Mechanism of Action of Wound Healing Activity of *Calendula officinalis*: A Comprehensive Review

Bhargab Deka¹, Bedanta Bhattacharjee¹, Anshul Shakya¹, Abu Md Ashif Ikbal^{2*}, Chayanika Goswami³, Santa Sarma³

¹Department of Pharmaceutical Sciences, Faculty of Science and Engineering, Dibrugarh University, Dibrugarh – 786 004, Assam, India

²Department of Pharmacy, Tripura University (A Central University), Suryamaninagar- 799022, Tripura (W), India

³Department of Pharmacology, Girijananda Chowdhury Institute of Pharmaceutical Sciences- 781017, India

ABSTRACT

Calendula officinalis is a short-lived aromatic herbaceous perennial plant. According to scientific literature, *Calendula officinalis* can also boost the wound healing activity. While the precise means it does is still unclear, it was assumed that the herb would increase the blood flow to the wound area, therefore supplying oxygen and nutrients necessary for tissue regeneration. The objective of the review is to understand and explore the relevant phytochemical and pharmacological information which will enhance its effective wound healing mechanism. The data were identified using PubMed, Google Scholar, Scopus and bibliographic reviews of recent and old articles from an English literature search. After independent analysis by co-authors of the identified articles, data were analysed and extracted for the stated purpose. *Calendula officinalis* with its high quantity of flavonoids, it can help to minimize inflammation and speed up the healing process. Additional usage for *Calendula officinalis* is that it can be a calming ointment, wash or tincture, since it can help to alleviate irritated wounds and minimize swelling and inflammation. Wound healing is a complex process, and *Calendula officinalis* have been historically used to treat minor wounds, skin irritation and minor burns. Data from large comparative clinical trials are needed before routine use can be recommended. Pharmacists and clinicians can effectively address patient questions about wound care and herbal therapies to help promote wound care practices that encourages wound healing and minimize poor outcomes such as infection or scarring.

Keywords: *Calendula officinalis*, Wound Healing, Tissue Regeneration

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Corresponding Author:

Abu Md Ashif Ikbal, Department of Pharmacy, Tripura University (A Central University), Suryamaninagar- 799022, Tripura (W), India

Email: abumd97@gmail.com

Mobile: +917002666727

INTRODUCTION

Wounds and skin disease can be both socially and financially burdensome to an individual. Skin ulcers and wounds ranked in the top 5 of the most economically burdensome skin diseases¹. Wound care products and therapies

can promote the healing process, decreased the formation of wounds and enhances the properties of the fresh skin. Certain natural compounds have demonstrated potential anti-inflammatory, antimicrobial, and cell-stimulating properties that

may aid wound healing^{2,3}. These complementary and alternative medicine (CAM) therapies using plant extracts have been used in wound healing for centuries. Homeopathic treatments as discussed here are a branch of CAM therapy. Approximately 33% of US adults use some form of CAM^{4,5}. In addition, over 15 million Americans use CAM (herbal products [including homeopathic] or high-dose vitamins) with their prescription medications⁴. Comparative clinical trials for homeopathic medications are becoming more common; however, the complexity of standardizing scientific methods for CAM therapies is difficult. The evidence-based data supporting the use of CAM is lacking⁴. CAM therapies for wound healing are typically less expensive than prescription medications but have not been associated with bacterial resistance^{2,3}. Several CAM therapies have been used historically for potential effects on skin healing; however, these products have not shown clear benefits in clinical trials. Some of these well-known products include aloe vera, ginkgo biloba, St. John's wort, and honey. Additionally, other plant extracts such as tea tree oil, oak bark, and *Calendula officinalis* extract have also been used for their effects on wound healing. This article focus on CAM in wound healing and, more specifically, the use of *Calendula officinalis*.

WOUND HEALING

Skin disorders and wounds are generally defined based on the depth of injury, healing time, healing progression, underlying pathology, associated risk of mortality, and the effect on quality of life^{6,7}. Surgical and traumatic wounds, burns, radiation dermatitis, and abrasions (including scrapes and microdermabrasion) are considered acute wounds, while venous and arterial leg ulcers, fungating wounds, pressure ulcers, and diabetic ulcers are classified as chronic wounds. Healing time and sequence also delineates acute versus chronic wounds. In general, acute wounds can repair themselves in an orderly and timely manner unlike chronic wounds⁸.

