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Advances in *Calendula officinalis* Applications: Innovations in Wound Healing and Novel Drug Delivery Systems

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Abstract

A member of the *Asteraceae* family, *Calendula*, commonly known as marigold, has a longstanding history of medicinal use. This plant contains a wide variety of bioactive substances, including steroids, terpenoids, triterpenoids, flavonoids, phenolic acids, carotenoids, and essential oils. These compounds confer significant anti-inflammatory, antibacterial, antimicrobial, and anticancer properties, making *Calendula* a promising option for the treatment of various skin disorders, particularly wounds. Potential uses for *Calendula* extracts exist in the food, cosmetic, and pharmaceutical sectors. These extracts can be used as natural materials that offer helpful benefits for many health problems. This review highlights how *Calendula* helps in wound healing and medicine delivery, giving a clear and updated summary of its healing and medical uses. This review aims to highlight the potential of *C. officinalis* in wound healing and drug delivery, while addressing the limited research on its active compounds and the lack of standardised formulations and dosage guidelines. The review found that *Calendula* has strong healing potential because of its anti-inflammatory, antioxidant, and wound-healing properties, and it is generally safe to use. However, future studies should aim to identify its active compounds and conduct more clinical trials to explore its wider medical uses.

Major Findings: *Calendula officinalis* demonstrates strong anti-inflammatory, antioxidant, and wound-healing properties, making it effective in treating skin injuries and promoting tissue repair. It is safe and versatile for use in pharmaceuticals, cosmetics, and food industries, though further research is needed to identify active compounds and standardize formulations.

Keywords: Anticancer, Antimicrobial, Antioxidant, Anti-inflammation, Biomaterial, Biopolymers, *Calendula*, Drug delivery

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1. Introduction

Calendula officinalis is a member of the *Asteraceae* family and is generally referred to as pot marigold. It is a blooming plant with beautiful yellow blossoms. Since ancient times, this herb has been used medicinally to heal a variety of wounds and skin irritations[1]. Figure 1 shows *C. officinalis* pharmacological properties and applications. *C. officinalis* usually has between 10 and 25 species[2]. Field marigold, or *C. officinalis* ardencies, is a wild *Calendula* variety that is indigenous to North Africa, Asia, and Europe[3]. *C. officinalis* suffruticosa is one of the other species; its complicated shape makes it difficult to classify 2[4].

A species with a wide range of genetic variants, *C. officinalis* can adapt to a variety of settings. Because it is a polyploidy species[5], each gene is present in multiple copies, leading to a large number of alleles and a high level of genetic variation within the species. Chromosome doubling can be induced by colchicine, oryzalin, and trifluralin, according to research. This results in a chromosome set of two, demonstrating that *C. officinalis* is an all-tetraploid plant. According to another study, colchicine can cause mutations in

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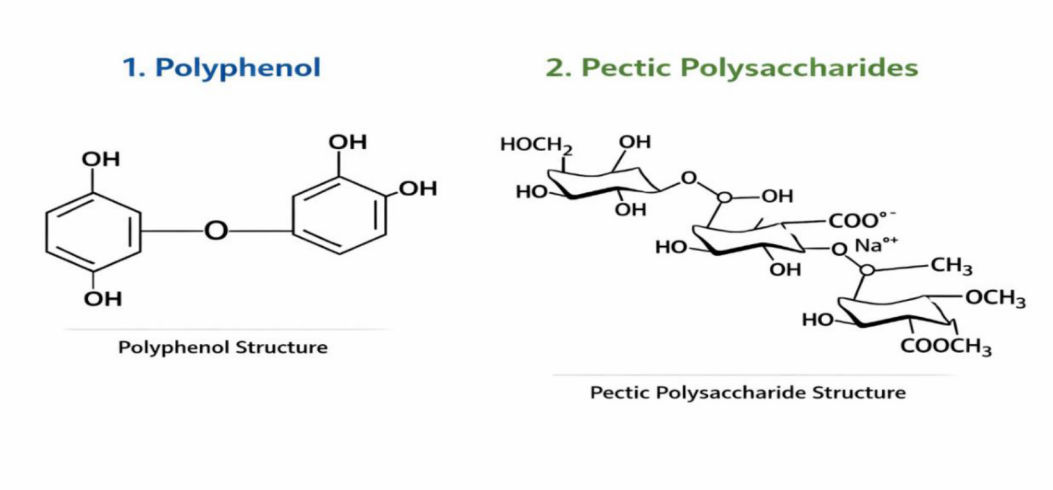


Figure 1. Pharmacological properties of *C. officinalis* and applications 1-polyphenol and 2- pectic polysaccharides.

Calendula plants, which improves yield, quality, and the ability to detect molecular similarities between species. These mutations also have a high heritability[6].

Light green leaves and yellow or orange oblong-spatulate petals characterise the fragrant herb *Calendula* flos. The plant has tube-shaped, projecting ligulae florets and produces curved achenes. The plant material, including composite flowers, dried ligulae florets, different trichomes, and oil droplets, is described in depth in the World Health Organisation's monograph on selected therapeutic plants[7].

According to the European Medical Agency's Committee on Herbal Medicinal Products (HMPC), *Calendula* flower medicines have been used traditionally to heal minor wounds, mouth or throat irritation, and skin inflammations. The fact that drugs containing *Calendula* have been used safely for at least 30 years lends credence to this notion, even in the absence of sufficient clinical data. Although clinical studies for skin conditions were considered, the outcomes were not totally clear due to issues with the study design.

According to the British Herbal Pharmacopoeia, *Calendula* is also used as an herbal medicine for duodenal ulcers, sebaceous cysts, swollen or irritated lymphatic nodes, and acute and chronic inflammatory skin lesions[8]. According to EMA monographs and the European Scientific Cooperative on Phototherapy (ESCOP), *Calendula* can be administered topically or eaten orally. To give a remedy, national authorities must assess an application and consider the scientific results of the HMPC. Examples of appropriate dosage forms include gels, creams, liquids, ointments, solutions, and sprays[9].

The World Health Organisation's (WHO) compendium on medicinal plants recommends a tincture or infusion of 12g/150 mL for topical application, a 40% alcohol extract for external use, and a 25% ointment for wounds and compresses Health Canada's *Calendula* monograph and other easily accessible monographs cover a variety of preparation methods designed for topical application, such as decoction, infusion, and oil infusion. 90-100% of the extract should be present in these processes. Two to twenty per cent of the dried flower should be present in semi-solids (dry powder, cream, gel, ointment, and salve)[10,11], five to ten per cent in tinctures and fluid extracts and one to one hundred per cent in tinctures and fluid extracts.

