

# A Review of *Calendula officinalis*- Magic in Science

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## ABSTRACT

*Calendula officinalis* (*Calendula*), a member of the Asteraceae family, is often known as English Marigold or Pot Marigold. Marigold is a fragrant herb that has been used in traditional medicine for centuries. *Calendula* species have been highlighted in order to better understand their diverse biological activities and modes of action. Carotenoids, flavonoids, glycosides, steroids and sterols, quinines, volatile oil, and amino acids are all found in abundance in this plant. *Calendula* oil is still used as an antitumour agent in medicine, which is also a wound healing agent. Among herbal medicines, *Calendula* suspension or tincture is used to treat acne locally, reduce inflammation, control bleeding and soothe irritated tissues. This *Calendula* plant's extract, a pure chemical extracted from it, have been shown to have a variety of pharmacological properties including anti-inflammatory, antioedematous, antioxidant activity, antibacterial and antifungal activity, anti-Human Immunodeficiency Virus (HIV) and antiviral activity, wound healing and immunostimulant activity. Anticytotoxic, hepatoprotective, spasmolytic properties and also impacts on exhibiting increased levels of proinflammatory cytokines Interleukin (IL)-1 beta, IL-6, Tumor Necrosis Factor (TNF)-alpha and Interferons (IFN)-gamma and acute phase protein, C-reactive protein. *C.officinalis* may have an important future impact on the development of new cancer treatment strategies, and until now it has been specifically used to reduce the side-effects of radiotherapy. This review looked at the organoleptic, in-vitro, and in-vivo pharmacological activities, as well as the description, cultivation, and active chemical constituents of *Calendula officinalis* in order to fill in the gaps in current knowledge about this plant and to highlight its potential applications as a medicinal agent.

**Keywords:** Chemical constituents, Medicinal plant, Oral mucositis, Preparations, Therapeutic effects, Traditional medicine

## INTRODUCTION

*Calendula officinalis* is a well-known therapeutic herb that was used for millennia and belongs to the kingdom plantae, family Asteraceae. English marigold, pot marigold, Bride of the Sun, bull flower, and butterwort are some of its other names [1]. *Calendula officinalis* is widely grown in sunny areas and in a variety of soils. *Calendula officinalis* is a tall plant with sparsely branching erect stems, rectangular lance leaflets with tubular disc florets, and thorns curving achene that is yellow or orange in colour. Carotenoids, flavonoids, saponins, sterols, phenolic acids, lipids, and other biological active elements found in numerous components of the plant such as leaves and flowers, are employed both in-vitro and in-vivo [1]. It is believed to have medicinal properties and is widely used as an anti-inflammatory, diaphoretic, analgesic, and antiseptic. It is used to treat gastrointestinal issues, gynaecological issues, oral disorders, eye diseases, skin injuries, and certain burns, among other things [1]. Fifteen amino acids were discovered in the free state in the leaves, stems, and flowers. Flowers were turned into extracts, tinctures, and balms for external application, and were therapeutically used to treat skin inflammations, open, lacerated wounds, and bleeding wounds [2].

*Calendula officinalis* has medicinal capabilities that have been stated in the Ayurvedic and Unani systems of medicine. Carophyllenic ointment (containing carotenoids obtained from the flowers) and pot marigold tincture are two recent *Calendula officinalis* treatments. It is one of the ingredients in the homoeopathic drug, which is used to relieve the pain and oedema associated with acute musculoskeletal injuries. Herbal ear drop formulations containing *Calendula* flowers have been beneficial for ear pain in children with acute otitis media. On liposomal lipid peroxidation generated by ferrous ion and ascorbic acid, extracts of *Calendula* flowers of various polarity displayed antioxidative properties. Lipoxxygenase was inhibited by isorhamnetin 3-glycosides from *Calendula* flowers. As *Calendula*

*officinalis* is high in medicinal active ingredients, it increases blood and lymphatic circulation, which aids in the removal of toxins from the body [2]. There have been no reported contraindications or drug interactions, although people who have a known sensitivity to the compositae family may be more susceptible to allergic responses. *Calendula* mouthwash has anti-inflammatory characteristics that fight swollen, irritated gums, as well as antibacterial properties that fight periodontopathic germs. Fresh chemical compounds such as isorhamnetin, rutin, and quercetin glucoside which are biologically engaged and employed for various purposes, have been isolated using advanced analytical technique [3].

