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The Potential Effect of *Daun Sirih* (*Piperaceae Leaf*) on the Burn Wound Healing: A Literature Review

Elvita Rahmawati[1], Ahmad Fawzy[2]

[1]Faculty of Medicine, University of Jenderal Soedirman. Indonesia

[2]Department of Surgery, Margono Soekarjo Country Hospital - Faculty of Medicine, University of Jenderal Soedirman, Indonesia

ABSTRACT

Introduction: Burn injuries, particularly among children and the elderly, result from heat, chemicals, or electricity, leading to skin and tissue damage. The wound healing process involves several stages, and infections from bacteria such as Pseudomonas aeruginosa and Staphylococcus aureus can complicate healing. While burns are typically treated with antiseptics, traditional remedies like Piper betle (Piperaceae) are commonly used in Indonesia. Compounds in Piper betle—including flavonoids, saponins, and tannins—possess antioxidant, antibacterial, and anti-inflammatory properties that may enhance burn wound healing.

Methods: This literature review synthesized data from various open-access online databases to evaluate the effects of Piper betle on burn wound healing.

Results and Discussion: Piper betle, a medicinal plant from the Piperaceae family, accelerates wound healing through several mechanisms. Flavonoids form complexes with proteins, damaging bacterial cells; saponins enhance collagen production, and tannins disrupt bacterial cell walls. Studies confirm that Piper betle reduces inflammation and fosters tissue regeneration via antioxidant activity. Animal trials demonstrate significant improvements in burn wound healing, including faster wound contraction and recovery.

Conclusion: Piper betle shows promise in accelerating burn wound healing due to its bioactive compounds. While existing studies support its effectiveness, further research is needed to assess the long-term safety and potential toxicity of Piperaceae-based treatments.

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INTRODUCTION

High-risk burns frequently affect children and the elderly, particularly in domestic settings during activities such as cooking, heating, or handling electrical devices. Burns, defined as tissue injuries caused by exposure to heat, chemicals, electrical currents, or radiation, can significantly impair the skin and impact multiple body systems. The severity of epidermal, dermal, and subcutaneous tissue damage depends largely on the duration of exposure to the causative heat source or other harmful agents.[1]

Wound healing progresses through distinct phases: hemostasis, inflammation, proliferation, and remodeling. Aerobic bacterial infections can significantly hinder and disrupt this healing process. Common contaminants in burn wounds include *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella spp.*, and *Enterococcus spp.*, all of which pose challenges to effective recovery. While antiseptic drugs are frequently employed in burn treatment, natural ingredients in traditional medicine also offer promising wound-healing properties and have shown effectiveness in supporting tissue repair.[2]

Numerous traditional Indonesian plants demonstrate wound-healing properties, with *daun sirih* (piper betle leaf, *Piperaceae*) emerging as a promising treatment option for burns. Widely cultivated in home gardens, *daun sirih* (piper betle) is both accessible and cost-effective. This plant contains bioactive compounds, including alkaloids, saponins, tannins, phenols, and flavonoids, which actively contribute to wound healing by

promoting cellular regeneration and supporting tissue repair. These bioactive molecules also function as antioxidants, directly inhibiting oxidative reactions caused by free radicals, which further protects tissues and enhances the healing process.[3]

Image 1. *Daun sirih* (piper betle leaf, *Piperaceae*)

Daun sirih (piper betle leaf, *Piperaceae*) has gained attention for its potential in promoting burn wound healing. This plant contains a range of bioactive compounds with therapeutic effects. Flavonoids in piper betle leaf act as anti-inflammatory, antioxidant, anti-allergic, and anti-carcinogenic agents, while its alkaloids provide antibacterial activity. Saponins serve as natural cleansers and antiseptics, effectively eliminating microorganisms and inhibiting their growth. Tannins further enhance wound healing by disrupting bacterial cell permeability, constricting skin pores, halting exudate production, and controlling minor bleeding.[4] Considering the potential supportive effect of this plant to wound healing, authors try to furher explore the effects of *daun sirih* (piper betle leaf, *Piperaceae*) on the burn wound healing process.

METHODS

We conducted a comprehensive literature review by analyzing data from multiple online databases. Our inclusion criteria required (1) openly accessible journals and (2) articles directly relevant to the scope of this review. Using keywords such as "Piper betle (Piperaceae) for burn wound healing" and "efficacy of Piper betle (Piperaceae) for wound healing," we performed searches across platforms including Google Scholar, PubMed, and Elsevier. We systematically collected, organized, and synthesized the resulting data to form a cohesive analysis.

