases such as Chemical Abstracts, Medicinal and Aromatic Plant Abstracts, PubMed, King's American Dispensatory, Henriette's Herbal Homepage, Duke's Phytochemical and Ethnobotany. The available information on *Calendula* has been divided into six sections, i.e., ethnopharmacology, morphology and microscopy, phytoconstituents, pharmacological reports, clinical studies and toxicology.

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THE GENUS CALENDULA

The genus *Calendula* (*Asteraceae*) includes approximately 25 *herbaceous* annual or perennial species, most common being *Calendula officinalis* Linn., *Calendula arvensis* Linn., *Calendula suffruticosa* Vahl., *Calendula stellata* Cav., *Calendula alata* Rech., *Calendula tripterocarpa* Rupr.[1] The genus is native to the Mediterranean countries.[2]

Ethnopharmacology

Traditional uses

C. alata Rech.f., aerial parts are used for the treatment of kidney stones and gall stones.[3]

C. arvensis Linn. (Field marigold) has been used as disinfectant, antispasmodic and diuretic.[4] In Italian folk medicine, the plant is used as anti-inflammatory, anticancer and antipyretic agent.[5] In Spain, the leaves are considered sudorific. Traditionally, it is used as an emmenagogue, diaphoretic and sedative.[6] It is known to have wound healing properties and crushed leaves are topically applied on wounds.[7] The decoction of the flower heads has been used for treating burns.[8]

C. officinalis Linn. (Pot marigold) has been traditionally

used in the treatment of inflammations of internal organs, gastrointestinal ulcers and dysmenorrhea and as a diuretic and diaphoretic in convulsions. It is also used for inflammations of the oral and pharyngeal mucosa, wounds and burns.[9] *Calendula* is a cleansing and detoxifying herb and the infusion treat chronic infections.[10] The dried flower heads have been used for their antipyretic, anti-tumor and cicatrizing effects.[11] Topical application of infusion of flowers is used as antifungal and antiseptic in wounds, marks, freckles, sprain and conjunctivitis.[12] *Calendula* tea is used as eyewashes, gargles, diaper rashes and other inflammatory conditions of the skin and mucous membranes.[13] Mother tincture of *C. officinalis* is used in homoeopathy for the treatment of mental tension and insomnia.[14]

Medicinal properties of *C. officinalis* have been mentioned in Ayurvedic and Unani system of medicine indicating that leaves and flowers are antipyretic, anti-inflammatory, antiepileptic and antimicrobial.[15] In traditional and homoeopathic medicine, *C. officinalis* has been used for poor eyesight, menstrual irregularities, varicose veins, hemorrhoids and duodenal ulcers.[16] In the middle ages, *Calendula* flowers were used for liver obstructions, snake bites and to strengthen the heart. It was used in the 18th century as a remedy for headache, jaundice and red eyes. The plant was employed in the civil war to treat wounds and as a remedy for measles, smallpox and jaundice.[17]

Decoction and infusion of *Calendula persica* C.A. Mey aerial parts are employed for the treatment of kidney stones.[3]

Alternative and *complementary* medicinal uses

Among the various species of the genus *Calendula*, *C. officinalis* is the only one, which is extensively used clinically throughout the world. The plant is listed in German Commission E, European Scientific Co-operative on Phytotherapy, British Herbal Pharmacopoeia, World Health Organization monographs for wound healing and anti-inflammatory actions.[18] *C. officinalis* preparations are used in various complementary and alternative medicine systems mainly for burns, cuts, rashes, dermatitis and varicosis.[19] It is also included as part of treatment for dry skin, bee stings and foot ulcers.[20] The essential oil of the plant is used for soothing central nervous system and as a wound healer.[21]

C. officinalis preparations currently in use include carophyllenic ointment (containing carotenoids extracted from the flowers) and pot marigold tincture. It is one of the constituents of proprietary homoeopathic medicine Traumeel®, used for treating the symptoms associated with acute musculoskeletal injuries including pain and swelling.[22] Otikon otic solution and naturopathic herbal extract ear drops solution, ear drop formulations of naturopathic origin containing *Calendula* flowers, have been reported to be effective for the management of otalgia associated with acute otitis media in children.[23,24]