2. Active Compounds of *C. officinalis*

Triterpenoids (its main natural group , triterpene alcohols, and triterpene saponins), polyphenolic compounds (phenolic material acids and flavonoids), carotenoids, and polysaccharides are the main active ingredients in *C. officinalis*. These substances offer the plant a wide range of therapeutic applications in addition to extensive potential in the food, pharmaceutical, and cosmetic sectors[12-14]. The molecular structure of some of the main active ingredients is shown in Figure 1. The metabolites of terpenoids

Table 1. Basic structure for each terpenoid compound present in *C. officinalis*[18-20]

Compound name	Type of compound	Chemical class/series	Functional group/ derivative	Molecular formula	Basic structural description
3-O-Laurate	Terpenoid ester	Oleanane-type triterpenoid	Laurate (C_{12} fatty acid) ester at position 3	Approx. $C_{42}H_{70}O_3$	Oleanane skeleton esterified with lauric acid at the 3-hydroxyl group
Arnidiol-3-O-Myristate	Triterpenoid ester	Oleanane-type	Myristate ester of Arnidiol at position 3	$C_{46}H_{80}O_3$	Arnidiol backbone esterified with myristic acid; long C_{14} chain
Arnidiol-3-O-Laurate	Triterpenoid ester	Oleanane-type	Laurate ester of Arnidiol at position 3	$C_{44}H_{76}O_3$	Arnidiol with lauric acid chain; similar to Myristate but shorter chain
*Calendula*diol-3-O-Palmitate	Triterpenoid ester	Oleanane-type	Palmitate ester of *Calendula*diol at position 3	$C_{48}H_{84}O_3$	Calenduladiol with a C_{16} palmitic acid moiety; increases lipophilicity
Calenduladiol-3-O-Myristate	Triterpenoid ester	Oleanane-type	Myristate ester of Calenduladiol at position 3	$C_{46}H_{80}O_3$	*Calendula* diol with C_{14} myristic acid; typical of *Calendula* triterpenes
Triterpenic Oleanolic Acid Saponins	Saponin (glycoside)	Oleanane triterpenoid	Glycosidic derivative of oleanolic acid	$C_{30}H_{48}O_3$ (aglycone) + sugar moieties (commonly glucose, rhamnose)	Oleanolic acid with sugar units linked to hydroxyl groups; amphiphilic
Saponins of Oleanane Triterpene Glycosides	Saponin	Oleanane-type triterpenoid	Glycosidic linkage with sugars	Variable; typically $C_{48}C_{60}$ range depending on sugar type	Contain oleanane aglycone bound to one or more sugar residues
Glucuronides (of triterpenoids)	Glycosidic conjugate	Triterpenoid derivative	Glucuronic acid conjugate	Variable; ~$C_{36}C_{52}H_{6084}O_{816}$	Triterpenoid backbone with a glucuronic acid moiety, enhancing solubility
Cornulacic Acid Acetate 21	Triterpenic ester	Oleanane series	Acetate ester of cornulacic acid	$C_{32}H_{52}O_5$	

exhibit a diverse array of chemical structures[15]. Terpenoids are derived from the polymerisation of the five-carbon precursor isoprene[16,17] and include the following subgroups: monoterpenes, sesquiterpene, triterpenes, triterpenes, and tetra terpenes (Table 1).

This group also includes steroids. Sterols like cholesterol and ergosterol are used in investigations on plant growth, development, and synthetic biology Steroids typically include 17 carbon atoms in their nucleus, which has four rings, one more than most other terpenes. These are essential signalling molecules that are created as the body breaks down cholesterol [21].

Calendula plants are among the many different types of plants that contain polyphenols, often known as phenolic chemicals. Both flavonoids and phenolic acid are polyphenols and share molecular similarities[22]. They both contain at least one aromatic ring and one complicated molecule. One or more hydroxyl groups are present in the aromatic ring that makes up phenolic acids. The flavone structure of flavonoids is made up of two aromatic rings connected by a bridge of three carbons[23,24].

They contain antioxidants called polyphenols, which assist your body aerobicize fat by lowering insulin resistance. According to reports, they mediate several cellular and molecular signalling pathways that contribute to their anti-oxidative, anti-inflammatory, and anti-cancer properties[25]. By affecting the tumour both inside and externally, these substances have the capacity to affect the development of cancer and its progression at every stage[26]. In one study, polyphenols showed a chemo preventive effect by regulating a

number of molecular processes, such as apoptosis, autophagy, cell cycle progression, inflammation, invasion, and metastasis.

The fact that they can cooperate with clinically approved drugs further demonstrates their potential for clinical usage in the treatment of various human malignancies. By focusing on the viral maturation cycle rather than viral entrance, polyphenolic substances, in particular curcumin, hesperidin, and quercetin, showed possible inhibitory effects on SARS-CoV-2, according to another study[27]. By supplying carbon sources, creating proton motive forces during metabolism, and encouraging the growth of advantageous probiotic bacteria like Lactobacilli and Bifidobacterium, polyphenols also have a good impact on gut health. Rodriguez-Daza *et al.*'s review[28] states that polyphenols alter gut microbiota in a number of ways. Among them are interactions with bacterial proteins that change the fluidity and structure of cell membranes, impact the synthesis and integrity of cell walls, interfere with bacterial metabolism, and prevent the formation of biofilms[29]. Additionally, by decreasing the activity of metalloenzymes and interfering with oxidative phosphorylation and cytochrome home production, polyphenols can chelate important metals such as iron, copper, and zinc, which are crucial cofactors for bacterial enzymes and hence hinder pathogen colonisation in the gut.

All things considered, polyphenols have a major impact on gut health through modifying the integrity of the intestinal barrier, immunological responses, intracellular signalling pathways, and microbiota composition. Another significant family of bioactive metabolites are carotenoids, which are distinguished by a complex conjugated double bond system that gives them their unique hue[30]. Carotenoids are structurally categorised as either carotenes or xanthophylls and have a C40 backbone made up of eight isoprene units. These substances have high levels of provitamin A, which is necessary for good vision, and they have potent antioxidant qualities that help prevent and resist disease[31]. Carotenoids generated from *Calendula* can be found in the stems, leaves, and petals of plants. These carotenoids include lutein, 9/9′A-lutein, 13/13′Z-lutein, α-kryptoxanthin, β-kryptoxanthin, Z-kryptoxanthin, lycopene, 9Z-neoxanthin, Violaxanthin, luteoxanthin, auroxanthin, 9Z-violaxanthin, Flavoxanthin, mutatoxanthin, 9Z-anthroxanthin, lutein, and lutein.

