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Advancing the Therapeutic Landscape of Calendula officinalis: A Critical Review of Phytoconstituents, Biological Mechanisms, Clinical Evidence, and Translational Perspectives

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ABSTRACT:

Calendula officinalis L. (pot marigold) is one of the most extensively investigated medicinal plants owing to its long-standing use in traditional medicine and its growing relevance in evidence-based herbal therapeutics. Rich in biologically active constituents, including flavonoids, triterpenoids, carotenoids, phenolic acids, essential oils, polysaccharides, and sterols, the plant exhibits a broad spectrum of pharmacological properties that have attracted considerable scientific interest. This review critically synthesizes current knowledge on the phytochemical composition, biological activities, molecular mechanisms, therapeutic applications, pharmaceutical formulations, safety profile, and future research directions of *C. officinalis*. Relevant literature was collected from major scientific databases, with emphasis on peer-reviewed studies investigating phytochemical characterization, experimental pharmacology, preclinical investigations, clinical evidence, and formulation strategies. Available findings demonstrate that *C. officinalis* possesses significant anti-inflammatory, antioxidant, antimicrobial, antifungal, wound-healing, immunomodulatory, hepatoprotective, and anticancer potential through the coordinated action of multiple bioactive metabolites. The review further discusses the molecular pathways underlying these effects, including modulation of inflammatory mediators, oxidative stress, cytokine signaling, collagen synthesis, angiogenesis, and tissue regeneration. Particular attention is given to its expanding applications in dermatology, wound management, oral healthcare, cosmetic products, and advanced herbal drug delivery systems such as hydrogels, liposomes, nanoparticles, and nanoemulsions, which may enhance the stability and

therapeutic performance of plant-derived constituents. In addition, the article highlights current challenges associated with phytochemical variability, extract standardization, quality assurance, regulatory requirements, and the limited availability of large-scale clinical studies. Collectively, the available evidence supports the considerable therapeutic promise of *C. officinalis* as a multifunctional medicinal plant. Nevertheless, future investigations integrating standardized phytochemical profiling, mechanistic studies, robust clinical validation, and innovative pharmaceutical technologies are essential to facilitate its successful translation into modern healthcare and evidence-based phytomedicine.

INTRODUCTION:

Calendula officinalis, commonly known as pot marigold, is an important medicinal herb belonging to the family Asteraceae. The plant has been extensively utilized in traditional and modern medicine because of its anti-inflammatory, antimicrobial, antioxidant, wound healing, antifungal, hepatoprotective, and immunomodulatory activities.[1,2] Calendula flowers contain several biologically active phytoconstituents including flavonoids, triterpenoids, carotenoids, phenolic acids, tannins, glycosides, volatile oils, and polysaccharides that contribute significantly to its therapeutic potential.[3]

Medicinal plants continue to play a major role in healthcare systems worldwide due to increasing demand for natural therapeutics with fewer adverse effects compared to synthetic drugs.[4] Among various herbal medicines, Calendula officinalis has gained substantial scientific interest because of its broad-spectrum pharmacological activities and extensive applications in dermatology, wound management, cosmetics, oral healthcare, and inflammatory disorders.[5]

Traditionally, calendula was used by Greek, Roman, and Ayurvedic practitioners for treatment of wounds, burns, ulcers, skin infections, gastrointestinal disorders, fever, and inflammatory diseases.[6] Herbal preparations containing calendula flowers such as ointments, oils, tinctures, creams, gels, teas, and lotions were commonly applied to accelerate tissue repair and reduce infections.[7] Ancient medicinal systems considered calendula as a cleansing and regenerative herb capable of promoting healing and improving skin health.[8]

Modern pharmacological investigations have validated many of these traditional claims. Experimental studies demonstrated that calendula extracts enhance collagen synthesis, fibroblast proliferation, epithelialization, angiogenesis, and granulation tissue formation, thereby accelerating wound healing.[9] Anti-inflammatory activity of calendula is primarily associated with triterpenoids such as faradiol esters, which inhibit cyclooxygenase pathways and inflammatory mediators.[10] Furthermore, flavonoids and phenolic compounds present in calendula exhibit potent antioxidant activity by scavenging reactive oxygen species and reducing oxidative stress-associated tissue injury.[11]

Several clinical studies have also highlighted therapeutic importance of calendula in dermatological conditions. Pommier et al. reported that Calendula officinalis ointment significantly reduced radiation-induced dermatitis in breast cancer patients receiving radiotherapy.[12] Patel et al. further demonstrated that calendula cream improved skin hydration, reduced erythema, and alleviated symptoms associated with dermatitis and eczema.[13]

In addition to dermatological applications, calendula exhibits broad antimicrobial activity against bacterial and fungal pathogens including *Staphylococcus aureus*, *Escherichia coli*, and *Candida albicans*.[14] These antimicrobial properties support its use in wound care, oral hygiene preparations, and skin protective formulations. Recent research has also investigated hepatoprotective, anticancer, anti-ulcer, and immunomodulatory effects of calendula extracts.[15]

The pharmaceutical and cosmetic industries increasingly incorporate calendula into creams, gels, ointments, mouthwashes, shampoos, sunscreens, moisturizers, anti-aging products, and advanced herbal formulations because of its soothing, protective, and regenerative properties.[16] Despite extensive pharmacological investigations, several challenges remain including lack of standardized extraction procedures, variability in phytochemical composition, insufficient toxicological evaluation, and limited large-scale clinical trials.[17]

Therefore, the present review aims to comprehensively evaluate the phytochemistry, pharmacological activities, therapeutic applications, mechanism of action, pharmaceutical significance, and future prospects of Calendula officinalis based on evidence from published Scopus-indexed scientific literature.

2. Traditional and Ethnomedicinal Uses of Calendula officinalis:
Calendula officinalis has been extensively used in traditional medicine systems for several centuries because of its remarkable healing, cleansing, and protective properties. Historical records indicate that calendula was widely utilized in Greek, Roman, Egyptian, Persian, and Ayurvedic systems of medicine for management of wounds, burns, ulcers, infections, inflammatory disorders, and gastrointestinal ailments.[18] The medicinal importance of calendula primarily originates from its flower heads, which contain numerous bioactive phytoconstituents capable of producing anti-inflammatory, antimicrobial, antioxidant, and tissue regenerative effects.[19]

Traditional healers considered calendula a valuable medicinal herb for promoting tissue repair and preventing wound infections. In European folk medicine, fresh flower petals and extracts were applied externally to cuts, abrasions, burns, bruises, and ulcerative lesions to accelerate healing and reduce pain.[20] Calendula poultices and ointments were commonly used to treat inflamed skin conditions because the plant was believed to possess cooling and soothing properties.[21]

In Ayurvedic medicine, calendula was traditionally used for blood purification, wound cleansing, treatment of skin disorders, and reduction of inflammatory symptoms.[22] Herbal preparations containing calendula flowers were prescribed for management of eczema, dermatitis, acne, rashes, boils, and fungal infections. Ayurvedic practitioners also recommended calendula infusions and herbal teas for treatment of digestive disorders including gastric irritation, peptic ulcers, intestinal inflammation, and menstrual discomfort.[23]

Ancient Egyptian civilizations incorporated calendula into cosmetic and beauty formulations because of its rejuvenating and anti-aging properties.[24] Calendula oils and extracts were used to improve skin texture, maintain moisture, reduce wrinkles, and protect skin against environmental damage. Traditional cosmetic preparations containing calendula were also applied to maintain skin elasticity and reduce signs of aging.[25]
Calendula additionally gained importance in traditional oral healthcare systems. Herbal mouthwashes, gargles, and oral gels containing calendula were used for treatment of gingivitis, mouth ulcers, throat infections, oral inflammation, and periodontal irritation.[26] Traditional practitioners believed that calendula reduced microbial growth and promoted healing of damaged oral tissues.
In traditional home remedies, calendula tea was frequently consumed for fever, sore throat, liver disorders, menstrual irregularities, and gastrointestinal discomfort.[27] The flowers were also incorporated into herbal baths and compresses for relief of muscular pain, swelling, inflammation, and skin irritation.[28]
The ethnomedicinal importance of calendula significantly contributed to its later scientific investigation. Many traditional therapeutic claims associated with calendula have now been supported by modern pharmacological and clinical studies demonstrating wound healing, antioxidant, antimicrobial, anti-inflammatory, hepatoprotective, and immunomodulatory activities.[29]

2.1 Traditional Uses in Skin Disorders
Skin diseases and inflammatory dermatological conditions represent one of the most common traditional applications of calendula. Calendula flower extracts and oils were widely used for treatment of eczema, dermatitis, psoriasis, acne vulgaris, burns, sunburn, insect bites, rashes, and allergic skin reactions.[30]

Traditional herbal medicine practitioners observed that calendula reduced redness, swelling, itching, and irritation associated with inflammatory skin disorders. The anti-inflammatory effects were believed to accelerate healing and prevent scar formation.[31] Calendula oils were frequently applied to cracked skin, dry skin, and minor wounds because of moisturizing and tissue protective properties.

Several traditional medicinal systems also used calendula in management of diaper rash and sensitive skin conditions in infants.[32] Herbal ointments prepared from calendula flowers were considered safe and soothing for delicate skin tissues.

Modern scientific studies have validated many of these traditional observations. Experimental investigations demonstrated that calendula extracts suppress inflammatory mediators, reduce oxidative stress, and enhance tissue regeneration.[33]

2.2 Traditional Use in Wound Healing:
One of the most important ethnomedicinal applications of calendula is wound healing. Calendula preparations were traditionally used to clean wounds, stop bleeding, reduce inflammation, and accelerate tissue regeneration.[34] Fresh flower extracts, herbal oils, tinctures, and poultices were commonly applied directly to wounds and ulcers.

Traditional healers observed that calendula-treated wounds healed faster and showed reduced infection compared to untreated wounds.[35] The herb was extensively utilized for treatment of burns, cuts, surgical wounds, diabetic ulcers, bed sores, and traumatic injuries.

Calendula was also used in military medicine during historical periods because of its antiseptic and tissue reparative properties.[36] Traditional battlefield healers frequently applied calendula extracts to injured tissues to reduce suppuration and promote recovery.

Current wound healing research strongly supports these traditional claims. Scientific studies reported that calendula stimulates fibroblast proliferation, collagen synthesis, angiogenesis, granulation tissue formation, and epithelialization.[37]

2.3 Traditional Gastrointestinal Applications:
Calendula has historically been used for treatment of gastrointestinal disorders due to its soothing and anti-inflammatory effects on mucosal tissues.[38] Herbal teas and decoctions prepared from calendula flowers were commonly administered for gastric ulcers, gastritis, indigestion, abdominal cramps, constipation, and inflammatory bowel irritation.

Traditional practitioners believed that calendula reduced gastric inflammation and protected gastrointestinal mucosa from irritation.[39] The herb was also used to stimulate bile secretion and improve digestive function.
Several experimental studies later demonstrated that calendula possesses gastroprotective and anti-ulcer activities because of antioxidant and anti-inflammatory phytochemicals.[40]

2.4 Traditional Gynecological and Reproductive Uses
Calendula flowers were traditionally used in women's healthcare for management of menstrual irregularities, dysmenorrhea, menopausal discomfort, and vaginal inflammation.[41] Herbal infusions prepared from calendula flowers were believed to improve circulation and reduce uterine inflammation.

