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REVIEW ARTICLE

Potential of natural bioactives in wound healing: A comprehensive review

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Abstract

The wound healing process encompasses three key phases: inflammation, tissue regeneration and remodeling. Natural bioactive compounds have garnered significant interest due to their anti-inflammatory, antioxidant and antimicrobial properties, which facilitate healing. Compounds such as polyphenols, flavonoids and peptides aid wound repair by reducing oxidative stress, encouraging angiogenesis and stimulating cellular proliferation. Natural antimicrobials like honey and chitosan also play a vital role by preventing infections that commonly hinder healing. Bioactive-based wound dressing materials embedded with biologically active agents, including natural extracts, antimicrobials and growth factors, offer dual benefits: they protect while actively promoting healing. These dressings work by minimizing infection risk, modulating inflammation and enhancing tissue regeneration. Such innovations have demonstrated promise in managing chronic wounds and diabetic ulcers. Despite their potential, the clinical translation of bioactive-based therapies faces challenges, primarily concerning the stability and controlled release of active compounds. These limitations restrict their broader application. Emerging advancements in nanotechnology and biomaterials engineering are emerging as solutions to these challenges. By enabling targeted delivery, sustained release and improved bioavailability of natural bioactives, these technologies are set to significantly boost their therapeutic impact and reliability in modern wound care strategies.

Keywords: angiogenesis; bioactives; natural products; phytochemicals; regenerative therapy; wound healing

Introduction

Wounds are defined as disruption of the cellular, anatomical and functional integrity of the living tissue caused by physical, chemical, thermal, microbial, or immunological factors, or they can be more serious and extend into subcutaneous tissue, impairing other tissues like bones, muscles, tendons, arteries, nerves and parenchymal organs (1). Wound healing is a complex biological process that restores the integrity of damaged tissues via a coordinated series of cellular and molecular activities (2). Four phases overlap: remodeling, proliferation, inflammation and hemostasis. The earliest processes of hemostasis are vasoconstriction and clot formation, which prevent blood loss as soon as an injury occurs. Following that, the inflammatory phase begins, with immune cells infiltrating to clear debris and pathogens (3). During proliferation, fibroblasts, keratinocytes and endothelial cells promote angiogenesis, tissue regeneration and extracellular matrix deposition. The final remodeling stage uses collagen maturation and reformation to strengthen the newly formed tissue (4). Wound healing is critical for developing targeted therapeutics that improve recovery and prevent side effects such as persistent wounds or excessive scarring (5, 6).

Wound healing is controlled by a variety of intrinsic and extrinsic factors, as seen in Fig. 1 (7), which might provide hurdles to recovery. Persistent wounds, which are usually associated with vascular diseases, diabetes and pressure ulcers, cause extended inflammation and poor angiogenesis, delaying healing. Infection is another significant obstacle, as bacterial colonization and biofilm formation impede tissue regeneration and raise the risk of sepsis (8). Excessive scar development caused by aberrant fibroblast activity and collagen deposition can lead to hypertrophic scars or keloids, which compromise both function and appearance (5). Aging and impaired immune responses impede healing, limiting the skin's ability to repair effectively. Environmental variables, including hunger and inadequate wound care, worsen difficulties, resulting in longer hospital stays and higher healthcare expenses. Although advancements in regenerative medicine, bioactive dressings and growth factor-based therapies have improved wound management, these challenges continue to limit optimal outcomes (9, 10).

Bioactive compounds enhance wound healing by modulating cellular responses, reducing inflammation and promoting tissue regeneration (11). Growth regulators, including epidermal growth factor (EGF) and platelet-derived growth factor (PDGF), promote the formation of collagen,