Polysaccharides, the most abundant class of carbohydrates, can be categorised based on their chemical composition and structural complexity. They consist of monosaccharide units linked via Glycosidic bonds and may also be covalently bound to other biomolecules such as peptides, amino acids, and lipids. Structurally, polysaccharides are classified into two main groups: homopolysaccharides, which are composed of identical monosaccharide units, and heteropolysaccharides, which contain a variety of monosaccharides[32]. Although the precise mechanisms of action of pectic polysaccharides (pectins) found in *Calendula* remain under investigation, these compounds have shown potential in therapeutic applications, particularly in the biopharmaceutical field. *In vitro* studies on cultured cancer cells have revealed that pectin preparations exhibit both cytotoxic and anti-migration effects. The anticancer properties of pectic polysaccharides extend beyond direct inhibition of tumour growth or induction of apoptosis; they also include indirect mechanisms such as modulation of immune responses, gut microbiota, and metabolic pathways[33].

It is thought that the synergistic interactions between *C. officinalis* many active components increase its bioactivity. When the combined effects of several substances are greater than the sum of their individual activities, this is known as synergy. For example, research has shown that the phytoconstituents in *Calendula* work together to increase their biological efficacy. The combination of carotenoids, polyphenols, and flavonoids in *Calendula* extract, for instance, produced a hydrophilic cream formulation with excellent antioxidant activity and showed both chemical and microbiological stability.[34]

Furthermore, *Calendula* extracts have shown variable bioactivity depending on their composition. An extract rich in polyphenols and β-carotene displayed superior nephroprotective effects compared to aqueous floral extracts, likely due to its higher concentration of bioactive compounds[35]. This highlights the significance of compound profile in determining therapeutic potential.

In general, the diverse bioactive constituents of *Calendula*, including triterpenoids, polyphenols, carotenoids, and flavonoids, contribute collectively to its broad spectrum of health benefits. Triterpenoids possess

Table 2. Pharmacological activities of *C. officinalis*, associated bioactive compounds, mechanisms, models, and key references

Activity	Bioactive compounds	Proposed mechanism of action	Experimental/ clinical model	Basic structural description	References
Anti-inflammatory	Faradiol monoesters, Arnidiol, Calenduladiol	Inhibition of COX and LOX pathways; downregulation of NF-κB and TNF-α	Carrageenan-induced paw edema, topical application models	Faradiol monoesters, arnidiol, and Calenduladiol inhibit COX/ LOX enzymes and suppress NF-κB, reducing inflammation effectively.	41
Antioxidant	Quercetin, Isorhamnetin, Rutin, Chromogenic acid	Free radical scavenging, inhibition of lipid peroxidation, and enhancement of antioxidant enzymes	DPPH and ABTS assays; cell culture oxidative stress models	Quercetin, isorhamnetin, rutin, and chromogenic acid scavenge free radicals and enhance cellular antioxidant defence enzymes.	42
Wound healing	Faradiol esters, Calenduladiol, Oleanolic acid saponins	Collagen synthesis stimulation, angiogenesis, and fibroblast proliferation	Incision and burn wound models; clinical wound trials	Faradiol esters, Calenduladiol, and oleanolic acid saponins enhance collagen synthesis and tissue regeneration, promoting wound healing.	43
Antimicrobial/ Antifungal	Oleanolic acid glycosides, Flavonoids	Disruption of microbial membranes, inhibition of bacterial adhesion	Cultures of *S. aureus, P. aeruginosa*, and *C. albicans*	Oleanolic acid glycosides and flavonoids disrupt microbial membranes, inhibit enzymes, and suppress pathogen growth, exhibiting strong antimicrobial and antifungal activities.	44
Anticancer/ Immuno modulatory	Triterpenoids, Flavonoids, Polysaccharides	Induction of apoptosis; activation of caspase cascade; enhancement of immune cell activity	Tumour cell lines; macrophage assays	Triterpenoids, flavonoids, and polysaccharides exhibit anticancer and immunomodulatory effects by inducing apoptosis, inhibiting proliferation, and enhancing immune cell activity and cytokine regulation.	45
Gastro protective	Oleanolic acid, Flavonoids	Maintenance of mucosal integrity, suppression of oxidative stress	Ethanol-induced gastric ulcer model	Oleanolic acid and flavonoids provide gastro protective effects by reducing gastric acidity, enhancing mucus secretion, and preventing oxidative and inflammatory gastric mucosal damage.	46
Hepato protective	Oleanolic acid saponins, Phenolic acids	Reduction of serum transaminases, lipid peroxidation inhibition	CCl_4-induced hepatotoxicity model	Oleanolic acid saponins and phenolic acids protect the liver by reducing oxidative stress and stabilising hepatocyte membranes.	47
Antiviral	Flavonoids, Saponins	Inhibition of viral replication, interference with viral envelope proteins	HSV-1 and influenza virus models	Flavonoids and saponins inhibit viral replication, block entry, and enhance host antiviral immune responses.	48

notable antibacterial and anti-inflammatory properties, supporting their use in infection control and inflammation management, while polyphenols are renowned for their antioxidant and anti-inflammatory activities.

3. Pharmacological Activities of *Calendula*

Because of its anti-inflammatory, antioxidant, and antibacterial qualities, research shows that *C. officinalis* is useful in the treatment of a number of skin conditions. An overview of *C. officinalis* pharmacological effects is given in Figure 2[36]. Flavonoids and phenolic acids are among the plant's notable polyphenolic components, which have been linked to strong anti-inflammatory and antioxidant properties[37]. Apart from polyphenols, *Calendula* also includes carotenoids, which are widely recognised for their anti-ageing and UV protection qualities[38].

Moreover, *C. officinalis* has been demonstrated to alter the control of enzymes crucial to the wound-healing process, particularly Matrix Metalloproteinases (MMPs), which play a vital role in tissue remodelling and repair[39]. *Calendula* extract showed promise in preventing and repairing UV-damaged skin by modulating the activity and production of MMP-2 and MMP-9 after exposure to UVB radiation in a mouse model experiment[40] (Table 2).