Traditional medicine systems also used calendula in management of postpartum wound healing and minor infections because of its antimicrobial and tissue regenerative properties.[42]

2.5 Traditional Immunological and Fever Applications
Traditional healers considered calendula an immune-supportive herb capable of enhancing resistance against infections and inflammatory diseases.[43] Calendula teas and extracts were commonly consumed during fever, cold, sore throat, influenza, and respiratory infections.

The herb was believed to possess detoxifying and cleansing effects which helped eliminate harmful substances from the body.[44] Modern studies later identified immunomodulatory polysaccharides and flavonoids in calendula that may contribute to immune regulation.

3. Phytochemistry and Analytical Characterization
Calendula officinalis contains a wide variety of biologically active phytochemicals responsible for its extensive pharmacological and therapeutic activities. Phytochemicals are naturally occurring secondary metabolites produced by plants for defense, protection, and physiological regulation. In medicinal plants, these compounds exhibit therapeutic effects including antioxidant, anti-inflammatory, antimicrobial, anticancer, hepatoprotective, and wound healing activities.[45]

The flowers of Calendula officinalis are considered the most pharmacologically active part of the plant and contain significant concentrations of flavonoids, triterpenoids, carotenoids, phenolic acids, tannins, glycosides, coumarins, saponins, quinones, sterols, polysaccharides, volatile oils, and fatty acids.[46] These compounds work

synergistically to produce broad-spectrum pharmacological effects.

Modern phytochemical investigations using chromatographic and spectroscopic techniques such as HPLC, GC-MS, TLC, LC-MS, UV spectroscopy, FTIR, and NMR have identified numerous active compounds in calendula flowers.[47] The qualitative and quantitative composition of phytochemicals may vary depending on cultivation conditions, geographical origin, harvesting season, extraction method, drying conditions, and solvent system used.[48]

The major classes of phytochemicals identified in Calendula officinalis are discussed below.

3.1 Major Phytochemical Classes Present in Calendula officinalis

Table 1: Major phytochemical constituents present in Calendula officinalis and their therapeutic importance.

Phytochemical Class	Major Compounds Identified	Pharmacological Importance
Flavonoids	Quercetin, rutin, narcissin, isorhamnetin	Antioxidant, anti-inflammatory
Triterpenoids	Faradiol, arnidiol, calenduladiol	Anti-inflammatory, wound healing
Carotenoids	Beta-carotene, lutein, lycopene	Antioxidant, skin protection
Phenolic compounds	Caffeic acid, chlorogenic acid	Free radical scavenging
Essential oils	α-cadinol, γ-cadinene	Antimicrobial activity
Saponins	Oleanolic acid glycosides	Immunomodulatory
Polysaccharides	Arabinogalactans	Immune stimulation
Sterols	Stigmasterol, β-sitosterol	Anti-inflammatory
Coumarins	Umbelliferone, scopoletin	Antioxidant, vascular protection
Tannins	Condensed tannins	Astringent and antimicrobial

3.2 Flavonoids:

Flavonoids represent one of the most important groups of phytochemicals present in Calendula officinalis flowers. These polyphenolic compounds are primarily responsible for antioxidant, anti-inflammatory, antimicrobial, and wound healing activities.[49]

The major flavonoids identified in calendula include:

- Quercetin
- Rutin
- Isorhamnetin
- Narcissin
- Kaempferol
- Isoquercitrin

These compounds possess strong free radical scavenging properties and protect tissues from oxidative stress-induced cellular damage.[50]

Oxidative stress results from excessive production of reactive oxygen species (ROS) including superoxide radicals, hydroxyl radicals, and hydrogen peroxide. These reactive species damage proteins, lipids, DNA, and cellular membranes, leading to inflammation, aging, and chronic diseases.[51]

Flavonoids neutralize free radicals through electron donation and stabilization mechanisms, thereby reducing oxidative tissue injury.[52] Additionally, flavonoids inhibit cyclooxygenase (COX) and lipoxygenase pathways responsible for inflammatory mediator production.[53]

Experimental studies demonstrated that quercetin and rutin significantly reduce inflammatory cytokines such as:

- Tumor necrosis factor-alpha (TNF-α)
- Interleukin-1β (IL-1β)
- Interleukin-6 (IL-6)

These mechanisms contribute significantly to anti-inflammatory and tissue regenerative activities of calendula.[54]

Chinese Journal of Health Management
Volume 20 Issue 5, Year of Publication 2026, Page 1118-1163 | DoI-10.564220/1674-0815.2026.139

3.3 Triterpenoids

Triterpenoids are considered the principal anti-inflammatory compounds of Calendula officinalis.[55] These compounds are mainly present in flower petals and are responsible for suppression of inflammatory responses and promotion of wound healing.
The major triterpenoids identified in calendula include:

Table 2: Major triterpenoids identified in Calendula officinalis.

Triterpenoid Compound	Therapeutic Role
Faradiol monoester	Potent anti-inflammatory activity
Faradiol diester	Inhibition of inflammatory edema
Arnidiol	Tissue regeneration
Calenduladiol	Wound healing support
Oleanolic acid	Hepatoprotective activity
Ursolic acid	Antioxidant and anti-inflammatory

Della Loggia et al. demonstrated that faradiol esters significantly inhibit experimentally induced inflammation and edema.[56] The anti-inflammatory activity of faradiol esters was reported to be comparable to certain synthetic anti-inflammatory agents.

Triterpenoids suppress:

- Cyclooxygenase enzymes (COX-1 and COX-2)
- Prostaglandin synthesis
- Nitric oxide production
- Histamine release
- Cytokine-mediated inflammatory pathways

These actions reduce swelling, redness, tissue irritation, and pain associated with inflammatory conditions.[57]
Triterpenoids additionally stimulate fibroblast proliferation and collagen deposition, thereby accelerating wound contraction and tissue remodeling.[58]

3.4 Carotenoids:

Calendula flowers possess characteristic bright yellow-to-orange coloration due to presence of carotenoids.[59] Carotenoids are natural pigments with strong antioxidant and photoprotective properties.
Major carotenoids identified include:

- Beta-carotene
- Lycopene
- Lutein
- Flavoxanthin
- Auroxanthin
- Violaxanthin

These compounds protect skin tissues against ultraviolet radiation and oxidative injury.[60]
Beta-carotene additionally acts as a precursor of vitamin A, which is essential for epithelial cell differentiation, tissue repair, and maintenance of healthy skin and mucosal surfaces.[61]
arotenoids reduce lipid peroxidation and oxidative damage associated with:

- Skin aging

- Ultraviolet radiation
- Inflammatory disorders
- Cancer development
- Cellular degeneration

Several studies demonstrated that calendula carotenoids improve skin hydration, elasticity, and photoprotection.[62]

3.5 Phenolic Compounds:

Phenolic compounds contribute significantly to antioxidant and antimicrobial activities of calendula.[63]
Major phenolic acids include:

Table 3: Important phenolic compounds present in Calendula officinalis.

Phenolic Compound	Biological Activity
Caffeic acid	Antioxidant
Chlorogenic acid	Anti-inflammatory
Ferulic acid	UV protection
Gallic acid	Antimicrobial
Coumaric acid	Tissue protection

Phenolic compounds inhibit oxidative stress by neutralizing reactive oxygen species and protecting cellular biomolecules.[64] They additionally stabilize cellular membranes and reduce inflammatory tissue injury.
Recent studies demonstrated that phenolic compounds also contribute to antimicrobial activity against bacterial and fungal pathogens.[65]

3.6 Essential Oils and Volatile Constituents:

Calendula flowers contain small quantities of volatile oils responsible for antimicrobial and aromatic properties.[66]

The major volatile constituents identified include:

- α-Cadinol
- γ-Cadinene
- T-muurolol
- Caryophyllene
- Cadinene derivatives

Essential oils exhibit antimicrobial activity against both Gram-positive and Gram-negative bacteria.[67]
These compounds damage microbial cell membranes, interfere with enzymatic systems, and inhibit microbial growth.[68]

3.7 Polysaccharides and Immunomodulatory Compounds

Calendula contains biologically active polysaccharides including arabinogalactans and rhamnoarabinogalactans.[69] These compounds exhibit immunomodulatory activity by stimulating macrophage activation and enhancing phagocytic function.
Polysaccharides contribute to:

- Immune stimulation
- Tissue regeneration
- Inflammation regulation
- Wound healing enhancement

Several studies reported that calendula polysaccharides increase cytokine production involved in immune defense mechanisms.[70]

3.8 Mechanism of Phytochemical Synergism

The therapeutic efficacy of Calendula officinalis results from synergistic interaction among multiple phytochemicals rather than activity of a single compound.[71]
For example:

- Flavonoids reduce oxidative stress
- Triterpenoids suppress inflammation

- Carotenoids protect tissues against UV damage
- Essential oils inhibit microbial growth
- Polysaccharides stimulate immunity

The combined action of these phytochemicals enhances overall therapeutic effectiveness and promotes faster tissue healing.[72]

3.9 Factors Affecting Phytochemical Composition

Several factors influence phytochemical concentration in calendula flowers:

Table 4: Factors affecting phytochemical composition of Calendula officinalis.

Factor	Effect on Phytochemical Content
Climate	Alters carotenoid and flavonoid synthesis
Soil composition	Influences mineral uptake
Harvesting stage	Affects triterpenoid concentration
Drying conditions	Excess heat reduces volatile oils
Extraction solvent	Determines compound recovery
Storage conditions	Oxidation decreases activity

Hydroalcoholic extraction methods are generally considered most effective for obtaining maximum phytochemical yield because both polar and semi-polar compounds are efficiently extracted.[73]

4. Pharmacological Activities of Calendula officinalis

Calendula officinalis possesses a broad spectrum of pharmacological activities because of the synergistic interaction of flavonoids, triterpenoids, carotenoids, phenolic acids, polysaccharides, tannins, glycosides, and volatile oils present in its flowers.[74] Numerous in vitro, in vivo, and clinical investigations have demonstrated that calendula exhibits anti-inflammatory, antioxidant, antimicrobial, antifungal, wound healing, hepatoprotective, immunomodulatory, anticancer, anti-ulcer, and dermatoprotective activities.[75]

The therapeutic significance of calendula has increased substantially in recent years because of growing interest in herbal therapeutics with fewer adverse effects compared to synthetic drugs.[76] Modern pharmacological studies have validated many traditional medicinal claims associated with calendula and have identified several molecular mechanisms responsible for its biological activities.[77]

The major pharmacological activities of Calendula officinalis are discussed below.

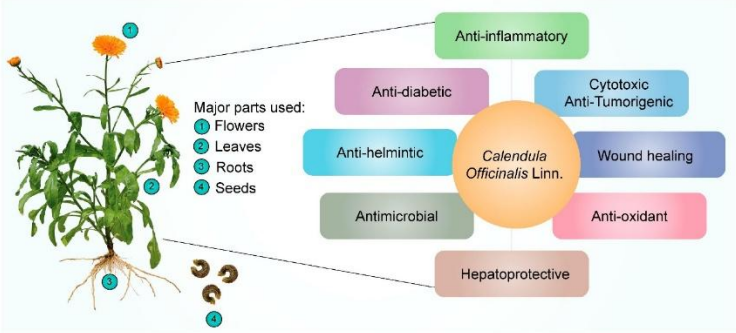

Image 2 Different application of *Calendula Officinalis*

4.1 Anti-inflammatory Activity

Inflammation is a protective physiological response against infection, injury, toxins, and tissue damage. However, excessive or chronic inflammation contributes significantly to development of pathological conditions including arthritis, dermatitis, cardiovascular diseases, diabetes, autoimmune disorders, and cancer.[78]
Calendula officinalis demonstrates significant anti-inflammatory activity primarily because of triterpenoids, flavonoids, carotenoids, and phenolic compounds present in the flowers.[79]

The major anti-inflammatory mechanisms include:

- Inhibition of cyclooxygenase (COX) enzymes
- Suppression of prostaglandin synthesis
- Reduction of inflammatory cytokines
- Stabilization of lysosomal membranes
- Reduction of nitric oxide production
- Inhibition of histamine release
- Suppression of reactive oxygen species generation

$$\boldsymbol{COX\text{-}2 + Arachidonic\ Acid \rightarrow Prostaglandins \rightarrow Inflammation}$$

Della Loggia et al. demonstrated that faradiol esters isolated from calendula flowers exhibited potent anti-inflammatory activity comparable to indomethacin in experimental animal models.[80] Triterpenoids significantly reduced experimentally induced edema and inflammatory swelling.