REVIEW RESULT AND DISCUSSION

PIPERACEA PLANT-BASED ACTIVE SUBSTANCE AND WOUND HEALING

Medicinal plants possess significant potential in promoting burn wound healing by preventing infection, accelerating epithelial cell regeneration, and facilitating wound closure. Among the active compounds in these plants, flavonoids serve as potent antibacterial agents. Flavonoids form complexes with extracellular bacterial proteins, compromising bacterial cell membrane integrity and resulting in irreversible damage. Saponins also contribute antibacterial effects, exerting bacteriostatic action by destabilizing bacterial cell membranes, ultimately leading to cell lysis. Furthermore, saponins play a critical role in collagen synthesis, which supports connective tissues, including cartilage, capillary membranes, and skin, thereby expediting the wound healing process.[3] Tannins exhibit unique antibacterial mechanisms, particularly effective against *Porphyromonas gingivalis*. By targeting bacterial polypeptide cell walls, tannins inhibit proper cell wall formation, causing structural weaknesses that lead to bacterial cell lysis and death. Additionally, tannins inactivate bacterial enzymes and disrupt intracellular proteins, further impairing bacterial function. Together, these mechanisms underscore the therapeutic potential of medicinal plant metabolites in enhancing wound healing through infection control and tissue repair.[3]

The Piperaceae family, a group of dicotyledonous plants, is characterized by distinct organs including roots, stems, and leaves. Among its varieties, the betel plant includes types such as green betel, red betel, and Chinese betel. Red betel leaf (*Piper crocatum*) has been traditionally used in medicine, primarily for its leaves, which contain beneficial compounds like flavonoids, alkaloids, polyphenols, tannins, saponins, and essential oils. Flavonoids in red betel leaves are known for their antioxidant activity, while tannins offer both antioxidant and anti-inflammatory effects. Specifically, antioxidants exert anti-inflammatory actions by inhibiting the production of oxidants such as O_2 by neutrophils, monocytes, and macrophages. This inhibition reduces hydrogen peroxide (H_2O_2) and subsequently suppresses hypochlorous acid and hydroxyl radical (OH) production. Saponins enhance collagen production, essential for wound healing, and essential oils contribute antibacterial properties that help prevent infections in burn wounds. Additionally, flavonoids have notable anti-inflammatory properties. During the preparation process, red betel leaves underwent maceration with 96% ethanol for three days, followed by filtration to separate the extract. This liquid extract was then concentrated using a rotary evaporator, resulting in an extraction yield of 6.14%. In one study, researchers applied 200 mg of the resulting gel to burn wounds measuring an average of 20.61 mm in diameter on rabbits. They administered the gel once daily over a 21-day period. Observational results showed significant changes in the treated wounds, initially forming a crust of congealed blood, which developed into a protective scab layer. This study highlights the wound-healing potential of red betel leaf extract, suggesting its applicability in managing burn injuries.[6]

Green betel leaf (*Piper betle* Linn) is widely recognized for its antiseptic properties, frequently employed in traditional medicine to treat wounds, including those on the feet. Its therapeutic efficacy stems from a rich composition of bioactive compounds, such as saponins, tannins, and flavonoids, which together promote wound healing through various mechanisms. Tannins in green betel leaf exert astringent effects that effectively control bleeding, reduce mucosal membrane inflammation, and accelerate tissue regeneration. Saponins

contribute to wound healing by initiating the formation of collagen, a key protein essential for tissue repair and wound closure. Furthermore, the flavonoids in betel leaf possess significant antioxidant activity, which imparts antimicrobial and anti-inflammatory effects, particularly beneficial in the management of burn wounds. The cumulative actions of these compounds underline the medicinal value of green betel leaf as a potent agent for wound healing and antiseptic treatment.[7]

Chinese betel (*Peperomia pellucida*) has a long history of traditional use, particularly for its medicinal properties in treating various ailments. Its leaves have been widely recognized for their extensive pharmacological benefits, including antibacterial, analgesic, antipyretic, anti-inflammatory, hypoglycemic, antifungal, antimicrobial, anticancer, antioxidant, antidiabetic, and antihypertensive effects. The bioactive compounds in Chinese betel include alkaloids, tannins, calcium oxalate, lipids, and essential oils, which contribute to its therapeutic effects.[8] Additionally, the plant is rich in flavonoids, saponins, phenolics, steroids, glycosides, and triterpenoids. Essential oils present in *Peperomia pellucida* exhibit potent antimicrobial properties, while its flavonoid compounds act as powerful antioxidants, supporting its role in reducing oxidative stress and enhancing cellular defense mechanisms.[9]