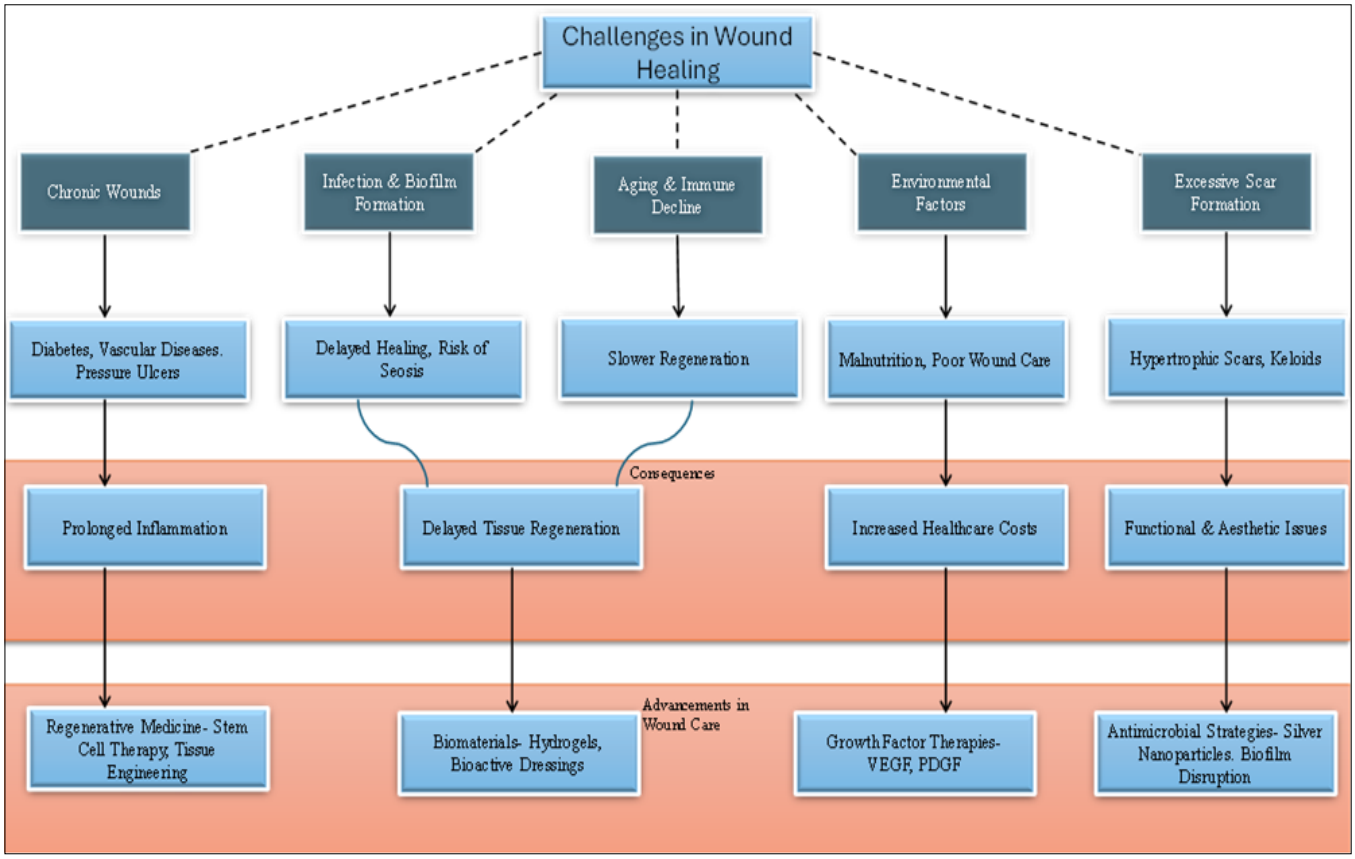


Fig. 1. Challenges in wound healing.

fibroblast expansion and re-epithelialization (10). Recombinant PDGF, used in Becaplermin gel, has shown efficacy in treating diabetic foot ulcers by stimulating angiogenesis and granulation tissue formation (12). Additionally, bioactive peptides like thymosin beta-4 enhance keratinocyte migration and reduce oxidative stress, expediting wound closure. Natural bioactives, including honey, curcumin and aloe vera, exhibit antimicrobial and anti-inflammatory properties, preventing infections and promoting healing (13). Advanced wound dressings incorporating bioactive compounds, such as silver nanoparticles and antimicrobial peptides, provide a controlled-release system for sustained therapeutic effects. Despite promising results, challenges remain regarding stability, delivery and patient-specific responses to bioactive therapies (14). Clinical studies and additional investigations are required to optimize formulations and improve wound healing outcomes, particularly in chronic wounds and burns. Given the complexity of wound healing and its varied roles.

This review aims to provide a comprehensive understanding of the significance of bioactives in this field. A literature search was conducted in several databases (Scopus, PubMed, Health and Medical, Web of Science and Clinical Trials). Using search strategy terms: 'wound healing', 'bioactive' and 'phytoconstituents', the search was limited to English-language articles released within the previous fifteen years (2010-2025) and it discusses the spectrum of bioactive compounds, their mechanisms of action across different wound healing phases and their clinical potential in overcoming current limitations to achieve more effective and personalized wound care.

Types of bioactive and their sources

Bioactives alter biological processes, lessen problems and speed up recovery, so it is essential for wound healing. These compounds can be broadly classified into two categories: synthetic or engineered bioactives, which are designed to mimic or enhance natural molecules and natural bioactives, which are derived from plant, animal, or microbial sources. A comprehensive understanding of their origins and mechanisms of action is essential for the development of effective and targeted wound care strategies (15).

Since ancient times, natural bioactives have been employed in both conventional and contemporary medicine. These consist of chemicals originating from plants, animals and microorganisms. Plant-based remedies offer a sustained supply that is highly effective in treating and curing a variety of illnesses, including highly virulent or life-threatening pathogens.

The present review thus focuses on beneficial phytochemical elements from different chemical families, including phenolic compounds, terpenoids and flavonoids (16). The healing process is often modulated by these bioactive substances in one or more phases. Their multifunctional properties make them promising candidates for inclusion in advanced wound care formulations.

Plant-derived bioactive

Plants have been a rich source of therapeutic agents for centuries, with more than half of modern clinical drugs originating from natural sources, many demonstrating efficacy in wound healing (17). Numerous substances with a range of biological characteristics that aid in wound healing may be found in plants. Important categories consist of:

Flavonoids: Flavonoids are plant-derived polyphenolic compounds with strong antioxidant, anti-inflammatory, antimicrobial and tissue-regenerative properties. In wound healing, they reduce oxidative stress, suppress inflammatory mediators (e.g., COX, LOX, TNF-α) and inhibit microbial growth (18). Flavonoids also promote angiogenesis, fibroblast proliferation, collagen synthesis and extracellular matrix remodeling by modulating growth factors like VEGF and TGF-β. These combined effects accelerate healing and make flavonoids valuable in advanced wound care, especially for chronic or infected wounds (19). Quercetin and kaempferol are two examples that lower oxidative stress, block pro-inflammatory mediators and encourage angiogenesis and fibroblast growth, as shown in Table 1 (20).

