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Calendula and aloe Vera in wound healing: A review

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Abstract
Introduction: Calendula and Aloe vera contain valuable metabolites due to their anti-inflammatory properties and ability to stimulate fibroblasts, supporting their use in medicine.
Objective: To analyze the literature regarding key aspects of wound healing, with an emphasis on Calendula and Aloe vera.
Methodology: The search was conducted in PubMed and Google Scholar using the terms *"Calendula","Aloe vera", "wound healing", "bacteria", "inflammation,"* combined with the Boolean operators *OR* and *AND*.
Results: Wound management requires proper assessment, cleaning, disinfection, and debridement to prevent infections, provided the patient follows treatment and aftercare. The skin microbiota, which varies depending on anatomical location and environment, changes in acute wounds (thermophilic bacteria) and chronic wounds (anaerobes), affecting healing. Its study is crucial for clinical management. *Calendula officinalis* and *Aloe vera* are plants with anti-inflammatory, antiseptic, and wound-healing properties, supported by their historical use in both traditional and modern medicine. Calendula officinalis exhibits anti-inflammatory, antimicrobial, wound-healing, and antioxidant properties, backed by scientific studies demonstrating its efficacy in wound care and inflammation, establishing it as a promising therapeutic agent in natural medicine. Aloe vera accelerates healing by stimulating cell proliferation, collagen synthesis, and reducing inflammation, though results vary. Its components inhibit pro-inflammatory cytokines and protect keratinocytes, supporting its use in dermatology. Its therapeutic potential lies in its anti-inflammatory and regenerative capabilities.
Conclusions: Effective wound care requires proper management and microbiota study, with *Calendula officinalis* and *Aloe vera* offering proven anti-inflammatory, antimicrobial, and healing benefits. These natural treatments are valuable in dermatology but need more research for optimal use.

Keywords: Calendula, healing, Aloe Vera, inflammation, bacteria, wound.

1. Introduction
Plant metabolites are considered key compounds due to their anti-inflammatory, anti-edematous properties, and their ability to stimulate fibroblasts [1]. Wounds are a growing medical problem requiring specialized care and are classified as acute, chronic, or burns. Wound healing occurs in three phases: inflammation, proliferation, and maturation. Acute wounds typically heal within 5 to 10 days, whereas chronic wounds take longer than 4 weeks due to unresolved healing phases. Burns are considered a separate category due to their distinct pathophysiology and progression [2].
Medicinal plants have been used since ancient times, and it is estimated that about 80% of the world's population relies on traditional herbal medicine for primary healthcare. Recently, there has been growing interest in herbal therapies for treating various ailments, alongside advancements in modern medicine. Today, numerous new drugs and treatments derived from these plants are being developed and prescribed. According to the World Health Organization (WHO), nearly 25% of modern medications originate from plants used in traditional medicine [3].
When performing primary wound closure in any region of the facial structure, the goal is to

achieve the most aesthetic healing possible to avoid a permanent lifelong scar. Therefore, investigating relevant aspects of wound healing is crucial. This study reviews the literature on wound management, the role of bacteria, and the use of plant extracts such as Calendula and Aloe vera.

2. Methodology

Information was collected from articles published in PubMed, Scopus and Google Scholar servers, with emphasis on the last 5 years. The quality of the articles was evaluated based on the standard guidelines, i.e., identification, review, choice and inclusion. The quality of the review was assessed using the measurement instrument for evaluating systemic reviews. Boolean logical operators AND, OR and NOT were used in the search. It was performed with the words "healing", "Calendula", "Aloe vera", "wound", "inflammation", "bacteria". The keywords were used individually, as well as each of them related to each other.

3. Results

3.1 Wound Management

Before performing primary or delayed closure, it is essential to assess skin viability. This evaluation is conducted clinically by observing skin color, the presence of bleeding, and the sensation of pain and warmth [4]. Non-viable skin tends to be less flexible and has a harder texture compared to viable skin. Additionally, it will not show capillary bleeding at the wound edges and may appear bluish, black, or white [5].

Wound irrigation is a crucial step to remove contamination and often allows for a more detailed wound assessment [6]. This procedure helps eliminate devitalized tissue, reduce bacterial contamination, and remove macroscopic debris. Various irrigation solutions have been proposed, with or without the addition of antiseptics such as povidone-iodine [7].

When closing a contaminated or dirty-infected wound, the placement of a drain should be considered, as it allows for the drainage of blood and serum that could otherwise accumulate and promote bacterial proliferation [8]. Drainage should also be considered if there is an unusually large amount of dead space, regardless of wound classification. Additionally, drains should not be placed directly beneath the wound closure or incision [4].

