International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 3 May-June 2025, pp: 1695-1703 www.ijprajournal.com ISSN: 2456-4494

Mechanism of action of wound healing activity and properties of calendula officinalis

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Date of Submission: 10-06-2025 Date of Acceptance: 20-06-2025

ABSTRACT
Calendula officinalis (Calendula, marigold) is a medicinal plant widely recognized for its wound-healing properties. This review paper delves into the multifaceted mechanisms underlying Calendula's efficacy in wound management, properties, chemical composition, traditional uses, pharmacological activities and future applications. The flowering plant Calendula officinalis belongs to the Asteraceae family. Through an extensive review of literature, we explore the key bioactive compounds responsible for its therapeutic effects, including triterpenoids, flavonoids, carotenoids, and polysaccharides. Although the exact mechanism is still unknown, it was assumed that the herb would improve blood flow to the injured location, carrying with it the oxygen and nutrients required for tissue repair. We analyze the impact of these compounds on inflammation, angiogenesis, collagen synthesis, granulation tissue formation, and epithelialization. Furthermore, we discuss the potential of Calendula in treating various types of wounds, highlighting its anti-inflammatory, antioxidant, antimicrobial, and immune stimulatory properties. Calendula officinalis promotes wound closure, reduces inflammation, combats infection, and fosters tissue regeneration. This comprehensive review aims to provide a understanding of the intricate mechanisms that contribute to the wound-healing activity of Calendula officinalis.

KEYWORDS: Calendula officinalis, wound healing, mechanism of action, triterpenoids, flavonoids, inflammation

I. INTRODUCTION

Calendula officinalis, commonly known as pot marigold, has been used for centuries in traditional medicine, particularly for its wound healing properties. Modern research has begun to unravel the complex mechanisms underlying its effectiveness, supporting its continued use and highlighting its potential for further development. This review aims to summarize the current understanding of calendula's wound healing activity and properties. A person may experience financial and social hardship as a result of wounds and skin conditions. Among the top five most economically burdensome skin conditions were wounds and ulcers. Treatments for wound care can speed up the healing process, reduce the risk of new wounds, and improve the qualities of newly formed skin. Potential anti-inflammatory, antibacterial, and cell-stimulating qualities of several natural substances have been shown to help promote wound healing.[1]

Historically, a number of alternative medicine treatments have been employed for their possible effects on skin healing, however, clinical research have not clearly demonstrated the advantages of these products. Among these commonly used products are honey, ginkgo biloba, aloe vera, and St. John's wort. Furthermore, various plant extracts have been utilised for their benefits on wound healing, including Calendula officinalis extract, oak bark, and tea tree oil.[2]

Wound healing is a complex biological process involving a cascade of molecular and cellular events, aiming to restore tissue integrity after injury. This process is broadly categorized into four overlapping phases: hemostasis, inflammation, proliferation, and remodeling. Disruptions in any phase of this process can lead to chronic wounds, posing a significant burden on healthcare systems and negatively impacting the quality of life. Traditional medicine has long utilized plant-derived remedies to promote wound healing. Calendula officinalis, commonly known as Calendula or marigold, is one such plant that has been used for centuries for its therapeutic benefits, particularly in the treatment of wounds, burns, and skin irritations. The bright orange flowers of Calendula are rich in a variety of bioactive compounds, including triterpenoids, flavonoids, carotenoids, and polysaccharides, which collectively contribute to its remarkable wound-healing properties. Traditionally, it has been used

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 3 May-June 2025, pp: 1695-1703 www.ijprajournal.com ISSN: 2456-4494

topically to treat a variety of skin ailments, including burns, ulcers, eczema, and, most notably, wounds.[3]

Calendula officinalis is a well known medicinal plants, and it is native to Asia and southern Europe, but commonly found in gardens around the world. It is commonly known as Pot marigold , has been used in many forms and for centuries as an herbal remedy belonging to the family Asteraceae used for the treatment of wounds, burns, abrasions and dermatitis.[4]

Calendula officinalis is a member of the Asteraceae family and has been used for many, many years as a medicine. Other names for it include English marigold, pot marigold, bull flower, butterwort, and bride of the sun. Originally derived from the Latin word "calendas," meaning "first of the month," calendula Often utilised in traditional medicinal system such as european herbalism, traditional Chinese medicine, and Ayurveda.[5]