Flavonoids such as quercetin and rutin suppress inflammatory mediators including:

- Tumor necrosis factor-alpha (TNF-α)
- Interleukin-1β (IL-1β)
- Interleukin-6 (IL-6)
- Nuclear factor-kappa B (NF-κB)

These mechanisms reduce tissue irritation, redness, pain, and swelling associated with inflammatory disorders.[81]
Clinical investigations additionally demonstrated that calendula ointments significantly reduce radiation-induced dermatitis in cancer patients undergoing radiotherapy.[82]

Table 5: Anti-inflammatory Phytochemicals and Their Mechanisms

Phytochemical	Mechanism of Action	Therapeutic Effect
Faradiol esters	COX inhibition	Reduces edema
Quercetin	Cytokine suppression	Anti-inflammatory
Rutin	Antioxidant activity	Tissue protection
Carotenoids	ROS scavenging	Reduces oxidative injury
Oleanolic acid	NF-κB inhibition	Decreases inflammation

4.2 Antioxidant Activity

Oxidative stress results from imbalance between production of reactive oxygen species (ROS) and antioxidant defense systems.[83] Excessive oxidative stress damages proteins, DNA, lipids, and cellular membranes, leading to inflammation, aging, degenerative diseases, cancer, and delayed wound healing.[84]
Calendula officinalis possesses strong antioxidant activity because of high concentrations of flavonoids, carotenoids, phenolic acids, and polyphenolic compounds.[85]

The major antioxidant mechanisms include:

- Free radical scavenging
- Inhibition of lipid peroxidation
- Chelation of transition metal ions
- Protection of cellular membranes
- Enhancement of endogenous antioxidant enzymes

$$\boldsymbol{ROS + Antioxidants \rightarrow Neutralized\ Free\ Radicals}$$

Studies demonstrated that calendula extracts significantly increase activity of antioxidant enzymes including:

- Superoxide dismutase (SOD)
- Catalase (CAT)
- Glutathione peroxidase (GPx)

These enzymes play an important role in neutralizing reactive oxygen species and preventing cellular damage.[86]
Fonseca et al. reported that calendula extracts protected skin cells against oxidative stress-induced injury and

reduced lipid peroxidation.[87]

Antioxidant activity of calendula contributes significantly to:

- Anti-aging effects
- Tissue regeneration
- Wound healing
- Cancer prevention
- Hepatoprotection
- Cardiovascular protection

Table 6: Important Antioxidant Compounds in Calendula

Compound	Antioxidant Function
Quercetin	Free radical scavenging
Rutin	Lipid peroxidation inhibition
Beta-carotene	Photoprotection
Lutein	Cellular protection
Chlorogenic acid	Oxidative stress reduction

4.3 Antimicrobial Activity

Microbial infections represent a major complication in wounds, skin disorders, oral diseases, and inflammatory conditions.[88] Increasing antibiotic resistance has created substantial interest in plant-derived antimicrobial agents.

Calendula officinalis exhibits broad-spectrum antimicrobial activity against bacteria, fungi, and certain viral pathogens.[89]

Studies demonstrated antimicrobial activity against:

Gram-positive bacteria:

- Staphylococcus aureus
- Streptococcus pyogenes
- Bacillus subtilis

Gram-negative bacteria

- Escherichia coli
- Pseudomonas aeruginosa
- Klebsiella pneumoniae

Fungal organisms

- Candida albicans
- Aspergillus niger
- Dermatophytes

The antimicrobial activity is mainly attributed to:

- Essential oils
- Flavonoids
- Phenolic compounds
- Triterpenoids
- Tannins

These compounds damage microbial cell membranes, alter permeability, inhibit protein synthesis, and interfere with microbial enzymatic pathways.[90]

Efstratiou et al. demonstrated that calendula petal extracts possess substantial antibacterial and antifungal activity.[91]

Table 7: Antimicrobial Activity of Calendula Against Pathogens

Microorganism	Type	Observed Activity

Staphylococcus aureus	Gram-positive	Strong inhibition
Escherichia coli	Gram-negative	Moderate inhibition
Candida albicans	Fungus	Antifungal effect
Pseudomonas aeruginosa	Gram-negative	Growth suppression
Aspergillus niger	Fungus	Antifungal activity

4.4 Wound Healing Activity

Wound healing is one of the most extensively studied pharmacological activities of Calendula officinalis.[92] The wound healing process consists of four major phases:

1. Hemostasis
2. Inflammation
3. Proliferation
4. Remodeling

$$Hemostasis \rightarrow Inflammation \rightarrow Proliferation \rightarrow Remodeling$$

Calendula accelerates wound healing through:

- Stimulation of fibroblast proliferation
- Increased collagen synthesis
- Promotion of angiogenesis
- Enhanced epithelialization
- Reduction of oxidative stress
- Prevention of microbial contamination

Preethi and Kuttan demonstrated that calendula-treated wounds showed faster wound contraction and significantly improved epithelialization compared to untreated controls.[93]
Calendula additionally enhances hydroxyproline content, indicating increased collagen formation necessary for tissue repair.[94]

Table 8: Effects of Calendula on Wound Healing Parameters

Wound Healing Parameter	Effect of Calendula
Fibroblast proliferation	Increased
Collagen deposition	Enhanced
Granulation tissue formation	Accelerated
Epithelialization	Faster
Inflammatory edema	Reduced
Oxidative damage	Minimized

4.5 Antifungal Activity

Fungal infections of skin and mucosal tissues are common complications in immunocompromised individuals and chronic inflammatory conditions.[95]
Calendula extracts demonstrated antifungal activity against:

- Candida albicans
- Microsporum species
- Trichophyton species

The antifungal mechanism involves disruption of fungal membrane integrity and inhibition of fungal metabolic pathways.[96]

Several studies reported that ethanolic extracts exhibit stronger antifungal activity than aqueous extracts because of better extraction of lipophilic compounds.[97]

4.6 Immunomodulatory Activity

Calendula contains polysaccharides and flavonoids capable of modulating immune responses.[98]
Immunomodulatory effects include:

- Activation of macrophages
- Increased phagocytic activity
- Cytokine regulation
- Enhanced lymphocyte proliferation

- Immune defense stimulation

Wagner et al. reported that polysaccharides isolated from calendula stimulated macrophage activity and enhanced immune responses.[99]
These findings suggest potential applications of calendula in immune-supportive herbal therapies.

4.7 Hepatoprotective Activity

The liver is highly susceptible to oxidative stress and toxic injury caused by drugs, alcohol, infections, and environmental toxins.[100]
Calendula extracts demonstrated hepatoprotective activity through:

- Reduction of lipid peroxidation
- Antioxidant enzyme enhancement
- Suppression of inflammatory mediators
- Stabilization of hepatic cell membranes

Experimental studies showed that calendula significantly reduced elevated liver enzymes including:

- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Alkaline phosphatase (ALP)

These effects indicate protection against hepatocellular injury.[101]

4.8 Anticancer Activity

Recent investigations suggest that calendula possesses anticancer and antiproliferative activity.[102]
Potential anticancer mechanisms include:

- Induction of apoptosis
- Cell cycle arrest
- Antioxidant protection
- Suppression of tumor-promoting inflammation
- DNA protection against oxidative damage

$$\textit{Cancer Cell} \xrightarrow{\textit{Calendula Phytochemicals}} \textit{Apoptosis}$$

Triterpenoids and flavonoids present in calendula demonstrated cytotoxic effects against several cancer cell lines in experimental studies.[103]
However, additional molecular and clinical investigations are still required to establish therapeutic applications in oncology.

4.9 Anti-ulcer Activity

Calendula exhibits gastroprotective and anti-ulcer activity because of antioxidant, anti-inflammatory, and mucosal protective properties.[104]
Experimental studies demonstrated that calendula extracts:

- Reduce gastric acid-induced injury
- Protect gastric mucosa
- Accelerate ulcer healing
- Reduce oxidative tissue damage

Flavonoids and triterpenoids play an important role in maintaining integrity of gastric mucosal tissues.[105]

5. Wound Healing Activity and Mechanism of Action of Calendula officinalis

Calendula officinalis is one of the most extensively investigated medicinal plants for wound healing applications. Wound healing is a complex biological process involving coordinated interaction among inflammatory cells, fibroblasts, extracellular matrix proteins, cytokines, growth factors, and vascular tissues.[106] Delayed wound healing may result in chronic wounds, infections, tissue necrosis, and severe complications particularly in diabetic, immunocompromised, and elderly patients.[107]
Traditional medicinal systems have utilized calendula preparations for treatment of cuts, burns, abrasions, ulcers, surgical wounds, traumatic injuries, and skin infections for centuries.[108] Modern scientific studies have validated these traditional claims and demonstrated that calendula significantly accelerates wound contraction,

epithelialization, collagen synthesis, fibroblast proliferation, angiogenesis, and granulation tissue formation.[109] The wound healing activity of calendula is mainly attributed to flavonoids, triterpenoids, carotenoids, polysaccharides, phenolic compounds, and essential oils present in flower extracts.[110] These phytoconstituents exhibit synergistic anti-inflammatory, antioxidant, antimicrobial, and tissue regenerative properties that collectively promote rapid healing.

5.1 Physiology of Wound Healing

Wound healing occurs through four overlapping phases:

1. Hemostasis
2. Inflammation
3. Proliferation
4. Remodeling or maturation

$$\textit{Hemostasis} \rightarrow \textit{Inflammation} \rightarrow \textit{Proliferation} \rightarrow \textit{Remodeling}$$

Each phase involves highly regulated cellular and biochemical events necessary for restoration of tissue integrity.[111]

5.1.1 Hemostasis Phase

The hemostatic phase begins immediately after tissue injury and primarily functions to stop bleeding through vasoconstriction and clot formation.[112]

Major events include:

- Platelet aggregation
- Fibrin clot formation
- Activation of coagulation cascade
- Release of growth factors

Platelets release several growth factors including:

- Platelet-derived growth factor (PDGF)
- Transforming growth factor-beta (TGF-β)
- Epidermal growth factor (EGF)

These growth factors initiate cellular migration and tissue repair mechanisms.[113]

Calendula phytochemicals indirectly support this phase by protecting tissues against oxidative injury and microbial contamination.