3.2 Bacteria

An individual's skin microbiota is established during birth, with the maternal process playing a crucial role in microbial composition. The most common bacterial phyla in the epidermis are *Actinobacteria* (52%), *Firmicutes* (24%), *Proteobacteria* (17%), and *Bacteroidetes* (7%) [9]. The most representative genera include *Corynebacteria* (*Actinobacteria*), *Propionibacteria* (*Actinobacteria*), and *Staphylococci* (*Firmicutes*) [10].

Microbial composition varies depending on skin location, influenced by factors such as moisture and anatomy [11]. For example, areas with numerous sebaceous glands—such as the glabella, nasal folds, and external ear canal—tend to have a higher bacterial load, primarily dominated by *Propionibacterium* and *Staphylococci* spp. In contrast, moist sites are typically dominated by *Corynebacteria* and *Staphylococci* spp [10].

3.2.1 Bacteria in Acute Wounds

Although most clinical research on wound microbiome healing has focused on chronic wounds, acute wounds—such as burns and trauma—are also relevant [12]. In burn wounds, a higher abundance of thermophilic microbes like *Aeribacillus*, *Caldalkalibacilus*, and *Nesterenkonia* has been observed, along with a lower presence of *Corynebacterium*, both in the wound center and edges [10]. Similarly, wounds resulting from blunt or penetrating trauma show changes in skin microbial composition and significant differences in beta diversity compared to healthy controls. The most predominant microbes in open fracture wounds and surrounding skin include *Staphylococcus*, *Corynebacterium*, *Streptococcus*, *Acinetobacter*, *Anaerococcus*, *Finegoldia*, and *Pseudomonas* [10].

3.2.2 Bacteria in Chronic Wounds

Human skin microbial composition is dynamic and varies depending on wound type [13]. In pressure ulcers, the three main phyla of microbes present are similar to those found in healthy skin, such as *Firmicutes*, *Proteobacteria*, and *Actinobacteria* [10]. Chronic wounds, which are typically more oxygenated, show a notable presence of anaerobic bacteria compared to acute wounds. Among the anaerobes identified as part of the chronic wound microbiome are *Finegoldia*, *Prevotella*, *Peptoniphilus*, *Peptostreptococcus*, and *Anaerococcus* [10].

3.3 Healing

3.3.1 Calendula

Calendula officinalis L. (Asteraceae) is an annual herb native to the Mediterranean region. It was introduced to England in the 13th century and has since been cultivated across Europe, though wild specimens are rare [14]. Its medicinal use became widespread starting in the 13th century, particularly for wound treatment [15]. During the American Civil War and World War I, it was incorporated into balms and creams as an antiseptic and anti-inflammatory agent [16].

The anti-inflammatory activity of *C. officinalis* flowers cultivated in Europe and Asia has been demonstrated through edema induction models, such as croton oil-induced ear edema and carrageenan-induced paw edema [17]. Additionally, the angiogenic activity of aqueous extracts from *C. officinalis* grown in England has been confirmed [15].

3.3.2 Aloe Vera

Aloe vera (AV), belonging to the Liliaceae family, is best known by its species name *Aloe barbadensis* Miller. It has been used in traditional medicine for thousands of years and is regarded as a "miracle gift of nature" due to its numerous therapeutic benefits [2]. Its medicinal use dates back 4,000 years, with references found in Sumerian tablets (2100 BCE) and the Ebers Papyrus (1552 BCE), where it was described as a laxative [18]. Egyptians, Romans, Greeks, Arabs, and Indians were among the first to recognize its healing properties. Legends claim that Egyptian Queen Nefertiti (1353 BCE) and Cleopatra VII (69-30 BCE) used it in their beauty and medicinal treatments [19]. Reportedly, Aristotle advised Alexander the Great in 333 BCE to capture the island of Socotra for its aloe vera plantations, which were essential for treating wounded soldiers [2].

Both *Calendula officinalis* and *Aloe vera* have historically demonstrated medicinal properties, particularly as anti-inflammatory, antiseptic, and wound-healing agents. Their documented use across ancient cultures supports their therapeutic efficacy, solidifying their value in traditional and modern medicine.

3.4 Calendula

3.4.1 Components

Extracts of *C. officinalis* are associated with diverse pharmacological actions, most notably anti-inflammatory, antiedematous, antioxidant, antibacterial, antifungal, and immunostimulatory properties [20]. Its chemical composition includes terpenoids, flavonoids, phenolic acids, carotenoids, coumarins, quinones, volatile oils, amino acids, and lipids. Additionally, *C. officinalis* exhibits antimicrobial and antiviral activity, is considered an effective treatment for breast cancer, and possesses antioxidant and immunomodulatory properties [21]. It is also used for acne treatment, shows potent anti-gastric ulcer activity, promotes wound healing, combats bacterial infections in animals, and provides hepatoprotective and nephroprotective effects [22].