Figure 1: *Calendula officinalis* L

Morphology and microscopy

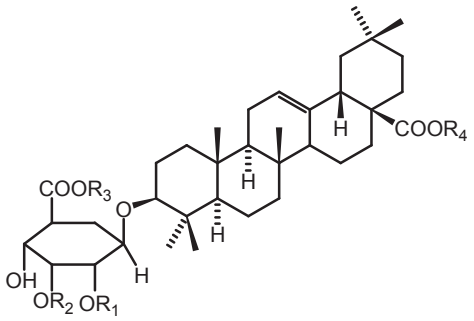
C. arvensis Linn. is an annual herb, not generally exceeding 15 cm in height. Leaves lance-shaped; stem slender, hairy; inflorescence single flower head up to 4 cm wide with bright yellow to yellow-orange ray florets around a center of yellow disc florets.[25,26]

C. officinalis Linn. [Figure 1] is an annual or biennial plant attaining height of 30-60 cm. Leaves lower spatulate, 10-20 cm long and 1-4 cm wide; higher oblong and mucronate, 4-7 cm long; stem angular, hairy and solid; flower heads bright yellow to orange; marginal flowers in cultivated plants multi-seriate, corolla oblong spatulate, 15-25 mm long and 3 mm wide; corolla of disc flowers rounded, at the top tridentate, 1.5-2.5 cm long and 4-7 mm in diameter with 5 mm long tubular florets.[27,28]

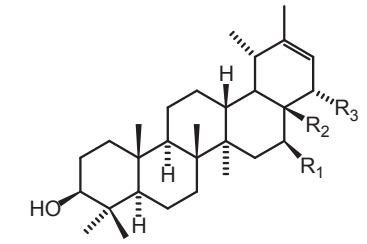
The powdered *C. officinalis* is yellowish brown with a characteristic, aromatic odor and a slightly bitter taste; comprises fragments of the corolla, anomocytic stomata in the apical region of outer epidermis, covering and glandular trichomes, elongated sclerenchymatous cells, pollen grains, fragments of the walls of the ovaries containing brown pigment, fragments of stigma, fragments of the fibrous layer of the others.[29,30]

C. stellata Cav., is a small, attractive annual growing to a height of 30 cm or more. Leaves oval or oblong, somewhat pointed, wavy-toothed;[31] stems scabrous; achenes outer five with membranous toothed margins, the five inner ones "boat-shaped" and smooth on the back, the rest angular and muricated on the back.[32]

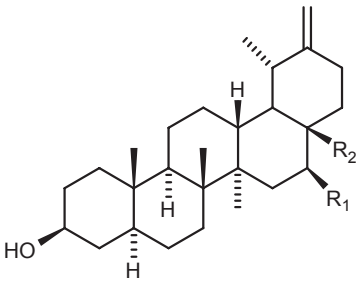
C. suffruticosa Vahl., is a perennial plant reaching a height between 20 cm and 40 cm. Leaves lance-shaped, slightly toothed, covered with short sticky hairs; stem young one first erected, later begin to hang and spread to the soil; flowers bright yellow, each measuring about 2.5 cm in diameter.[31,33]



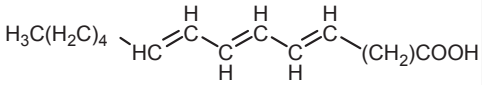
	R_1	R_2	R_3	R_4
Calendulaglycoside A	Glc	Gal	H	Glc
Calendulaglycoside A 6′-*O*-methylester	Glc	Gal	CH_3	Glc
Calendulaglycoside A 6′-*O*-n-butylester	Glc	Gal	n-Bu	Glc
Calendulaglycoside B	Glc	Gal	H	H
Calendulaglycoside B 6′-*O*-n-butylester	Glc	Gal	n-Bu	H
Calendulaglycoside C	H	Gal	H	Glc
Calendulaglycoside C 6′-*O*-methylester	H	Gal	CH_3	Glc
Calendulaglycoside C 6′-*O*-n-butylester	H	Gal	n-Bu	Glc
Calendulaglycoside D	H	Gal	H	H
Calendulaglycoside D 2	H	H	H	Glc
Calendulaglycoside F	H	H	H	H
Calendulaglycoside F 6′-*O*-n-butylester	H	H	n-Bu	H
Calendulaglycoside G 6′-*O*-methylester	H	Gal	CH_3	H



