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The Potential Therapeutic Role of Flavonoids and Mangiferin in Mango Peel for Burn Wound Healing: A Comprehensive Literature Review

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ABSTRACT

Background: Approximately 11 million burn injuries occur worldwide each year, causing significant morbidity and emotional distress. Burn wounds heal slowly, impacting quality of life. Mango peel contains flavonoids and mangiferin, which may aid burn wound healing.

Objectives: This literature review aims to explore flavonoids and mangiferin in mango peel for burn wound healing.

Methods: We searched PubMed, Google Scholar, Scopus, and Web of Science using keywords like burn wound, thermal injuries, flavonoid, mangiferin, and mango peel. We included accessible articles in Bahasa Indonesia or English, including research articles, systematic reviews, meta-analyses, and literature reviews.

Discussion: Flavonoids enhance collagen synthesis and increase fibroblast basic growth factor and vascular endothelial growth factor, promoting granulation tissue formation. Mangiferin has anti-inflammatory properties, suppressing COX-1, COX-2, and PGE-2 production, and deactivating the NLRP3 inflammasome. These actions suggest potential for improving burn wound healing.

Conclusion: Flavonoids and mangiferin in mango peel show promise for wound healing due to their anti-inflammatory, antibacterial properties, and ability to stimulate collagen and VEGF formation. Further research is needed for clinical application and better outcomes.

KEYWORDS: flavonoids, mangiferin, mango peel, burn wound healing

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INTRODUCTION

Mangifera indica L., commonly known as mango, is cultivated globally. Mango comprises three distinct parts: peel, pulp, and kernel. Although people usually discard the mango peel, it possesses significant nutritional value, containing biocomponents such as mangiferin, flavonoids, polyphenols, protocatechuic acids, and β-carotene. These biocomponents in the mango peel exhibit various functions, including anti-inflammatory and antimicrobial properties, which play a crucial role in wound healing.[1]

Burn injury associates with high morbidity and mortality, mainly affecting patients with a total body surface area (TBSA) of 30% or greater. Furthermore, it causes emotional distress and imposes an extra burden on patients, their families, or caregivers. Additionally, treating burn injury requires considerable time.[2] Pathological scars often occur in burns, especially in deep partial-thickness or full-thickness burns. Hypertrophic scars and keloids usually develop following burn injury, with hypertrophic scars being more common. Contracture can also develop.[3]

Research on the use of plant-based medicine for treating burn injuries remains limited and requires further investigation. Our paper examines the potential therapeutic role of mangiferin and flavonoids in mango peel for promoting burn wound healing.

Biological Basis of Burn Wound Healing

Phases of wound healing

Wound healing involves a complex series of cellular events aimed at repairing damaged tissues. This process relies on an individual's intrinsic healing capacity. Researchers have categorized the main cellular events into either three overlapping phases—inflammation, proliferation, and remodeling—or four overlapping phases—hemostasis, inflammation, proliferation, and remodeling.[4,5]

- Hemostasis

Hemostasis precedes the first phase. After an injury occurs, blood vessels contract to decrease blood flow to the injured area. Platelets become activated upon encountering the vascular subendothelial matrix. Platelet receptors, such as glycoprotein VI, interact with collagen, fibronectin, von Willebrand factor, and other extracellular matrix (ECM) proteins to enhance platelet adherence to the endothelium. Thrombin activates platelets immediately after this interaction, leading to the release of dense and alpha granules that carry bioactive molecules promoting coagulation. Dense granules contain several small molecules, including adenosine diphosphate (ADP), adenosine triphosphate (ATP), guanosine diphosphate (GDP), serotonin (5-HT), pyrophosphate, magnesium, and calcium. Along with thromboxane A2, these molecules act on circulating platelets, promoting the positive feedback signaling that sustains ongoing platelet aggregation. Platelet secretions also contain growth factors that activate resident skin cells, such as keratinocytes and fibroblasts. The coagulation process terminates once the platelet plug has formed to prevent excessive thrombosis. Prostacyclin inhibits platelet aggregation, antithrombin III inhibits thrombin, and activated protein C degrades coagulation factors V and VII. Hemostasis does not always occur in burn wounds because there is no bleeding, so it is sometimes not considered in burn injuries. However, vasoconstriction significantly prevents fluid loss from the burn wound. After a burn injury, increased capillary permeability causes a high loss of fluid and protein into the interstitial space. Without vasoconstriction interference, this fluid loss leads to hypotension, potentially causing end-organ damage.[4,6,7]