Typical wound healing progresses through key phases. All phases must occur in an overlapping sequence and progress until healing is complete^{9,10}. Minor wounds are superficial, shallow, noninfected wounds that occur in patients without comorbid conditions that could complicate treatment (such as diabetes or immune deficiencies). Phase 1

of wound healing controls bleeding^{9,11}. Vascular constriction, platelet migration, and fibrin clot formation reestablish hemostasis shortly after vascular injury and provide an extracellular matrix for cell migration. Through this process, mediators of wound healing attract inflammatory cells to the area of injury progressing into the next phase of inflammation¹⁰. Phase 2 overlaps with the previous hemostasis and coagulation phase and begins within a few hours of injury. It is primarily defined by the accumulation of leukocytes and macrophages^{11,12}. Macrophages enter the wound site and release growth factors, such as platelet-derived growth factor, which facilitate the formation of new connective tissue (i.e. granular tissue)¹¹. Macrophages also help resolve inflammation and stimulate tissue regeneration, facilitating the transition from the inflammatory to reparative phases of proliferation and remodeling⁹. Occurring between 3 to 21 days post injury, phase 3 (proliferation) is characterized by granulation tissue formation, re-epithelialization of the wound surface, and contraction of the wound margins^{9,12}. Granulation tissue will contain macrophages, fibroblasts, and immature collagen, all of which stimulate granulation tissue formation. Concurrently, blood vessels will stimulate capillary growth. Fibroblasts within the wound bed stimulate the production of collagen, one of the key components of the extracellular matrix.

The final phase of wound healing (phase 4) can last for years and involves the reorganization of collagen fibers to create new skin^{9,12}. New skin may gain less than a quarter of its final strength in the first 3 weeks and rarely ever reaches the same strength as uninjured skin¹¹.

MOLECULAR MECHANISM OF WOUND HEALING

Molecular Mechanism of Platelets on Wound Healing

In the initial stage of injury platelets were activated and it has an important role in clot formation during hemostasis after aggregation and attachment to the exposed collagen surfaces. The cytokines and other growth factors regulate the process. Cytokines acts on target cells by various routes like endocrine, paracrine, autocrine or intracrine routes and activate target cells thereby activating other cell signalling

pathway. Cytokines can play various roles by acting on different targets.

Molecular Mechanism in the Inflammatory Cells on Wound Healing

Chemokines, which are small heparin binding proteins, promotes the movement of circulating inflammatory cells to the injury sites through the interaction with specific membrane bound receptors. Neutrophils are the main cell type in the initial inflammation phase and begins to disappear after 24 – 36 h by cell death in the time of circulating monocytes enter the wound and mature into tissue macrophages that play crucial role in the healing of wounds. This mechanism is regulated by the chemokines IL – 8 which is released by neutrophils which attracts the macrophages and other cells to the wound site.

Molecular biology in repair cells on wound healing

In correlation to macrophage – synthesized growth factors viz. PDGF, FGF, VEGF, TGF- α , TGF- β , KGF etc. the fibroblast a component of granulation tissue, starts to migrate, proliferate and produce the components of ECM, such as glycosaminoglycans and proteoglycans as well as collagen, a critical event in the proliferation phase and wound healing in general. Collagen is secreted to the extracellular space in the form of procollagen and then cleaved of its terminal segments, which is known as tropocollagen. Tropocollagen aggregates with other similar molecules to form collagen filaments that are enriched in hydroxylysine and hydroxyproline moieties and enable it to form strong cross links.

The stability of the collagen fiber is based on the intermolecular cross – links makes collagen fiber more resistant. Higher the cross – links of collagen, more will be the bursting strength in wound healing. Thus, collagen forms close cross – links with other collagens and with protein molecules thereby increasing the tensile strength of the healing wound¹³.

REGULATIONS OF HERBAL MEDICINES

WHO has updated and released the guidelines and policies regarding herbal medicines time to time including the areas ranging from GACP (Good Agricultural and Collection Practices), GMP (Good Manufacturing Practices) etc. These guidelines and policies taken by WHO will help to address the

variations in regulations and place the herbal medicine in the Global Market. Under the Drug and Cosmetic Act 1940 and Rules 1945 in India, herbal drugs are regulated which controls licensing, formulations, manufacturing, labeling, packing, import and export¹⁴.

