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A Narrative Review of Natural Bioactive Agents for Wound Healing: Mechanistic Insights on Anti-Inflammatory, Angiogenic, Antimicrobial, and Tissue Regeneration Pathways

Nur Afni[1*]

[1]Department of Chemistry, Faculty of Mathematics and Natural Science, Universitas Negeri Makassar, Makassar, Jalan Mallengkeri Makassar, 90244, Indonesia

**Corresponding Address: nur.afni@unm.ac.id*

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ABSTRACT

Wound healing is a complex biological process involving the coordinated progression of hemostasis, inflammation, proliferation, and extracellular matrix (ECM) remodeling. Chronic and infected wounds often fail to progress through these stages due to persistent inflammation, oxidative stress, and microbial biofilm formation. In recent years, natural bioactive compounds have gained attention as potential therapeutic agents due to their multi-target biological functions and biocompatibility. This review synthesizes evidence from original in vitro, in vivo, and clinical studies to evaluate the mechanisms of natural bioactive agents in modulating the wound-healing process. The findings demonstrate that natural agents can enhance platelet-mediated hemostasis, suppress inflammatory cytokines through NF-κB inhibition and Nrf2 activation, stimulate angiogenesis via VEGF and TGF-β signaling, promote fibroblast proliferation and collagen synthesis, and exert antimicrobial and antibiofilm effects against drug-resistant pathogens. Formulation strategies such as hydrogels and nanoparticle delivery systems were also shown to improve compound stability, tissue penetration, and therapeutic outcomes. These results indicate that natural bioactive wound-healing agents provide a promising avenue for managing both acute and chronic wounds, particularly in contexts where antibiotic resistance or delayed healing presents clinical challenges.

Keywords**:** *natural bioactives, wound healing, angiogenesis, antibiofilm, anti-inflammatory*

I. INTRODUCTION

Chronic and hard-to-heal wounds, including diabetic foot ulcers, venous leg ulcers, and pressure injuries, represent a growing global health burden, associated with prolonged hospitalization, reduced quality of life, and substantial healthcare costs. In United States, chronic wounds affect 10.5 million of U.S Medicare beneficiaries and impact the quality of life of nearly 2.5% of the total population. These reports highlight that chronic wounds frequently fail to progress through orderly phases of repair, in part due to persistent inflammation, ischemia, and recurrent infection. (Eriksson et al., 2022; Sen, 2023). Microbial biofilms are now recognized as a central barrier to healing, creating protected microenvironments that sustain inflammation and confer tolerance to conventional antiseptics and antibiotics (Falcone et al., 2021; Shen et al., 2025). In the context of rising antimicrobial resistance, these factors

collectively underscore the need for alternative or adjunctive wound therapies that extend beyond traditional antibiotic-centric approaches.

Conventional wound management relies heavily on debridement, topical antiseptics, systemic antibiotics, and passive dressings, yet these strategies often show limited efficacy against biofilm-associated infections and may further disturb the local tissue microenvironment (Falcone et al., 2021; Larson et al., 2025). In response, recent work has explored "antibiotics-free" or antibiotic-sparing approaches, in which bioactive compounds reduce bacterial burden and inflammation while simultaneously supporting tissue regeneration (Oluwole et al., 2022). Natural products are particularly attractive in this regard because they typically exhibit multi-target activities, combining antimicrobial, antiinflammatory, antioxidant, and pro-regenerative effects within a single therapeutic platform.

Recent findings of laboratory and clinical investigations reveal that natural bioactive agents can modulate fundamental molecular pathways involved in different phases of wound healing. These agents exert multifunctional therapeutic effects, including suppression of excessive inflammation through NF-κB inhibition, activation of antioxidant defenses via Nrf2 signaling, stimulation of angiogenesis through upregulation of VEGF and TGF-β pathways, and enhancement of extracellular matrix remodeling and collagen maturation. In addition, several natural compounds possess antimicrobial and antibiofilm capabilities that support wound healing in the presence of infection and multidrug-resistant pathogens. For example, curcumin-based formulations, *Centella asiatica* derivatives such as asiaticoside, honey-based dressings, and chitosan-based hydrogels have shown significant improvements in epithelialization, regulation of inflammatory cytokines, angiogenic response, and collagen deposition across in vitro, in vivo, and clinical models (Gościniak et al., 2025; Utoyo et al., 2025; Wu et al., 2023; Wulandari et al., 2025; Xiao et al., 2025; Yang et al., 2024).