Terpenoids: Terpenoids, a large class of naturally occurring chemical substances, have antibacterial, anti-inflammatory and antioxidant properties that make them crucial for wound healing. Plant essential oils such as tea tree, eucalyptus and lavender contain these chemicals (21) as seen in Table 2, they can be categorized as monoterpenoids, sesquiterpenoids, diterpenoids, triterpenoids and tetraterpenoids. Monoterpenoids and sesquiterpenoids provide antimicrobial protection, thereby preventing wound infection. Diterpenoids and triterpenoids promote re epithelialization and tissue remodeling, while carotenoids classified as tetraterpenoids-serve as potent antioxidants that mitigate oxidative stress. Collectively, terpenoids enhance angiogenesis, support fibroblast activity and modulate inflammatory responses, leading to improved wound healing outcomes (22).

Table 1. Classification of flavonoids

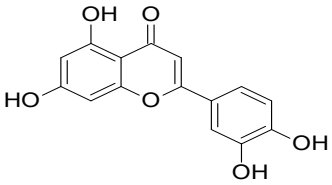
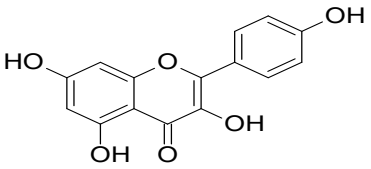
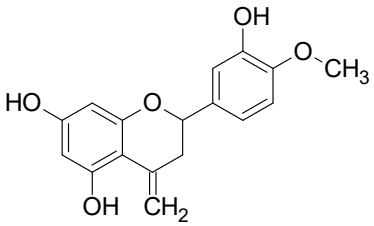
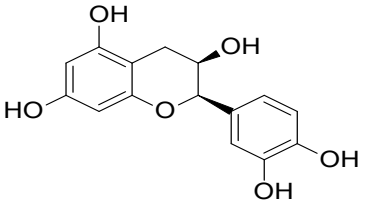
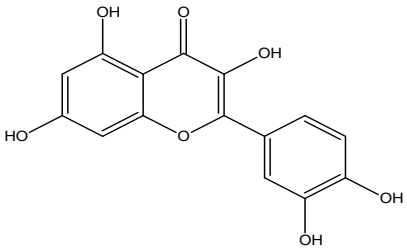
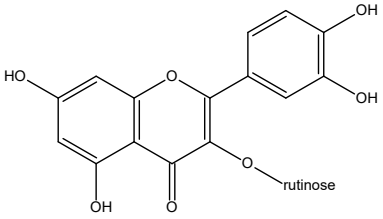
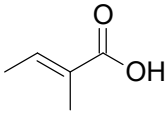
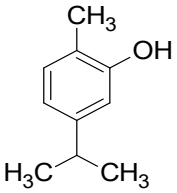
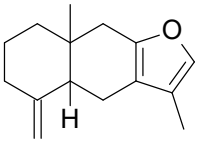
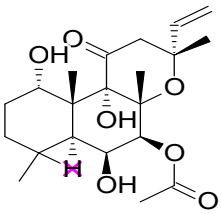
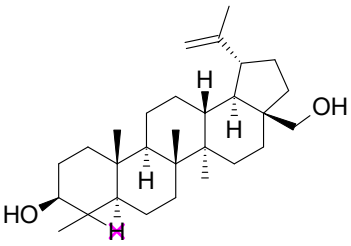
Flavonoid Type	Mechanism of Action	Chemical Structure	References
Luteolin	Antioxidant, anti-inflammatory, anticancer		(51)
Kaempferol	Free radical scavenging, enzyme inhibition		(52)
Hesperidin	Anti-inflammatory, neuroprotective		(53)
Epicatechin	Antioxidant, cardioprotective, antimicrobial		(54)
Quercetin	Anti-inflammatory, anti-diabetic, stimulating fibroblast proliferation, enhancing collagen synthesis and improving angiogenesis at the wound site		(55)
Rutin	Reducing oxidative stress and inflammation and anticancer, improving angiogenesis at the wound site		(56)

Table 2. Classification of terpenoids

Terpenoid Type	Mechanism of Action	Chemical Structure	References
Tiglic Acid	The gel contains glycoproteins and vitamins that create a protective layer on damaged areas, accelerating wound healing and reducing infection risk		(57)
Carvacrol	It exhibits antimicrobial activity by inhibiting microorganisms' RNA and protein biosynthesis. It also possesses anti-inflammatory properties by decreasing IL-6 and TNF-α production		(58)
Atractylone	Promotes re-epithelialization of scratched HaCat monolayers, enhancing tissue repair processes		(59)
Forskolin	Activates cyclic adenosine monophosphate (cAMP) signaling, which improves cell migration and re-epithelialization		(60)
Betulin	Exhibit antimicrobial and anti-inflammatory properties, preventing infections and modulating cytokine activity to accelerate healing		(61)