4. Antioxidant and Anti-inflammatory Synergy of *C. officinalis*

The antioxidant and anti-inflammatory properties of *C. officinalis* are closely interconnected and represent key mechanisms underlying its therapeutic efficacy. Many of its bioactive constituents, including flavonoids (quercetin, isorhamnetin, apigenin), carotenoids, triterpenoids (faradiol, *Calendula* diol, arnidiol), and saponins (oleanolic acid derivatives), act synergistically to reduce oxidative stress and suppress inflammatory responses. These compounds collectively form a potent defence system that mitigates cellular injury caused by free radicals and inflammatory mediators.

The antioxidant defence of *Calendula* plays a crucial role in modulating inflammation. Reactive Oxygen Species (ROS) are major mediators of inflammatory processes, and *Calendula* compounds counteract this by scavenging free radicals, protecting lipids and proteins from oxidative damage, and maintaining intracellular redox balance. This ant oxidative modulation downregulates key pro-inflammatory pathways such as NF-κB, COX-2, and iNOS, thereby reducing the synthesis of prostaglandins, TNF-α, and interleukins responsible for pain, swelling, and tissue injury. Furthermore, these compounds enhance the activity of endogenous antioxidant enzymes, including Superoxide Dismutase (SOD), Catalase (CAT), and

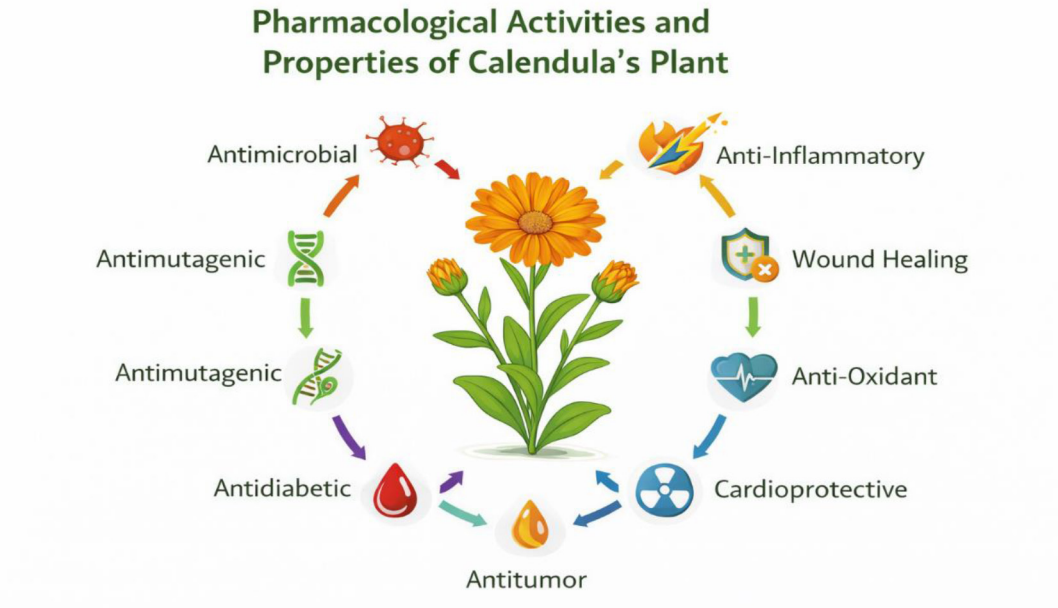


Figure 2. The pharmacological activities and properties of *Calendula*'s plant[36].

Ascorbate Peroxidase (APX), helping to preserve cellular homeostasis during oxidative and inflammatory stress.

Several experimental and clinical studies have confirmed the dual antioxidant and anti-inflammatory potential of *C. officinalis*. In extract-based antioxidant assays such as FRAP, DPPH, and ABTS, both metabolic and alcoholic extracts demonstrated strong antioxidant capacity, largely attributed to their phenolic and flavonoid content. The highest activity was noted in extracts derived from bracts and fruits, associated with hydroxycinnamoyl compounds and oleanolic acid saponins. Similarly, plants grown in substrates containing heavy metals (Ni, Cr, Co, Cd) exhibited significantly increased SOD, CAT, APX, and POD activity, indicating an adaptive enzymatic antioxidant defence mechanism under oxidative stress conditions.

In models of UV-induced skin damage and exercise-induced muscle stress, *Calendula* extract enhanced Glutathione (GSH) levels, preserved antioxidant enzyme activity, and protected tissue integrity. In combination with Ribes nigrum and Vaccinium myrtillus, it reduced markers of muscle injury such as Ammonia (NH_3), Blood Urea Nitrogen (BUN), and Creatine Kinase (CK), demonstrating its systemic antioxidant capability. Anti-inflammatory studies further revealed that *Calendula* extracts significantly reduced paw edema and nitric oxide production in LPS-stimulated macrophages, suggesting effective suppression of inflammatory mediator release. Notably, a 50% inhibition of nitrite production was achieved at 147 µL/mL without affecting macrophage viability, highlighting both potency and safety.

The anti-inflammatory mechanism of *Calendula* also extends to modulation of the peripheral opioid pathway. Topical creams containing 1030% *Calendula* extract reduced formalin-induced pain by activating peripheral opioid receptors and alleviating oxidative and inflammatory responses. This dual action was accompanied by a decrease in TNF-α levels and reduced histopathological damage, mechanical hypersensitivity, and edema in both acute and chronic inflammation models. In clinical settings, a chitosan-silver nanoparticle hydrogel enriched with *Calendula* extract promoted wound healing in diabetic patients by enhancing fibrinolysis, maintaining a moist healing environment, reducing edema, and minimising infection risk.

Overall, the synergistic antioxidant and anti-inflammatory activities of *C. officinalis* can be attributed to the integrated actions of its flavonoids, triterpenoids, carotenoids, and saponins. These bioactive compounds act in concert to scavenge ROS, enhance antioxidant enzymes, and inhibit inflammatory mediators such as COX-2, TNF-α, and iNOS. Through this multifaceted mechanism, *C. officinalis* offers significant potential in wound healing, tissue repair, pain management, and oxidative stress-related disorders. Its ability to regulate both oxidative and inflammatory pathways underscores its value as a multifunctional therapeutic agent in modern psychopharmacology and as a promising component of advanced drug delivery systems[49-61].