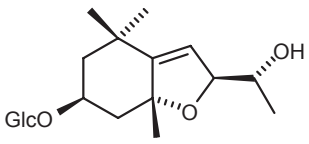
	R_1	R_2	R_3
Ψ-Taraxasterol	H	CH_3	H
Faradiol	OH	CH_3	H
Heliantriol B_0	OH	CH_2OH	H
Heliantriol C	OH	CH_3OH	OH



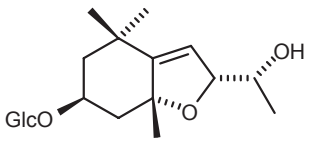
	R_1	R_2
Taraxasterol	H	CH_3
Arnidiol	OH	CH_3
Heliantriol B_1	OH	CH_2



Calendic acid

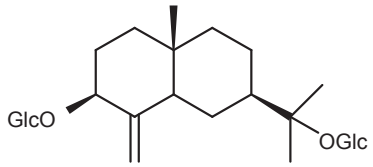


Officinoside A

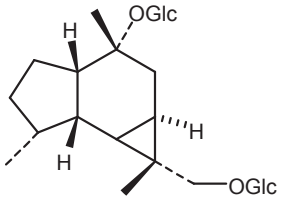


Officinoside B

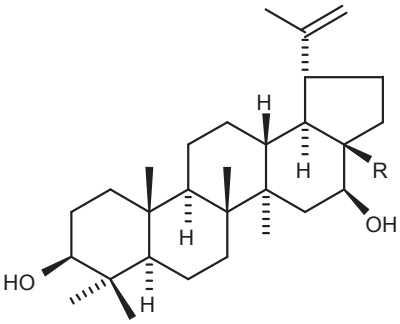
Figure 2: Chemical structures of some phytoconstituents reported from the genus *Calendula*



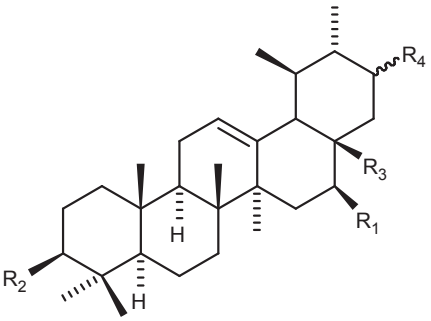
Officinoside C



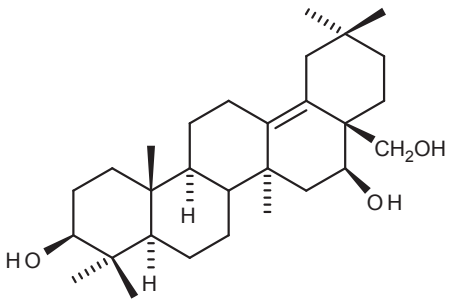
Officinoside D



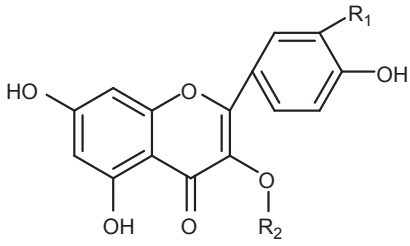
	R
Lupeol	H
Calenduladiol	CH_3
HeliantriolB2	CH_2OH



	R_1	R_2	R_3	R_4
α-Amyrin	H	OH	CH	H
Brein	H	OH	CH	H
Ursadiol	H	OH	CH	OH
Ursatriol	OH	OH	CH_2OH	H

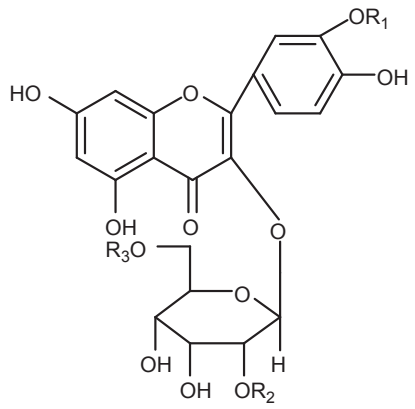


Heliantriol A_1

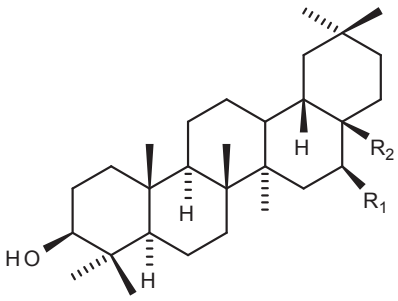


	R_1	R_2
Quercetin	OH	H
Isorhamnetin	OCH_3	H
Kaempferol	H	H
Rutin	OH	Rha-(1→ 6)-Glc
Hyperoside	OH	Gal
Isoquercitrin	HO	Glc
Astragalin	H	Glc

Figure 2: Contd...