In homoeopathy, Calendula officinalis is frequently used to treat a range of ailments. Numerous pharmacological characteristics, including antiviral, antibacterial, antifungal, anti-inflammatory, and antioxidant qualities, have been reported. Moreover, it possesses cytotoxic and tumor-suppressive qualities. Its applications include strengthening the immune system and acting as an analgesic, anthelmintic, antifungal, anti-inflammatory, antipyretic, antibacterial, disinfectant, spasmolytic, antiviral, emetrol, costringent, bitter, cardiotonic, flatus-relieving, diuretic, lymphatic, gall bladder contraction stimulant, uterotonic, and vasodilator. It is frequently used to treat open wounds, lacerated wounds, and skin inflammations. Inflammations of the mucous membranes, gastrointestinal spasms, peptic and duodenal ulcers, neurotic or anaemic women, intestinal and duodenal mucosa, splenic and hepatic inflammations, and dysmenorrheal (painful menstruation) are all treated internally.[6,7]

Fifteen free amino acids were found in the stems, leaves, and flowers. Flowers were used to cure open, lacerated wounds, bleeding wounds, and skin inflammations. They were also made into extracts, tinctures, and balms to be used topically. Using herbal ear drops infused with calendula flowers has been shown to reduce ear pain in children with acute otitis media. Extracts from calendula flowers with different polarities showed antioxidative effects on liposomal lipid peroxidation caused by ferrous ions and ascorbic acid.[8]

The purpose of this study is to review all the available information on Calendula officinalis in a single document. This review summarizes various aspects such as morphological features, geographical distribution, traditional uses, phytochemistry, pharmacological studies, mechanism of wounds healing, toxicology and future aspects. The search for effective and safe wound-healing agents has led to a renewed interest in natural remedies, with Calendula officinalis emerging as a promising candidate. This paper aims to comprehensively review and analyze the current understanding of the mechanisms of action underlying the wound-healing activity of Calendula officinalis.

Figure No. 1: Leaves of Calendula officinalis

MORPHOLOGICAL FEATURES

Calendula officinalis can grow either monthly or eternally, and it has a woody base. It typically grows to a height of 30 to 60 cm. It has a solid, hairy, angular stem; its lower, spatulate leaves are 10–20 cm long and 1- 4 cm wide; its upper, oblong and mucronate leaves are 4–7 cm long; the apical region of the external epidermis contains bright, unheroic to orange anomocytic stomata that cover glandular trichomes, stretched sclerenchyma cells, and borderline flower heads; the corolla of the slice flowers is oblong, spatulate, and measures 15–25 mm long and roughly three mm wide; at its stylish, it is tridentate, 1.5–2.5 cm long and 4–7 mm in periphery, with tubular boutonnieres that are 5 mm long. Pulverised sienna from C. officinalis has a pleasant bitter taste and a unique, sweet aroma. Calendula officinalis is distinguished by its flower heads, which can be carried alone or in loose corymbs. The outside row

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 3 May-June 2025, pp: 1695-1703 www.ijprajournal.com ISSN: 2456-4494

of ray florets, or ligulate flowers and the inner disc of tubular florets, which are usually bright yellow to deep orange in colour, make up each flower head. A curving, boat-shaped achene is the fruit.[9]

BOTANICAL DESCRIPTION AND CULTIVATION

Calendula officinalis is an annual herbaceous plant belonging to the Asteraceae family. Native to the Mediterranean region, it is now widely cultivated globally. The plant is characterized by its bright orange or yellow daisy-like flowers, which are the primary source of medicinal properties. Calendula officinalis is relatively easy to cultivate, thriving in sunny locations and well-drained soil. Different varieties exist, varying in flower size, color intensity, and resin content, influencing their therapeutic efficacy.