3.4.2 Anti-Inflammatory Effects

Current research focuses on *C. officinalis* due to its notable anti-inflammatory activity [23]. The plant contains secondary metabolites such as alkaloids, tannins, flavonoids, essential oils, sterols, saponins, carotenoids, triterpene alcohols, mucilages, polysaccharides, and resins, which correlate with its anti-inflammatory effects [24].

Garrido-Suárez investigated the antinociceptive effects of a *C. officinalis* cream on inflammatory hypernociception. In rat studies, topical application of the cream (20% or 30% w/w) significantly reduced TNF-α levels and suppressed COX-2 expression. Furthermore, pharmaceutical formulations like nanoemulsions have been developed to enhance *C. officinalis*'s anti-inflammatory effects [25].

3.4.3 Wound-Healing Activity

C. officinalis may significantly enhance wound angiogenesis and collagen metabolism, leading to scar softening and emollient properties [26]. Floral extracts, whether applied topically or taken orally, show therapeutic effects on burns and wounds [27]. Increased collagen, hydroxyproline, and hexosamine levels indicate improved wound healing in treated individuals or animals [28].

Studies on albino rats confirm *C. officinalis*'s efficacy in wound healing. Findings reveal that herbal ointments containing *C. officinalis* inhibit macrophage activation while accelerating keratinocyte and fibroblast migration and proliferation—key factors in wound repair [29]. This is achieved by preventing proinflammatory cytokine release and reducing oxidative stress in the wound area [21].

Clinical trials have evaluated *C. officinalis* in second-intention wound healing (e.g., hand and finger injuries). Results indicate that calendula extract reduces epithelialization time and accelerates healing [30]. For chronic wounds like venous ulcers, topical *C. officinalis* treatment reduces lesion size, promotes faster epithelialization, and speeds up recovery [24].

Calendula officinalis stands out for its pharmacological properties, including anti-inflammatory, antimicrobial, wound-healing, and antioxidant effects, supported by its rich chemical composition. *In vivo* and clinical studies demonstrate its efficacy in accelerating healing, reducing inflammatory markers, and treating chronic wounds, positioning it as a promising therapeutic agent in natural medicine and pharmacology.

3.5 Aloe Vera

3.5.1 Wound-Healing Activity

Aloe vera significantly stimulates fibroblast and keratinocyte proliferation and migration [32]. Surprisingly, it also exhibits strong protective effects against preservative-induced keratinocyte death [33]. Keratinocytes cultured in preservative media with aloe vera showed dramatically higher viability than controls [34].

3.5.2 Anti-Inflammatory Activity

Recent studies on aloe vera's anti-inflammatory mechanisms focus on isolated compounds in murine macrophage RAW264.7 cells and LPS-stimulated mice [35]. Aloin's anti-inflammatory effect is linked to its ability to inhibit cytokines, reduce reactive oxygen species (ROS) production, and block JAK1-STAT1/3 signaling [36]. Additionally, aloe-emodin sulfates/glucuronides (0.5 μM), rhein sulfates/glucuronides (1.0 μM), aloe-emodin (0.1 μM), and rhein (0.3 μM) inhibit proinflammatory cytokines, nitric oxide production, iNOS expression, and MAPK phosphorylation [37].

3.5.3 Wound-Healing Effects

While some studies report positive effects of aloe vera gel on wound healing, others show contradictory results, even suggesting delayed healing [38]. These discrepancies may stem from ingredient stability and post-harvest treatment duration [39]. Proposed mechanisms include maintaining wound moisture, promoting epithelial cell migration, accelerating collagen maturation, and reducing inflammation [40]. A glycoprotein isolated from aloe vera (5.5 kDa) accelerates healing and cell proliferation in human keratinocytes and hairless mice, stimulating epidermal tissue formation [41].

Aloe vera promotes wound healing by stimulating cell proliferation and protecting keratinocytes, while its anti-inflammatory activity involves cytokine inhibition and proinflammatory pathway suppression. Despite variable results, its components enhance cell migration, collagen synthesis, and inflammation reduction, supporting its therapeutic potential in dermatology.

4. Conclusion

Clinical skin assessment and meticulous cleansing are essential for safe wound closure, while drains minimize infection in contaminated cases. The dynamic skin microbiota, influenced by wound type, affects healing and requires targeted management. Plants like *Calendula officinalis* and *Aloe vera*—with anti-inflammatory, antimicrobial, and wound-healing properties—offer valuable complementary therapies, supported by scientific evidence and medical tradition. Their integration into wound care can optimize recovery, highlighting the potential of natural medicine in modern clinical practice.

Conflict of Interest

Not available

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Not available

5. References

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