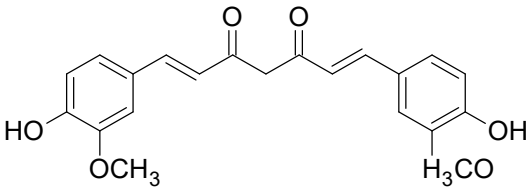
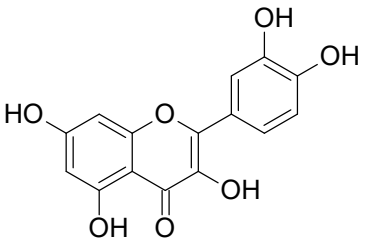
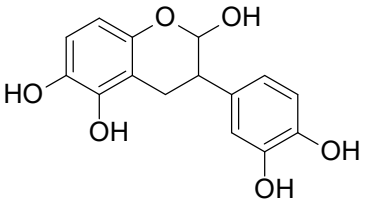
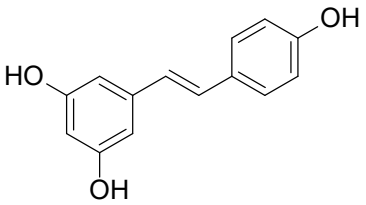
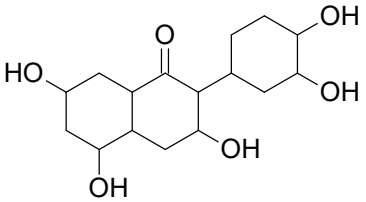
Polyphenols: Polyphenols like resveratrol and catechins, which are found in berries, grapes and green tea, are potent antioxidants that improve vascularization, shield cells from oxidative stress and encourage the production of collagen-all of which are critical for the remodeling and proliferation phases of wound healing (23). Based on Table 3, the main categories of polyphenols include lignans (secoisolariciresinol), stilbenes (resveratrol), flavonoids (quercetin, epicatechins and catechins) and phenolic acids (ferulic acid, caffeic acid). By reducing inflammatory processes, managing oxidative stress, encouraging collagen synthesis and inducing angiogenesis, these substances improve wound healing (24).

Mechanistically, polyphenols enhance growth factors like transforming beta growth factor (TGF-beta) and vascular endothelial growth factor (VEGF), scavenge reactive oxygen species (ROS) and decrease anti-inflammatory mediators like TNF-alpha and IL-6. Polyphenols also promote extracellular matrix remodeling and fibroblast multiplication, which speeds up wound closure (25). Numerous studies demonstrate their effectiveness in treating diabetic ulcers, burns and chronic wounds. For example, quercetin reduces inflammation, resveratrol increases neovascularization and catechins encourage fibroblast migration. In regenerative medicine, their use in hydrogels and wound dressings has produced encouraging outcomes (26).

Microbial-derived bioactives

Microbial-derived bioactives are essential to the recovery of wounds by exhibiting antimicrobial, anti-inflammatory and tissue-regenerative properties. Various microorganisms, including bacteria, fungi and actinomycetes, produce bioactive compounds such as bacteriocins, enzymes, polysaccharides and secondary metabolites that enhance wound healing. Bacteriocins and bacterial exopolysaccharides, such as alginate from *Pseudomonas* species, promote cell proliferation and tissue regeneration (27). Actinobacteria-derived antibiotics, like actinomycin D, inhibit pathogenic bacterial growth and reduce inflammation (28). Probiotic-derived metabolites and Fungal-derived enzymes, such as chitinase, help degrade necrotic tissue and accelerate wound repair (29). Moreover, biofilm-disrupting agents from *Bacillus* species help in chronic wound healing (30). Marine and microbial sources offer a diverse array of bioactive compounds with significant wound healing potential due to their antioxidant, anti-inflammatory and regenerative properties. Marine-derived peptides and proteins, such as collagen peptides from fish skin and sulfated polysaccharides like fucoidan, promote fibroblast proliferation, collagen synthesis, angiogenesis and epithelial regeneration (31). Similarly, microbial-derived metabolites, including undecylprodigiosin from *Streptomyces* and recombinant growth factors like EGF, enhance tissue repair by reducing oxidative stress and stimulating fibroblast and keratinocyte activity. These bioactives can be incorporated into advanced

Table 3. Classification of polyphenols

Polyphenol	Mechanism of Action in Wound Healing	Chemical Structure	References
Curcumin	Antioxidant, anti-inflammatory, increases collagen deposition and encourages fibroblast proliferation		(62)
Quercetin	Increases fibroblast migration, encourages angiogenesis and lowers oxidative stress		(63)
Proanthocyanidins	Contain antioxidant activity, eliminating free radicals and helping to restore redox equilibrium		(64)
Resveratrol	Improves vascularization, minimizes scarring and promotes granulation tissue development		(65)
Tannins	Antimicrobial qualities help to prevent infection and promote healing		(66)

delivery systems such as hydrogels and nanofibers for localized, controlled release. Despite their therapeutic promise, clinical application is limited by challenges such as extraction variability, low bioavailability and the need for thorough safety validation. Ongoing innovations in biotechnology and formulation science are expected to drive their integration into next generation wound care therapies (32).

Probiotics: Probiotic-derived metabolites from *Lactobacillus* species stimulate immune modulation and enhance epithelialization (33). Commensal bacteria like *Bifidobacterium* and *Lactobacillus* help restore the epithelial barrier, lower inflammation and alter the wound microenvironment to stop infections. Therapies based on probiotics are becoming more popular as wound care adjuncts. Early efforts focused on developing solid scientific evidence for the effectiveness of these probiotic bacteria, which primarily consist of species of *Bifidobacterium* and *Lactobacillus*. Probiotic bacteria's mechanisms of action are currently the subject of extensive investigation due to these evidence-based functional approaches. Immune modulation, competitive exclusion of infections and the activation of host defense systems are the key mechanisms that have been discovered thus far. (Probiotics and other useful microorganisms: from mechanisms to markets.)