- Inflammation

Damage-associated molecular patterns (DAMPs), also known as alarmins or endogenous ligands, arise from necrotic cells and damaged tissues. Pathogen-associated molecular patterns (PAMPs), also known as exogenous ligands, originate from microbial components. These signals, induced by injury, activate resident immune cells. Specific Toll-Like Receptors (TLRs) on resident immune cells, such as mast cells, Langerhans cells, T cells, and macrophages, bind to these signals. TLR2, TLR3, and TLR4 significantly contribute to wound healing. TLR3 activation triggers genes involved in all aspects of wound healing. From six hours to three days post-injury, keratinocytes at the wound edge express TLR4. The TLR4-p38 and JNK MAPK signaling pathways stimulate cytokine production, promoting inflammation. A study in TLR4-deficient mice demonstrated significantly impaired wound healing due to a decrease in cytokines (IL-1β and IL-6). Subsequently, pro-inflammatory cytokines and chemokines attract circulating leukocytes and stimulate vasodilation. Vasodilation, along with selectin expression on the endothelial wall, facilitates neutrophil and monocyte adhesion and diapedesis. Interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF-α), and lipopolysaccharide (LPS) attract neutrophils, which then release cytokines, reactive oxygen species (ROS), antimicrobial peptides, eicosanoids, proteolytic enzymes, and phagocytose necrotic tissues and pathogens. Monocytes enter the injury site and differentiate into macrophages, often referred to as wound macrophages. These macrophages also phagocytose necrotic tissues and pathogens, known as M1 (pro-inflammatory). Due to their high level of plasticity and polarization, macrophages facilitate tissue repair and are referred to as M2 (anti-inflammatory). M2 macrophages release arginase, a key factor for effective wound repair. Macrophages play a critical role in transitioning from inflammation to proliferation. Without macrophages, the transition to the next phase fails. Distinct differences exist between the inflammatory response during burn injury wound healing and the standard wound healing process. Histamine presence causes protein leakage, stimulating kinin formation by tissue kallikrein on kininogens. Kinin then binds with kinin B1 or B2 receptors. During inflammation, kinin B1R and B2R expressions are upregulated. Kinin also activates the kallikrein-bradykinin system, complement cascade, arachidonic cascade, and coagulation-fibrinolytic cascade. Increasing levels of prostaglandins, prostacyclins, and TXA2 result in edema retention, vasoconstriction, and local ischemia. Prolonged or unrestrained edema, along with the inflammatory response, exacerbates pain and slows wound healing.[5,8-15]

- Proliferation

When the inflammation phase ends, the proliferation phase starts. The migration and differentiation of keratinocytes in the basal layer of the wound edge and epithelial stem cells from skin appendages such as neighboring hair follicles or sweat glands mark the beginning of the proliferation phase. In a first-degree burn wound, the basement membrane remains intact, so the epithelial cells move upward following a normal pattern. The epidermis restores in 2 to 3 days. Deeper

burn injuries disrupt the basement membrane, allowing normal epidermal cells to migrate from skin appendages and re-epithelialize the wound from the wound's periphery. Angiogenesis also occurs during this phase. The process of proliferation requires a lot of oxygen and nutrients, necessitating angiogenesis. The expression of hypoxia-inducible factors (HIFs), cyclooxygenase 2 (COX-2), vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and other factors direct endothelial cells to proliferate and migrate into the wound bed, creating new blood vessels that unite and develop into more stable blood vessels. Fibroblasts mainly replace the hemostatic plug with granulation tissue. Platelets, endothelial cells, and macrophages send signals such as transforming growth factor beta (TGF-β) and platelet-derived growth factor (PDGF) to the fibroblasts. Then, fibroblasts either build fibrosis, compose extracellular matrix (ECM) proteins, or transform into myofibroblasts. Fibroblasts produce matrix metalloproteinases (MMPs) which help in the hydrolysis of ECM molecules such as collagen, elastin, laminin, fibronectin, cytokines, and growth factors. This process produces granulation tissue, serving as a temporary platform for the migration and differentiation of wound cells.