TAXONOMICAL PROFILE

Kingdom : Plantae
Subkindom : Tracheobionta
Division : Magnoliophyta
Class : magnoliopsida
Subclass : Asteridae
Order : Asterales
Family : Asteraceae
Tribe : Calendulea
Genus : Calendula
Species : Officinalis[10]

MECHANISMS OF ACTION IN WOUND HEALING

Calendula officinalis exerts its wound-healing effects through a multi-pronged approach, targeting different stages of the healing cascade

Anti-inflammatory Activity

Inflammation is a crucial initial phase of wound healing. However, excessive or prolonged inflammation can hinder tissue regeneration. Triterpenoids, especially faradiol esters, are potent anti-inflammatory agents. Studies have shown that faradiol esters inhibit the activation of NF-κB, a key transcription factor involved in the expression of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6. Flavonoids also contribute to anti-inflammatory effects by inhibiting cyclooxygenase (COX) and lipoxygenase (LOX) enzymes, reducing the production of prostaglandins and leukotrienes, respectively. By modulating the inflammatory response, Calendula prevents excessive inflammation and promotes a more conducive environment for tissue repair.[11,12]

Stimulation of Angiogenesis

Angiogenesis, the formation of new blood vessels, is essential for delivering oxygen and nutrients to the wound site, supporting cell proliferation and tissue regeneration. Calendula extracts have been shown to stimulate angiogenesis in vitro and in vivo. The underlying mechanisms involve the upregulation of Vascular Endothelial Growth Factor (VEGF), a key regulator of angiogenesis. Triterpenoids and flavonoids contribute to this effect by promoting endothelial cell proliferation, migration, and tube formation.[13]

Enhanced Collagen Synthesis

Collagen is the major structural protein of the extracellular matrix (ECM) and plays a crucial role in wound strength and tissue integrity. Calendula promotes collagen synthesis by stimulating fibroblast proliferation and increasing the expression of collagen genes. Triterpenoids are particularly effective in enhancing collagen production by fibroblasts. The increased collagen deposition leads to improved wound closure and reduced scar formation.[14]

Granulation Tissue Formation

Granulation tissue is a temporary tissue that fills the wound defect during the repair process. It consists of fibroblasts, blood vessels, and inflammatory cells embedded in a collagen matrix. Polysaccharides in Calendula stimulate macrophage activity, promoting the clearance of debris and facilitating the formation of granulation tissue. These polysaccharides also enhance fibroblast proliferation, further contributing to the formation of granulation tissue.[15]

Epithelialization

Epithelialization is the process of re-establishing the epithelial barrier over the wound surface. It involves the migration and proliferation of keratinocytes from the wound edges. Calendula promotes epithelialization by stimulating keratinocyte proliferation and migration. Vitamin A, derived from carotenoids, plays a critical role in this process by regulating keratinocyte differentiation and promoting the formation of new epithelial tissue.[16]

Antioxidant Activity

Wound healing is associated with increased oxidative stress, which can damage cells and impair tissue repair. Calendula contains potent antioxidants, such as flavonoids and carotenoids, that scavenge free radicals and protect cells from oxidative damage. By reducing oxidative stress, Calendula promotes a more favorable environment for wound healing.[17]

Antimicrobial Activity

Wound infection is a major complication that can delay healing. The volatile oils and other constituents of Calendula exhibit antimicrobial activity against a range of bacteria and fungi, including Staphylococcus aureus and Candida albicans. This antimicrobial activity helps to prevent wound infection and promote faster healing.[18]

Immunomodulatory Activity

Calendula polysaccharides stimulate the immune system by activating macrophages and promoting the production of cytokines. This immunostimulatory effect enhances the body's natural defenses against infection and promotes efficient wound healing.

CHEMICAL CONSTITUENTS

Calendula officinalis's complex chemical composition provides to its wide range of pharmacological actions. The plant includes a wide range of chemical classes, including terpenoids, quinones, coumarins, flavonoids, essential oils, carotenoids, and amino acids, according to several phytochemical studies. The chemical composition of Calendula officinalis includes flavonoids, triterpeneol esters, and saponins. Numerous chemical components that are also used in the food and cosmetic industries include isorhamnetin, rutin, quercetin, and glucoside.[19]
The major bioactive constituents identified in the plant, particularly in the flowers, include:

- **Triterpenoids:** These compounds, particularly faradiol monoesters, are believed to be the primary drivers of Calendula's anti-inflammatory and wound-healing activities. Triterpenoids have demonstrated the ability to stimulate collagen synthesis, accelerate wound epithelization, and modulate the inflammatory response. These are considered the primary active constituents of Calendula, particularly oleanolic acid glycosides and faradiol esters. These include saponins (e.g., calendulosides A-H), which contribute to the plant's anti-inflammatory and wound-healing properties.[20]
- **Flavonoids:** Quercetin, rutin, and isorhamnetin are among the prominent flavonoids found in Calendula. These potent antioxidants protect against oxidative stress, a key factor in delayed wound healing. They also possess anti-inflammatory and antimicrobial properties, contributing to a healthier wound environment. They also exhibit antimicrobial and anticancer properties.[21]
- **Carotenoids:** β-carotene, lycopene, and lutein contribute to Calendula's vibrant color and act as antioxidants, protecting cells from free radical damage. β-carotene, in particular, can be converted to vitamin A, which is crucial for epithelial cell growth and differentiation, essential in the proliferative phase of wound healing. The bright orange and yellow colors of Calendula officinalis flowers are due to the presence of carotenoids, which act as antioxidants and contribute to skin protection.[22]
- **Essential Oils:** Composed of a complex mixture of volatile compounds like α-terpineol and linalool, these oils contribute to Calendula's antimicrobial and antiseptic properties. They can inhibit the growth of various bacteria and fungi, preventing wound infection and promoting a cleaner healing environment.[23]
- **Polysaccharides:** These complex carbohydrates, including mucilage, can contribute to wound hydration and promote fibroblast proliferation. They can also stimulate immune cell activity, contributing to the overall immune response in the wound bed.
- **Coumarins:** Coumarin derivatives such as umbelliferone are present in Calendula and contribute to its anti-inflammatory and anticoagulant properties.

TRADITIONAL USES

Calendula officinalis has a rich history of use in traditional medicine systems worldwide. Some of the most common traditional applications include:[24,25]

- **Wound Healing:** Arguably the most well-known application, calendula has been used to promote wound closure, reduce inflammation, and prevent infection in cuts, burns, ulcers, and bedsores.
- **Skin Conditions:** It has been employed to treat various skin ailments, including eczema, dermatitis, psoriasis, and acne, due to its

purported anti-inflammatory, antimicrobial, and moisturizing properties.

- **Gastrointestinal Issues:** Internally, calendula has been used to soothe digestive discomfort, treat gastric ulcers, and alleviate inflammatory bowel conditions.
- **Oral Health:** Calendula extracts have been utilized in mouthwashes and gargles to treat gingivitis, stomatitis, and sore throats.
- **Menstrual Issues:** In some traditional medicine systems, calendula has been used to regulate menstruation and alleviate menstrual pain.

CLINICAL APPLICATIONS OF CALENDULA OFFICINALIS IN WOUND MANAGEMENT

The wound-healing properties of Calendula have been demonstrated in various clinical studies. Calendula preparations, such as ointments, creams, and tinctures, have been used to treat:[26,27]

- **Burns:** Calendula has been shown to accelerate the healing of burns, reducing pain and inflammation**.**
- **Surgical wounds:** Calendula promotes faster healing of surgical wounds, reducing the risk of infection and scarring.
- **Venous leg ulcers:** Calendula may be beneficial in treating venous leg ulcers, although further research is needed.
- **Radiation-induced dermatitis:** Calendula cream has been shown to be effective in preventing and treating radiation-induced dermatitis in breast cancer patients.
- **Episiotomies:** Calendula can promote the healing of episiotomy wounds after childbirth.
- **Radiation Dermatitis:** Calendula has shown promise in preventing and treating radiation dermatitis, a common side effect of cancer radiation therapy. Several studies have found that Calendula cream is more effective than conventional treatments, such as trolamine, in reducing the severity of radiation dermatitis.
- **Diaper Rash:** Calendula ointments are commonly used to treat diaper rash in infants. Studies have shown that Calendula is effective in reducing inflammation and promoting healing of diaper rash.
- **Oral Mucositis:** Calendula mouthwashes have been investigated for the treatment of oral mucositis, an inflammation of the oral mucosa that can occur as a result of chemotherapy or radiation therapy. Some studies have found that Calendula mouthwashes can reduce the severity and duration of oral mucositis.