	R_1	R_2	R_3
Quercetin 3-*O*-glucoside	H	H	H
Quercetin 3-*O*-rutinoside	H	H	Rha
Quercetin 3-*O*-neohesperidose	H	Rha	H
Quercetin 3-*O*-2^G-rhamnosylrutinoside	H	Rha	Rha
Isorhamnetin 3-*O*-glucoside	CH_3	H	H
Isorhamnetin 3-*O*-rutinoside	CH_3	H	Rha
Isorhamnetin 3-*O*-neohesperidoside	CH_3	Rha	H
Isorhamnetin 3-*O*-2^G-rhamnosylrutinoside	CH_3	Rha	Rha



	R_1	R_2
β-amyrin	H	CH_3
Maniladiol	OH	CH_3
Erythrodiol	H	CH_2OH
Longispinogenin	OH	CH_2OH

Figure 2: Contd...

Table 1: Phytoconstituents of different species of *Calendula*

Species	Phytoconstituents
C. officinalis	Triterpene glycosides: Calendulaglycoside A, calendulaglycoside A 6'-*O*-methyl ester, calendulaglycoside A 6'-*O*-n-butyl ester, calendulaglycoside B, calendulaglycoside B 6'-*O*-n-butyl ester, calendulaglycoside C, calendula glycoside C 6'-*O*-methyl ester, calendulaglycoside C 6'-*O*-n-butyl ester, calendulaglycoside D, calendulaglycoside D_2, calendulaglycoside F, calendulaglycoside F 6'-*O*-butyl ester, calendulaglycoside G 6'-*O*-methyl ester, calendasaponins A-D;[9,11] triterpene alcohols: Free and esterified (with fatty acids) monols, diols and triols of *ψ*-taraxastane-type including *ψ*-taraxasterol, faradiol, heliantriol B_0, heliantriol C, taraxastane-type including taraxasterol, arnidiol, heliantriol B_1, lupine-type including lupeol, calenduladiol, heliantriol B_2, ursane-type including *α*-amyrin, brein, ursadiol, ursatriol, oleanane-type including *β*-amyrin, maniladiol, erythrodiol, longispinogenin, heliantriol A_1;[34,35] flavonoids: Quercetin, isorhamnetin, kaempferol, rutin, hyperoside, isoquercitrin, astragalin, quercetin 3-*O*-glucoside, quercetin 3-*O*-rutinoside, quercetin 3-*O*-neohesperidose, quercetin 3-*O*-2^G-rhamno-sylrutinoside, isorhamnetin 3-*O*-glucoside, isorhamnetin 3-*O*-rutinoside, isorhamnetin 3-*O*-neohesperidoside, iso-rhamnetin 3-*O*-2^G-rhamnosylrutinoside;[11] ionone glucosides: Officinosides A and B; sesquiterpene glycosides: Officinosides C and D;[36] carotenoids: Lutein, zeaxanthine, flavoxanthin, auroxanthin, β-carotene, luteoxanthin, violaxanthin, *β*-cryptoxanthin, mutaxanthin;[37] hydroxycoumarins: Scopoletin, umbelliferone, esculetin; phenolic acids: Chlorogenic acid, caffeic acid, coumaric acid, vanillic acid;[38] volatile oils: α-cadinol, T-cadinol;[39] *α*-cadinene, limonene, 1,8-cineol;[40] quinones: *α*-tocopherol, phylloquinone;[41] fatty acids: Calendic acid, dimorphecolic acid;[42] others: Sterols, mucilage, carbohydrates, resin, tannins, amino acids, bitter principle calendin[43]
C. arvensis	Triterpenoid saponins: Arvensoside A and B,[44] arvensoside C,[45] calenduloside C and D,[46] calendulaoside G and H;[43] sesquiterpene glycosides: Arvoside A and B;[47,48] flavonoids: Isoquercitroside, rutoside, narcissoside;[49] volatile oils: *δ* cadinene, *α*-cadinol;[26] fatty acids: Calendic acid,[50] dimorphecolic acid; others: Amino acids,[51] alkaloids,[43] lutein,[52] phenolic acids, tannins, malic acid, salicylic acid, mucilages[53]
C. persica	Fatty acids: Palmitic acid, linoleic acid[54]
C. stellata	Fatty acid: Calendic acid;[55] volatile oils: Linalool, linalyl acetate, limonene[2]