The traditional usage and clinical significance of *Calendula* species are highlighted in this review paper. It is aimed to attract attention of natural product researchers from around the world to the enormous potential and diverse biological activities in treatment aspects. Furthermore, the authors emphasise its key function in both general and oral treatment.

## CHEMICAL CONSTITUENTS

Saponins, triterpeneol esters, and flavonoids were found in the chemical make-up of the *Calendula officinalis* plant. *Calendula officinalis* has high carotenoids in its blossom, which is mostly orange in colour. Fatty acids, chloroform extracts, triterpens, and sterols are all present in *Calendula officinalis* leaf extract. *Calendula officinalis* water extract contained saponins, phenolic compounds, and tannin [1]. Alkaloids, flavonoids, and saponins were found in ethanolic extract. Flavonoids and saponins were found in aqueous extract. Plastoquinone, phyloquinone, tocopherol, and ubiquinone were isolated from quinone in different sections of *Calendula officinalis*. Terpenoids were isolated from the petroleum ether extract of *Calendula officinalis* flowers [4].

In general, roughly 5% of amino acids were found in the leaves, 3.5 percent in the stems, and 4.5 percent in the flowers. Alanine,

arginine, aspartic acid, asparagine, valine, histidine, glutamic acid, leucine, lysine, proline, serine, tyrosine, threonine, methionine, and phenylalanine were among the fifteen amino acids found in the flowers. Quercetin, isorhamnetin, isoquercetin, and other flavonoids were also extracted from *Calendula officinalis* [Table/Fig-1] [5]. Inflorescences of *Calendula officinalis* acquired significant levels of carotenoids. Carotenoids are primarily responsible for the yellow-to-orange hue of inflorescences. *Calendula officinalis* orange types have more hydrocarbons, while yellow varieties have mostly oxygenated derivatives [4].

Main components	Sub-components
Calenduladiol-3-O-palmitate	
Calenduladiol-3-O-myristate	
Oleanolic acid saponins	Calenduloside AH
Oleanane triterpene glycoside	Calendula-glycoside A
Calendula-glycoside A6'-O-n-methyl ester	
Calendula-glycoside A6'-O-n-butyl ester	
Calendula glycoside B	
Calendula glycoside B 6'-O-n-butyl ester	
Calendula glycoside C	
Calendula-glycoside C 6'-O-n-butyl ester	
Calenduloside F6'-O-n-butyl ester	
Calenduloside G6'-O-n-methyl ester	
3-monoesters of taraxasterol	
Erythrodiol	
Lupeol	
Brein	
Ursadiol	
Faradiol-3-O-palmitate	
Faradiol- 3-O-myristate	
Faradiol-3-O-laurate	
Amidiol-3-O-palmitate	
Amidiol-3-O-myristate	
Amidiol-3-O-laurate	
Glucosides of oleanolic acid I, II, III, VI, VII	
Glucuronides F, D, D2, C, B and A	
Ester of oleanane.	

[Table/Fig-1]: Constituents of *Calendula officinalis* flower extract [5].

The main pigments identified were flavoxanthin, lutein, rubixanthin,  $\beta$ -carotene,  $\gamma$ -carotene and lycopene. The total oils extracted from the dried flowers of *Calendula officinalis* compounds isolated from *Calendula officinalis* flower were also be added in part of its chemical constituents [4].

## PHARMACOLOGICAL EFFECTS OF CALENDULA OFFICINALIS

The pharmacological effects of *Calendula officinalis* are listed as:

- Antimicrobial and antihelminthic effects
- Anti-inflammatory effects
- Antioxidant and photoprotective effects
- Cytotoxic effects
- Genotoxic and antigenotoxic effects
- Cardiovascular effect
- Neuroprotective effect
- Hepatoprotective effect

**Antimicrobial effects:** Methanol and ethanol extracts from *Calendula* petals has been tested for antibacterial activity against clinical pathogens, including bacteria and fungi such as *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumonia*,

*Candida albicans* and *Aspergillus niger* [1]. The methanol extract of *Calendula officinalis* showed better antibacterial activity than against most of the bacteria tested and was better than the ethanol extract. Both methanol and ethanol extract showed excellent antifungal activity against the fungal test strain [5].