PATHOPHYSIOLOGY OF BURN WOUND HEALING

Burns are classified into three main categories based on the depth of tissue damage: first-degree, second-degree, and third-degree burns. First-degree burns (superficial burns) involve only the epidermis, leading to dry skin, erythema, and pain due to irritation of sensory nerve endings; however, blisters are not present. Ultraviolet (UV) radiation from sunlight is the primary cause of this superficial skin damage. First-degree burns typically heal within a week through self-limited processes and leave no scar tissue. Second-degree burns (partial-thickness burns) extend through the epidermis and into the dermis, resulting in painful erythema and exudation. This category includes two subtypes: superficial partial-thickness and deep partial-thickness burns, each of which exhibits varying healing characteristics and depths of dermal involvement.[10] Third-degree burns (full-thickness burns) entail complete destruction of the epidermis and dermis, as well as subdermal structures, including skin appendages like hair follicles, sweat glands, and sebaceous glands. Full-thickness burns often appear dry, gray, or brown, without blistering or pain due to extensive nerve damage. Healing is significantly prolonged as epithelialization does not occur spontaneously.[10]

The wound healing process in burns involves four dynamic and overlapping phases: hemostasis, inflammation, proliferation, and remodeling. The **hemostasis phase** begins immediately after injury and focuses on blood vessel constriction and clot formation. Damaged vessels release blood to flush out microorganisms and antigens. Platelet activation initiates clotting cascades and vasoconstriction to minimize blood loss, while exposed collagen triggers platelet adhesion. As platelets aggregate, they release cytokines and growth factors, forming a blood clot composed of fibrin, fibronectin, and vitronectin. This temporary matrix supports cellular migration essential for subsequent healing phases.[11] Following hemostasis, **the inflammatory phase** aims to cleanse the wound and prepare it for new tissue formation. This phase, lasting two to five days, is primarily mediated by neutrophils, which phagocytize bacteria and release proteases, including elastase, cathepsin G, and proteinase 3, to degrade pathogens and clear cellular debris. Neutrophils also release inflammatory mediators like TNF-α, IL-1, and IL-6, which enhance the immune response and promote vascular endothelial growth factor (VEGF) and IL-8 production to facilitate tissue repair. Macrophages then assume a crucial role by phagocytizing debris, secreting growth factors, chemokines, and cytokines, thereby reducing apoptosis, promoting inflammation, and supporting cell proliferation and tissue regeneration. During this phase, symptoms such as edema, erythema, and pain are common.[11] The **proliferation phase** is critical for tissue regeneration and lasts approximately 6 to 21 days. During this phase, new collagen and extracellular matrix (ECM) components are deposited within the wound, which contracts as granulation tissue forms. Angiogenesis, or blood vessel formation, supplies nutrients and oxygen to the granulation tissue, promoting a healthy healing environment. Fibroblasts transition into myofibroblasts, which synthesize ECM components and exert contractile forces, thereby facilitating wound contraction.[12] In the early proliferative stage, granulation tissue appears pink or red with a slightly irregular texture, though darker discoloration may indicate infection, ischemia, or inadequate perfusion. Towards the end of this phase, epithelial cells migrate across the wound bed, effectively closing the wound. This epithelialization process can be enhanced by applying occlusive or semi-occlusive dressings within 48 hours of injury, which create a moist environment conducive to cell migration. The initial fibrin matrix is gradually replaced by a robust collagen-rich matrix comprising proteoglycans and fibronectin, which restore structural integrity and function to the tissue. Throughout the proliferation phase, fibroblasts must recognize and bind to specific ECM components to initiate migration. Normally, fibroblasts in the dermis are sparse and remain dormant; however, during wound healing, they become highly active, facilitating ECM reorganization and advancing wound closure.[13] The **remodeling phase** is the final stage of burn wound healing, lasting from several months to years. During this phase, collagen fibers reorganize, mature, and align along tension lines, strengthening the wound area. Fibroblasts continue to synthesize collagen, while myofibroblasts contract the wound further, improving tissue structure. The newly formed tissue gradually gains tensile strength, though it rarely reaches the full strength of uninjured skin. Scar tissue may form as the wound continues to remodel, and the appearance of the scar can improve over time with ongoing collagen reorganization.