Calendula officinalis

Calendula officinalis is a well known medicinal plants, and plant image display in Fig 1. It is native to Asia and southern Europe, but commonly found in gardens around the world. It is commonly known as Pot marigold, has been used in many forms and for centuries as an herbal remedy belonging to the family Asteraceae used for the treatment of wounds, burns, abrasions and dermatitis¹⁷. *Calendula officinalis* leaves, flowers, extract possess wide range of pharmacological activity viz wound healing, diaphoretic, analgesic, anti-inflammatory, anti-HIV¹⁸.

Fig 1: Various parts of *Calendula officinalis*

The chemical components include triterpenoids, saponins, flavonoids, carotenoids, fatty acids, polysaccharides, essential oils. The concentrations of these compounds vary depending on geographical area, although the observed physiological effects of topical *Calendula officinalis* appear to be consistent. *In vitro* studies shown that plant extract of *Calendula officinalis* show cytotoxic and tumor reducing potential on various tumor cell lines derived from cervix, breast, leukemias, prostate, fibrosarcomas^{17,19}. Generally, for the

treatment of peptic ulcer, duodenal ulcer, gastritis, colitis, mucous membrane inflammation it has also been used internally. *Calendula officinalis* is available in various formulations including creams, lotions, ointments, and gels. For general use, 2%-5% ointment may be applied 3 to 4 times daily as needed. After tooth extraction it is also used as a mouth wash²⁰. The Pharmacognostical profile and Organoleptic properties of the *Calendula officinalis* have been compiled in the Table 1.

Table 1: Scientific classification and organoleptic properties used for the *Calendula officinalis*

Biological Profile	
Kingdom	Plantae ²¹
Subkingdom	Tracheobionta ²¹
Division	Magnoliophyta ²²
Class	Magnoliophyta ²¹
Subclass	Asteridae ²²
Order	Asterales ²³
Family	Asteraceae ²³
Tribe	Calenduleae ²²
Genus	<i>Calendula</i> ²⁴
Species	<i>officinalis</i> ²⁴
Synonyms	
English	Pot marigold, Halligold ²³
Hindi	Genda ²⁴
Urdu	Gul-e- ashrafi ²³
Organoleptic Properties	
Odour	Aromatic and Faint ²¹
Taste	Bitter ²³
Height	3 feet
Texture	Medium to dull green oblong leaves

PHYTOCHEMISTRY OF *Calendula officinalis*

Calendula officinalis flower, leaves, root is a rich source of secondary plant metabolites and they differ in different part of the plant²⁵. The amount of these phytometabolites may vary according to the season, soil composition and harvesting time^{25,27,28}. Terpenoids, Flavonoids, quinones, coumarins and volatile oils are commonly present in *Calendula officinalis*^{29,30}. The major phytochemicals present in different parts of the plants are mentioned in Table 2. The structure of some important bioactive components are illustrated in Fig 2.

WOUND HEALING ACTIVITY OF *Calendula officinalis*

In ayurvedic system of medicine, it seems like *Calendula officinalis* possess scar easing and emollient properties by significantly raising the amount of collagen metabolism, wound angiogenesis in wound areas⁴³. By addition of *Calendula officinalis* flower extract, Hill *et al.*, demonstrated an experimentation conducted on scar reducing and massage emollient properties produce promising effective results⁴⁴. Ethanolic, hexane and dichloromethane fraction of *Calendula officinalis* in experimental model enhance wound healing and angiogenic activities. Treatment with ethanolic extract of *Calendula officinalis* increased the amount of blood vessel and decreased in wound area compared to reference group⁴⁵. Another study suggested that application of *Calendula officinalis* extract profoundly enhances epithelization in chronic venous ulceration. In the thermal induced burns in rats, treatment with ethanolic floral extract of *Calendula officinalis* showed significant improvement in wound healing activity by increasing the level of hexosamine and collagen hydroxyproline content. Similarly, the levels of tissue damage markers (alanine and aspartate amino transferase, alkaline phosphatase), acute phase protein (orosomycin, heptaglobulin), lipid peroxidation should be decreased due to its potential antioxidant property⁴⁶. Ethanolic extract of *Calendula officinalis* significantly increases collagen synthesis and blood flow to the effectively wounded sites⁴⁷. Due to its antimicrobial and antioxidant action, 2% *Calendula officinalis* gel and its daily application produces better healing of wounds⁴⁸.

Antiseptic and anti-inflammatory properties of *Calendula officinalis* extract heals wound along with internal as well as external ulcers. Because of its

good stability, penetrability and ease of application the ointment base of *Calendula officinalis* is more acceptable in hydrophobic medium^{49,50}.