- Maturation/remodelling

Maturation, also known as remodeling, represents the final phase of wound healing. This phase can extend for months or even years and remains relatively consistent across all wound types. During this phase, fibroblasts migrate out of the wound bed, and collagen is rearranged into a more ordered matrix. Mechanical tension and the differentiation of fibroblasts to myofibroblasts cause wound contraction. Collagen fibrils cross-link to enhance mechanical tension. Transforming growth factor beta (TGF-β) stimulates the differentiation of fibroblasts to myofibroblasts, leading to the expression of alpha-smooth muscle actin (α-SMA), which induces wound contraction. Myofibroblasts develop pseudopodial extensions that assist in wound contraction by facilitating the binding of cytoplasmic actin to fibronectin in the matrix. Myofibroblasts secrete the extracellular matrix (ECM), matrix metalloproteinases (MMPs), and tissue inhibitors of metalloproteinases (TIMPs) to remodel the ECM. Collagen I exhibits higher mechanical tension strength compared to collagen III, and collagen I replaces collagen III during this phase, although complete deposition in the ECM takes time. Upon completion of this final stage, myofibroblasts undergo apoptosis. The composition of wounded skin, which later forms a scar, never entirely returns to normal. Scar dermis contains large parallel bundles of collagen fibrils, whereas normal dermis exhibits a basket weave orientation of collagen fibrils. Consequently, the strength of scar tissue ranges from more than 80% to less than 100% of the strength of normal uninjured skin. This final phase also occurs in burn wounds, with outcomes varying depending on the depth and severity of the burn. Superficial burns can lead to hyperpigmentation due to excessive melanocyte activity in response to the burn, while deeper wounds may result in hypopigmentation due to melanocyte damage. In second-degree deep dermal and full-thickness burns, prolonged wound healing duration or natural healing increases the likelihood of developing hypertrophic scars and contractures.[8,15,18]

Flavonoids and Mangiferin as Bioactive Compounds in Mango Peel

Mangifera indica L., commonly known as mango, is a prevalent species within the *Mangifera* genus, belonging to the *Anacardiaceae* family. This medium-to-large evergreen tree features a multitude of utilizable parts, including roots, barks, leaves, ripe and unripe pulps, seeds, and flowers, integral to ethnomedicinal practices. Over 1000 identified varieties of mango thrive primarily in tropical regions of South and Southeast Asia. In recent years, global mango production and export volumes have surged, cementing its status as a leading tropical fruit commodity. Beyond its palatable taste, mango exhibits extensive pharmacological potential due to a rich array of bioactive compounds in its various parts, encompassing proteins, vitamins A and C, carotenoids, phenolic compounds (e.g., mangiferin, catechin, quercetin, gallotannins, and iriflophenone), gallic acid, benzoic acid, fiber, carbohydrates, and minerals. The phytochemical composition and subsequent biological effects of mango exhibit significant variation influenced by factors such as variety, maturity stage, and cultivation locale. These bioactive compounds contribute to the fruit's sensory appeal and confer potential health benefits due to their antioxidant capacity, making mango a promising candidate in functional foods and nutraceutical formulations.[19–23]

Figure 1. Mango (*Mangifera indica L.*), peeled.

Globally, mango processing, which involves roughly 20% of total mango output, produces various products such as nectar, puree, pickles, and canned slices. This processing also results in the production of peel and seed by-products. The

Indonesian Central Bureau of Statistics has reported a notable increase in mango production in Indonesia, escalating from 2.8 million tons in 2021 to 3.3 million tons in 2022. Remarkably, industries discard 7-10% of fruit peels as waste. Estimates suggest that annually, mango fruit processing generates waste ranging from approximately 196,000 to 330,000 tons. This quantity is considerable, especially since numerous studies have identified high levels of flavonoids and mangiferin in mango peels.[24,25]