Bacteriocins: Bacteriocins, particularly nisin from *Lactococcus lactis*, are ribosomally synthesized peptides produced by lactic acid bacteria with potent antimicrobial activity against drug-resistant pathogens like MRSA and *Clostridium difficile*. Nisin acts by binding lipid II, disrupting bacterial cell wall synthesis and forming membrane pores, effectively inhibiting biofilms and reducing resistance development. To improve stability and localized delivery, nisin has been incorporated into advanced wound dressings such as hydrogels, liposomes, nanofibers and chitosan-based films. It also exhibits synergistic effects with silver nanoparticles, honey and antibiotics, enhancing efficacy while minimizing doses. However, clinical translation faces challenges including degradation by proteases, immunogenic risks and regulatory complexities. Despite these hurdles, bacteriocins hold strong potential as next-generation antimicrobial agents for managing infected and chronic wounds, pending further clinical validation and standardization (34).

Synthetic and engineered bioactives

Natural bioactive compounds such as polyphenols, plant-derived peptides and herbal extracts have demonstrated considerable promise in enhancing wound healing, their translation into clinical practice remains limited due to challenges including poor stability, low bioavailability and variability in composition. To overcome these constraints,

recent advances have focused on synthetic and engineered bioactive strategies that allow for precise control over molecular design, targeted delivery and pharmacokinetics. These engineered approaches aim to replicate or surpass the biological efficacy of natural compounds while offering greater reproducibility, scalability and formulation versatility.

Importantly, synthetic bioactives are often better aligned with regulatory requirements, as their well-defined structures and standardized manufacturing processes facilitate quality control, batch consistency and safety assessment. Nevertheless, achieving clinical readiness requires rigorous preclinical validation, long-term safety studies and harmonization with existing clinical workflows. Moreover, the regulatory landscape remains complex, particularly for combination products involving nanocarriers, scaffolds, or biologically active polymers. A more integrated strategy linking material science, regulatory compliance and clinical trial design is essential to accelerate the translation of engineered bioactive therapies from bench to bedside.

Peptide-based drugs

Peptide-based drugs promote cell migration, angiogenesis and extracellular matrix remodeling. These peptides, such as growth factor mimetics and antimicrobial peptides, accelerate tissue regeneration and reduce infection risk. Key mechanisms involve activating signaling pathways like PI3K/Akt and MAPK, which enhance fibroblast proliferation and keratinocyte migration. For instance, peptides like LL-37 exhibit broad-spectrum antimicrobial activity and are effective in managing chronic wound infections (35). Collagen-derived peptides also contribute by stimulating collagen synthesis and enhancing wound closure. Synthetic peptides provide tailored activity with improved stability by mimicking the actions of natural peptides (36).

Thymosin beta-4: Tβ4, a low molecular weight, naturally occurring peptide, plays a vital role in the repair and regeneration of injured cells and tissues. After injury, Tβ4 is released by platelets, macrophages and many other cell types to protect cells and tissues from further damage and reduce apoptosis, inflammation and microbial growth. Tβ4 binds to actin and promotes cell migration, including the mobilization, migration and differentiation of stem/progenitor cells, which form new blood vessels and regenerate the tissue. Tβ4 also decreases the number of myofibroblasts in wounds, resulting in decreased scar formation and fibrosis (37).

LL-37: LL-37 is a synthetic immunomodulatory antimicrobial peptide that plays multiple roles in wound healing. It is derived from the C-terminal of the human cationic antimicrobial protein hCAP-18-the only known human cathelicidin-which is primarily expressed by neutrophils and epithelial cells (38).

Biomimetic scaffolds

Examples of genetically engineered bioactives include hydrogels embedded with vascular endothelial growth factor (VEGF) that encourage angiogenesis or scaffolds filled with epidermal growth factor (EGF) to encourage re-epithelialization. For instance, hydrogels embedded with vascular endothelial growth factor (VEGF) promote angiogenesis, while scaffolds containing epidermal growth factor (EGF) facilitate re-epithelialization (39, 40).

Integration of natural and synthetic bioactives

By combining the advantages of both natural and synthetic bioactives, a potential strategy for wound treatment has evolved. For example, scaffolds made of chitosan and supplemented with synthetic peptides or polyphenols produced from plants work in concert to improve tissue regeneration and antimicrobial defense (41). Researchers and physicians may create specialized therapies to address certain wound healing issues, ranging from acute injuries to chronic wounds, by comprehending the origins and processes of these bioactives. This integration highlights the possibility of bioactive to transform wound care and enhance patient outcomes (42).

Impact of natural products on wound healing

Bioactive metabolites from plants and marine organisms, such as polyphenols, carotenoids, terpenoids, alkaloids and vitamins, have antibacterial, anti-inflammatory and antioxidant qualities that are critical for wound healing, as shown in Fig. 2. Oxidative stress, in which immune responses are overpowered by reactive oxygen species (ROS), leads to chronic wounds (43). Natural antioxidants improve endogenous antioxidant responses, stabilize free radicals and lessen ROS damage. Polyphenols protect cell integrity by preventing lipid peroxidation and inflammation. Additionally, plant-derived antimicrobial compounds-many of which are Generally Recognized as Safe (GRAS)-are effective against microbial biofilms that often complicate chronic wounds (44). In chronic wounds, they contribute to antibiotic resistance, by addressing oxidative stress, inflammation and infections, these natural extracts provide a multipurpose strategy that enhances healing, as shown in Table 4.