5. Antimicrobial Properties

The propensity of plant-based extracts to have less adverse effects is one of their noteworthy benefits as antibacterial agents[62]. Extracts from *C. officinalis* have demonstrated effectiveness against a variety of gram-positive and gram-negative bacteria[63]. Terpenes included in the plant's essential oils are largely responsible for this antibacterial activity[64]. Its efficacy against different pathogens is being supported by an increasing amount of research. Many studies have documented the capacity of *Calendula* to suppress the growth of pathogens, including Salmonella spp., Aspergillus spp., Bacillus subtilis, Enterococcus faecalis, Enterococcus faecium, Propionibacterium acnes, and Klebsiella pneumoniae[65]. In a single investigation, *Calendula* extracts exhibited potent antibacterial activity against coagulase-positive and coagulase-negative Staphylococcus species, *E. coli*, Pseudomonas aeruginosa, and Enterococcus species. Furthermore, fluconazole was found to have comparable antifungal action against Candida albicans and Candida parapsilosis[66]. Another study found that using *C. officinalis* to treat tooth root canals reduced the growth of Streptococcus mutans[67].

In addition to its direct antibacterial properties, *Calendula* contains helpful endophytic bacteria that are efficient against fungal infections in plants, including Pseudomonas and Agrobacterium. The antifungal activities of *Calendula* may be attributed to the bioactive substances produced by these bacteria, including chitinase, protease, β-1,3-glucanase, lipase, hydrogen

cyanide, indole-3-acetic acid, and ACC deaminase[68]. This implies that *Calendula* may be used to treat fungal infections in people via comparable methods. All things considered, *Calendula* extracts' antibacterial properties make them viable options for the treatment of bacterial and fungal illnesses, providing therapeutic efficacy with a decreased chance of side effects.

6. Anticancer Properties

Substantial evidence supports the anticancer potential of *Calendula* demonstrated that the ethyl acetate extract from *Calendula* ardencies flowers exhibited cytotoxic effects against both estrogen receptor-positive and triple-negative breast cancer cell lines, with IC_{50} values of 70 µg/mL and 78 µg/mL, respectively[69]. The observed anticancer activity was linked to the induction of apoptosis via the caspase signalling pathway, involving DNA fragmentation, increased Bax/Bcl-2 ratios, cell shrinkage and detachment, nuclear condensation, and activation of caspases 3 and 7. Notably, even at non-cytotoxic doses, the extract inhibited the migration of MCF-7 breast cancer cells. Similarly, extracts from *C. officinalis* flowers demonstrated even stronger cytotoxic effects on breast cancer cell lines[70].

In addition to flower extracts, the leaves of *Calendula* also possess anticancer properties. One study investigated iron nanoparticles synthesised using *Calendula arvensis* leaf extract and found them effective against cholangiocarcinoma cells, showcasing both cytotoxic and antioxidant activities[71]. Importantly, *Calendula* has been reported to selectively target cancer cells while sparing healthy ones. Methanolic extracts of *C. officinalis* leaves ardens inhibited the proliferation of breast cancer cells without affecting normal cells[72], suggesting that its flavonoid-rich composition may serve as a promising natural agent for broad-spectrum cancer therapy.

Furthermore, *Calendula* may alleviate complications associated with cancer treatments. In a clinical trial, a topical cream containing *C. officinalis* was used to manage radiation-induced dermatitis in breast cancer patients[73]. The study assessed the effectiveness of three herbal formulations, including *Calendula* oil, in preventing skin toxicity during radiotherapy among 59 patients, 53 with invasive breast cancer and 6 with head and neck cancer. Results showed that the prophylactic application significantly reduced the severity of radiation-induced skin damage during treatment and up to four weeks post-therapy. None of the participants developed grade III dermatitis, and outcomes varied based on treatment and patient specific factors[74].

In summary, *C. officinalis* demonstrates a wide range of anticancer activities, including the ability to induce apoptosis, inhibit cell proliferation, and prevent metastasis, all while showing minimal toxicity to healthy tissues. Moreover, its inclusion in advanced drug delivery systems offers promising potential for

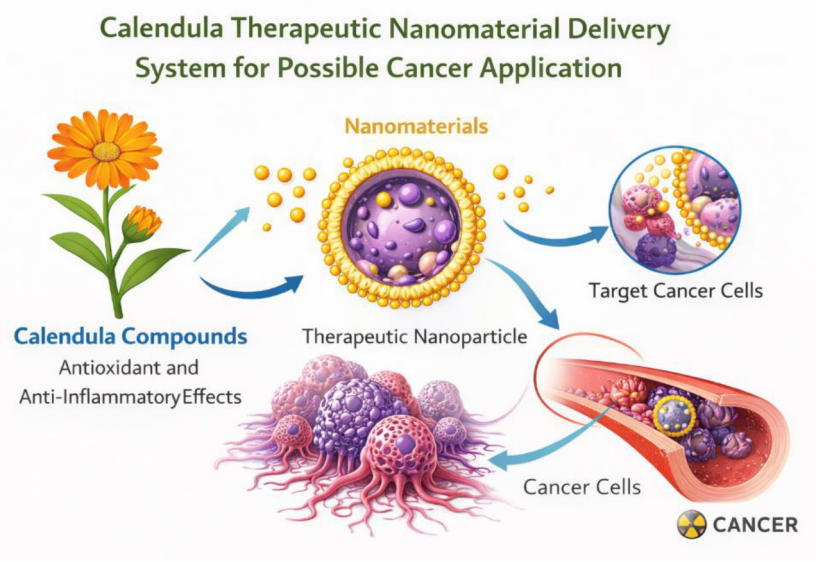


Figure 3. *Calendula* therapeutic nanomaterial delivery system for possible cancer application.

improving the efficacy and safety of breast cancer therapies. Figure 3 illustrates prospective delivery systems incorporating *Calendula* and its bioactive constituents for breast cancer treatment[75].

7. Delivery Systems Containing *Calendula*

Because *Calendula* has anti-inflammatory, antioxidant, and anti-tumour properties, research using it to treat conditions like cancer, skin infections, inflammation, and wound healing has shown promising results[76]. Illustrates how *Calendula* works to promote wound healing 52. These pathways involve critical molecules such as NF-κB, TNF-α, IL-1β, VEGF-C, SMAD, and PI3K/Akt, which collectively contribute to inflammation reduction, cell proliferation, and tissue regeneration (Figure 4). In support of these mechanisms, various studies have developed *Calendula*-based wound healing systems[77]. For instance, hydrogels made from chitosan, sodium alginate, and polyvinyl alcohol infused with Ag_2O, SiO_2 nanoparticles, and *Calendula* extract significantly improved healing. Similarly, collagen films loaded with *Calendula* flower extract accelerated wound contraction in rats and were shown to be non-toxic[78]. A green synthesis method using *Calendula* extract to create titanium oxide nanoparticles showed dose-dependent cytotoxicity against colorectal cancer cells[79], indicating both antioxidant and anticancer potential. Additionally, collagen scaffolds embedded with *Calendula* micro particles enhanced extract stability and release, showing promise for chronic wound treatment[80].