Table 2: Phytoconstituent of *Calendula officinalis*

Plant part / Secondary metabolite	Active constituents
Flower	
Terpenoids	Lupeol ³¹ , Erythrodil ³² , Calendulose ³³ , <i>Calendula officinalis</i> glycoside A ³⁴ , <i>Calendula officinalis</i> glycoside B, Cornulacic acid acetate ³⁵
Flavonoids	Isoquercitrin, Rutin, Calendoflavoside ³⁴ , Quercetin ³⁶ , Isorhamnetin, Isorhamnetin-3-O-β-D-glycoside, Narcissin ²⁸
Coumarins	Esculetin, Scopoletin, Umbelliferone ³⁷
Volatile oils	Cubenol, α-cadinol, Oplopanone, Methylnoleate ³⁸ , Sabinene, Limonene, p-cymene, Carvacrol, Geraniol, Nerolidol ³⁹
Leaves	
Quinones	Phylloquinone, α-tocopherol, Ubiquinone, Plastoquinone ⁴⁰
Root	
Terpenoid	Calendulose A ⁴¹
Petal and Pollens	
Carotenoids	Flavoxanthin, Luteoxanthin, Auroxanthin, 9Z-antheraxanthin, Violaxanthin ⁴²

10% *Calendula officinalis* ointment prescribed for Cheilitis exfoliative⁵¹. In vivo model of excisional wounds of BALB/c mice, *Calendula officinalis* may help to induce granulation tissue formation by altering the appearance of connective tissue growth factor (CTGF) and α-smooth muscle actin (α-SMA)⁵². An overview of wound healing mechanism of *Calendula officinalis* as presented in Fig 3.

THERAPEUTIC USES OF *Calendula Officinalis*

Minor Wounds, Burns, And Abrasions

Historically, topical *Calendula officinalis* was used to treat minor wounds, burns, and abrasions; however, few clinical trials have been conducted to assess its efficacy and safety for these indications.

An animal study suggests that *Calendula officinalis* is beneficial for wound healing, though, such conclusions cannot be reasonably extrapolated to humans⁸⁷. Currently, more clinical studies need to be conducted in humans for this specific indication⁴⁸.

Venous Ulcers

Venous ulcer or stasis ulcer is the most common etiology of lower extremity ulceration and affects approximately 1% of Americans⁸⁸. Venous ulcers are irregular, shallow, and usually recurrent. Treatment typically includes leg elevation, compression therapy, wound dressings, pentoxifylline, and aspirin⁸⁸. *Calendula officinalis* has been studied as a possible treatment for venous leg ulcers.

In an open, comparative clinical trial, 34 patients with venous leg ulcers were treated with either an ointment containing 7.5% marigold extract in a neutral petrolatum base (from a local source in

Serbia and Montenegro) applied twice daily for 3 weeks or saline solution dressings applied for 3 weeks⁸⁹.

At the end of the 3-week study period, patients treated with the *Calendula officinalis* ointment

had a statistically significant reduction in the aggregate ulcer surface area compared with those in the placebo group (-41.71% vs -14.52%, respectively; $P < 0.05$). The number of wounds achieving complete epithelialization was similar in both groups (7/21 *Calendula officinalis* vs 4/13 placebo). Adverse effects were not reported. Despite the positive results, this study lacked an adequate control group, was not blinded, and had a small study population. Further clinical trials are warranted as benefit was shown⁸⁹.

Lupeol

Narcissin

Rutin

Isoquercetin

Esculetin

Scopoletin

Nerolidol

α-cadinol

Oplopanone

Umbelliferone

Sabinene

Plastoquinone

Violaxanthin

Flavoxanthin

Cubenol

Calendulose A

Fig 2: Struture of chief active constituents

Fig 3: Graphical representation of *Calendula officinalis* accelerates wound healing mechanisms

Radiation Dermatitis in Patients With Breast Cancer

Radiation dermatitis is a cutaneous repercussion of the external beam ionizing radiation used to treat malignancies⁹⁰. Also called “radiation skin damage” or a “radiation burn,” it affects approximately 95% of patients receiving radiotherapy. Skin changes after radiotherapy may be minor, reversible, and self-limiting, but can be serious and lead to ulceration, infection, or permanent skin damage in some patients. Protective

agents have been investigated. Controlled studies have not shown conclusive results in favor of specific agents, but patients have anecdotally noted satisfaction with ointments⁹⁰. *Calendula officinalis* has also been studied in the prevention of radiation dermatitis.