Despite this rapidly expanding evidence, current knowledge remains fragmented across individual compounds, wound models, and delivery systems, making it difficult to compare mechanisms or to rationally design next-generation therapies. While many studies focus on single endpoints, such as bacterial load, inflammatory markers, or collagen content, fewer investigations integrate these outcomes within the broader framework of the hemostasis–inflammation–proliferation–remodeling cascade (Deng et al., 2025; Oluwole et al., 2022). Therefore, a mechanistic synthesis of how natural bioactive compounds act on key molecular pathways, such as NF-κB signaling, oxidative stress responses, growth factor regulation, extracellular matrix remodeling, and biofilm disruption, is urgently needed to guide the rational development of natural product–based, multifunctional strategies for acute and chronic wound management.

II. METHODS

This narrative literature review was conducted to identify and synthesize current evidence regarding natural bioactive compounds used in wound healing and their mechanisms of action. Relevant literature published between 2016 and 2025 was searched across PubMed, Scopus, Web of Science, and Google Scholar using combinations of keywords including *natural compounds*, *phytochemicals*, *wound healing*, *angiogenesis*, *anti-inflammatory*, and *antibiofilm*. Eligible articles included original experimental research (in vitro, in vivo, or clinical studies) and systematic reviews written in English that clearly investigated natural extracts, purified compounds, or biomaterial-based formulations and reported mechanistic or biological outcomes relevant to wound repair. Studies focusing solely on synthetic pharmaceuticals, with insufficient mechanistic analysis, or lacking peer review were excluded. Data extracted from the selected studies included compound source, formulation, experimental model, mechanistic pathways involved, and wound healing outcomes. The evidence was then synthesized and categorized according to the phases of wound healing, including hemostasis,

inflammation, proliferation/angiogenesis, and remodeling, as well as emerging delivery strategies such as nanotechnology-enhanced and biomaterial-based systems.

III. RESULTS AND DISCUSSION

Natural Compound Supporting Hemostatis and Early Wound Stabilization

Experimental studies indicate that several tannin- and polyphenol-rich natural extracts can promote hemostasis by enhancing clot formation and stabilizing the early wound matrix. In a rat excisional wound model, a tannin-rich Jaft (oak) extract ointment significantly shortened bleeding time, increased fibrin density, and improved early wound closure compared with control, suggesting direct effects on platelet aggregation and protein precipitation in the wound bed (Samavati et al., 2025). Similarly, an ethanolic bark extract of *Butea monosperma* demonstrated dose-dependent reductions in bleeding time and clotting time in rodent models, supporting its potential as a natural hemostatic agent. (Singhmura et al., 2025). Jatropha-derived products have also shown combined hemostatic and wound-healing effects; crude extracts or sap of *Jatropha multifida* accelerated cessation of bleeding and enhanced re-epithelialization in traumatic ulcers in rats, likely through astringent precipitation of proteins and stimulation of local tissue repair (Mpenda et al., 2024; Swastini et al., 2025). Collectively, these findings suggest that plant-derived astringent compounds can reinforce the hemostatic phase and create a more stable environment for subsequent inflammatory and proliferative events.

Anti-Inflammatory and Antioxidant Actions of Natural Bioactive Compounds

A number of in vivo studies have demonstrated that natural bioactive compounds exhibit potent anti-inflammatory and antioxidant effects that are crucial for resolving the early inflammatory phase of wound healing. Curcumin has been extensively investigated in this context: in a murine full-thickness skin wound model, topical curcumin accelerated wound closure and increased re-epithelialization while significantly reducing TNF-α, IL-1β, and IL-6 levels via activation of Nrf2 signaling and inhibition of NF-κB (Wu et al., 2023). Similar anti-inflammatory effects were reported in diabetic wound models, where curcumin treatment lowered oxidative stress markers and improved histological architecture of the regenerating skin (Deng et al., 2025). *Centella asiatica* also exhibits strong immunomodulatory activity. Xiao et al. (2025) showed that oral administration of *C. asiatica* extract in diabetic mice suppressed macrophage-driven inflammation by downregulating AKT/MAPK/NF-κB signaling, thereby decreasing pro-inflammatory cytokines and facilitating transition into the proliferative phase.

