

Phytochemical Composition and Biological Activities of *Calendula officinalis* L. – A Review

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ABSTRACT

Calendula officinalis L. (Marigold) is globally known for its medicinal importance containing various phytochemicals including carbohydrates, amino acids, lipids, fatty acids, carotenoids, terpenoids, flavonoids, quinones, coumarins and other constituents, showing some important biological activities like wound healing, immunostimulant, spasmogenic and spasmolytic, hepatoprotective, genotoxic and antigenotoxic, anti-amylase, anti-inflammatory, anti-oedematous, anti-bacterial and anti-fungal, antioxidant, antidiabetic, anti-HIV and anti-cancerous, nephron-protective, prevention of oropharyngeal mucositis, hypoglycemic and gastroprotective activities with no toxic effect. In this review, a detailed account of different phytochemicals and the medicinal properties of *C. officinalis* have been addressed.

Keywords: *Calendula officinalis*, Asteraceae, Marigold, Phytochemicals

INTRODUCTION

Calendula officinalis

Calendula word derives from the Latin “*calendas*”, meaning “**first of the month**” because it refers to the plant blooms every month and long flowering period [1]. *Calendula officinalis* L. (Pot marigold) is a perennial plant in the tribe *Calendula* belongs to the Asteraceae family [2,3]. It is mostly seen in the Mediterranean Sea region, China, North Africa, Western Asia, America [4], US, India, Egypt and Southern Europe [5,6]. It is believed to be the result of natural hybridization among other types of marigolds, probably from *Calendula arvensis*. It is a self-seeding plant that grows in any kind of soil. It grows between 30-70 cm long with multiple branching stem, a long tap root and secondary roots, alternate leaves and inflorescent flowers [7-9].

The plant is used to make medicine for treatment of various diseases. Its flower is used to reduce fever, treating muscle spasms, menstrual cramps, cancer, sore throat and mouth, and stomach, duodenal and leg ulcers [10]. It is applied to the skin to reduce swelling (inflammation), pain and to treat healing wounds [11]. It is also used topically to the skin for nosebleeds, hemorrhoids, inflammation of the lining of the eyelid (conjunctivitis) and the rectum (proctitis) [12]. The major active constituents of calendula flowers include triterpenoid

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esters, saponins, alkaloids, flavonoids and carotenoids [13,14]. The taxonomic classification of calendula plant is shown in Table 1 as follows.

Taxonomic Classification

Table 1: Taxonomic Classification of Calendula Plant [15]

Kingdom	Plantae
Subkingdom	Tracheobionta
Division	Magnoliophyta
Class	Magnoliopsida
Subclass	Asteridae
Order	Asterales
Family	Asteraceae
Tribe	Calenduleae
Genus	Calendula

Botanical Description

Description of Calendula Plant [12,16]

- Pot marigold or calendula is an annual or seldom biennial plant grows with multiple branching erect stems up to 30-70cm. tall.
- Calendula has a deep, thin, long taproot and some secondary roots.
- The leaves are oblong, alternate, petiolate, spatulate, margins entire or with few teeth, and hairy.
- Calendula is known for its large flower heads, 5–7 cm diameter surrounded by two rows of hairy bracts; in the wild plant they have a single ring of ray florets surrounding the central disc florets. The disc florets are tubular and hermaphrodite, and generally of a more intense orange-yellow colour than the female, tridentate, peripheral ray florets.
- The fruits are a thorny curved achene because they have no pappus.
- Common name in other languages (see Table 2).

Common Name in Other Languages

Table 2: Common name of CO in other languages [18,19]

Spanish	maravilla, calendula, maravillas, mejicanas, tudescas, reinita, flamenquilla, rosa de muertos, flor de muerto
Galician	maravalla, calendula, pampullo
Potuguese	wonders, boninas
Euskara	illen, ilherrilili

Catalan	calendula, gojat, gaujat, boixac, gauget, groguet, jaumet, galldiro, garronada, llevama, carnation of mort d' Albat flower, boixac of jardi, goja, galdirons, pet of frare, lligama
French	Calendula fleur, fleur de tous les mois, souci des jardins, souci des vignes, souci officinal.
Italian	Calendula, fiorrancio
German	Ringelblume, Garten-Ringelblume, Ackerringelleume, gemeine Ringelblume.