Flavonoids, notable for their diverse chemical structures, constitute a broad group of plant-derived compounds renowned for their strong antioxidant properties and extensive health benefits. These bioactive molecules, found abundantly in a variety of fruits, vegetables, and beverages such as tea and wine, actively contribute to the vibrant colors and flavors in nature's offerings. By neutralizing harmful free radicals, flavonoids are crucial in enhancing cellular health and resilience. Research has linked dietary flavonoid intake with several positive health outcomes, including reduced risk of chronic diseases and enhanced overall well-being. As multifaceted compounds, flavonoids consistently attract the interest of scientists and health aficionados, emphasizing their significance in sustaining optimal health and vitality. Biochemically, flavonoids consist of two aromatic rings (A and B rings) linked by a three-carbon chain that forms an oxygenated heterocyclic ring (C ring), and may display a wide variety of structures (see **Figure 2**). These structural differences lead to the formation of various subclasses including flavones, flavonols, flavanols, flavanones, isoflavones, anthocyanins, and chalcones, each characterized by distinct hydroxylation and conjugation patterns. The complex molecular structures of flavonoids make them particularly compelling for addressing dermatological issues. The therapeutic effectiveness of flavonoids in skincare originates from their complex structure-activity relationships (SAR). Hydroxyl groups, particularly when located at specific positions such as 5, 7, 3, and 4 in the chemical structure, play a crucial role. These hydroxylation sites significantly enhance the antibacterial, antifibrotic, antioxidant, and anti-inflammatory capabilities of flavonoids, highlighting their importance in the treatment of various skin conditions.[26-32]

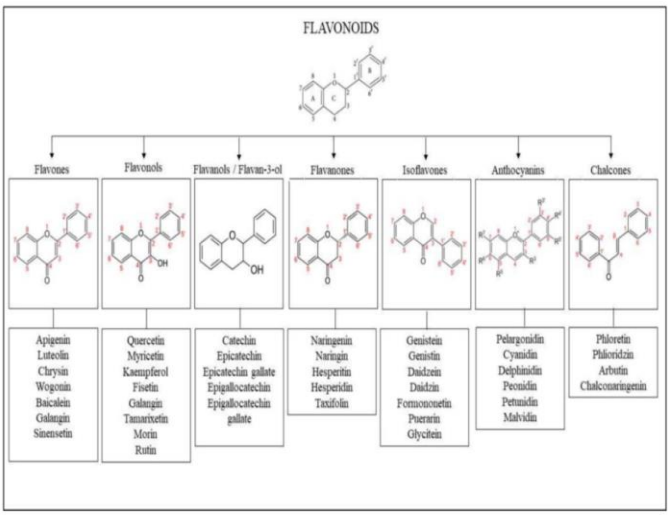

Figure 2. Chemical structure of flavonoids and its derivatives[31]

Mangiferin ($C_{19}H_{18}O_{11}$), a natural glucosyl xanthone within the flavonoid group of polyphenols, occurs naturally in mango fruit, particularly concentrated in the mango peel. This compound significantly enhances the nutritional value of mangoes, showing great promise for advancing human health. Mangiferin possesses four hydroxyl groups in its molecular structure and actively exhibits strong antioxidant properties by neutralizing harmful free radicals. Both the C-glucosyl linkage and the hydroxyl groups in mangiferin contribute significantly to its free radical scavenging ability. Mangiferin is widely acknowledged for its profound antioxidant capacity, actively scavenging free radicals and reducing oxidative stress, thereby protecting cellular integrity and function. Additionally, anti-inflammatory properties of mangiferin enhance its therapeutic potential, showing effectiveness in addressing inflammation-related disorders. These collective properties of mangiferin highlight its important role in delivering health benefits from mango consumption, making it a focus of increasing interest and investigation in scientific and medical research fields.[20,21,26,33,34]