5.1.2 Inflammatory Phase

The inflammatory phase involves infiltration of neutrophils, macrophages, and inflammatory mediators at the wound site.[114]

Major functions include:

- Removal of debris and pathogens
- Prevention of infection
- Activation of repair pathways
- Cytokine signaling

Excessive inflammation may delay wound healing and cause tissue destruction.[115]

Calendula significantly modulates inflammatory responses through:

- Inhibition of cyclooxygenase enzymes
- Reduction of prostaglandin synthesis
- Suppression of inflammatory cytokines
- Antioxidant protection

$$\textit{Inflammation} \xrightarrow{\textit{Calendula Triterpenoids}} \textit{Reduced Cytokine Production}$$

Faradiol esters and flavonoids present in calendula inhibit inflammatory mediators including:

- TNF-α
- IL-1β
- IL-6

- NF-κB

This anti-inflammatory activity reduces tissue edema, pain, redness, and oxidative damage.[116]

5.1.3 Proliferative Phase

The proliferative phase is characterized by tissue regeneration, fibroblast proliferation, angiogenesis, collagen synthesis, and epithelialization.[117]
Calendula significantly enhances this phase through stimulation of:

- Fibroblast migration
- Collagen deposition
- Granulation tissue formation
- Keratinocyte proliferation
- Blood vessel formation

$$\boldsymbol{Fibroblasts + Collagen\ Synthesis \rightarrow Tissue\ Repair}$$

Fibroblasts are essential connective tissue cells responsible for extracellular matrix formation and collagen production.[118]
Experimental studies demonstrated that calendula increases hydroxyproline content, indicating enhanced collagen synthesis.[119]
Angiogenesis is another critical process during wound healing because newly formed blood vessels supply oxygen and nutrients necessary for tissue repair.[120] Calendula extracts stimulate vascular endothelial growth factor (VEGF)-mediated angiogenesis and improve circulation at wound sites.

5.1.4 Remodeling Phase

The remodeling phase involves maturation of collagen fibers, tissue strengthening, and scar formation.[121]
During this stage:

- Type III collagen converts to Type I collagen
- Tensile strength increases
- Extracellular matrix reorganizes
- Scar tissue stabilizes

Calendula improves remodeling through antioxidant protection and enhanced collagen maturation.[122]

5.2 Molecular Mechanism of Wound Healing by Calendula officinalis

The wound healing mechanism of calendula involves multiple molecular pathways and biological targets.

Table 9: Molecular Mechanisms Involved in Calendula-Mediated Wound Healing

Mechanism	Biological Effect	Responsible Phytochemicals
COX inhibition	Reduced inflammation	Faradiol esters
ROS scavenging	Reduced oxidative stress	Flavonoids
Fibroblast stimulation	Enhanced collagen synthesis	Triterpenoids
VEGF activation	Increased angiogenesis	Polyphenols
Antimicrobial activity	Infection prevention	Essential oils
Cytokine modulation	Controlled inflammation	Flavonoids
Keratinocyte proliferation	Faster epithelialization	Carotenoids

5.3 Role of Antioxidants in Wound Healing

Oxidative stress significantly delays wound healing by damaging cellular proteins, lipids, and DNA.[123]
Reactive oxygen species generated during inflammation cause:

- Lipid peroxidation
- Cellular membrane injury
- Fibroblast dysfunction
- Delayed epithelialization

Calendula antioxidants neutralize free radicals and protect regenerating tissues from oxidative injury.[124]

$$\boldsymbol{ROS + Flavonoids \rightarrow Reduced\ Oxidative\ Damage}$$

Important antioxidant compounds include:

- Quercetin

- Rutin
- Beta-carotene
- Lutein
- Chlorogenic acid

These compounds additionally improve survival and proliferation of fibroblasts and keratinocytes.[125]

5.4 Role of Collagen in Calendula-Mediated Wound Healing

Collagen is the principal structural protein required for tissue repair and wound contraction.[126]
Calendula enhances collagen metabolism through:

- Fibroblast activation
- Hydroxyproline synthesis
- Extracellular matrix stabilization
- Increased tensile strength

Hydroxyproline is an important biochemical marker of collagen formation.[127]
Experimental investigations demonstrated significantly elevated hydroxyproline levels in calendula-treated wounds compared to untreated controls.[128]

Table 10: Effect of Calendula on Important Wound Healing Biomarkers

Biomarker	Effect Observed
Hydroxyproline	Increased
Collagen deposition	Enhanced
Fibroblast proliferation	Increased
VEGF expression	Elevated
Inflammatory cytokines	Reduced
Lipid peroxidation	Decreased
Epithelialization time	Reduced

5.5 Antimicrobial Contribution in Wound Healing

Microbial infection is one of the most important factors delaying wound healing.[129]
Wounds infected with bacterial or fungal organisms exhibit:

- Delayed epithelialization
- Excessive inflammation
- Tissue necrosis
- Increased exudate formation

Calendula exhibits antimicrobial activity against several wound-associated pathogens including:

- Staphylococcus aureus
- Pseudomonas aeruginosa
- Escherichia coli
- Candida albicans

The antimicrobial effect prevents secondary infections and creates favorable conditions for tissue regeneration.[130]

5.6 Experimental Studies on Wound Healing Activity

Several in vivo animal studies demonstrated significant wound healing activity of calendula extracts and formulations.[131]
Preethi and Kuttan reported that calendula-treated excision wounds showed:

- Faster wound contraction
- Increased granulation tissue formation
- Reduced epithelialization time
- Enhanced collagen synthesis

compared to untreated controls.[132]
Parente et al. additionally demonstrated that calendula extract significantly reduced inflammatory infiltration and accelerated tissue remodeling in animal wound models.[133]

Table 11: Important Experimental Studies on Wound Healing Activity

Study	Experimental Model	Major Findings
Preethi and Kuttan	Excision wound model	Faster epithelialization
Parente et al.	Animal wound model	Reduced inflammation
Leach	Systematic review	Enhanced tissue repair
Or Givol et al.	Clinical review	Improved wound healing outcomes

5.7 Clinical Studies and Human Applications

Several clinical studies evaluated calendula formulations in management of wounds, burns, radiation dermatitis, diabetic ulcers, and post-surgical injuries.[134]

Pommier et al. demonstrated that calendula ointment significantly reduced incidence and severity of radiation-induced dermatitis in breast cancer patients receiving radiotherapy.[135]

Calendula formulations have additionally shown beneficial effects in:

- Venous leg ulcers
- Diabetic foot ulcers
- Pressure sores
- Postoperative wounds
- Burn injuries

because of combined anti-inflammatory, antimicrobial, and tissue regenerative activities.[136]

5.8 Pharmaceutical Formulations Used in Wound Healing

Calendula is incorporated into various pharmaceutical formulations including:

Table 12: Pharmaceutical formulations of calendula used in wound management.

Formulation Type	Therapeutic Application
Ointments	Burns and wounds
Creams	Dermatitis and ulcers
Gels	Moist wound healing
Hydrogel dressings	Controlled drug release
Herbal sprays	Antiseptic applications
Nanoformulations	Enhanced penetration

Hydrogels and nanoformulations containing calendula have recently gained attention because they improve:

- Bioavailability
- Sustained release
- Skin penetration
- Moist wound environment
- Stability of phytoconstituents[137]

5.9 Limitations and Challenges in Wound Healing Research

Despite promising findings, several limitations remain:

- Lack of standardized extracts
- Variability in phytochemical composition
- Limited large-scale clinical trials
- Inadequate toxicological evaluation
- Insufficient molecular studies
- Variability in extraction techniques

Further research is required to establish standardized therapeutic protocols and evidence-based clinical applications.[138]

6. Dermatological and Cosmetic Applications of Calendula officinalis

Calendula officinalis has gained substantial importance in dermatology and cosmetic science because of its anti-inflammatory, antioxidant, antimicrobial, moisturizing, wound healing, soothing, and photoprotective properties.[139] The flower extracts of calendula are widely incorporated into pharmaceutical dermatological preparations and cosmetic formulations including creams, lotions, ointments, gels, shampoos, sunscreens, facial cleansers, moisturizers, anti-aging products, baby care products, and herbal skincare preparations.[140]

Skin represents the largest organ of the human body and serves as a primary protective barrier against

environmental toxins, ultraviolet radiation, microbial invasion, and physical injury.[141] Various dermatological conditions such as dermatitis, eczema, psoriasis, acne vulgaris, skin infections, burns, wounds, and photoaging are associated with inflammation, oxidative stress, microbial colonization, and impaired tissue regeneration.[142]

Calendula officinalis possesses multiple pharmacological properties that directly target these pathological mechanisms, making it an important medicinal herb in modern dermatology and cosmetology.[143]

6.1 Role of Calendula in Skin Physiology

The skin consists of three major layers:

1. Epidermis
2. Dermis
3. Hypodermis

$$Epidermis \rightarrow Dermis \rightarrow Hypodermis$$

The epidermis acts as the outer protective barrier, while the dermis contains collagen fibers, blood vessels, fibroblasts, sebaceous glands, and connective tissues responsible for structural integrity and elasticity.[144]
Damage caused by ultraviolet radiation, oxidative stress, microbial infection, and inflammation disrupts skin homeostasis leading to:

- Dryness
- Wrinkles
- Hyperpigmentation
- Inflammation
- Dermatitis
- Premature aging
- Reduced elasticity

Calendula phytochemicals help restore skin integrity by:

- Reducing oxidative stress
- Suppressing inflammatory mediators
- Enhancing collagen synthesis
- Improving hydration
- Promoting epithelial regeneration

6.2 Anti-inflammatory Dermatological Effects

Inflammatory skin disorders such as eczema, dermatitis, psoriasis, allergic reactions, and acne involve excessive production of inflammatory cytokines and oxidative mediators.[145]
Calendula exhibits significant anti-inflammatory activity because of triterpenoids, flavonoids, carotenoids, and phenolic compounds.[146]
The anti-inflammatory mechanisms include:

- Cyclooxygenase inhibition
- Reduction of prostaglandin synthesis
- Cytokine suppression
- Histamine release inhibition
- Reduction of inflammatory edema

$$Inflammatory\ Cytokines \xrightarrow{Calendula} Reduced\ Skin\ Inflammation$$

Faradiol esters present in calendula flowers significantly reduce skin inflammation and erythema.[147]
Clinical studies demonstrated that calendula creams effectively reduce:

- Redness
- Swelling
- Itching
- Irritation
- Burning sensation

associated with inflammatory skin disorders.[148]

Table 13: Dermatological Conditions Treated with Calendula Formulations

Dermatological Condition	Therapeutic Effect of Calendula
Dermatitis	Reduces inflammation
Eczema	Soothes irritated skin
Psoriasis	Reduces scaling and redness
Acne vulgaris	Antimicrobial and anti-inflammatory
Burns	Accelerates healing
Diaper rash	Skin protection
Radiation dermatitis	Tissue regeneration
Sunburn	Cooling and anti-inflammatory effect

6.3 Antioxidant and Anti-aging Effects

Skin aging is associated with oxidative stress, collagen degradation, ultraviolet radiation exposure, and chronic inflammation.[149]

Reactive oxygen species generated by UV radiation damage:

- Cellular DNA
- Collagen fibers
- Elastin proteins
- Lipid membranes

This leads to:

- Wrinkle formation
- Pigmentation
- Loss of elasticity
- Dryness
- Photoaging

Calendula contains potent antioxidants including:

- Quercetin
- Rutin
- Beta-carotene
- Lutein
- Chlorogenic acid

These compounds neutralize reactive oxygen species and protect skin tissues from oxidative injury.[150]

$$\boldsymbol{UV\ Radiation \rightarrow ROS \rightarrow Skin\ Aging}$$

$$\boldsymbol{ROS + Antioxidants \rightarrow Reduced\ Photoaging}$$

Carotenoids present in calendula additionally provide photoprotective effects by absorbing harmful ultraviolet radiation.[151]