Synonyms

Synonyms of *Calendula officinalis* [20]

- *Calendula arvensis*
- *Calendula officinalis*
- *Calendula aurantiaca* Kotschy ex Boiss.
- *Calendula eriocarpa* DC.
- *Calendula hydruntina* (Fiori) Lanza
- *Calendula officinalis* var. *prolifera* Hort.
- *Calendula prolifera* Hort. ex Steud.
- *Calendula* × *santamariae* Font Quer
- *Calendula sinuata* var. *aurantiaca* (Klotzsch ex Boiss.) Boiss

Phytochemistry

Common Chemical Constituents of *Calendula officinalis* [21]

- Polysaccharides: Galactans
- Fiber: Insulin, mucilage
- Salicylic acid
- Saponins (25%): calendulosides A, D, F, D2; oleanolic acid derivatives.
- Terpenoids and triterpene alcohols: lupeol, taraxerol, taraxasterol, faradiol, alpha and beta amyryl, aenadiol [22]
- Phytosterols: betasitosterol, campesterol, stigmasterol, cholestanol
- Flavonoids: isorhamnetin, quercetin, and rutoside glycosides (isoquercetin, narcisina, neoheperidosido).
- Carotenoids: liofilide (calendula), carotenoids (betacarotene, lycopene, lutein, violaxanthin, crisanthemaxantina) [16]
- Alkaloids
- Organic acids: caffeic acid, chlorogenic acid, gentistic acid and malic acid.
- Tannins

- Chinones and polyprenylchinones: heterocyclic aromatic compounds responsible for the strong scent of the plant, qualities that give it antioxidant properties to fight free radicals. It is used in cosmetic creams (Table 3).

Table 3: Chemical structure of various components presents in plant *Calendula officinalis*

Phytochemical Constituents	Chemical Structure
Carbohydrate	
Flavonoid	
Triterpenoid	
Volatile oil	

Amino acid	
Lipid	
Coumarin	
Quinone	

The major components of *Calendula officinalis* are carbohydrates, terpenoids, flavonoids, coumarins, quinones, volatile oils, carotenoids, and amino acids [19,23]

Carbohydrates: Carbohydrates class of *Calendula officinalis* contain polysaccharides and monosaccharides. The water soluble polysaccharides of *Calendula officinalis* inflorescence contain moisture, acidic sugar, ash, reducing sugars and pectic substances and various monosaccharides including glucose, galactose and galacturonic acid, arabinose, rhamnose and xylose [24]. The ethanolic extract of *C. officinalis* inflorescence containing monosaccharides along with polysaccharides, PS-I, -II, -III with (1→3)-β-D-galactam backbone and a side chain at C-6 consisting of α-L-rhamnan-(1→3)-araban and α-araban-(1→3)-araban form [23].

Flavonoids: Flavonoids include quercetin, isorhamnetin [24,25], isoquercetin, isorhamnetin-3-O-D-glycoside, narcissin, calendoflaside [26], calendoflavoside, calendoflavobioside, rutin, neoherperidoside, isorhamnetin-3-O-neoherperidoside, isorhamnetin-3-O-2G-rhamnosyl, rutinoid, isorhamnetin-3-O-rutinoid, quercetin-3-O-glucoside and quercetin-3-O-rutinoid [27,28].

Amino acids: The ethanolic extract of *Calendula officinalis* flower showed the presence of 15 free amino acids including alanine, arginine, asparagine, aspartate, glutamate, histidine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tyrosin, and valine [15,29].

Lipids: The leaves, seeds, and flowers of *Calendula officinalis* contain phospholipids and glycolipids, fatty acids of flowers contain monols, sterol esters, 3-monoesters and 3-monoester diols including lauric, myristic, palmitic, stearic, oleic, linoleic and linolenic acid. The fatty acids of seeds contain conjugated trienic (trans-8,trans-10, cis-12) acid and 9-hydroxy-18:2 (trans- 9,cis-11) acid - dimorphecolic acid [30,31], one oxygenated fatty acid also reported from the seed oil that is D-(+)-9-hydroxy-10,12-octadecadienoic acid [32,33].