PHARMACOLOGICAL PROPERTIES OF CALENDULA OFFICINALIS

Calendula officinalis, commonly known as pot marigold, exhibits a wide range of therapeutic activities, making it a significant plant in traditional and modern medicine. Modern scientific research has investigated the pharmacological properties of Calendula officinalis, providing evidence to support its traditional uses and uncovering new potential applications.

Anti-inflammatory

Multiple studies have demonstrated the wound-healing properties of Calendula officinalis. The plant's triterpenes and flavonoids stimulate collagen synthesis, promote angiogenesis (formation of new blood vessels), and reduce inflammation, thereby accelerating wound closure and tissue regeneration. In vivo studies have shown that Calendula officinalis significantly improves wound healing in various animal models of skin injuries, including burns, incisions, and ulcers. Because of its superior anti-inflammatory properties, Calendula officinalis is presently the subject of research. The plant contains a variety of secondary metabolites that are linked to its anti-inflammatory properties, including alkaloids, tannins, flavonoids, essential oils, sterols, saponins, carotenoids, triterpene alcohols, mucilage, polysaccharides, and resin. Mostly used as a component of tinctures, ointments, and infusions, Calendula officinalis is used as a wound healing remedy for blisters, scars, mucous membranes, skin inflammations, tissue repair, and allergic responses.[28]

Antioxidant activity

The flavonoids and carotenoids present in Calendula officinalis are potent antioxidants that protect against oxidative stress. They can neutralize free radicals, prevent lipid peroxidation, and protect cells from damage. This antioxidant activity may contribute to the anti-inflammatory, wound-healing, and anti-aging effects of Calendula.[29]

Anti cancer activity

One of Calendula officinalis's isolated active ingredients, saponin, has been demonstrated to have antimutagenic properties. Several in vitro and in vivo studies have suggested that Calendula officinalis possesses anticancer activity. The plant's triterpenoids and flavonoids have been shown to inhibit the growth and proliferation of various cancer cell lines, including breast cancer, colon cancer, and leukemia cells. Furthermore, Calendula officinalis has been shown to induce apoptosis (programmed cell death) in cancer cells and inhibit angiogenesis, thereby suppressing tumor growth and metastasis.[30]

Wound-healing activity

Numerous studies have demonstrated the wound-healing properties of Calendula officinalis. It has been shown to accelerate tissue regeneration, promote collagen synthesis, and increase blood flow to the wound site. These effects are attributed to the combined action of triterpenoids, flavonoids, and other bioactive compounds. In vitro studies have shown that Calendula extracts can stimulate fibroblast proliferation and migration, key processes in wound repair. Animal studies have confirmed these findings, demonstrating faster wound closure and improved scar formation in Calendula-treated animals. Calendula officinalis may significantly boost collagen metabolism and wound angiogenesis, leading to emollient properties and softer scars. Calendula officinalis flower extract provides therapeutic benefits for burns and wounds when applied topically and taken orally.[31]

Antimicrobial activity

Calendula extracts have demonstrated antimicrobial activity against a range of bacteria, fungi, and viruses. The volatile oils and flavonoids are thought to be responsible for these effects. Studies have shown that Calendula can inhibit the growth of Staphylococcus aureus, Escherichia coli, and Candida albicans, among other pathogens. This antimicrobial activity may contribute to the wound-healing properties of Calendula by preventing infection. Broad-spectrum antibacterial action against a variety of bacteria, fungi, and viruses is exhibited by Calendula officinalis. By rupturing microbial cell membranes and interfering with microbial metabolism, the plant's essential oil and flavonoid contents help to produce its antimicrobial actions. Calendula officinalis plants have demonstrated the anthelmintic effect of saponins, demonstrating their anthelminthic properties.[32]

Immunomodulatory

Calendula officinalis has been shown to modulate the immune system, enhancing immune responses and promoting wound healing. Polysaccharides present in Calendula can stimulate macrophage activity and increase the production of antibodies.