Other delivery platforms, such as solid lipid nanoparticles containing *Calendula* and biocompatible compounds, proved beneficial for eye surface repair. Electrospun nanofibers with chitosan, polyethylene glycol, or PVA and sodium alginate combined with *Calendula* extract promoted cell adhesion and proliferation, achieving up to 87.5% wound closure in rats by day 14[81]. These findings demonstrate *Calendula*'s versatility in advanced wound healing formulations.

8. *Calendula officinalis* Mode of Action in Wound Healing

Through potential mechanisms like decreased inflammation, enhanced blood flow, and antimicrobial activity, *Calendula* aids in wound healing. *Calendula* supports wound healing through flavonoids, such as quercetin, which have potential applications in reducing inflammation, improving blood flow, and antibacterial activity. *C. officinalis* flavonoids, which include quercetin, have beneficial properties that reduce swelling and inflammation, so the wound remains focused on healing. In order to give vital nutrients and oxygen for tissue regeneration, *Calendula* may enhance blood flow to the wound site[82].

By breaking the cell membrane of microorganisms (fungi and bacteria), it may also have some direct

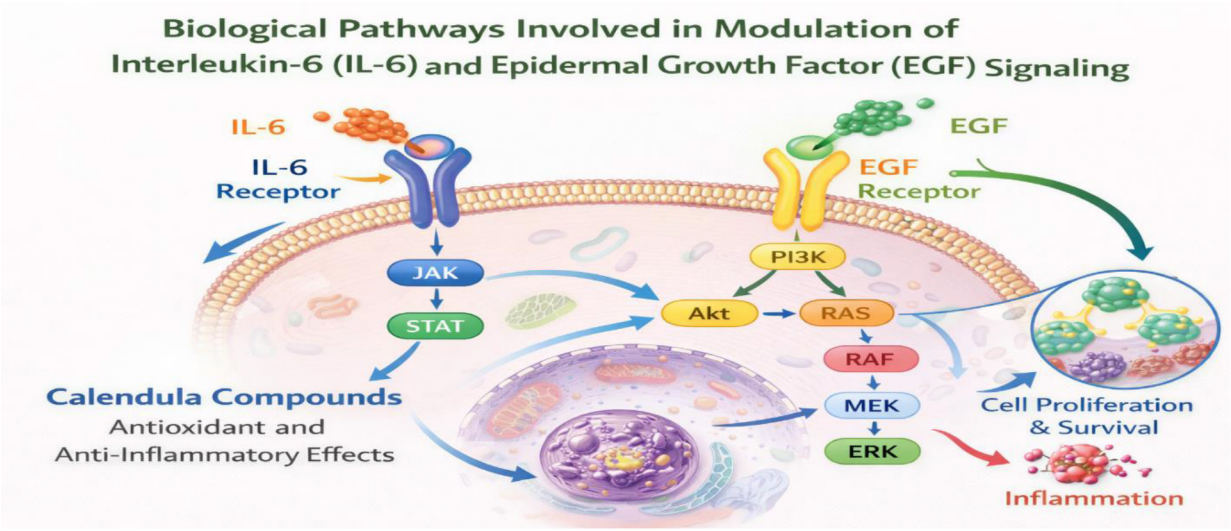


Figure 4. Biological pathways involved in the modulation of interleukin-6 (IL-6) and Epidermal Growth Factor (EGF) signalling.

antibacterial actions, preventing wound infections that can slow healing. Cell death results from this disruption because it increases permeability and lets vital components escape. The precise mechanism of blood flow and antibacterial action is still being studied and is not fully known. A key component of the inflammatory response, NF-κB, is one of the pro-inflammatory cytokines released by activated platelets upon damage[83]. By preventing the activation of these cytokines, *C. officinalis* reduces neutrophil recruitment and stops the subsequent release of Myeloperoxidase (MPO). The oxidative stress and tissue damage usually linked to the early inflammatory stage of wound healing are lessened by this decrease in neutrophil activity.

Additionally, by reducing the synthesis of pro-inflammatory cytokines like IL-6, TNF-α, and IL-1β, *Calendula* may also affect macrophage function. By downregulating bcl-2-like protein 4 (BAX), a pro-apoptotic protein that is essential to apoptosis, this modulation lowers oxidative stress and the incidence of apoptosis (programmed cell death)[84]. As a result, this reduces excessive inflammation and cell death, which improves the healing environment.

Re-epithelialization and the creation of granulation tissue depend on the proliferative and migratory ability of keratinocytes and fibroblasts, which is improved when oxidative stress is downregulated[85]. Further supporting increased keratinocyte activity and the subsequent epithelialization of the wound mediated by cues received from IL-6, as well as fibroblast migration and proliferation, is increased production of transforming growth factor-β (TGF-β) 66 and Vascular Endothelial Growth Factor (VEGF-c). These elements are necessary for the development of fresh granulation tissue as well as the general structural. By upregulating the production of collagen-1 and the anti-decapentaplegic homolog 3 (Smad-3) protein in mothers, *C. officinalis* may also promote angiogenesis, which is crucial for the formation of new blood vessels and tissue remodelling. *C. officinalis's* role in fortifying the wound's structural framework and encouraging quicker, more complete healing is highlighted by the increase in hydroxyproline, a crucial component of collagen.

The balance between the Smad-3 and mothers against decapentaplegic homolog 7 (Smad-7) pathways is crucial for wound healing. While Smad-7 functions as a negative feedback regulator, Smad-3 promotes collagen deposition and fibrosis[86]. Because *Calendula* can alter these pathways, extracellular matrix components are deposited in a balanced manner, avoiding excessive fibrosis and encouraging the best possible wound healing. It's crucial to remember that additional study is required

9. Utilising *Calendula* in Clinical Trials

Clinical research has thoroughly examined *Calendula*'s potential therapeutic benefits for a range of illnesses. These investigations demonstrate its encouraging anticancer qualities, especially in *C. officinalis*[87]. Clinical evidence indicates that *Calendula* may significantly aid wound healing, alleviate inflammation, and help manage symptoms of several medical conditions. For instance, in breast cancer patients, a clinical trial comparing *Calendula* with trolamine showed that *C. officinalis* was more effective in reducing acute radiation-induced dermatitis and pain during radiotherapy, despite being more difficult to apply. Furthermore, *Calendula*-based creams have demonstrated anti-inflammatory effects and have shown comparable efficacy to standard corticosteroid creams in treating mild to moderate dermatitis[88]. These findings suggest that *Calendula* may play a valuable role in preventing and treating radiation-related skin damage, ultimately enhancing the quality of life for cancer patients undergoing radiotherapy.