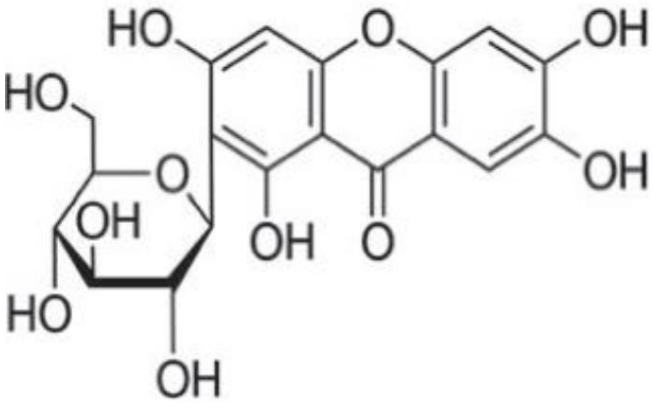

Figure 3. Chemical structure of mangiferin[22]

Experimental Evidence Supporting the Role of Flavonoids and Mangiferin in Wound Healing

Mango peel harbors a significant concentration of phytochemicals such as flavonoids and mangiferin, both of which have attracted attention for their health-promoting properties. Flavonoids, a diverse group of polyphenolic compounds, exhibit antioxidant, anti-inflammatory, and antimicrobial activities, playing a crucial role in various therapeutic contexts including wound healing. Researchers predominantly find mangiferin, a xanthone glycoside, in mango peel, noting its strong antioxidative and anti-inflammatory effects. Researchers have thoroughly investigated the healing properties of flavonoids in both in vitro and animal model studies, highlighting their considerable potential to enhance the wound healing process. These studies shed light on the mechanistic actions of flavonoids and their practical applications in therapeutic interventions. Researchers have utilized in vitro studies to uncover the cellular and molecular mechanisms by which flavonoids facilitate wound healing. Specifically, flavonoid C-glycosides, as those found in oil palm leaves, enhance the proliferation and migration of 3T3 fibroblast cells during wound healing. The in vitro study presented results indicating that flavonoid C-glycosides, including orientin, isoorientin, vitexin, and isovitexin, might be further developed as therapeutic bioactive agents due to their ability to promote fibroblast proliferation and migration in wound healing. Flavonoids of the quercetin type increase wound healing rates while significantly reducing levels of inflammatory factors, such as Tumor Necrosis Factor-alpha (TNF-α), Interleukin-1 beta (IL-1β), and Interleukin-6 (IL-6), through the Wnt/β-catenin pathway, which plays a critical role in tissue remodeling and cell growth. Additionally, other types of flavonoids including hesperidin, glycitin, naringin, genistein, and quercetin have been shown to enhance wound healing and participate in processes such as inflammation, angiogenesis promotion, fibroblast growth, collagen synthesis and deposition, and new extracellular matrix remodeling through the Transforming Growth Factor-beta (TGF-β) pathway.[35-41] In clinical trials, researchers have observed various effects of flavonoids on wound healing. A recent 2022 study revealed that flavonoids from unspecified classes exhibit the most potent wound-healing properties for chronic venous leg ulcers by diminishing ulcer size. Quercetin, when formulated as a cream, has shown the capability to alleviate pain and promote complete healing in oral ulcers. Another investigation into quercetin demonstrated that a nano-hydrogel formulation containing quercetin could lessen skin lesions, enhance the viscoelastic properties of the wound, and expedite the treatment of chronic wounds. Furthermore, anthocyanins formulated as a gel have accelerated wound closure, alleviated pain, and improved quality of life for patients with oral wounds.[42-45]