Flavonoid-rich botanical extracts have also demonstrated efficacy in modulating inflammatory cascades. Topical application of a flavonoid-rich formulation significantly reduced COX-2 and TNF-α expression in rat incisional wounds, accompanied by reduced edema and leukocyte infiltration (Pratiwi et al., 2025). Vernonia (*Vernonia amygdalina*) leaf extract administered to type-2 diabetic mice not only improved glycemic control but also enhanced macroscopic and microscopic wound healing, indicating that systemic metabolic improvement and local anti-inflammatory effects may act synergistically in chronic wounds (Sharfina et al., 2025). These data support the view that natural compounds can modulate inflammatory and oxidative pathways early in the healing cascade, preventing chronic inflammatory states that often underlie non-healing wounds.

Promotion of Proliferation, Granulation, and Angiogenesis

Several studies have shown that natural compounds promote fibroblast proliferation, keratinocyte migration, and new vessel formation during the proliferative phase. Hydromethanolic extract of *Dioscorea bulbifera* significantly enhanced wound contraction,

granulation tissue formation, and re-epithelialization in rats, with histological analysis revealing increased fibroblast density and neovascularization compared with controls (Chinko & Precious-Abraham, 2024). Topical *Centella asiatica* preparations have consistently demonstrated pro-angiogenic effects. In a second-degree burn model in mice, *C. asiatica* cream (5%) significantly reduced wound size and increased VEGF expression and microvessel density, suggesting direct stimulation of angiogenesis (Utoyo et al., 2025). These findings align with studies in which topical *C. asiatica* application enhanced collagen synthesis and angiogenesis in rodent excisional wounds, as evidenced by upregulated VEGF-A and improved histological scores (Millah Shofiah et al., 2024; Witkowska et al., 2024). African leaf extract (*Vernonia amygdalina*) similarly improved wound contraction and histopathological indicators of granulation and re-epithelialization in diabetic mice, indicating that some phytochemicals may act both systemically (through metabolic control) and locally (through pro-proliferative signaling) (Sharfina et al., 2025). These studies support a role for plant-derived triterpenoids, saponins, and polyphenols in activating growth factor pathways such as VEGF and TGF-β, thereby enhancing granulation tissue formation and vascularization.

Modulation of Extracellular Matrix Remodeling and Tensile Strength

Beyond early closure, high-quality wound healing requires organized collagen deposition and remodeling of the extracellular matrix (ECM). Recent in vivo and clinical studies highlight the ability of natural-bioactive dressings and compounds to improve ECM remodelling and increase tensile strength in healed wound tissue. For example, El-Kased et al. (2017) developed a honey-chitosan hydrogel (75% honey) and demonstrated superior wound contraction, thicker granulation tissue and more mature collagen deposition in a burn-wound model compared to commercial silver sulfadiazine dressings. Another study by Nikolić et al. (2025) reported that CHI/honey/gelatin hydrogels achieved complete epidermal repair by day 12 with improved mechanical strength and organized ECM fibre alignment in a rat burn model. In a diabetic wound model, Li et al. (2025) reported that topical administration of a chitosan hydrogel enriched with *Lactiplantibacillus plantarum* metabolites significantly increased collagen type I and III deposition and improved tissue alignment, resulting in superior tensile strength compared with untreated wounds.

In human clinical settings, natural-compound treatments also show promise for improving functional tissue strength. For instance, a randomized study involving honey-based advanced dressings demonstrated improved wound-bed collagen density and higher elasticity in post-surgical patients, with earlier tensile strength recovery than standard care (Gościniak et al., 2025). Complementing this, a recent study by Yang et al. (2024) found that antioxidant-enriched chitosan hydrogel increased hydroxyproline levels (a marker of collagen content) and yielded more aligned, mature collagen fibres, resulting in greater tensile strength compared to untreated or standard dressing groups (Zainuddin et al., 2025). These results support the concept that natural-based therapies not only accelerate closure but also enhance ECM remodeling, improve biomechanical integrity, and support functionally stronger skin regeneration.

Antimicrobial and Antibiofilm Protection by Natural Products and Biomaterials

Control of infection and biofilm formation is critical for successful healing, particularly in chronic and diabetic wounds. Experimental studies show that natural products, particularly honey, exhibit potent antibacterial and antibiofilm effects against wound-associated pathogens. Study by Balázs et al. (2021) demonstrated that three unifloral Hungarian honeys (black locust, linden, sunflower) inhibited the growth of *Haemophilus* spp., *Pseudomonas aeruginosa*, and *Streptococcus pneumoniae* and significantly reduced biofilm biomass in vitro, with linden honey showing the strongest activity and clear evidence of membrane damage on treated cells.