Clinical application

Bioactive compounds are increasingly integrated into clinical wound management strategies due to their ability to modulate specific biological processes essential for tissue repair. Among these, growth factor-based therapies such as recombinant platelet-derived growth factor (PDGF-BB) and epidermal growth factor (EGF) have demonstrated significant clinical utility. Notably, PDGF-BB gel (becaplermin) is FDA-approved for the treatment of diabetic foot ulcers, with multiple randomized controlled trials (RCTs) indicating improved wound closure rates and reduced healing time. EGF formulations have similarly been employed in the management of pressure ulcers and burn injuries, primarily by enhancing angiogenesis and epithelial regeneration.

Advanced bioactive dressings incorporating antimicrobial agents-including silver nanoparticles, medical-grade honey and iodine-are widely adopted in clinical practice to minimize infection and promote granulation tissue formation. RCTs have shown that honey-based dressings significantly reduce healing duration in venous leg ulcers and postoperative wounds, while offering broad-spectrum antimicrobial activity. Peptides such as thymosin beta-4 are also being investigated for their capacity to stimulate keratinocyte migration, modulate inflammatory signaling and promote extracellular matrix remodeling, all of which are pivotal for effective wound repair.

Natural bioactives-including curcumin, aloe vera and green tea polyphenols-are frequently formulated into topical applications due to their potent anti-inflammatory, antioxidant and pro-regenerative effects. However, these agents often face

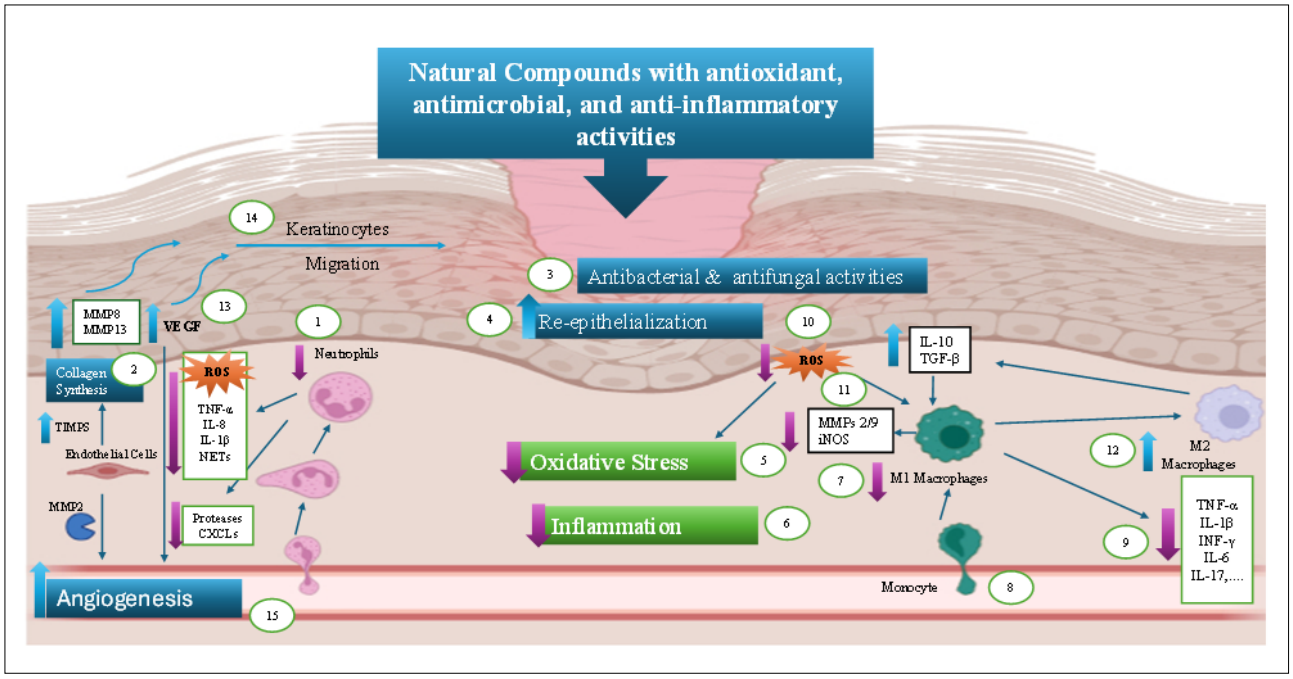


Fig. 2. An illustration of infected wounds being treated using natural bioactive substances. The primary targets and molecular pathways impacted by the natural substances mentioned in the manuscript are highlighted. The arrows show how therapy affects the targets. The numbers refer to respective targets and the natural compounds that seem to be best for the treatment. 1: α-Terpineol, Vitamin C; 2: Delphinidin, Tannins, Lignans, β-carotene, Astaxanthin, Berberine, Vitamin C, Vitamin E; 3: Curcumin, Gallic acid, Tannins, Resveratrol, Borneol, Thymol, α-Terpineol, Berberine, Palmatine, Vitamin E; 4: Catechins, Kaempferol, Curcumin, Lignans, Thymol, Astaxanthin, Berberine, Vitamin C, Vitamin E; 5: Catechins, Quercetin, Delphinidin, Curcumin, Gallic acid, Tannins, Resveratrol, Lignans, Borneol, Thymol, D-Limonene, β-carotene, Lycopene, Lutein and Zeaxanthin, Berberine, Palmatine, Vitamin C, Vitamin E; 6: Flavanols, Kaempferol, Quercetin, Delphinidin, Curcumin, Gallic acid, Tannins, Resveratrol, Lignans, Borneol, Thymol, α-Terpineol, D-Limonene, Lycopene, Astaxanthin, Lutein and Zeaxanthin, Berberine, Palmatine, Vitamin C, Vitamin E; 7: Catechins; 8: Kaempferol; 9: Catechins, Delphinidin, Curcumin, Resveratrol, Borneol, α-Terpineol, D-Limonene, Berberine, Vitamin E; 10: Quercetin, Curcumin, Resveratrol, Lignans, Borneol, Thymol, D-Limonene, β-carotene, Lycopene, Vitamin C, Vitamin E; 11: Quercetin; 12: Curcumin, Borneol, β-carotene, Berberine; 13: Kaempferol, Curcumin, Tannins, Resveratrol; 14: Kaempferol, Astaxanthin; 15: Catechins, Tannins, Resveratrol, Vitamin E.