Phytoconstituents

Four species of *Calendula* have been investigated phytochemically. Table 1 summarizes the phytoconstituents of different species of *Calendula*. Figure 2 represents chemical structures of some phytoconstituents reported from the genus *Calendula*.

Pharmacological reports

The available literature reveals that amongst 12-20 species of *Calendula*, only three species, i.e., *C. officinalis, C. arvensis* and *C. suffruticosa* have been evaluated for their pharmacological activities.

Tincture of *C. arvensis* was active against *Staphylococcus aureus* at concentrations of 10 mg/ml or 25 mg/ml.[56] Sesquiterpene glycosides from *C. arvensis* were able to inhibit vesicular stomatitis virus infection.[57] A saponin containing fraction from the aerial parts of *C. arvensis* had hemolytic activity *in vitro* and anti-inflammatory activity against carrageenan induced paw edema in rats.[58] Saponins showed antimutagenic activity against benzo (a) pyrene 1 μg and mutagenic urine concentrate from a smoker (SU) 5 μL with a dose-response relationship.[59]

Preparations of *C. officinalis* are mainly applied in the form of infusions, tinctures and ointments as a wound healing remedy for inflammations of the skin, mucous membranes, for poorly healing wounds, bruises, boils and rashes, e.g., pharyngitis and leg ulcers.[27] In the mixed lymphocyte reaction, 70% ethanol extract showed stimulatory effects at 0.1-10 μg/ml, followed by inhibition at higher concentrations.[60] Phagocytosis of human granulocytes was stimulated by polysaccharides isolated from aqueous extract of *Calendula* flowers.[61] Extracts of *Calendula* flowers of differing polarities exhibited anti-oxidative effects on liposomal lipid peroxidation induced by Fe^{2} + and ascorbic acid.[62,63] Isorhamnetin 3-glycosides from *Calendula* flowers inhibited lipoxygenase from rat lung cytosol at a concentration of 1.5×10^{-5} M.[64] In a test system based on porcine buccal membranes, strong concentration dependent adhesive processes were observed with a low viscosity polysaccharide enriched extract (98% carbohydrates) of *Calendula* flowers. These findings suggested that the polysaccharides may contribute to therapeutic effects in the treatment of irritated mucosa.[65] A triterpene enriched fraction given orally to mice inoculated with Ehrlich mouse carcinoma prevented the development of ascites and increased survival time compared to control.[66] Triterpenes such as faradiol and taraxasterol inhibit experimental tumor promotion and are therefore considered as inhibitors of tumor growth.[67] A saponin rich fraction administered orally at 50 mg/kg body weight to hyperlipemic rats reduced the serum lipid level.[68,69] The aqueous alcohol extract of *C. officinalis* showed central nervous system inhibitory effect with marked overall sedative activity as well as hypotensive effect.[70] The alcohol extract of flowers of *C. officinalis* possesses anti-HIV properties.[71] A cream containing *calendula* extract has been reported to be effective in dextran and burn edemas as well as in acute lymphedema in rats. Activity against lymphedema was primarily attributed to enhancement of macrophage proteolytic activity.[72] The essential oil of the flowers inhibited the growth *in vitro* of *Bacillus subtilis*, *Escherichia coli*, *S. aureus*, *Pseudomonas aeruginosa* and *Candida albicans*.[73] Acetone, ethanol or water extracts inhibited the growth *in vitro* of the fungus *Neurospora* crass.[74] A flavonoid fraction isolated from the flowers inhibited the *in vitro* growth of *S. aureus*, *Sarcina lutea*, *E. coli*, *Klebsiella pneumonia* and *Candida monosa*.[75] The 50% ethanol extract of the plant showed spermicidal activity in rats at 2% concentration.[76]

C. suffruticosa inhibited pathogenic micro-organisms, especially *Pseudomonas syringae, Pseudomonas fluorescens, Xanthomonas campestris, Agrobacterium tumefaciens*.[77]