Several cosmetic studies demonstrated that calendula-containing formulations improve:

- Skin hydration
- Elasticity
- Smoothness
- Barrier function
- Skin firmness

while reducing fine lines and oxidative tissue damage.[152]

6.4 Moisturizing and Skin Barrier Protective Effects

Maintenance of skin hydration is essential for preserving skin barrier integrity and preventing transepidermal water loss.[153]

Calendula oils and extracts contain fatty acids, polysaccharides, flavonoids, and sterols that help maintain skin moisture and barrier function.[154]

The moisturizing mechanisms include:

- Enhancement of epidermal hydration
- Prevention of water loss
- Restoration of lipid barrier

- Reduction of skin dryness and irritation

Calendula is therefore extensively incorporated into:
- Moisturizers
- Baby creams
- Sensitive skin formulations
- Dry skin preparations
- Herbal lotions

because of its gentle soothing properties.[155]

Table 14: Cosmetic Properties of Calendula Constituents

Phytochemical	Cosmetic Benefit
Carotenoids	Photoprotection
Flavonoids	Antioxidant activity
Essential oils	Skin cleansing
Polysaccharides	Moisturization
Triterpenoids	Anti-inflammatory action
Fatty acids	Barrier protection

6.5 Antimicrobial and Anti-acne Activity

Acne vulgaris is a chronic inflammatory skin disorder associated with:
- Excess sebum production
- Follicular obstruction
- Bacterial proliferation
- Inflammation

The primary microorganism involved is Cutibacterium acnes (formerly Propionibacterium acnes).[156]
Calendula exhibits antimicrobial activity against several skin pathogens including:
- Staphylococcus aureus
- Candida albicans
- Cutibacterium acnes

The antimicrobial activity is mainly attributed to essential oils, flavonoids, and phenolic compounds.[157]
Calendula formulations help:
- Reduce microbial colonization
- Minimize inflammation
- Promote healing of acne lesions
- Reduce post-inflammatory irritation

Because of these effects, calendula is frequently included in herbal anti-acne gels and cleansers.[158]

6.6 Calendula in Radiation Dermatitis

Radiation dermatitis is a common complication in cancer patients receiving radiotherapy.[159]
Clinical symptoms include:
- Erythema
- Dryness
- Burning
- Ulceration
- Skin peeling
- Pain

Pommier et al. demonstrated that calendula ointment significantly reduced incidence and severity of acute radiation dermatitis in breast cancer patients compared to trolamine treatment.[160]
The protective effects are associated with:
- Anti-inflammatory activity
- Antioxidant protection
- Tissue regenerative effects
- Enhanced epithelial repair

Calendula is therefore considered a promising supportive care agent in oncology dermatology.[161]

6.7 Calendula in Burn and Scar Management

Burn injuries involve severe oxidative stress, inflammation, microbial contamination, and tissue destruction.[162]
Calendula preparations accelerate burn healing through:

- Reduction of inflammation
- Prevention of infection
- Enhanced collagen synthesis
- Improved epithelialization
- Reduced scar formation

$$\textit{Burn Injury} \xrightarrow{Calendula} \textit{Enhanced Tissue Regeneration}$$

Experimental studies demonstrated faster healing and reduced inflammatory infiltration in calendula-treated burn wounds.[163]
Calendula additionally improves collagen remodeling and may help minimize hypertrophic scar formation.[164]

6.8 Applications in Cosmetic Industry

The cosmetic industry extensively utilizes calendula because of its safety profile and multifunctional dermatological benefits.[165]
Calendula is incorporated into:

Table 15: Major cosmetic applications of Calendula officinalis.

Cosmetic Product	Function
Moisturizers	Hydration
Sunscreens	Photoprotection
Face creams	Anti-aging
Cleansers	Skin soothing
Baby products	Skin protection
Lip balms	Healing and moisturization
Hair products	Scalp protection
Herbal soaps	Antimicrobial cleansing

The increasing consumer demand for herbal and natural cosmetics has further expanded commercial utilization of calendula extracts.[166]

6.9 Safety and Dermatological Tolerability

Calendula is generally considered safe for topical use with relatively low incidence of adverse effects.[167]
However, rare allergic reactions may occur in sensitive individuals, especially those allergic to plants belonging to the Asteraceae family.[168]
Reported adverse effects include:

- Contact dermatitis
- Skin irritation
- Allergic rash
- Hypersensitivity reactions

Patch testing is recommended for highly sensitive individuals before extensive topical application.[169]

6.10 Future Prospects in Dermatology and Cosmetology

Recent advances in pharmaceutical technology have increased interest in:

- Nanoemulsions
- Liposomal gels
- Hydrogel dressings
- Nanofibers
- Polymeric films
- Controlled release systems

containing calendula extracts.[170]

These advanced systems improve:

- Skin penetration
- Stability of phytoconstituents
- Sustained drug release
- Bioavailability
- Therapeutic efficacy

Future dermatological research should focus on large-scale clinical trials, molecular investigations, and standardized formulations for evidence-based therapeutic applications.[171]

7. Oral Healthcare Applications of Calendula officinalis

Calendula officinalis has emerged as an important medicinal herb in oral healthcare because of its antimicrobial, anti-inflammatory, antioxidant, wound healing, antifungal, and immunomodulatory activities.[172] Oral diseases such as gingivitis, periodontitis, dental plaque, oral ulcers, mucositis, halitosis, and fungal infections are highly prevalent worldwide and are often associated with microbial colonization, inflammatory responses, oxidative stress, and tissue destruction.[173]

Conventional oral care products including chlorhexidine mouthwashes, antibiotics, corticosteroids, and synthetic anti-inflammatory agents are associated with several adverse effects such as tooth staining, altered taste sensation, microbial resistance, mucosal irritation, and hypersensitivity reactions.[174] Therefore, increasing attention has been directed toward herbal therapeutics that provide safer and effective alternatives for long-term oral healthcare management.[175]

Calendula officinalis has been traditionally utilized in oral medicine for treatment of:

- Gingivitis
- Mouth ulcers
- Oral inflammation
- Sore throat
- Periodontal infections
- Mucosal wounds
- Oral candidiasis

Modern scientific studies have validated many of these traditional applications and demonstrated significant therapeutic benefits of calendula-based oral formulations.[176]

7.1 Importance of Oral Health and Oral Microbiota

The oral cavity contains a highly complex microbial ecosystem composed of bacteria, fungi, viruses, and protozoa.[177]

Under healthy conditions, oral microbiota remain in balance; however, poor oral hygiene, dietary factors, systemic diseases, smoking, and immunosuppression may disrupt this balance and contribute to oral diseases.[178]

The major oral pathogens associated with dental diseases include:

Table 16: Common oral diseases and associated microorganisms.

Oral Disease	Major Microorganisms Involved
Dental caries	Streptococcus mutans
Gingivitis	Porphyromonas gingivalis
Periodontitis	Aggregatibacter actinomycetemcomitans
Oral candidiasis	Candida albicans
Halitosis	Anaerobic bacteria

Calendula extracts exhibit broad-spectrum antimicrobial activity against many of these pathogens and help maintain oral microbial balance.[179]

7.2 Antimicrobial Activity in Oral Healthcare

The antimicrobial activity of calendula plays a major role in prevention and management of oral infections.[180]

Calendula extracts demonstrated inhibitory activity against:

- Streptococcus mutans
- Candida albicans
- Staphylococcus aureus

- Porphyromonas gingivalis

These microorganisms contribute significantly to dental plaque formation, gingivitis, periodontal disease, and oral fungal infections.[181]
The antimicrobial mechanisms include:

- Disruption of microbial cell membranes
- Inhibition of bacterial adhesion
- Alteration of membrane permeability
- Inhibition of microbial enzymes
- Suppression of biofilm formation

$$\textit{Bacterial Biofilm} \xrightarrow{\textit{Calendula Extract}} \textit{Reduced Microbial Growth}$$

Flavonoids, phenolic compounds, essential oils, and tannins present in calendula contribute substantially to antimicrobial activity.[182]
Several studies reported that calendula mouthwash effectively reduces dental plaque accumulation and bacterial load.[183]

7.3 Anti-inflammatory Effects in Gingivitis and Periodontitis

Gingivitis and periodontitis are inflammatory diseases affecting gingival tissues and supporting structures of teeth.[184]
The inflammatory process involves:

- Cytokine release
- Neutrophil infiltration
- Oxidative stress
- Tissue destruction
- Bone resorption

Calendula exhibits significant anti-inflammatory effects through inhibition of:

- Cyclooxygenase pathways
- Pro-inflammatory cytokines
- Histamine release
- Oxidative mediators

$$\textit{Inflammatory Cytokines} \rightarrow \textit{Gingival Inflammation}$$
$$\textit{Calendula Flavonoids} \rightarrow \textit{Reduced Gingival Edema}$$

Clinical studies demonstrated reduction in:

- Gingival bleeding
- Plaque index
- Gingival inflammation
- Oral mucosal irritation

following use of calendula mouthwash formulations.[185]

Table 17: Therapeutic Oral Effects of Calendula

Therapeutic Activity	Clinical Benefit
Antimicrobial activity	Reduces oral pathogens
Anti-inflammatory activity	Reduces gingivitis
Antioxidant activity	Protects oral tissues
Wound healing activity	Accelerates ulcer healing
Antifungal activity	Controls candidiasis
Immunomodulatory effect	Supports oral immunity

7.4 Role in Oral Ulcers and Mucositis

Oral ulcers and mucositis are painful inflammatory conditions commonly associated with trauma, chemotherapy, radiotherapy, infections, and autoimmune diseases.[186]

Chemotherapy-induced oral mucositis is particularly common among cancer patients and significantly affects nutrition, speech, swallowing, and quality of life.[187]
Calendula formulations help in management of oral ulcers through:

- Reduction of inflammation
- Promotion of epithelial regeneration
- Antimicrobial protection
- Reduction of oxidative stress
- Enhanced collagen synthesis

$$\textit{Oral Ulcer} \xrightarrow{\textit{Calendula}} \textit{Faster Epithelialization}$$

Calendula gels and mouthwashes demonstrated beneficial effects in reducing pain, erythema, ulcer size, and healing time in patients with oral mucosal lesions.[188]
The wound healing effect is attributed to:

- Fibroblast stimulation
- Increased granulation tissue formation
- Enhanced collagen deposition
- Cytokine modulation

7.5 Antifungal Activity in Oral Candidiasis
Oral candidiasis is a fungal infection primarily caused by Candida albicans.[189]
Risk factors include:

- Diabetes mellitus
- Immunosuppression
- Denture use
- Antibiotic therapy
- Xerostomia

Calendula extracts possess antifungal activity against Candida species because of phenolic compounds, flavonoids, and essential oils.[190]
The antifungal mechanisms include:

- Membrane disruption
- Inhibition of fungal growth
- Alteration of fungal enzyme systems
- Suppression of fungal adhesion

Experimental studies demonstrated that ethanolic calendula extracts exhibit stronger antifungal activity compared to aqueous extracts.[191]

7.6 Antioxidant Protection in Oral Tissues
Oxidative stress contributes significantly to periodontal tissue destruction and oral inflammatory disorders.[192]
Reactive oxygen species generated during inflammation damage:

- Gingival tissues
- Periodontal ligaments
- Cellular DNA
- Oral mucosal membranes

Calendula antioxidants neutralize free radicals and reduce oxidative injury in oral tissues.[193]
Major antioxidant compounds include:

- Quercetin
- Rutin
- Carotenoids
- Chlorogenic acid
- Polyphenols

These compounds help preserve integrity of gingival and mucosal tissues.[194]

7.7 Calendula-Based Oral Pharmaceutical Formulations

Calendula is formulated into various oral healthcare products including:

Table 18: Calendula-based oral pharmaceutical formulations.