The *Calendula officialises* anticancer potential, showing *in vitro* effects like cell cycle arrest and growth inhibition, *in vivo* antitumor and chemo preventive actions, and palliative benefits reducing breast cancer treatment side effects.

A number of clinical studies have explored the therapeutic potential of *C. officinalis* for a variety of health conditions. One such study involved 240 participants aged 20 to 40 with gingivitis and bleeding gums[89]. Participants were randomly divided into two groups: one used a *Calendula* tincture mouthwash, and the other used a placebo. Clinical assessments were conducted at baseline, three months, and six months. Although the reductions in plaque and gingivitis were modest, *Calendula* mouthwash still showed a positive impact over time, even in the absence of dental scaling.

In a separate double-blind trial with 16 participants, subjects used both a *Calendula*-based and a chlorhexidine mouth rinse over two separate test periods. After each cycle, plaque was measured, and taste preferences were recorded using a Visual Analogue Scale (VAS). Results indicated that the *Calendula* mouth rinse was not only more effective in plaque control but also better tolerated in terms of taste. Another study showed that a *Calendula* mouthwash helped reduce oropharyngeal mucositis in head-and-neck cancer patients undergoing radiotherapy[90]. *Calendula* has also demonstrated effectiveness in wound care. In a clinical trial with 72 first-time mothers recovering from caesarean sections, those treated with *Calendula* ointment experienced faster healing based on the REEDA scale (redness, Edema, ecchymosis, discharge, and approximation) compared to those receiving standard hospital care[91].

Calendula officinalis potential to reduce menstrual pain is being studied in the field of women's health. Since anti-inflammatory drugs that block prostaglandins are frequently used to treat dysmenorrhea, *Calendula* is a good option because of its active ingredient, curcumin. A clinical trial evaluating curcumin for menstrual pain relief found it effective and well-tolerated, suggesting *C. officinalis* potential utility for this purpose[92]. *C. officinalis* has also proven beneficial for postpartum recovery. A study found that *Calendula* ointment helped reduce discomfort, bleeding, and dyspareunia following episiotomy in women with full-term, singleton pregnancies[93]. Moreover, *Calendula* may have therapeutic benefits for gastrointestinal issues like inflammatory bowel disease, gastric ulcers, and peptic ulcers due to its anti-inflammatory and tissue-repair properties.

Despite these promising findings, further research is necessary to determine the most effective dosages, delivery forms, and treatment durations for various conditions. Table 3 provides a summary of selected clinical studies on *Calendula* conducted from 2019 to the present.

Table 3. Selected *Calendula* use in human clinical trials published since 2019 upwards

S. No.	Study type	Number of participants	Agent	Outcome	References
1	triple-blind clinical trial	60	Oral *C. officinalis*	Accelerated the healing of burn wounds	[94]
2	Open-label	59	Radiation dermatitis cream, ointment, shower gel (*Aloe vera* gel, *C. officinalis* and *Hypercom perforatum* oil extract)	Reduction in the severity of radiation dermatitis	[95]
3	triple-blind randomised clinical trial	54	Topical cream including *Calendula*, chamomile (*Anthemis nobilis*), rose geranium (*Pelargonium graveolens*), cocoa butter (*Theobroma* oil), and soybean	Low prevalence and severity of Striae Gravidarum	[96]
4	randomised, double-blind study	66	face serum (*C. officinalis, Glycyrrhizins glaba* root extract, and snail secretion filtrate)	Treatment of face acne due to face masks	[97]
5	Randomised clinical trial	90	*Aloe vera* gel, *C. officinalis* ointment and prophylactic dressing	Prevention of pressure injury in intensive care patients	[98]
6	Controlled randomised clinical trial	20	*C. officinalis* extract	Healing of an acute hand wound	[99]
7	Randomised controlled trial	82	Topical *C. officinalis*	Efficacy against radiation-induced dermatitis	[100]
8	Randomised controlled trial	15	*Calendula* based topical formula	Improvement of palatal wound healing	[101]
9	Single-centre parallel group randomised trial	100	*Calendula* ointment	Improved wound healing and pain due to episiotomy	[102]

10. Safety, Regulatory, and Potential Adverse Effects of *C. officinalis*

The primary goal of topical wound therapy is complete wound closure and proper epithelial regeneration. *C. officinalis* has repeatedly demonstrated strong efficacy in achieving these outcomes[103]. However, despite its well-documented therapeutic benefits, a comprehensive safety evaluation remains essential to ensure safe use in diverse populations. Both clinical and preclinical studies consistently support the excellent safety profile of *C. officinalis*, particularly in topical formulations[104].

10.1 General Safety and Toxicological Evidence

The prevailing consensus is that *C. officinalis* is a safe medicinal plant with minimal side effects and no reported fatal outcomes. Topical application, its most common mode of use, carries an extremely low risk of systemic toxicity, allergic contact dermatitis, or irritation. The Cosmetic Ingredient Review Expert Panel concluded that *Calendula*-derived compounds are non-genotoxic, non-sensitising, and non-phototoxic, with only occasional mild eye discomfort.

Toxicological assessments indicated that flavonoids such as quercetin and isorhamnetin slightly exceed the Cramer Class III threshold (>90 mg/day), but their high NOAELs (*e.g.*, 400 mg/kg/day for quercetin)[105] confirm minimal systemic risk. A condensed overview of key toxicological parameters of representative *Calendula* constituents is provided in Table 4.

10.2 Sensitisation and Cross-reactivity

Allergic sensitisation to *C. officinalis* is extremely rare. A multicentre trial by de Groot *et al.*[107] 121 involving 119 participants found only one positive reaction to a 10% alcoholic extract. Similarly, tested 1,032 individuals and reported just two mild reactions 120. Patch testing with a 10% *Calendula* formulation in petrolatum resulted in a single positive response among 15 volunteers. While Paulsen noted sensitisation in some patients exposed to sesquiterpene-lactone mixtures, these findings are exceptional and may be linked to prior exposure to *Asteraceae*-derived compounds.

Clinically, practitioners should consider cross-reactivity within the *Asteraceae* (Composite) family, including plants such as chrysanthemum, daisy, ragweed, and marigold. Though rare, patients with known sensitivity to these species should undergo allergy screening before using *Calendula*-based products. This is particularly important for individuals with a history of atopic dermatitis or occupational exposure to botanical extracts.