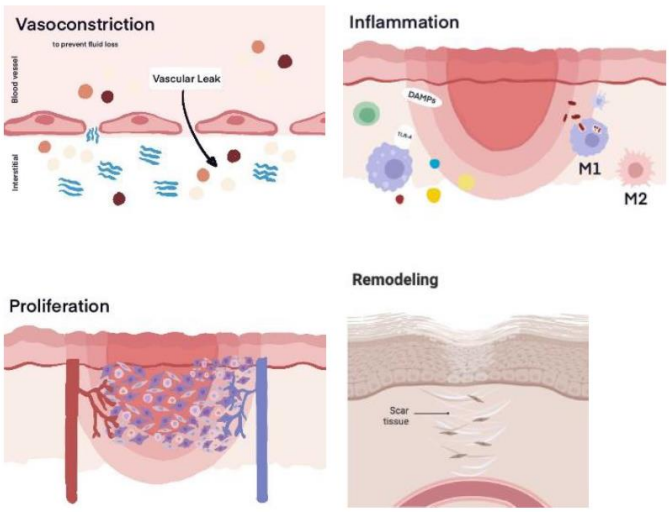

Figure 4. Mechanism of action of flavonoid and mangiferin in burn wound healing

In a rat model, researchers discovered that the methanolic extract of Mangifera indica, rich in mangiferin, exhibits anti-inflammatory, antibacterial, and oxidative stress regulatory properties. It also enhances resistance to stretching and either inhibits or promotes enzymes critical for the synthesis and maturation of collagen. Another investigation involving streptozotocin-nicotinamide-induced type-2 diabetic male rats revealed that topical application of mangiferin significantly increases the expression and distribution of Epidermal Growth Factor (EGF), Fibroblast Growth Factor (FGF), Transforming Growth Factor-beta (TGF-β), Vascular Endothelial Growth Factor (VEGF), Phosphoinositide 3-kinases (PI3K), Matrix Metalloproteinases (MMP), and Nuclear factor (erythroid-derived 2)-like 2 (Nrf2). Concurrently, it reduces the expression and distribution of Tumor Necrosis Factor alpha (TNFα) and Nuclear Factor kappa-light-chain-enhancer of activated B cells p65 (NF-κB p65), leading to a notable decrease in wound size and an increase in the thickness of the skin surrounding the wound.[46,47]

CLINICAL RELEVANCE AND POTENTIAL APPLICATION

Researchers must perform in vitro and in vivo pre-clinical studies before initiating clinical trials. In 2023, Shanthi and colleagues conducted an in vivo study that confirmed the high flavonoid content in *Dodonaea viscosa Jacq*. (*D. viscosa*) has a significant wound healing effect. Applying 2.5% and 5% *D. viscosa* ointment topically for several days significantly enhances wound healing, as evidenced by accelerated wound contraction rates, increased hydroxyproline levels, and faster granulation tissue development. This study demonstrates that flavonoids stimulate collagen formation and enhance the upregulation of basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF), thereby speeding up granulation tissue formation. Histopathological findings

support this result. Valdy and colleagues conducted another experimental study in 2023, revealing that the bioactive fraction of mangiferin extracted from mango peel significantly accelerates wound healing in burns, leveraging its anti-inflammatory, analgesic, and antibacterial properties. Mangiferin inhibits cyclooxygenase-1 (COX-1), cyclooxygenase-2 (COX-2), and prostaglandin E2 (PGE-2) production and deactivates the NLRP3 inflammasome. They considered a 10% mangiferin concentration as the most effective, supported by the notable reduction in burn area from the 1st to the 21st day. Despite extensive studies, translating preclinical findings to clinical practice presents significant challenges and limitations. Comparing pre-clinical and clinical results can support research outcomes. Chronic wound cases require long-term monitoring to assess clinical outcomes. Additionally, most in vivo and in vitro studies do not accurately reflect human body mechanisms, often leading to the production of irrelevant and distorted facts, despite clinical trials. Research on using flavonoids and mangiferin for burn wound healing often incorporates other active substances to promote cell development, potentially leading to biased results. [31,47,48]

FUTURE DIRECTIONS AND RESEARCH IMPLICATIONS

Most studies expect flavonoids and mangiferin to have potential in wound repair. Researchers must comprehend and combine natural ingredient extracts with sophisticated technology to achieve promising results. Thus far, researchers have primarily conducted in vivo testing instead of clinical trials. Several clinical studies yielded inconsistent outcomes. Moreover, clinical trials failed to progress beyond Phase 3. We are hopeful that the results of our study may initiate and recommend further research, including clinical trials, to validate the efficacy and safety of mango peel extracts in burn wound healing. More research is highly needed to explore and establish the potency of flavonoids and mangiferin as therapeutic agents.

CONCLUSION

The biocomponents mangiferin and flavonoids, found in mango peel, potentially assist in burn wound healing by virtue of their anti-inflammatory and antimicrobial properties, along with their capacity to promote collagen and VEGF formation. Nevertheless, additional research and investigation are imperative to comprehensively grasp the potential therapeutic utility of mangiferin and flavonoids in burn wound healing.

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