Formulation	Application
Mouthwash	Gingivitis and plaque control
Oral gel	Ulcer management
Toothpaste	Antimicrobial oral hygiene
Gargles	Throat inflammation
Lozenges	Oral soothing
Herbal sprays	Oral antiseptic application

Herbal mouthwashes containing calendula have gained popularity because they provide therapeutic effects with comparatively fewer side effects than synthetic antiseptic mouthwashes.[195]

7.8 Clinical Studies on Oral Applications

Several clinical investigations evaluated efficacy of calendula formulations in oral diseases.[196]
Studies demonstrated significant reduction in:

- Gingival index
- Plaque index
- Bleeding index
- Oral inflammation
- Pain associated with ulcers

after regular use of calendula-based mouthwashes and gels.[197]
Calendula mouthwash was additionally reported to improve healing of radiation-induced oral mucositis in cancer patients.[198]

Table 19: Clinical Outcomes of Calendula Oral Formulations

Clinical Parameter	Observed Outcome
Gingival bleeding	Reduced
Dental plaque	Decreased
Oral ulcer healing time	Shortened
Oral inflammation	Reduced
Pain and discomfort	Improved
Oral microbial load	Lowered

7.9 Advantages of Calendula in Oral Healthcare

Calendula-based oral formulations provide several advantages:

- Natural herbal origin
- Broad-spectrum antimicrobial activity
- Reduced adverse effects
- Anti-inflammatory action
- Wound healing support
- Lower probability of microbial resistance
- Better patient acceptance

These characteristics make calendula a promising alternative in herbal dentistry and preventive oral healthcare.[199]

7.10 Limitations and Future Prospects

Despite promising findings, certain limitations still exist:

- Limited large-scale randomized clinical trials
- Lack of standardized oral formulations
- Variability in extraction methods
- Insufficient long-term safety studies

- Limited molecular investigations

Future research should focus on:
- Nanoformulations for oral delivery
- Controlled release herbal gels
- Bioadhesive systems
- Clinical standardization
- Comparative studies with conventional oral therapeutics[200]

8. harmaceutical Formulations and Novel Drug Delivery Systems of Calendula officinalis

Calendula officinalis has been widely incorporated into various pharmaceutical and cosmeceutical formulations because of its anti-inflammatory, antioxidant, antimicrobial, wound healing, antifungal, and tissue regenerative properties.[201] The increasing demand for herbal therapeutics with improved efficacy, safety, and patient compliance has significantly enhanced research interest in development of advanced calendula-based drug delivery systems.[202]

Traditional formulations such as ointments, creams, decoctions, tinctures, and poultices have been utilized for centuries in management of wounds, burns, inflammatory skin disorders, ulcers, and oral diseases.[203]
However, conventional herbal formulations often suffer from limitations including:

- Poor solubility of phytoconstituents
- Low bioavailability
- Instability of active compounds
- Poor penetration through biological barriers
- Short residence time
- Variable therapeutic efficacy

Recent pharmaceutical advancements have therefore focused on development of novel drug delivery systems capable of improving stability, controlled release, penetration, therapeutic efficacy, and patient acceptability of calendula formulations.[204]

8.1 Importance of Herbal Drug Delivery Systems

Herbal medicines contain multiple phytoconstituents with varying physicochemical properties.[205]
Efficient drug delivery systems are essential for:

- Enhancing bioavailability
- Improving stability of phytochemicals
- Sustained and controlled release
- Site-specific targeting
- Improved therapeutic response
- Reduction of dosing frequency
- Enhanced patient compliance

Novel pharmaceutical carriers additionally protect herbal compounds from oxidation, hydrolysis, and photodegradation.[206]

8.2 Conventional Pharmaceutical Formulations of Calendula

Calendula officinalis is incorporated into numerous conventional dosage forms depending on intended therapeutic applications.[207]

Table 20: Conventional Pharmaceutical Formulations of Calendula

Dosage Form	Major Application
Ointments	Wounds and burns
Creams	Dermatitis and inflammation
Gels	Moist wound healing
Tinctures	Oral and topical use
Mouthwashes	Gingivitis and oral ulcers

Poultices	Traditional wound care
Lotions	Skin soothing
Herbal sprays	Antiseptic applications
Oils	Skin moisturization
Decoctions	Traditional medicinal use

8.2.1 Ointments

Ointments are semisolid topical preparations commonly used for wound healing and dermatological applications.[208]

Calendula ointments exhibit:

- Occlusive effects
- Enhanced skin hydration
- Protection against microbial contamination
- Prolonged contact time

Clinical studies demonstrated effectiveness of calendula ointments in management of:

- Radiation dermatitis
- Minor burns
- Surgical wounds
- Skin irritation

because of their anti-inflammatory and tissue regenerative activities.[209]

8.2.2 Creams

Creams are emulsified semisolid systems suitable for cosmetic and dermatological applications.[210]

Calendula creams provide:

- Better patient acceptability
- Ease of application
- Enhanced spreadability
- Moisturizing effects

They are widely used in:

- Eczema
- Psoriasis
- Dry skin
- Diaper rash
- Acne management

because of soothing and anti-inflammatory properties.[211]

8.2.3 Gels

Hydrophilic gels containing calendula extracts are increasingly preferred because they provide:

- Non-greasy texture
- Better patient comfort
- Enhanced drug release
- Improved wound moisture balance
- Cooling effect

$$\boldsymbol{Hydrogel + Calendula\ Extract \rightarrow Sustained\ Wound\ Healing}$$

Calendula gels demonstrated promising applications in:

- Burn wounds
- Oral ulcers
- Diabetic wounds
- Periodontal inflammation

because of improved hydration and penetration characteristics.[212]

8.3 Novel Drug Delivery Systems

Advances in nanotechnology and biomaterials have enabled development of sophisticated calendula-based drug delivery systems.[213]
These systems enhance:

- Drug stability
- Bioavailability
- Controlled release
- Skin penetration
- Cellular uptake
- Therapeutic efficacy

8.3.1 Nanoemulsions

Nanoemulsions are thermodynamically stable colloidal systems with droplet size generally ranging from 20–200 nm.[214]
Calendula nanoemulsions offer several advantages:

- Enhanced solubility of phytochemicals
- Improved skin penetration
- Increased bioavailability
- Controlled release
- Better physical stability

Nano-sized droplets provide larger surface area which facilitates enhanced absorption through biological membranes.[215]

$$\textit{Reduced Particle Size} \rightarrow \textit{Increased Surface Area} \rightarrow \textit{Enhanced Drug Penetration}$$

Nanoemulsion formulations demonstrated superior antimicrobial and wound healing activity compared to conventional formulations.[216]

Table 21: Advantages of Calendula Nanoemulsions

Property	Therapeutic Benefit
Small droplet size	Better penetration
Increased surface area	Improved absorption
Controlled release	Prolonged action
Improved stability	Longer shelf life
Enhanced solubility	Better bioavailability

8.3.2 Liposomes

Liposomes are phospholipid vesicles capable of encapsulating both hydrophilic and lipophilic compounds.[217]
Calendula-loaded liposomes provide:

- Improved stability of phytoconstituents
- Controlled drug release
- Enhanced dermal penetration
- Reduced irritation
- Site-specific delivery

Liposomes additionally mimic biological membranes and facilitate deeper penetration into skin layers.[218]
These systems are especially useful in:

- Dermatitis
- Anti-aging products
- Burn management
- Wound healing applications

8.3.3 Nanoparticles

Polymeric and metallic nanoparticles loaded with calendula extracts have gained attention for advanced therapeutic applications.[219]
Nanoparticles provide:

- Sustained release

- Enhanced permeability
- Increased therapeutic concentration
- Improved stability
- Better targeting efficiency

Nanoparticles → Controlled Drug Release

Calendula-loaded nanoparticles demonstrated improved antimicrobial and wound healing activities in experimental studies.[220]
Polymeric nanoparticles additionally protect sensitive phytochemicals against degradation caused by environmental factors.

8.3.4 Hydrogels

Hydrogels are three-dimensional polymeric networks capable of retaining large amounts of water.[221]
Calendula hydrogels provide:

- Moist wound environment
- Enhanced epithelialization
- Cooling and soothing effect
- Controlled drug release
- Improved oxygen permeability

Hydrogel dressings containing calendula extracts are particularly useful in:

- Chronic wounds
- Burn injuries
- Diabetic ulcers
- Surgical wounds

because maintenance of moist wound environment accelerates tissue repair.[222]

Table 22: Therapeutic Benefits of Calendula Hydrogels

Hydrogel Property	Clinical Benefit
Moist environment	Faster epithelialization
Controlled release	Sustained therapeutic action
Cooling effect	Reduced pain and irritation
High water content	Better hydration
Oxygen permeability	Improved tissue repair

8.3.5 Nanofibers and Polymeric Films

Electrospun nanofibers and polymeric wound dressings represent advanced wound management systems.[223]
Calendula-loaded nanofibers provide:

- Large surface area
- High porosity
- Controlled drug release
- Enhanced cell attachment
- Improved tissue regeneration

These systems mimic extracellular matrix architecture and support cellular proliferation and migration.[224]
Polymeric films additionally protect wounds against microbial contamination while maintaining suitable moisture balance.

8.4 Transdermal Delivery of Calendula

Transdermal delivery systems provide controlled release of phytoconstituents across the skin barrier.[225]
Advantages include:

- Avoidance of first-pass metabolism
- Sustained plasma concentration
- Improved patient compliance
- Reduced dosing frequency

Calendula transdermal systems are particularly promising in management of chronic inflammatory and

dermatological disorders.[226]

8.5 Bioavailability Enhancement Strategies

Many calendula phytochemicals exhibit limited oral bioavailability because of poor solubility and rapid metabolism.[227]
Several approaches are used to enhance bioavailability:

Table 23: Bioavailability enhancement strategies for calendula formulations.

Strategy	Purpose
Nanoencapsulation	Improved stability
Liposomal delivery	Better penetration
Polymeric carriers	Sustained release
Phospholipid complexes	Enhanced absorption
Hydrogel systems	Localized delivery

8.6 Stability Considerations in Calendula Formulations

Stability is an important pharmaceutical parameter because phytoconstituents may degrade under environmental conditions.[228]
Factors affecting stability include:

- Temperature
- Light exposure
- Oxidation
- Moisture
- pH changes

Carotenoids and flavonoids are particularly susceptible to oxidative degradation.[229]
Novel delivery systems such as nanoparticles and liposomes help improve chemical stability of calendula phytoconstituents.