10.3 Systemic Interactions and Special Populations

While *Calendula* is generally safe, co-administration with Central Nervous System (CNS) depressants may enhance sedative effects or prolong sleep duration[108]. Due to limited data, pregnant and lactating women are advised to avoid use unless prescribed by a healthcare professional. More targeted safety trials are required in these populations.

Table 4. Comparative toxicological and safety profile of major *C. officinalis* constituents[106]

Constituent class	Representative compounds	Cramer toxicity class	Estimated systemic exposure (mg/day)	Safety assessment summary
Flavonoids (<1.5%)	Quercetin, Isorhamnetin, Rutin	III	<108	Non-mutagenic; safe within normal use concentrations; high NOAEL (400 mg/kg/day)
Triterpenic Alcohols (<5%)	Faradiol, Arnidiol, *Calendula*diol	I	<90	Low systemic absorption; non-irritant and non-sensitising in dermal assays
Triterpenic Glycosides (210%)	Calenduloside	II	<180	Non-toxic; no evidence of dermal or ocular irritation
Carotenoids (<1%)	β-carotene, Lycopene, Lutein	III	<90	Non-toxic; antioxidant and photoprotective; negligible absorption
Tannins (610%)	Catechol and pyrogallol types	III	<180	Safe at cosmetic exposure levels; minor irritation possible at high doses

10.4 Regulatory Approvals and Global Frameworks

Calendula officinalis is officially recognised for clinical use in several jurisdictions. The German Commission E approves topical *Calendula* preparations for the treatment of poorly healing wounds, leg ulcers, and mucosal inflammation[109]. Similarly, the European Scientific Cooperative on Phytotherapy (ESCOP) recommends its use for promoting wound healing and reducing skin and mucous membrane inflammation[110]. In the United States, while the FDA has not formally approved *Calendula* for medical indications, it is freely available in over-the-counter (OTC) products, including ointments, tinctures, and dietary supplements, under the Dietary Supplement Health and Education Act (DSHEA). For advanced applications such as *Calendula*-encapsulated nanomaterials, regulatory oversight is more complex. Agencies including the U.S. FDA, European Medicines Agency (EMA), and French ANSM enforce stringent standards for safety, efficacy, and quality[111,112]. These frameworks emphasise: Good Manufacturing Practices (GMP) to ensure product consistency, Comprehensive preclinical testing (*in vitro* and *in vivo*) to assess toxicity and bio-distribution, Post-market surveillance for long-term safety monitoring, and Transparency and public engagement in evaluating nanomedicine products. Global harmonisation efforts, led by the European Medicines Expert Group, focus on risk-benefit assessment, nanoparticle characterisation (size, surface charge, stability), and the establishment of uniform quality standards across regions.

10.5 Clinical Implications for Practitioners

For clinicians and pharmacists, *C. officinalis* remains a well-tolerated, evidence-backed botanical for wound healing and dermatologic applications. Nonetheless, patient screening for *Asteraceae* family allergies and medication review for potential CNS depressant interactions are advised. Its favourable safety record, together with formal European regulatory endorsement, supports its inclusion in evidence-based phototherapeutics practice.

11. Conclusions and Prospects for the Future

Calendula officinalis exhibits broad pharmacological potential, including antibacterial, anti-inflammatory, antioxidant, and wound-healing properties that collectively support its therapeutic value in mitigating inflammatory responses, preventing oxidative stress, and promoting tissue regeneration. These pharmacological effects, coupled with emerging evidence of anti-tumour and antifungal activities, position *C. officinalis* as a promising candidate for incorporation into modern drug delivery systems. Its extracts have been successfully formulated into scaffolds, hydrogels, and nanoparticle-based carriers, enhancing both safety and therapeutic efficacy.

Clinical research substantiates its benefits in diverse conditions such as radiation-induced dermatitis, gingival inflammation, caesarean wound recovery, dysmenorrhea, and gastrointestinal disorders. However, further investigation is required to establish optimal dosing regimens, formulation parameters, and treatment durations across different indications. Beyond its classical uses, new findings suggest additional therapeutic avenues, including modulation of gut microbiota, alleviation of cancer-related symptoms, and support of physiological stress adaptation mechanisms.

Calendula officinalis' safety profile is well established for topical applications and has been endorsed by multiple regulatory bodies. Nevertheless, its safety during pregnancy and lactation remains insufficiently characterised, and use is therefore not recommended in these populations. Similarly, the European Medicines Agency (EMA) advises caution due to limited data in children under six years. Individuals allergic to other *Asteraceae* family plants should seek medical guidance prior to use, as mild hypersensitivity reactions, though rare, have been reported.

Future research should prioritise the isolation and characterisation of specific bioactive compounds, optimisation of standardised extraction and formulation protocols, and well-controlled clinical trials across broader demographic groups, including paediatric and perinatal populations. Pharmacokinetic and toxicological assessments will be essential to ensure reproducibility and safety. Furthermore, expanding the exploration of *C. officinalis* within advanced drug delivery systems such as nanoformulations and targeted biopolymer carriers may facilitate its integration into mainstream wound management and systemic therapy paradigms.

Calendula officinalis demonstrates significant therapeutic promise through its antioxidant, anti-inflammatory, and wound-healing properties, supported by both preclinical and clinical evidence. The integration of Calendula-derived compounds into modern nanomedicine platforms presents new opportunities for targeted, sustained, and biocompatible drug delivery systems in wound care.

Future research should focus on the standardisation of extraction and formulation protocols to ensure consistent phytochemical profiles and regulatory compliance across products. Moreover, well-controlled paediatric and geriatric clinical trials are needed to establish safety, optimal dosage, and efficacy in these sensitive populations. Finally, comprehensive bioavailability and pharmacokinetic studies of *Calendula*'s triterpenoids and flavonoids will be essential for understanding systemic absorption and optimising therapeutic outcomes.

By addressing these key research gaps, *C. officinalis* can transition from traditional herbal applications to a scientifically standardised and clinically validated component of modern wound-healing therapeutics.

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Author Contribution

Ms. Shital Patel contributed to the conceptualization and study design. Dr. Anita Prakasam conducted the literature search and comprehensive review. Dr. Vruti Patel was responsible for the clinical studies and interpretation of findings, while Ms. Pinal Darji handled the data acquisition, organization, and compilation for the manuscript. All authors have read and agreed to the published version of the manuscript.