SAFETY AND TOXICITY

Calendula officinalis is generally considered safe for topical use. However, some individuals may experience allergic reactions, such as contact dermatitis. Oral consumption of Calendula is also generally considered safe, but pregnant and breastfeeding women should consult with a healthcare professional before using Calendula products.

- **Allergic Reactions:** Individuals with allergies to plants in the Asteraceae family (e.g., ragweed, chrysanthemums, daisies) may be more likely to experience allergic reactions to Calendula.
- **Drug Interactions:** There is limited information available regarding potential drug interactions with Calendula. However, it is always advisable to consult with a healthcare professional before using Calendula products, especially if you are taking other medications.
- **Pregnancy and Breastfeeding:** While Calendula is generally considered safe for topical use during pregnancy and breastfeeding, there is limited data on its safety when ingested. Therefore, pregnant and breastfeeding women should consult with a healthcare professional before using Calendula products internally.

PROPERTIES CONTRIBUTING TO WOUND HEALING

Besides the mechanisms, several inherent properties of Calendula further contribute to its wound healing efficacy:[33,34]

- **Emollient and Moisturizing:** Calendula preparations often have emollient properties, which help to soften and soothe the skin. This is particularly beneficial for dry or irritated skin, improving its elasticity and promoting faster healing.
- **Vulnerary:** Calendula is traditionally recognized as a vulnerary herb, meaning it promotes wound healing. This traditional use is supported by scientific evidence demonstrating its ability to accelerate wound closure and reduce scarring.
- **Safety Profile:** Calendula is generally considered safe for topical use, with a low incidence of adverse reactions. However,

individuals with allergies to plants in the Asteraceae/Compositae family (e.g., ragweed, chrysanthemums) may experience allergic contact dermatitis.

FUTURE APPLICATIONS

While significant progress has been made in understanding the therapeutic potential of Calendula officinalis, further research is warranted in several areas:

- **Clinical Trials:** Conducting well-designed clinical trials to validate the efficacy of calendula for specific conditions, such as wound healing, dermatitis, and gastrointestinal disorders.
- **Mechanism of Action:** Exploring the precise mechanisms by which calendula exerts its therapeutic effects at the molecular level.
- **Cosmetics and Skincare:** The anti-inflammatory, antioxidant, and wound-healing properties of Calendula officinalis make it a valuable ingredient in cosmetics and skincare products. It is commonly used in creams, lotions, and ointments for soothing irritated skin, promoting wound healing, and protecting against sun damage.
- **Pharmaceuticals:** Further research into the bioactive constituents of Calendula officinalis and their mechanisms of action could lead to the development of new pharmaceuticals for the treatment of various diseases, including skin disorders, inflammatory conditions, and cancer.
- **Food Industry:** Calendula officinalis is sometimes used as a natural food coloring agent and flavouring agent.
- **Agriculture:** Calendula officinalis has been investigated for its pesticidal and nematicidal properties, suggesting a potential role in sustainable agriculture.

II. CONCLUSION

Calendula officinalis exhibits remarkable wound-healing properties due to the synergistic action of its diverse bioactive compounds. Triterpenoids, flavonoids, carotenoids, and polysaccharides collectively contribute to its anti-inflammatory, antioxidant, angiogenic, collagen-stimulating, granulation tissue-promoting, and epithelialization-enhancing effects. The antimicrobial and immunomodulatory properties of Calendula further contribute to its efficacy in wound management. Calendula can be effective in treating various conditions, such as radiation dermatitis, diaper rash, and oral mucositis. While generally considered safe, some individuals may experience allergic reactions. The increasing body of evidence supporting the clinical effectiveness of Calendula highlights its potential as a valuable therapeutic agent for the treatment of various types of wounds. Further research is warranted to optimize the formulation and delivery of Calendula-based products to maximize their therapeutic benefits. Further investigations are also needed to elucidate the specific molecular mechanisms underlying its wound-healing activity. The continued investigation into Calendula's wound healing potential holds promise for the development of novel therapeutic strategies for wound management.

CONFLICT OF INTEREST

The authors have no conflicts of interest.

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International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 3 May-June 2025, pp: 1695-1703 www.ijprajournal.com ISSN: 2456-4494

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