Terpenoids: Various terpenoids of *Calendula officinalis* flowers. They include sitosterols, stigmasterol, 3-monoesters of taraxasterol, lupeol [34,35], erythrodiol, brein [36,37], faradiol-3-O-palmitate, faradiol-3-O-myristate, faradiol-3-O-laurate, arnidiol-3-O-palmitate, arnidiol-3-O-myristate, arnidiol-3-O-laurate, calenduladiol-3-O-palmitate, calenduladiol-3-O-myristate, diesters of diols [38,39], oleanolic acid saponins: calenduladuloside AH, ursadiol [40], oleanane triterpene glycoside: calendulaglycoside A, calendulaglycoside A6-O-n- methyl ester, glucosides of oleanolic acid [41,42].

Volatile Oil and its constituents: The flower heads of *C. officinalis* contain maximum volatile oils including p-cymen, cubenol, α -cadinol, γ -cadinene, δ -cadinene, oplopanonec, methylinoleate, methyltetradecanoate, methylhexanoate, methyloctadecanoate and methyl-9, 12, 15-octadecatrienoate^[43], epi- α -muurolol, α -cadinol, δ -cadinene, sesquiterpenols and sesquiterpene hydrocarbons^[44], p-cymene and various monoterpenes and sesquiterpenes: sabinene, limonene, α -pinene, β -pinene, α -thujene, p-cymene, γ -terpenene, tras- β -ocimene, δ -3-carene, 1,8-cineol, nonanal, carvacrol, geraniol, terpene-4-ol, α -terpeneol, 3-cyclohexene-1-ol, α -cadinol, bornyl acetate, calarene, aromadendrene, germacrene-D, endobourbonene muurolene, α -bourbonene, α - copaene, α -cubebene, α -gurjunene, α -humulene, α -phellandrene, α -cadinene, α -cadinol, β - cubebene, β -caryophyllene, β -saliene, nerolidol, t-muurolol and palustron [45].

Quinones: Leaves of *C. officinalis* contain phyloquinone and α -tocopherol, ubiquinone and plastoquinone are present in mitochondria and chloroplast [28].

Coumarins: Various coumarins like scopoletin, umbelliferone and esculetin are present in *Calendula officinalis* [15,46].

Carotenoids: Leaves, perals and pollens of *C. officinalis* flowers contain various forms of carotenoids: auroxanthin, 9Z-anthroxanthin, α -carotene, β -carotene, α -cryptoxanthin, β -cryptoxanthin, z-cryptoxanthin, flavoxanthin, lutein, lycopene, luteoxanthin, mutatoxanthin, neoxanthin, 9Z-neoxanthin, violxanthin and 9Z-violxanthin [47,48].

Other constituents: Some other constituents of *Calendula* include *n*-paraffins, calendulin, calendin and some bitter constituents [49].

Traditional Uses

- Traditionally, *Calendula officinalis* was used internally to reduce fevers, promote menstruation and treat jaundice. The flowers were used into various preparations like extracts, tinctures, balms and salves and these preparations were applied directly to the skin to prevent heal wounds, to soothe inflamed and damaged skin [6]. *Calendula arvensis* Linn. (Field marigold) act as disinfectant, antispasmodic and diuretic [28,51].
- In Europe, the leaves are used as resolvent and diaphoretic while the flowers are used as a stimulant, antispasmodic and emmenagogue [6,22].
- In England, for the treatment of smallpox and measles, the flowers decoction was used as a posset drink and for constipation, jaundice and suppression of menstrual flow, the fruit juice remedy is used.
- In India, Calendula ointments are used for treating wounds, herpes, ulcers, frostbite, skin damage, scars and blood purification. Infusion form of leaves is externally applied for treating varicose veins [52].
- In Italian, the plant is act as folk medicine in inflammation and cancer. It also act as antipyretic agent.
- In Spain, the leaves are act as sudorific. Traditionally, it is used as diaphoretic and sedative [53].
- Calendula is best known as an antiseptic, astringent, and an antimicrobial used on cuts, wounds, skin infections, varicose veins and hemorrhoids and is especially helpful in fungal conditions and sore nipples from breast feeding [6].