Clinical studies

In a randomized, open controlled study, the effects of three ointments were compared after topical treatment of patients with 2nd or 3rd degree burns for 17 days: *Calendula* flower ointment (prepared by digestion in vaseline) (n = 53) or vaseline only (n = 50) or a proteolytic ointment (n = 53). The success rates were considered to be 37/53 for *Calendula* flower ointment, 27/50 for vaseline and 35/53 for the proteolytic ointment.[78] In an open uncontrolled pilot study, 30 patients with burns or scalds were treated 3 times/day for up to 14 days with a hydrogel containing 10% of a hydro-ethanol extract. The symptoms reddening, swelling, blistering, pain, soreness and heat sensitivity were scored before, during and at the end of treatment. Total score and individual scores for each symptom improved.[79] In women with surgical wounds, local application of a mixture containing 70% oily extract of *Hypericum perforatum* and 30% oily extract of *C. arvensis* improved the rate of healing, compared with controls.[53] Phase III randomized single blinded trial of *C. officinalis* compared with trolamine for the prevention of acute dermatitis during irradiation for breast cancer was conducted. Patients who had been operated on for breast cancer and who were to receive post-operative radiation therapy were randomly allocated to application of either *Calendula* ointment containing 20% of fresh *Calendula* aerial parts in petroleum jelly (126 patients) or trolamine (128 patients) on the irradiated fields after each session. The primary end point was the occurrence of acute dermatitis of grade 2 or higher. Secondary end points were the occurrence of pain, the quantity of the topical agent used and the patient satisfaction. The occurrence of acute dermatitis of grade 2 or higher was significantly lower (41% vs. 63%; $P < 0.001$) with the use of *Calendula* than with trolamine. Moreover, patients receiving *Calendula* had less frequent interruption of radiotherapy and significantly reduced radiation-induced pain.[80] Clinical examination of an ointment with *C. officinalis* extract was carried out in 34 patients with venous leg ulcer. A total of 21 patients with

33 venous ulcers were treated with ointment, applied twice a day for 3 weeks. Control group that consisted of 13 patients with 22 venous ulcers were treated with saline solution dressings, applied to ulcers for 3 weeks. In the experimental group, the total surface of all the ulcers at the beginning of the therapy was 67,544 mm^2. After the 3rd week, the total surface of all the ulcers was 39,373 mm^2 (a decrease of 41.71%). In seven patients, complete epithelialization was achieved. In the control group, the total surface of all ulcers at the beginning of the therapy was 69,722 mm^2. After the 3rd week, the total surface of all ulcers was 58,743 mm^2 (a decrease of 14.52%). In four patients, complete epithelialization was achieved. There was a statistically significant acceleration of wound healing in the experimental group ($P < 0.05$), suggesting the positive effects of the ointment with marigold extract on venous ulcer epithelialization.[81]

Toxicology

Although rare, skin contact with *Calendula* preparations may result in an allergic reaction to the herb. Sensitization to *Calendula* and allergic contact reactions have been reported.[82,83] There have also been incidents of anaphylactic shock after gargling with an infusion of *Calendula*.[84]

CONCLUSION

About 12-20 species of the genus *Calendula* have been reported in various floras. Among these, most of the ethnopharmacological reports are available on *C. officinalis* and *C. arvensis*. Further, only four species of *Calendula* have been partially investigated for their phytoconstituents. A close scrutiny of literature on *Calendula* reveals that three species have been investigated pharmacologically. Pharmacological studies reveal that *C. officinalis* exhibits antibacterial, antiviral, anti-inflammatory, anti-tumor and antioxidant properties; *C. arvensis* possesses antibacterial, anti-inflammatory, antimutagenic and hemolytic activities; and *C. suffruticosa* exhibits antimicrobial activity. *C. officinalis* has been included in number of herbal formulations, which are in clinical use for the treatment of various ailments like central nervous system disorders. Keeping in view the ethnopharmacology, phytochemical and pharmacological reports, low toxicity and frequency of use, *C. officinalis* seems to hold great potential for in depth investigation for various biological activities. Few preliminary pharmacological reports support medicinal potential of some *Calendula* species. These species need to be investigated systematically with a view to establish their varied pharmacological activities and mode of actions.

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