Calendula officinalis was evaluated in an open, phase 3, single center clinical trial for the prevention of radiation dermatitis following radiotherapy for breast cancer⁹¹. Women (n = 254) were randomized to be treated with *Calendula officinalis* extract in

petroleum jelly (Pommade au *Calendula officinalis* par Digestion; n= 126) or trolamine, the standard of care, (n = 128) applied by patients at least twice daily. Patients with more pain or erythema applied the products more frequently.

At the end of the study, Radiation Therapy Oncology Group (RTOG) grade 2 or higher dermatitis was reported less by patients receiving *Calendula officinalis* compared with those in the trolamine group (41% vs 63%, respectively; $P < .001$). Fewer patients treated with *Calendula officinalis* vs trolamine experienced grade 3 toxicity (7% vs 20%, respectively; $P = .034$), required treatment interruption (1 vs 15 patients), or had an allergic reaction to the cream (0 vs 4 patients). Despite better overall outcomes, patients reported that it was more difficult to use the *Calendula officinalis* formulation than trolamine (30% vs 5%, respectively) and more physicians felt that there was less compliance with *Calendula officinalis* than with trolamine (84% vs 92%, respectively)⁹¹. Study limitations include a lack of treatment blinding and the use of petroleum jelly (which itself may have beneficial effects) in the *Calendula officinalis* formulation.

A randomized, phase 3 study compared a 10% *Calendula officinalis* cream to an aqueous cream (moisturizer) without parabens (standard of care) applied twice daily before, during courses, and after radiation therapy for breast cancer⁹². Each treatment was applied starting with the initial radiotherapy session and was continued until 2 weeks after the last session or until any acute radiation skin reaction was healed. There were 390 patients included in the study with 194 receiving *Calendula officinalis* cream and 196 receiving aqueous cream. No difference was observed between the use of *Calendula officinalis* cream compared with aqueous cream for the incidence of RTOG grade 2 or greater dermatitis (23% vs 19%, respectively; $P = .39$). In addition, no differences were reported for other efficacy outcomes such as patient-reported symptoms like itchiness and pain. However, patients reported that the *Calendula officinalis* product was not as easy to apply and had worse absorption quality than the aqueous cream⁹².

Antihypertensive drugs

Excessive doses of *Calendula officinalis* has been found to possess hypertensive effects. Thereby, in combination with hypertensive drugs may result in additive effects⁹³.

Sedative drugs

Excessive doses of ingested preparation of *Calendula officinalis* has been found to possess sedative effects. Thereby, in combination with sedative agents may attributed additive effects. *Calendula officinalis* has been shown to increase the sleep time caused by hexobarbital in rats⁹³.

Hypoglycemic drugs

Calendula officinalis can increased the activity of insulin or hypoglycemic drugs⁹³.

Lipid lowering agent

Agents that minimize lipids and triglycerides, *Calendula officinalis* can have an additive effect⁹³.

ROLE OF THE PHARMACIST AND CLINICIAN IN THERAPY

When recommending a topical product for wound care, one should consider the proper dosage and frequency of application, patient age and weight, and the physical form of the preparation to be applied. Various drug vehicles have specific advantages and disadvantages, as described previously⁶⁶.

Patient assessments and histories are necessary to develop a plan of care for any skin condition. Items identified through a patient interview should guide treatment and identify areas of additional need, such as patient and family support, education, and goals of care. Patient information that should be obtained include: chief complaint; a detailed medical history including concurrent illnesses; allergies and past medical conditions; medication history, as well as herbal and nutritional supplements; use of self-care products; current diet; tobacco use, alcohol consumption, and exercise routine; and social interactions, hobbies, and mobility, with a focus on the effects of these on wound healing.

Safety risks, such as allergic reactions, exist with any product, but may be increased with herbal

products. In addition, a lack of regulation in the production of herbal and alternative products could result in products having additives and preservatives⁹⁴. To address these concerns, pharmacists and other health care practitioners should always recommend using products from trusted manufacturers and, in the case of supplements taken by mouth, ensure that they are US Pharmacopeia (USP) verified. The label with USP Verified Mark shows that the product⁹⁵:

- Carries the proclaim potency and amount of the ingredients listed
- Does not have specified contaminants present in harmful levels
- Meets dissolution standards
- Has been manufactured according to FDA and USP guidelines for safe, sanitary, and well-controlled manufacturing practices

Advise patients to know and watch for symptoms of an allergic reaction and discontinue using the product if allergy symptoms appear. For minor skin wounds and abrasions, pharmacists and nurse practitioners may assist with proper selection of self-care products for appropriate wound dressing and infection prevention. Pharmacists and clinicians can help patients navigate the multitude of available preparations and recommend appropriate delivery systems that are best suited for particular skin conditions (as described previously). Additional *Calendula officinalis* and wound care resources for pharmacists, nurse practitioners, and patients are provided in the table. As front-line health care providers, pharmacists and nurse practitioners may also identify patients with more serious or nonhealing wounds that require the care of a physician. These patients should be referred immediately⁹⁶.