**Antioxidant and photoprotective effects:** *Calendula officinalis* leaves and petals may be a natural source of antioxidants. It was reported that *Calendula* extract scavenges hydroxyl radicals and superoxide radicals which is produced by photo reduction of riboflavin [6].

**Cytotoxic effects:** Although none of the extracts demonstrated a direct mitogenic impact on human lymphocytes or thymocytes, *C.officinalis* inhibited lymphocyte proliferation completely [1].

**Anthelmintic effects:** The *Calendula officinalis* plants contain saponins and have also demonstrated anthelmintic action, indicating that saponins have anthelmintic activity [7].

**Genotoxic and antigenotoxic effects:** All saponins were shown to be non toxic and non mutagenic and floral extract inhibits HIV-1 multiplication in acutely infected lymphocytic MOLT-4 cells [8,9].

**Neuroprotective effect:** *Calendula officinalis* extracts also have modest sedative effects and can work in conjunction with sedative drugs like barbiturates. The Central Nervous System (CNS) inhibitory impact of aqueous alcoholic extract of florets was also observed, as well as sedative action [2].

**Cardiovascular effect:** *Calendula* extract has been found to reduce the size of myocardial infarction. It seems that cardio protection is achieved by changing the ischaemia-reperfusion-mediated death signal into a survival signal [5].

**Anti-inflammatory effects:** *Calendula officinalis* preparations are mostly used as a wound healing medicine for inflammations of the skin, mucous membranes, tissue repair, scars, blisters, and allergic rashes in the form of infusions, tinctures, and ointments. *Calendula* extract cream has been shown to be beneficial in the treatment of burn oedemas. *Bacillus subtilis*, *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Candida albicans* were all inhibited in-vitro by the essential oil from the flowers [2,10].

**Hepatoprotective effect:** *Calendula officinalis* extracts were found to have potential hepatoprotective properties against cytotoxicity and oxidative stress caused by carbon tetrachloride. It raises total haemoglobin levels. The extract has a comparable consistency to insulin. As a result, the research clearly reveals that *Calendula officinalis* hydro alcoholic extract has both antidiabetic and antihyperlipidemic properties [11,12].

## TRADITIONAL AND GENERAL USES OF CALENDULA SPECIES

Only three species of *Calendula* such as *Calendula officinalis*, *Calendula arvensis*, and *Calendula suffruticosa* have been studied for their medicinal activity, according to the literature [2]. Field marigold, *Calendula arvensis* Linn, an annual herb, the height usually does not exceed 15 cm. The leaves are lance-shaped; the stem is thin and hairy; the inflorescence has a single flower head upto 4 cm wide, with bright yellow to orange-yellow ray flowers around the center of the yellow disk has been used as a disinfectant, antispasmodic, and diuretic. The plant is utilised as an anti-inflammatory, anticancer, and antipyretic agent in Italian medicine. It is been used for centuries as an emmenagogue, diaphoretic, and sedative. It has wound healing effects, and powdered leaves are administered directly to wounds. The flower blossoms decoction has been used to cure burns [2,13]. *Calendula officinalis* Linn. (Pot marigold) is an annual or biennial plant with a height of 30-60 cm. Lower spoon-shaped leaves, 10-20 cm long and 1-4 cm wide; the tallest oblong, 4-7 cm long; angular, hairy and solid stems; bright yellow to orange flower heads; marginal

flowers of many cultivated plants, spoon shaped oblong corolla, 15-25 mm long and 3 mm wide; corolla disc shaped, with three teeth on the upper part, 1.5-2.5 cm long, 4-7 mm in diameter, tubular flower length 5 mm which has traditionally been treated for internal organ inflammations, gastrointestinal ulcers, and dysmenorrhea, as well as to treat convulsions as a diuretic and diaphoretic. *Calendula* is a detoxifying and cleansing herb, and its infusion is used to treat chronic illnesses. The antipyretic, antitumour, and cicatrising properties of the dried flower heads have been used. In wounds, markings, freckles, sprains, and conjunctivitis, a topical application of floral infusion is utilised as an antifungal and antimicrobial. *Calendula* tea is used as gargles, eyewashes, diaper rashes, and various other mucous membrane and skin inflammatory diseases [14,15] in homoeopathy, tincture of *Calendula officinalis* is being used for the treatment of insomnia and mental tension [16].