IMPACT OF PIPERACEAE PLANT LEAF ON BURN WOUND HEALING

In a study conducted by Mu'nim and colleagues in 2010, wound healing showed a significant improvement in both the percentage of healing and the reduction of wound area at concentrations of 20% and 40% betel leaf extract, compared to the control group treated with normal saline. This enhancement is attributed to the anti-inflammatory properties of betel leaf, which effectively capture free radicals through its potent antioxidant activity. The ethanol extract of betel leaf demonstrates superior antioxidant capacity compared to ascorbic acid, dimethyl sulfoxide (DMSO), and butylated hydroxytoluene (BHT). Furthermore, betel leaf extract contains essential nutrients, such as vitamins A and C, which are crucial for wound healing. Vitamin A facilitates collagen formation, promotes epithelial cell differentiation, and boosts immune function. Specifically, it accelerates the transition from the inflammatory phase to the proliferation phase by increasing the recruitment of monocytes and macrophages to the wound site. Macrophages, which originate from monocytes, serve to clear bacterial pathogens and cellular debris from the wound, while also producing growth factors that stimulate fibroblast proliferation and angiogenesis. Additionally, macrophages support the regeneration and proliferation of the dermal layer. Vitamin C is indispensable for the hydroxylation of proline and lysine residues in procollagen, a critical step in collagen synthesis.[14]

Topical products derived from plants in the *Piperaceae* family have gained attention for their potential use in post-surgical care. Phytochemical analyses in previous studies have identified alkaloids as the primary secondary metabolites in *Piper vicosanum* and *Piper amalago*. Additionally, organic acids, tannins, steroids, and triterpenes were predominantly found in *Piper glabratum*. A study by Menon and colleagues in 2023 stated that the anti-inflammatory properties of *Piperaceae* plants may mitigate endothelial damage by preventing platelet aggregation and inhibiting lymphocyte adhesion, and therefore lower the risk of tissue ischemia and necrosis.[15] Previously, Carsono and colleagues in 2022 already highlighted the antioxidant properties of *Piperaceae* plants, which play a protective role during perfusion injury.[16] The combined anti-inflammatory and antioxidant activities of *Piperaceae* extracts exhibit a synergistic and multimodal mechanism that contributes to tissue protection.

However, subacute toxicity was observed in trials using *Piper amalago* extract, with signs such as decreased hematocrit, increased platelet count, elevated cholesterol levels, and raised serum alkaline phosphatase. These potential toxic effects may arise from prolonged use of the extract. Consequently, it may be advisable to limit the duration of treatment with *Piperaceae* extracts to minimize the risk of adverse effects.[16]

THERAPEUTIC TIMING RECOMMENDATION

Piperaceae extracts, with their antibacterial, antiplatelet, antioxidant, and anti-inflammatory properties, hold significant potential in enhancing burn wound healing. In the inflammatory phase of burn wound healing, the antibacterial properties of the plant extract can reduce the risk of infection, which is crucial during this early phase when the immune response is activated. By preventing bacterial colonization, the extract would help maintain a sterile wound environment, reducing complications that can impair healing. Additionally, its anti-inflammatory effects can modulate excessive inflammation, which is characteristic of the inflammatory phase, thereby preventing prolonged tissue damage and promoting faster recovery. The antiplatelet activity of Piperaceae extracts may also support wound healing by reducing unwanted clot formation, which could otherwise obstruct the proper blood flow to the injured tissue. Furthermore, the antioxidant properties of these extracts can neutralize reactive oxygen species (ROS) produced during inflammation, minimizing oxidative damage to the cells and surrounding tissues. As the wound progresses into the proliferative phase, these actions help to optimize the formation of granulation tissue and collagen deposition, both vital for tissue regeneration. The combined effects of reducing inflammation and oxidative stress during the early stages of healing suggest that *Piperaceae* extracts are most beneficial in the inflammatory phase, where they can effectively modulate the immune response and protect tissues from further damage, thus promoting faster and more efficient healing.

CONCLUSION

The use of traditional plants, particularly the *Piperaceae* family, such as betel leaf, has demonstrated significant potential in burn healing. Betel leaf contains a variety of bioactive compounds, including flavonoids, saponins, alkaloids, and tannins, which are known for their anti-inflammatory, antioxidant, antibacterial, and antiseptic properties. These compounds contribute to the accelerated healing of burns especially in acute inflammatory phase, as evidenced by numerous studies focusing on both red and green betel leaf varieties.

Despite these promising findings, the long-term use of *Piperaceae* plant-based products warrants caution due to potential toxicity, as highlighted in some studies. Notably, products derived from *Piper amalago* have raised concerns regarding safety. Therefore, further research is essential to thoroughly assess the safety profile and effectiveness of these plants in burn treatment, ensuring they can be used reliably and without adverse effects in clinical settings.

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