TOXICOLOGICAL EFFECT OF *Calendula officinalis*

Calendula officinalis extract has been found to be safe, non irritating, non genotoxic and nonmutagenic⁹⁷. Oral administration of floral extract of *C.officinalis* 0.15g/kg/day given for a period of 18 months in hamstr were found to be non toxic⁹⁸. Dermal application of floral extract of *C.officinalis* produces allergic reaction in human evaluated by

the patch testing method reported in clinical studies⁹⁹. Similarly, Bone; Braun and Cohen also advised to patients and use *Calendula officinalis* preparation with caution. Patients with low immunity who are in close contact with *Calendula officinalis* showed an allergic reaction¹⁰⁰. *Calendula officinalis* has the ability to stimulate labor, so pregnant women are specially recommended to take care when using *Calendula officinalis* preparation¹⁰¹.

CLINICAL STUDIES

In traditional medicine system, *C.officinalis* flowers are reported to be used for treating wounds, scars, skin damage, ulcers. The therapeutic application of *Calendula officinalis* having promising effect are assessed in human studies are compiled in Table 3.

Topical application of *Calendula officinalis* suspension or in tincture is used for the treatment of reducing inflammation, controlling bleeding, acne.

Additionally, it improve the blood flow to the affected areas and it heals internal as well as external ulcers.

FUTURE PROSPECTS OF HERBAL DRUGS

Now a days people are showing more interest towards the herbal medicines compared to synthetic drug due to its minimum side effects and economic. The various types of Phyto-pharmaceutical are present in the natural products which deliver different types pharmacological activities. The therapeutic efficacy of medicinal plant depends upon the concentration of phytochemical components such as alkaloid, glycoside, tannin, polyphenol, flavonoids, steroids, terpenoids, etc.

The extract of medicinal plant contains more than one phytoconstituents and produce synergistic effects along with antioxidant property. The flavonoids and polyphenol present in *Calendula officinalis* reduced the oxidative stress in the body and boost the normal cells to fight the diseases with more potency. These antioxidant components are used as nutrient supplement which keep body healthy by increasing the immunity system. It has been reported that the herbal medicines eradicate the diseases from the root level, while the synthetic drug suppressed the diseases. Presently, the novel

drug delivery system such as Phytosomes, Liposomes, Niosomes etc improved the bioavailability and therapeutic efficacy of herbal extract.

Table 3: Clinical studies conducted in human trial for *C. officinalis*

Preparation	Therapeutic utility
<i>Calendula officinalis</i> powder	Administered orally 1-2 gm in a cup of water for the GI disorders ¹⁰²
Tincture (1:9 in 20% alcohol)	Administered daily 2-4 ml in water 3times for the GI disorders ¹⁰³
Cream (0.9% <i>C.officinalis</i> extract)	Effective against ROS caused damaged long term protection of the skin ¹⁰⁴
<i>C.officinalis</i> containing cream	Irritant contact dermatitis induced by Sodium lauryl sulfate ¹⁰⁵
2% <i>Calendula officinalis</i> oral gel	Oropharyngeal mucositis induced by Radiation ¹⁰⁶
Ointment base of <i>C.officinalis</i> (2-5%)	Used to treat ringworm, candida infection and athletes foot ^{46,50,51,107}

CONCLUSION

Calendula officinalis is a important medicinal plant and used for the treatment of various diseases. *Calendula officinalis* is mostly used for the healing of wound by herbal practitioner and the data presented in the paper support significant wound healing activity. Further, health care practitioners should understand the use of CAM for wound healing to assist patients seeking self-care.

CONFLICT OF INTEREST

Nil

AUTHOR'S CONTRIBUTIONS

BD, BB, AS, AMAI, CG and SS equally contributed in the preparation of manuscript, and all author approved for the publication.

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