Study by Lu et al. (2019) further showed that well-characterized New Zealand honeys, including manuka-type honeys, were able not only to prevent *P. aeruginosa* biofilm formation but also to completely eradicate established biofilms at clinically achievable concentrations, highlighting their relevance for infected chronic wounds. More recently, Alshaybawee et al. (2025) reported that medical-grade thyme and citrus honeys displayed strong antibacterial and concentration-dependent antibiofilm activity against multidrug-resistant *P. aeruginosa* isolates, suggesting their usefulness as adjuncts or alternatives to antibiotics in infection management. In an ex vivo porcine-skin wound model, Guedes et al. (2023) confirmed that manuka honey significantly reduced *Staphylococcus aureus* and *P. aeruginosa* biofilm CFU counts and altered biofilm architecture, supporting the translational potential of honey for biofilm-associated wound infections. More recently, honey-loaded 3D-printed scaffolds demonstrated strong in vitro bactericidal activity, biofilm penetration, and in vivo promotion of granulation tissue in rodent models, indicating that integration of honey into advanced biomaterial platforms can overcome limitations related to viscosity and dosing (Firmanda et al., 2024).

Other natural-product-based biomaterials, such as chitosan hydrogels and composite dressings, also provide dual antimicrobial and wound-healing benefits. Yang et al. (2024) developed a chitosan-based hydrogel with intrinsic antibacterial and antioxidant properties and showed in an in vivo full-thickness rat wound model that the dressing significantly reduced bacterial load, accelerated wound closure, and increased collagen deposition compared with controls. In a murine MRSA biofilm-infected wound model, Fasiku et al. (2021) reported that a chitosan-based hydrogel system enabled dual delivery of natural agents and achieved faster wound contraction and a marked reduction in bacterial burden relative to standard treatment. Peng et al. (2017) similarly demonstrated that low molecular weight chitosan-coated silver nanoparticles effectively controlled MRSA infection and promoted nearly complete wound re-epithelialization in mice, outperforming commercial silver sulfadiazine cream. Complementing these findings, Assauqi et al. (2025) showed that a chitosan/PEG/ZnO nanoparticle hydrogel exhibited strong antibacterial activity and superior wound-healing performance over povidone-iodine in a 10-day rat model, reinforcing the concept that chitosan-based biomaterials can provide sustained antimicrobial protection while supporting tissue regeneration.

Integrated View of Multi-Target Mechanisms

Across the hemostatic, inflammatory, proliferative, and remodeling phases, experimental studies consistently indicate that natural compounds and biomaterials act via multi-target mechanisms, rather than through a single isolated pathway. Tannin-rich extracts and astringent saps stabilize the initial clot; polyphenols such as curcumin and Vernonia-derived metabolites modulate inflammatory and oxidative pathways; *Centella asiatica* and tuber extracts like *Dioscorea bulbifera* enhance fibroblast activity, angiogenesis, and granulation; and biomaterial platforms based on chitosan and honey provide combined antimicrobial, antioxidant, and ECM-regulating actions (Chinko & Precious-Abraham, 2024; Sharfina et al., 2025; Utoyo et al., 2025; Wu et al., 2023; Yang et al., 2024).This integrated profile is particularly relevant in the era of antimicrobial resistance, where strategies that simultaneously control infection, dampen excessive inflammation, and support regeneration are increasingly needed to treat chronic and hard-to-heal wounds effectively.

IV. CONCLUSION

Natural bioactive compounds demonstrate significant potential in enhancing wound healing through multi-mechanism actions. Evidence from experimental and clinical studies shows that these compounds support the healing process by regulating inflammation, reducing

oxidative stress, promoting angiogenesis, stimulating fibroblast activity, and improving extracellular matrix remodeling and tensile strength of regenerated tissue. Several natural agents also exhibit strong antimicrobial and antibiofilm effects, offering advantages particularly in chronic or infected wounds where conventional therapies may be limited. Although promising, further standardized formulation approaches and large-scale clinical validation are needed to ensure consistency, safety, and translational applicability in routine wound care.

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