*Calendula officinalis* has been used for impaired eyesight, menstrual irregularities, varicose veins, haemorrhoids, and duodenal ulcers in both traditional and homoeopathic treatment. *Calendula* flowers were used in the middle ages to treat liver blockages, snake bites, and to enhance the heart health. It was once used to treat headaches, jaundice, and red eyes. The herb is also used to cure wounds as well as to treat measles, smallpox, and jaundice. *Calendula persica* decoction and infusion, as well as its aerial parts, are used to cure kidney stones [16,17].

*C. suffruticosa vahl*, is a perennial plant with a height between 20 cm to 40 cm. The leaves are lance-shaped, slightly serrated and covered with short, sticky hairs; stem seedlings rise first, then begin to hang and spread to the ground; the flowers are bright yellow, each about 2.5 cm in diameter which is used traditionally in few of the herbal formulations [2].

*C. stellata cav*, is an attractive small annual plant that can reach 30 cm or higher in height. Leaves are elliptical or oblong, slightly pointed, with wavy teeth, thick stem; five outer achenes have membranous tooth margins, inner five "boat-shaped" and smooth backs, and the remaining backs are angular and jagged which inhibits pathogenic microorganisms, especially *Pseudomonas syringae*, *Pseudomonas fluorescens*, *Xanthomonas*, *Agrobacterium tumefaciens* [2].

In early animal studies, it was reported that a high dose preparation of *Calendula* can be used as a tranquiliser [5]. Therefore, the combination with sedatives can produce additive effects. Marigolds were shown to increase hexobarbital induced sleep times. The systemic effects of *Calendula* used locally on the human body are unclear [5].

The antioxidant potential of *Calendula* extract in-vitro and in-vivo was evaluated by Al-Snafi AE. It was found that *Calendula* extract scavenges superoxide free radicals and hydroxyl free radicals produced by riboflavin photoreduction and fenton reaction [5].

Induction of Unplanned DNA Synthesis (UDS) was determined for four different extracts of *Calendula officinalis*, Aqueous Ethanol (AE), Ethanol (EE), and Chloroform (CE). The reversal in the UDS assay in hepatocyte culture, Diethylnitrosamine (DEN) micromolecule produced the greatest increase in incorporation of 40% (3) H-thymidine, and both EE and AE showed a complete reversal of the effect of DEN. The concentration that produces genotoxic damage is three orders of magnitude higher than the concentration that provides complete protection against the DEN effect [5].

*Calendula* extract has significant anti-inflammatory activity on acute pedal oedema caused by carrageenan and dextran. It was found that faradiol 3 myristate and faradiol 3 palmitate have the same dose dependent anti-inflammatory activity. Unesterified faradiol is more active than esters. The effect on inflammation is equivalent to equimolar doses of indomethacin [5].

## TOXICOLOGY OF CALENDULA SPECIES

*C. officinalis* extract has been found to be non toxic, non mutagenic, and non genotoxic [1]. In rare cases, contact with *Calendula* supplements and topicals on skin can cause an allergic reaction. Sensitisation and allergic contact reactions to *Calendula* were reported [2]. There was also a case of anaphylactic shock after gargling with *Calendula* infusion [18].

## EFFECT OF CALENDULA OFFICINALIS IN DENTISTRY

*Calendula officinalis* is a medicinal herb with antiseptic, antibacterial, and anti-inflammatory effects. Triterpene saponins, triterpene alcohols and their fatty acid esters, carotenoids, flavonoids, coumarins, essential oil, hydrocarbons, and fatty acids are all found in the plant components and are utilised in pharmaceutical and cosmetic products [19].