Table 4. Mechanism of action of the natural products

Mechanism	Key Processes	Examples of Bioactives	Impact on Wound Healing
Anti-Inflammatory Effects	Controls immune cell activity and cytokine levels.	Curcumin, Resveratrol, Omega-3 fatty acids	Minimizes tissue damage, persistent wounds and excessive inflammation (67)
	Cytokine Regulation:		Numerous bioactives suppress pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-α and (IL-1beta) while boosting anti-inflammatory cytokines like IL-10. For instance, resveratrol and curcumin reduce tissue damage by reducing the release of IL-6 and TNF-alpha
	Immune Cell Modulation:		By lowering neutrophil infiltration and encouraging the shift from macrophages that promote inflammation (M1) to those that inhibit it (M2) (68), bioactives affect immune cell behavior. This change promotes tissue healing and speeds up the resolution of inflammation
Antioxidant Activity	Increases the activity of antioxidant enzymes and scavenges free radicals	Quercetin, Catechins, Ascorbic acid, EGCG	Keeps the redox equilibrium in the wound microenvironment stable and shields cells from oxidative damage (69)
	Scavenging Free Radicals		Polyphenols like quercetin and catechins neutralize ROS, protecting fibroblasts and keratinocytes from oxidative damage. By donating electrons, they stabilize reactive molecules, restore redox balance and create a healing-friendly environment. Their antioxidant action supports wound healing by promoting tissue formation, transformation and inflammation resolution
	Boosting Antioxidant Enzymes		Ascorbic acid (vitamin C) and EGCG, the main catechin in green tea, enhance the body's antioxidant defense by boosting key enzymes like superoxide dismutase (SOD) and glutathione peroxidase (GPx). Ascorbic acid plays a crucial role in the glutathione-ascorbate cycle, aiding glutathione regeneration and maintaining redox balance. EGCG further upregulates antioxidant enzyme expression, reducing oxidative stress and creating an optimal wound microenvironment for tissue repair and healing

Antimicrobial Properties	Breaks down the cell walls of bacteria, prevents the production of biofilms and boosts immunity	Honey, Chitosan, Terpenoids, Bacteriocins	Minimizes microbial colonization, prevents infections and encourages wound sterility (70)
	Direct Antimicrobial Action:		Bioactives that break down bacterial cell walls, prevent the development of biofilms and lessen microbial colonization include flavonoids, terpenoids and bacteriocins. These characteristics are best illustrated by the hydrogen peroxide and methylglyoxal concentrations of honey
	Support for the Immune System		Certain bioactives strengthen the innate immune response, which helps get rid of infections. Probiotics and chitosan, for instance, increase macrophage activity and fortify epithelial barriers
Angiogenesis Promotion	Boosts the generation of nitric oxide (NO) and growth factor expression	Curcumin, Thymosin beta-4, Resveratrol, Quercetin	Increases the wound's blood flow and the delivery of nutrients and oxygen (71)
	Upregulating Growth Factors		Substances like curcumin and thymosin beta-4 promote production of growth factors such as fibroblast growth factor (FGF) and the vascular endothelial growth factor (VEGF), which increases the movement and multiplication of cells that line the vessels
	Enhancing Nitric Oxide (NO) Production:		Bioactives like quercetin, resveratrol increases the synthesis of NO, which promotes angiogenesis and vasodilation
Extrusion and Reproduction of Cells	Increases keratinocyte activity and the functions of fibroblasts and endothelial cells	Aloe vera, LL-37 peptides, Ascorbic acid, Collagen peptides	Promotes wound closure, improves extracellular matrix and encourages re-epithelialization (72)
	Keratinocyte Migration and Proliferation		Synthetic peptides like LL-37 and natural substances like aloe vera encourage keratinocyte activation, which aids in re-epithelialization
	Fibroblast Activation		Bioactive like collagen peptides and ascorbic acid encourage the production of ECM (extracellular matrix) and fibroblast growth (73), which fortifies the wound bed
	Endothelial Cell Stimulation		Bioactive that increase VEGF stimulates endothelial cell activity, which enhances oxygen supply and vascularization
Synergistic Effects	Possesses angiogenic, antioxidant and anti-inflammatory properties	EGCG, Polyphenols, Multi-component bioactive formulations	Enhances total recovery by addressing several stages of wound healing at once (67)

formulation challenges such as poor aqueous solubility, instability under physiological conditions and limited shelf-life. To mitigate these issues, advanced carriers like liposomes, nanofibers and polymeric hydrogels are being utilized to enhance stability, bioavailability and targeted delivery.