8.7 Evaluation Parameters of Calendula Formulations

Pharmaceutical formulations containing calendula are evaluated using various physicochemical and biological parameters.[230]

Table 24: Evaluation Parameters for Calendula Formulations

Parameter	Importance
pH	Skin compatibility
Viscosity	Spreadability
Drug content	Dose uniformity
Stability	Shelf life
Particle size	Penetration efficiency
Zeta potential	Colloidal stability
In vitro release	Drug release pattern
Antimicrobial activity	Therapeutic efficacy
Skin irritation test	Safety assessment

8.8 Regulatory and Quality Control Considerations

Standardization of herbal formulations remains a major challenge because phytochemical composition varies depending on:

- Geographical conditions
- Harvesting season
- Extraction method
- Storage conditions

Quality control parameters include:

- Phytochemical profiling
- Microbial limit testing
- Heavy metal analysis

- Stability testing
- Uniformity studies

WHO and pharmacopeial guidelines recommend proper standardization for ensuring safety, efficacy, and reproducibility of herbal medicinal products.[231]

8.9 Future Perspectives in Calendula Drug Delivery Research

Future research directions include:

- Smart responsive delivery systems
- Nanotechnology-based targeting
- Bioadhesive oral formulations
- Stimuli-responsive hydrogels
- Tissue engineering scaffolds
- Combination therapies with biomaterials

Integration of nanotechnology and herbal medicine may significantly improve therapeutic potential of calendula formulations in wound healing, dermatology, oral healthcare, and regenerative medicine.[232]

9. Toxicological Profile, Safety Evaluation, and Regulatory Aspects of Calendula officinalis

Calendula officinalis is generally regarded as a safe medicinal herb with extensive traditional usage in dermatological, wound healing, oral healthcare, and cosmetic applications.[233] Despite its widespread therapeutic acceptance, comprehensive toxicological evaluation and standardization are essential for ensuring safety, efficacy, quality control, and regulatory compliance of calendula-based pharmaceutical formulations.[234]

The growing commercialization of herbal medicines and herbal cosmetics has increased global regulatory attention toward safety assessment, contamination control, phytochemical standardization, adverse effect monitoring, and evidence-based validation.[235]

Although calendula demonstrates comparatively low toxicity, improper formulation, contamination, allergic sensitivity, excessive dosing, and poor standardization may contribute to adverse reactions.[236] Therefore, toxicological investigations and regulatory guidelines are important for development of safe and effective herbal therapeutic products.

9.1 Importance of Toxicological Evaluation in Herbal Medicines

Herbal medicines contain multiple phytochemicals capable of producing beneficial therapeutic effects as well as potential toxicological responses under certain conditions.[237]

Safety evaluation of herbal products is important because of:

- Variability in phytochemical composition
- Risk of contamination
- Adulteration
- Improper extraction procedures
- Herb–drug interactions
- Long-term exposure risks
- Lack of standardization

Toxicological assessment helps establish:

- Safe dose range
- Therapeutic index
- Organ toxicity profile
- Mutagenic potential
- Carcinogenic risk
- Reproductive safety
- Dermal compatibility

9.2 Acute Toxicity Studies

Acute toxicity studies evaluate adverse effects occurring after administration of a single dose or multiple doses within 24 hours.[238]

Several experimental studies demonstrated that calendula extracts possess relatively low acute toxicity.[239]
Animal studies reported:

- High LD50 values
- Absence of severe behavioral abnormalities
- Minimal mortality at therapeutic doses
- Good dermal tolerability

These findings suggest a relatively wide safety margin for topical and oral applications of calendula formulations.[240]

Table 25: Important Toxicological Parameters Evaluated for Calendula

Toxicological Parameter	Purpose
Acute toxicity	Short-term safety evaluation
Subacute toxicity	Intermediate exposure assessment
Chronic toxicity	Long-term safety
Skin irritation test	Dermal compatibility
Sensitization study	Allergy assessment
Genotoxicity	DNA damage evaluation
Mutagenicity	Mutation risk assessment
Reproductive toxicity	Fertility and developmental safety

9.3 Subacute and Chronic Toxicity

Subacute and chronic toxicity studies evaluate toxic effects associated with repeated administration over extended periods.[241]

Available studies indicate that calendula extracts generally do not produce severe organ toxicity at therapeutic concentrations.[242]
Experimental observations revealed:

- Normal liver function parameters
- Minimal renal toxicity
- No major hematological abnormalities
- Absence of severe histopathological damage

However, long-term toxicological data in humans remain limited and additional investigations are required.[243]

9.4 Dermal Toxicity and Skin Irritation Studies

Because calendula is extensively used in topical formulations, dermal safety evaluation is critically important.[244]
Calendula creams, ointments, and gels generally demonstrate:

- Good skin compatibility
- Minimal irritation potential
- Low erythema incidence
- Good patient tolerability

Patch testing studies reported low irritancy in most individuals.[245]

$$\textit{Topical Calendula} \rightarrow \textit{Reduced Skin Irritation}$$

However, hypersensitivity reactions may occur in susceptible individuals, particularly those allergic to plants belonging to the Asteraceae family.[246]

9.5 Allergic Reactions and Hypersensitivity

Calendula belongs to the Asteraceae (Compositae) family, which includes several plants known to cause allergic contact dermatitis in sensitive individuals.[247]
Possible hypersensitivity reactions include:

- Contact dermatitis
- Skin rash
- Erythema
- Itching
- Swelling
- Allergic eczema

The allergic response is generally mediated through delayed-type hypersensitivity reactions involving immune

activation.[248]

$$Allergen + Immune\ Response \rightarrow Contact\ Dermatitis$$

Patients with known allergy to:

- Chamomile
- Ragweed
- Chrysanthemum
- Daisy family plants

may exhibit cross-reactivity with calendula preparations.[249]
Therefore, careful patient history and patch testing are recommended before prolonged use.

9.6 Genotoxicity and Mutagenicity Studies

Genotoxicity studies evaluate the ability of substances to damage genetic material, while mutagenicity studies determine mutation-inducing potential.[250]
Available evidence suggests that calendula extracts do not exhibit significant mutagenic or genotoxic effects at therapeutic concentrations.[251]
Several in vitro investigations demonstrated antioxidant-mediated DNA protective effects because flavonoids and carotenoids help neutralize reactive oxygen species responsible for oxidative DNA injury.[252]
However, additional molecular toxicological studies are still required for comprehensive evaluation.

9.7 Reproductive and Developmental Toxicity

Limited information is available regarding reproductive toxicity and use of calendula during pregnancy and lactation.[253]
Traditional medicine literature has occasionally suggested possible uterine stimulatory activity of calendula extracts, although scientific evidence remains insufficient.[254]
Because of limited clinical data:

- Excessive oral consumption during pregnancy is generally discouraged
- Controlled clinical studies are lacking
- Safety during lactation remains inadequately established

Topical use is generally considered comparatively safer when appropriately formulated.[255]

9.8 Herb–Drug Interactions

Herbal medicines may interact with conventional pharmaceuticals through pharmacokinetic or pharmacodynamic mechanisms.[256]
Potential interactions associated with calendula may involve:

Table 26: Potential herb–drug interactions associated with calendula.

Drug Category	Possible Interaction
Sedatives	Additive sedative effect
Anti-inflammatory drugs	Synergistic anti-inflammatory activity
Antihypertensive drugs	Mild additive hypotensive effect
Antidiabetic drugs	Possible glucose-lowering interaction
Immunomodulators	Altered immune responses

Although clinically significant interactions are relatively uncommon, caution is advised in polypharmacy patients.[257]

9.9 Microbial and Heavy Metal Contamination

Quality and safety of herbal formulations may be compromised by contamination.[258]
Potential contaminants include:

- Bacteria
- Fungi
- Pesticides
- Heavy metals
- Residual solvents
- Mycotoxins

Heavy metals such as:

- Lead

- Mercury
- Cadmium
- Arsenic

can accumulate in medicinal plants due to environmental pollution and improper cultivation practices.[259]
WHO guidelines therefore recommend strict quality control measures and contaminant monitoring in herbal medicinal products.[260]

9.10 Regulatory Guidelines for Herbal Medicines

Regulatory authorities across different countries have established guidelines for evaluation of herbal medicines.[261]
Important regulatory organizations include:

Table 27: Major regulatory authorities for herbal medicinal products.

Regulatory Authority	Country/Region
WHO	International
USFDA	United States
EMA	European Union
AYUSH	India
MHRA	United Kingdom

These organizations emphasize:

- Standardization of herbal extracts
- Safety evaluation
- Good manufacturing practices (GMP)
- Stability studies
- Labeling requirements
- Quality assurance
- Pharmacovigilance systems

9.11 WHO Guidelines for Herbal Products

The World Health Organization has established comprehensive guidelines for quality control and safety assessment of herbal medicines.[262]
WHO recommendations include:

- Botanical authentication
- Standardized extraction procedures
- Microbial limit testing
- Heavy metal analysis
- Pesticide residue testing
- Stability studies
- Toxicological evaluation

These measures help ensure reproducibility, efficacy, and patient safety of herbal medicinal products.[263]

9.12 Pharmacovigilance of Herbal Medicines

Pharmacovigilance refers to monitoring, detection, assessment, and prevention of adverse effects associated with medicinal products.[264]
Herbal pharmacovigilance is important because:

- Herbal products are widely consumed without prescription
- Adverse effects are often underreported
- Product quality varies significantly
- Polyherbal formulations complicate safety assessment

Healthcare professionals are encouraged to document and report adverse reactions associated with herbal products.[265]

9.13 Quality Control Parameters for Calendula Preparations

Quality control is essential to maintain therapeutic consistency and safety.[266]
Important quality parameters include:

Table 28: Quality control parameters for calendula formulations.

Quality Parameter	Importance
Botanical identification	Prevents adulteration
Phytochemical profiling	Standardization
Moisture content	Stability assessment
Ash values	Purity evaluation
Extractive values	Solvent efficiency
Microbial testing	Safety
Heavy metal testing	Toxicity prevention
Stability studies	Shelf-life determination

High-performance thin-layer chromatography (HPTLC), HPLC, GC-MS, and spectrophotometric methods are commonly utilized for phytochemical standardization.[267]

9.14 Safety Profile of Topical vs Oral Administration

Topical calendula formulations generally demonstrate better safety profiles compared to oral administration.[268]
Topical applications:

- Low systemic absorption
- Minimal systemic toxicity
- Good dermal compatibility
- Rare hypersensitivity reactions

Oral administration:

- Potential gastrointestinal effects
- Limited clinical safety data
- Possible herb–drug interactions
- Need for dosage standardization

Thus, most pharmaceutical and cosmetic applications focus primarily on topical therapeutic utilization.[269]

9.15 Future Perspectives in Toxicological Research

Future investigations should focus on:

- Long-term chronic toxicity studies
- Reproductive safety evaluation
- Nanoformulation toxicology
- Molecular toxicity mechanisms
- Clinical pharmacovigilance studies
- Herb–drug interaction analysis
- Standardized clinical safety protocols

Advanced toxicological assessment will strengthen evidence-based utilization of calendula in pharmaceutical and biomedical applications.[270]

10. Future Perspectives and Research Opportunities of Calendula officinalis

Calendula officinalis has gained remarkable scientific and commercial importance because of its broad spectrum of pharmacological activities including wound healing, anti-inflammatory, antimicrobial, antioxidant, antifungal, immunomodulatory, and dermatological properties.[271] Although substantial progress has been achieved in understanding the therapeutic potential of calendula, several research gaps still remain regarding molecular mechanisms, clinical validation, formulation standardization, and advanced biomedical applications.[272]

The growing global preference for herbal medicines, natural cosmetics, and plant-based therapeutics has created new opportunities for development of evidence-based calendula formulations. Modern pharmaceutical technologies combined with traditional medicinal knowledge may further expand the therapeutic scope of calendula in future healthcare systems.[273]

10.1 Need for Advanced Clinical Research

Most currently available studies on calendula are based on:
- In vitro investigations
- Experimental animal models
- Small-scale clinical studies

Although these studies demonstrate promising therapeutic activities, large multicentric randomized clinical trials are still limited.[274]

Future clinical research should focus on:
- Standardized dosage regimens
- Comparative efficacy studies
- Long-term safety assessment
- Patient-specific therapeutic outcomes
- Pharmacokinetic profiling
- Evidence-based clinical validation

Clinical trials involving:
- Chronic wound patients
- Diabetic ulcer management
- Oral mucositis
- Radiation dermatitis
- Psoriasis and eczema

may provide stronger scientific evidence for therapeutic acceptance of calendula-based formulations.