### Effect in Oral Health

*Calendula officinalis* was investigated as a possible treatment for exfoliative cheilitis [20]. After extraction of unerupted third molars, mouthwashes containing *Calendula officinalis* minimises the amount of micro-organisms adherent to the sutures. *Calendula* aqueous extract promotes wound healing by boosting neovascularisation and the rate of hyaluronic acid deposition. In bone wounds, hyaluronic acid can accelerate new bone creation by promoting mesenchymal cell differentiation [20].

### Effect in Gingivitis and Periodontitis

In the treatment of desquamative gingivitis, *Calendula officinalis* is used which may assist to reduce periodontal disease progression by reducing Hepatocyte Growth Factor (HGF) -mediated collagen breakdown and Matrix Metalloproteinases (MMP) activity [20].

### Effect in Oral Mucositis

*Calendula officinalis* has a cytotoxic effect on tumour cell lines, and its anticancer activity demonstrates its efficacy in the treatment of oral mucositis in radiation therapy patients [21]. It has its own efficacy by reducing the intensity of radiation with high radical scavenging activity, and it plays a crucial role in maximum safeguarding against oxidative stress caused by high levels of reactive oxygen species in the body [22,23].

### Effect in Dental Plaque

*Calendula's* anti-inflammatory, antioxidant, and immunomodulatory properties treat severe periodontal disease by regulating cytokine levels, reducing oxidative stress, and stimulating phagocytic activity of Polymorphonuclear (PMNs) leukocytes. This study showed that *Calendula* mouthwash is effective in reducing plaque and gingivitis as an adjunct to oral prophylaxis [3].

## VARIOUS TYPES OF STUDIES REVIEWED

### Clinical Trial Studies

Buzzi M and de Freitas F conducted a prospective non randomised control study on 57 non diabetic patients with venous ulcers for longer than ten weeks without infections with topical application of *Calendula officinalis* hydroglycolic extract spray twice per day and the outcome was ulcer reduction per week found to be higher level of wound healing in *Calendula* [24].

De Carvalho AF et al., done a prospective Randomised Controlled Trial (RCT) study on 32 patients aged 40 to 70 years with unbalanced diabetes and diabetic ulcer in lower limbs with Low-Level Laser Therapy (LLLT) with daily topical applications of *Calendula* oil and the outcome showed significant reduction in ulcer and pain by using both LLLT with *Calendula* oil was statistically significant [25].

Duran V et al., conducted a prospective control trial study on 34 patients with venous leg ulcers with topical application of *Calendula* ethanolic extract and the result revealed decreased ulcer surface area [26]. Eghdampour F et al., conducted a prospective, RCT study on 111 women with topical application using aloe vera ointment and *Calendula* ointment which exhibits a significant reduction in redness, oedema, ecchymosis, discharge and approximation [27]. A randomised controlled open trial on 156 patients by Lievre M et al., with partial to full thickness burns with daily topical application of *Calendula* ointment and the outcome was greatly decrease in fibrin and hyperemia. This showed marked increase in collagen amount and increased number of blood vessels [28].

Pommier P et al., conducted a blinded randomised controlled trial on 254 women undergoing postoperative adjuvant radiotherapy for breast cancer with topical application of *Calendula* ointment twice daily or more and it express the higher percent wound closure, period to re-epithelisation was also found to be faster [29]. A blinded randomised controlled trial by Sharp L et al., on 411 women undergoing postoperative adjuvant radiotherapy for breast cancer with topical application of *Calendula* cream twice daily showed improvement in tensile strength. After 14 days, granulation tissue had less immune cells, more fibroblasts, blood vessels and re-epithelisation completed after 14 days [30].

### Preclinical In-vivo Animal Model Studies

Details of Preclinical in-vivo animal model studies where *Calendula* was used has been given in [Table/Fig-2] [31-37].