Pharmacological Activities

Calendula officinalis has a broad range of pharmacological effects, some of which are very useful for possible future development [19,28].

1. Anti-Inflammatory activity: Calendula plant is used as anti-inflammatory agent to inhibit the increasing level of TNF- alpha, INF- gamma, proinflammatory cytokines IL-1beta and IL-6 [11]. The methanol extract of *Calendula officinalis* flowers had marked anti-inflammatory activity at a dose of 0.05-0.20 g/ear in mice against ear edema induced by the most potent inhibition of 12-o-tetradecanoyl phorbol-13-acetate (TPA) [54]. Calendula cream has been reported to be effective in burn oedemas and in acute lymphoedema in rats. Activity against lymphoedema was primarily attributed enhancement of macrophage proteolytic activity [55,56].

2. Anticancer activity:

The Laser Activated Calendula Extract (LACE) showed anti-tumor activity in nude mice against tumor growth of Ando-2 melanoma cells [28,57]. According to the *Journal of Clinical Oncology*, calendula is used to preventing the dermatitis caused by radiation used for breast cancer treatment [58].

3. **Analgesic activity:** Analgesic activity of hydroalcoholic extract of *Calendula officinalis* flowers evaluated by formalin and writhing test using 2.5 mg/kg subcutaneous dose of morphine [59].
4. **Antioxidant Activity:** Antioxidant activity of 70 % methanol extract of the plant *Calendula officinalis* was exhibited by liposomal lipid peroxidation-induced Fe²⁺ and ascorbic acid [60] Propylene glycol extracts of the petals was more potent than flower extract and indicated the inhibition lipid peroxidation [61].
5. **Hepatoprotective activity:** The hydroalcohol extract of the calendula flowers at a dose of 10mL/kg given to CCl₄-intoxicated liver in albino male Wistar rats showed the inhibition of hepatocytolysis due to reduction in glutamo-oxalate-transaminase (GOT) and glutamic-pyruvate-transaminase (GPT) [55,62].
6. **Insecticidal activity:** The acetone and methanol (2:1 v/v) extract of the *Calendula officinalis* flowers shows the insecticidal activity. The insecticidal activity is tested on milk weed bug [6,63].
7. **Cardiovascular activity:** The aqueous extract of *Calendula officinalis* flowers at a dose of 0.3mg/L in male Wistar rats reduced heart rate contractility [64].
8. **Hypoglycaemic activity:** In the presence of saponins, hypoglycaemic activity and gastroprotective activity showed by methanolic extract of calendula flowers against ethanol induced gastric mucosal lesions in the rats [65].
9. **Anti- HIV activity:** In an In-vitro study of organic extract of *Calendula officinalis* flowers showed the anti-HIV activity and the extract is also induced the 85% dose-and time-dependent reduction of HIV-1 reverse transcription (RT) activity [28].
10. **Toxicological activity:** The hydroalcohol extract of *Calendula officinalis* flowers at oral dose of 5.0 g/kg in rats and mice, does not show acute toxicity and at various doses of 0.025, 0.25, 0.5 and 1.0 g/kg didn't show hematological alterations [66,67], but the biochemical parameters, blood urea nitrogen (BUN) and alanine transaminase (ALT), were elevated [68].
11. **Immunostimulant activity:** Based on the *in vitro* granulocyte test, the polysaccharide fraction of *Calendula officinalis* extract showed immunostimulant activity due to presence of polysaccharides (PS)-I, II and III. At the concentration of 10.5 – 10.6 mg/mL, PS-III exhibited the highest phagocytosis (54 – 100 %), while PS-I and PS-II exhibited 40 – 57 and 20 – 30 % phagocytosis, respectively [48].
12. **Gingivitis activity:** Polysorb immobilized calendula act as astringent, reduced gum inflammation and chronic catarrhal gingivitis as well as fight against gingivitis, cavities, and plaque and promote a healthy oral environment [69].