10.2 Molecular Mechanism-Based Investigations

Several phytochemicals present in calendula such as flavonoids, triterpenoids, carotenoids, and phenolic acids contribute to its pharmacological effects.[275]
However, detailed molecular pathways associated with these activities still require further clarification.
Future mechanistic studies should investigate:
- Cytokine signaling pathways
- Gene expression modulation
- Growth factor regulation
- Cellular antioxidant pathways
- Matrix remodeling mechanisms
- Immune cell interactions
-

$$\textit{Phytochemicals} \rightarrow \textit{Molecular Signaling} \rightarrow \textit{Therapeutic Response}$$

Advanced omics technologies including:
- Genomics
- Proteomics
- Metabolomics
- Transcriptomics

may help identify specific biomarkers associated with calendula-mediated therapeutic effects.

10.3 Nanotechnology and Targeted Drug Delivery

Nanotechnology has emerged as one of the most promising areas for herbal medicine development.[276]
Future calendula-based nanoformulations may include:

Table 29: Emerging nanotechnology-based calendula delivery systems.

Advanced System	Potential Benefit
Nanoemulsions	Enhanced penetration
Liposomes	Controlled release
Polymeric nanoparticles	Improved stability
Nanofibers	Advanced wound dressing

Hydrogels	Sustained localized delivery
Bioadhesive systems	Improved mucosal retention

These advanced systems can improve:
- Bioavailability
- Stability of phytoconstituents
- Site-specific targeting
- Controlled release patterns
- Therapeutic efficacy

Nano-based wound healing scaffolds incorporating calendula extracts may become highly effective regenerative medicine tools in the future.[277]

10.4 Tissue Engineering and Regenerative Medicine

Regenerative medicine focuses on restoration of damaged tissues using biomaterials, cellular therapies, and bioactive compounds.[278]

Because calendula promotes:
- Fibroblast proliferation
- Collagen synthesis
- Angiogenesis
- Tissue regeneration

it has strong potential in tissue engineering applications.

Future research may involve incorporation of calendula extracts into:
- Biopolymeric scaffolds
- Electrospun nanofibers
- Hydrocolloid dressings
- Smart wound matrices
- Artificial skin substitutes

$$\boldsymbol{Calendula\ Extract + Biomaterial \rightarrow Enhanced\ Tissue\ Regeneration}$$

These systems may significantly improve management of:
- Chronic wounds
- Burns
- Diabetic ulcers
- Surgical injuries
- Tissue defects

10.5 Role in Personalized Herbal Medicine

Personalized medicine aims to optimize therapeutic outcomes based on individual patient characteristics.[279]

Future herbal therapeutics may incorporate:
- Genetic profiling
- Individual inflammatory markers
- Skin microbiome analysis
- Personalized dosage systems

Calendula formulations may therefore be customized according to:
- Patient sensitivity
- Disease severity
- Skin type
- Wound condition
- Oral microbiota composition

Such approaches could improve therapeutic precision and minimize adverse effects.

10.6 Artificial Intelligence and Herbal Drug Discovery

Artificial intelligence (AI) and computational pharmacology are rapidly transforming natural product research.[280]
AI-based tools can support:

- Phytochemical screening
- Molecular docking studies
- Toxicity prediction
- Drug-target interaction analysis
- Formulation optimization
- Predictive pharmacology

Computational modeling may help identify new therapeutic targets and optimize calendula-derived bioactive compounds for pharmaceutical development.

10.7 Sustainable Cultivation and Agricultural Research

Growing industrial demand for calendula has increased the need for sustainable cultivation practices.[281]
Future agricultural research should focus on:

- High-yield cultivars
- Organic cultivation methods
- Climate-resistant varieties
- Improved phytochemical productivity
- Sustainable harvesting techniques

Environmental conditions strongly influence phytochemical composition and medicinal quality of calendula flowers.
Standardized agricultural practices are therefore necessary to ensure consistency in pharmaceutical raw materials.

10.8 Standardization and Global Regulatory Harmonization

One of the major limitations in herbal medicine development is lack of universal standardization.[282]
Future advancements should focus on:

- Uniform extraction procedures
- Standard phytochemical markers
- Global quality standards
- Harmonized regulatory frameworks
- Advanced analytical profiling

Modern chromatographic and spectroscopic techniques such as:

- HPLC
- HPTLC
- LC-MS/MS
- GC-MS

will continue to play important roles in quality control and authentication of calendula products.

10.9 Commercial and Industrial Opportunities

The increasing global demand for natural therapeutics and herbal cosmetics has created substantial commercial opportunities for calendula-based products.[283]
Industries utilizing calendula include:

Table 30: Industrial applications and future commercial opportunities of calendula.

Industrial Sector	Applications
Pharmaceuticals	Wound healing formulations
Cosmetics	Anti-aging and skincare
Oral healthcare	Herbal mouthwashes and gels
Nutraceuticals	Antioxidant supplements
Veterinary medicine	Topical healing preparations
Biomedical industry	Tissue engineering materials

The herbal cosmeceutical industry particularly represents a rapidly expanding market for calendula-derived products.

10.10 Research Gaps and Challenges

Despite extensive therapeutic potential, several challenges remain:

- Insufficient large-scale clinical trials
- Variability in phytochemical composition
- Lack of standardized formulations
- Limited bioavailability studies
- Incomplete molecular investigations
- Regulatory inconsistencies
- Limited pharmacokinetic data

Addressing these limitations is essential for transforming calendula from a traditionally utilized medicinal herb into a scientifically validated evidence-based therapeutic agent.

10.11 Conclusion of Future Perspectives

Future integration of:

- Nanotechnology
- Molecular biology
- Regenerative medicine
- Artificial intelligence
- Precision therapeutics

with traditional herbal medicine may significantly enhance the therapeutic applications of calendula.[284]
The multifunctional pharmacological profile, comparatively favorable safety characteristics, and broad industrial applicability make calendula a highly promising medicinal plant for future pharmaceutical, biomedical, and cosmeceutical innovations.

11. DISCUSSION

Calendula officinalis is a medicinal plant with significant pharmacological and pharmaceutical importance due to the presence of bioactive compounds such as flavonoids, triterpenoids, carotenoids, phenolic acids, and essential oils.[296] These phytoconstituents collectively contribute to its wound healing, anti-inflammatory, antioxidant, antimicrobial, antifungal, and dermatoprotective activities.

The present review demonstrated that calendula possesses remarkable wound healing potential through enhancement of collagen synthesis, fibroblast proliferation, angiogenesis, and epithelialization.[297]

$$\textit{Collagen Synthesis} + \textit{Fibroblast Activity} \rightarrow \textit{Accelerated Wound Healing}$$

Its anti-inflammatory activity is mainly associated with inhibition of inflammatory mediators and reduction of oxidative stress.[298] The antioxidant properties further help protect tissues from reactive oxygen species and support tissue repair processes.[299]

Calendula also exhibited promising antimicrobial activity against several pathogenic microorganisms associated with skin infections and oral diseases including Staphylococcus aureus, Candida albicans, and Streptococcus mutans.[300] These properties support its applications in dermatology, oral healthcare, and wound management.
The review additionally highlighted the increasing importance of advanced pharmaceutical formulations such as nanoemulsions, liposomes, hydrogels, nanoparticles, and nanofibers for improving stability, bioavailability, controlled release, and therapeutic efficacy of calendula phytoconstituents.[301]
Despite extensive therapeutic potential, several limitations remain including lack of standardized formulations, variability in phytochemical composition, insufficient pharmacokinetic data, and limited large-scale clinical trials.[302] Therefore, further research focusing on clinical validation, molecular mechanisms, nanotechnology-based delivery systems, and regulatory standardization is necessary.
Overall, Calendula officinalis represents a promising medicinal herb with broad future potential in pharmaceutical sciences, dermatology, oral healthcare, regenerative medicine, and herbal drug delivery research.

12. Summary:

Calendula officinalis is an important medicinal plant widely used in traditional and modern medicine because of

its diverse pharmacological activities and broad therapeutic applications.[285] The plant contains several bioactive phytoconstituents such as flavonoids, triterpenoids, carotenoids, phenolic acids, tannins, saponins, essential oils, and polysaccharides, which collectively contribute to its medicinal properties.[286]

The present review summarized the botanical profile, phytochemistry, pharmacological activities, pharmaceutical formulations, dermatological applications, oral healthcare benefits, toxicological profile, and future biomedical potential of Calendula officinalis. Scientific evidence from experimental and clinical studies strongly supports its traditional medicinal uses.

Among its pharmacological properties, wound healing activity is one of the most significant therapeutic effects. Calendula promotes collagen synthesis, fibroblast proliferation, angiogenesis, epithelialization, and tissue regeneration, thereby accelerating the healing process.[287] The plant additionally exhibits anti-inflammatory activity by suppressing inflammatory mediators and oxidative stress pathways.[288]

Calendula also possesses significant antimicrobial and antifungal activities against pathogens such as Staphylococcus aureus, Candida albicans, Streptococcus mutans, and Cutibacterium acnes, which contribute to infection control and tissue protection.[289] Furthermore, its antioxidant activity helps neutralize reactive oxygen species and protects tissues from oxidative damage.[290]

The review also highlighted the increasing pharmaceutical and biomedical applications of calendula in creams, ointments, gels, mouthwashes, nanoemulsions, liposomes, nanoparticles, hydrogels, and nanofiber-based systems. These advanced delivery systems improve stability, bioavailability, tissue penetration, and therapeutic efficacy of calendula phytoconstituents.[291]

In addition, calendula demonstrates promising applications in dermatology, cosmeceuticals, oral healthcare, regenerative medicine, and tissue engineering because of its soothing, anti-aging, anti-inflammatory, and tissue regenerative properties. [292,293]

Although toxicological studies suggest relatively low toxicity and good dermal compatibility, proper standardization, quality control, and pharmacovigilance remain essential for ensuring safety and reproducibility of herbal formulations.[294]

The review further identified important future research opportunities including large-scale clinical trials, nanotechnology-based delivery systems, pharmacokinetic studies, molecular mechanism investigations, tissue engineering applications, and personalized herbal therapeutics.[295]

13. CONCLUSION

Calendula officinalis possesses significant pharmacological, pharmaceutical, dermatological, oral healthcare, and biomedical importance due to its rich phytochemical composition and multifunctional therapeutic activities. Scientific studies strongly support its wound healing, anti-inflammatory, antioxidant, antimicrobial, antifungal, and tissue regenerative properties.

The incorporation of calendula into advanced pharmaceutical formulations such as nanoemulsions, liposomes, hydrogels, nanoparticles, and nanofibers has further expanded its therapeutic and biomedical applications by improving drug delivery efficiency and therapeutic performance.

Despite considerable scientific progress, additional clinical validation, molecular studies, pharmacokinetic evaluation, and standardization protocols are still required to establish evidence-based therapeutic applications and regulatory acceptance of calendula-based formulations.

Overall, Calendula officinalis represents a highly promising medicinal plant with substantial future potential in evidence-based herbal medicine, advanced wound care, regenerative medicine, nanotechnology-based therapeutics, dermatology, oral healthcare, and cosmeceutical industries.
medicine, and cosmeceutical industries.

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