Authors name, year	Place of study	<i>Calendula</i> extract used	Route	Conclusion
Chandran PK and Kuttan R 2008 [31]	India	Ethanolic extract of <i>Calendula</i>	Orally to rats with burn wounds	Revealed higher rate of hexosamine, glutathione levels and hydroxy proline concentration.
Dinda M et al., 2016 [32]	India	Topical gel	Full thickness excisional wound on mice	Exhibits less necrotic tissue with more fibroblasts.
Fonseca YM et al., 2010 [33]	Brazil	Oral applications of <i>Calendula officinalis</i>	For ultraviolet irradiation at the range of 270-400 nm on mice	Showed increased glutathione concentration.
Parente LML et al., 2011 [34]	Brazil	Topicals of <i>Calendula officinalis</i>	Skin wounds done with circular metal punch on rats	Expressed higher vascular supply.
Parente LM et al., 2012 [35]	Brazil	Topical ointments	Normal skin wounds on rats	Revealed significant increase in collagen, less fibrin and hyperaemia.
Preethi KC and Kuttan R, 2009 [36]	India	Oral and topical preparations	Full thickness excisional wound, on rats	Showed greater amount of re-epithelisation and wound closure. Marked increase in hexosamine and hydroxy proline concentration.
Shafeie N et al., 2015 [37]	Iran	Topical application of <i>Calendula officinalis</i> gel	For skin excision and in all incisions only the skin was removed	Exhibits fewer immune cells, more fibroblast with blood vessels in granulation tissue. Complete re-epithelisation with greater tensile strength is significant after treatment.

[Table/Fig-2]: Preclinical in-vivo animal model studies [31-37].

### Studies Depicting use of Intraoral and Extraoral Preparations of *Calendula*

Details of studies where intraoral and extraoral preparations of *Calendula* was used has been given in [Table/Fig-3] [3,22,23,38,39].

Authors name, year	Place of study	<i>Calendula</i> preparation used	Effect	Conclusion
Tanideh N et al., 2013 [38]	Iran	Effect of topical <i>Calendula officinalis</i> extract	Healing of oral mucositis caused by 5-Fluorouracil (5-FU) in hamsters	Accelerated healing in hamsters.
Machado MA et al., 2010 [39]	Czechia	Clobetasol and <i>Calendula officinalis</i> gel	Desquamative gingivitis	Reduce the length and severity of symptomatic episodes.
Lima M et al., 2017 [22]	Brazil	<i>Calendula officinalis</i> extract	Effect on oxidative stress and bone loss in experimental periodontitis	Reduction in antioxidant capacity as well as an increase in oxidative damage. Anti-inflammatory and Antioxidant properties.
Saini P et al., 2012 [23]	USA	<i>Calendula officinalis</i> extract	Effects on Human gingival fibroblasts.	Reduces HGF-mediated collagen breakdown and MMP activity.
Khairnar MS et al., 2013 [3]	India	<i>Calendula officinalis</i> and <i>Camellia sinensis</i>	<ul style="list-style-type: none"> <li>Acts against microorganism adhesion to sutures after extraction of unerupted third molars</li> <li><i>Calendula mouthwash</i> is an effective adjuvant</li> </ul>	<ul style="list-style-type: none"> <li>Expresses anti-microbial effects of <i>Calendula officinalis</i>, <i>Camellia sinensis</i>.</li> <li>Reducing tooth plaque and gingivitis.</li> </ul>

[Table/Fig-3]: Studies with Intraoral and Extraoral Preparations [3,22,23,38,39].

HGF: Hepatocyte growth factor; MP: Matrix metalloproteinases

### CONCLUSION(S)

*Calendula officinalis* is found in a variety of herbal compositions that are used in clinical settings to treat a variety of diseases. The phytoconstituents of four *Calendula* species have been studied in part. In light of ethnopharmacology, phytochemical, and pharmacological findings as well as low toxicity and frequent use. *Calendula officinalis* appears to have a lot of potential for research into diverse biological processes. It can be found in a variety of forms including gel, cream, ointment, mouth washes, and systemic infusions. It is a very promising plant that needs indepth research and that can be used to extract active ingredients, to synthesise different drugs, to prevent various diseases, and also used to manage different pathologies.

This article addressed the botanical description, historical usage, pharmacological effects, outcome of studies with different combinations and applications of *Calendula officinalis*. Most importantly, it reveals its potential in terms of medical and dental elements for the benefit of humanity. Because of its effectiveness and safety, *Calendula officinalis* has considerable ability for the development of innovative medications to treat a variety of human ailments.

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