- 13. Antibacterial activity:** The methanol extract and 10% decoction of the *Calendula* flowers inhibited the growth of *Porphyromonas gingivalis*, *Prevotella* spp., *Furobacterium nucleatum*, *Caphocytophaga gingivalis*, *Veillonella parvula*, *Eikenella corrodens*, *Peptostreptococcus micros* and *Actinomyces odontolyticus* [70-72].
- 14. Antifungal activity:** Using disc diffusion technique, the essential oil extract *Calendula officinalis* flowers shows good potential antifungal activity (using disc diffusion technique) against various fungal strains, namely, *Candida albicans*(ATCC64548), *Candida dubliniensis* (ATCC777), *Candida parapsilosis* (ATCC22019), *Candida glabrata*(ATCC90030), *Candida krusei* (ATCC6258), and yeast isolated from humans, viz, *Candida albicans*, *Candida dubliniensis*, *Candida parapsilosis*, *Candida glabrata*, *Candida tropicalis*, *Candida guilliermondii*, *Candida krusei* and *Rhodotorella* spp., at 15 µl/disc [73,74].
- 15. Wound- healing activity:** Wound healing activity or property of *Calendula officinalis* is examined by hydroalcoholic extract of calendula herb. The volatile oils and xanthophyll's of calendula plant showed the tissue-healing effect [74].
- 16. Phagocytosis activity:** The phagocytosis activity is enhanced by administration of intraperitoneal injection (10 mg/kg in mice) of an aqueous extract of flowers [49,75].
- 17. Antispasmodic and spasmogenic effects:** Crude extracts of *Calendula officinalis* flowers showed both spasmolytic and spasmogenic constituents in rabbit jejunum and it exhibited these effect through calcium channel blocking [63].
- 18. Deodorant effects:** The components of marigold (*Calendula*) and other medicinal plants may act as oral deodorants by inhibiting salivary protein purification [76].
- 19. Antidiabetic and Antihyperlipidemic activities:** The hydroalcoholic extract of *Calendula officinalis* at dose 25 and 50 mg/kg body weight showed antidiabetic and antihyperlipidemic effect. It is significantly lowered the blood glucose, urine sugar and serum lipid in alloxan (150 mg/kg) diabetic rats [77].
- 20. Antiviral activity:** In vitro studies showed that a tincture of the hydroalcoholic extract of *Calendula officinalis* flowers suppressed the replication of herpes simplex, influenza A2 and influenza APR-8 virus [66].
- 21. Antianxiety activity:** Antianxiety effect produces by the various extract of aerial parts of *Calendula officinalis*. It decreases the motor activity of animals [78].
- 22. Nephroprotective activity:** *Calendula officinalis* flower extract inhibit or reduces the kidney damage and induce the protection against cisplatin induced oxidative stress [65].

23. Antiacne Activity: At the 0.04% concentration, the flavonoids of hydroalcoholic extract of *Calendula officinalis* showing antiacne effect [79].

24. Other effects: In animal studies, internal use of calendula is also lowering the blood pressure and increase the sedation [63,64].

CONCLUSION

Calendula officinalis also known as Marigold, is just an example, of the diversity of medicinal plants hold in the Medicine World. In this review, we have presented information on the botanical description, traditional uses, phytochemistry and pharmacology of *C. officinalis* Linn. (Asteraceae), a medicinal plant found in central and southern Europe, western Asia and the United States, amongst others. A variety of phytochemicals such as terpenoids, flavonoids, coumarins, quinones, volatile oil, carotenoids and others have been reported to be present in this plant. It exhibits several pharmacological activities such as anti-HIV, anti-cancer (dual activity), anti-inflammatory, hepatoprotective, spasmolytic and spasmogenic (dual activity), amongst others. Pharmacological studies reveal that *C. officinalis* exhibits antibacterial, antiviral, anti-inflammatory, anti-tumor and antioxidant properties, antimutagenic and hemolytic activities. *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. It is potentially an important medicinal plant for mankind. Keeping in view the 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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