Despite encouraging outcomes in preclinical models, the clinical translation of many bioactive therapies remains limited. A key barrier is the translational gap between animal models and human pathophysiology, with notable differences in immune function, skin structure and comorbidity profiles that can impact therapeutic efficacy. Additionally, a paucity of large-scale, multicenter clinical trials impedes definitive conclusions on the long-term safety and efficacy of bioactive compounds in heterogeneous patient populations.

Current research is directed toward addressing these challenges through the development of smart, controlled-release delivery systems, stabilization techniques for sensitive bioactives and the incorporation of personalized medicine approaches. These include tailoring bioactive therapies based on genetic profiles, wound-specific biomarkers and integration with real-time monitoring technologies. A comprehensive overview of bioactive agents and their delivery modalities is provided in Table 5.

Future directions

The future of bioactive-based wound healing therapies relies on advancements in nanotechnology and gene therapy to enhance efficacy and precision as shown in Table 6. Nanotechnology facilitates the encapsulation of bioactives in nanoparticles, improving stability, controlled release and bioavailability (45). Liposomes, dendrimers and gold nanoparticles aid in tissue regeneration, while silver nanoparticles exhibit antibacterial properties that prevent infections. Gene therapies further enable the targeted delivery of genes encoding bioactive proteins, such as fibroblast growth factor (FGF) and vascular endothelial growth factor (VEGF), promoting collagen synthesis, angiogenesis and tissue repair, particularly in chronic wounds (46).

The integration of bioactives with smart wound dressings and bioactive-embedded devices has transformed wound management. Smart dressings respond to physiological changes, such as temperature fluctuations indicating infection, by releasing therapeutic agents (47). Additionally, sensor-equipped dressings provide real-time data for personalized treatment. Bioactive-embedded hydrogel and hydrocolloid patches, coupled with micro-electromechanical systems (MEMS). MEMS are tiny devices that combine mechanical components, sensors, actuators and electronics on a single silicon chip using microfabrication techniques. In wound healing, MEMS enable smart, responsive systems often integrated into dressings or wearable patches that monitor wound conditions and actively support the healing process, facilitate controlled drug delivery and continuous monitoring, optimizing wound healing strategies (48).

Despite promising preclinical findings, extensive clinical trials are required to validate the safety and efficacy of bioactive-based wound therapies in diverse populations. Studies have explored the comparative effectiveness of honey versus povidone-iodine in acute wounds, highlighting honey's potential antimicrobial and wound-healing properties, though further trials are necessary for standardization (49). Translational research bridges laboratory discoveries with clinical applications, focusing on optimizing bioactive formulations for specific wound

Table 5. Clinical application of bioactives

Aspect	Description	Examples/Case Studies
Case Studies/Examples of Bioactive Formulations	To promote healing, bioactives are added to a variety of wound care treatments	**Topical Creams:** Honey, aloe vera, or essential oils are examples of bioactive-rich creams that are frequently used in wound treatment. Manuka honey and other honey-based lotions have antibacterial, anti-inflammatory and moisture-retaining qualities that make them ideal for healing burns and chronic wounds (74)
	These compositions lessen pain and infection while encouraging tissue regeneration	**Hydrogels:** Collagen-based hydrogels, hyaluronic acid and aloe vera offer an atmosphere of moisture that promotes wound healing. These products aid in pain relief, inflammation reduction and skin regeneration. For example, hyaluronic acid promotes tissue healing and speeds up fibroblast migration (75)
		Dressings: Because of their capacity to reduce bleeding, stop the growth of bacteria and encourage quicker wound healing, chitosan, a biopolymer made from crab shells, is used in wound dressings. Bioactive dressings containing iodine or silver also have antibacterial properties and are frequently used to treat diabetic foot ulcers and burns (76)
Restrictions in the Delivery of Bioactives	Significant obstacles stand in the way of bioactive compounds' regulated release, stability and bioavailability.	**Stability:** When subjected to environmental elements like heat, light, or air, many bioactives, including flavonoids and polyphenols, lose their stability. Over time, this reduces their efficacy in formulations. For instance, the strong anti-inflammatory bioactive curcumin degrades in the presence of light and oxygen, which may limit its therapeutic benefits (77)
		Bioavailability: The absorption of certain bioactives at the wound site is restricted due to their limited solubility or permeability. For example, since they are hydrophobic, curcumin, resveratrol and quercetin are not well absorbed via the skin or mucous membranes. This makes it difficult to guarantee the concentration of therapy at the site of the wound (78)
		Controlled release: To guarantee regulated, prolonged release at the location of wounds, many bioactives-particularly those contained in carriers like nanoparticles-need to be carefully formulated. To maximize their release patterns and guarantee their therapeutic benefits over time, bioactive-loaded carriers, such as liposomes or nano gels, continue to be the subject of intensive study (79)
Regulatory Challenges	For bioactive-based wound healing medicines, obtaining regulatory clearance can be a difficult and drawn-out procedure	**Safety and effectiveness:** To demonstrate their safety and effectiveness, all bioactive formulations must undergo a rigorous preclinical and clinical testing process. For instance, extensive testing in human subjects is frequently required for clinical trials of wound care products, which include growth factor-based treatments or bioactive dressings and these trials might take years to finish. The introduction of potentially life-saving assistance products may be delayed by this drawn-out approval process (80)
		Manufacturing Standards: One of the most important challenges in producing bioactive-based goods is making sure that Good Manufacturing Practices (GMP) are followed. For example, strict control procedures may be necessary to avoid contamination, degradation and fluctuation in the bioactive content when scaling up the manufacture of biologically loaded wound dressings to fulfill GMP criteria (81)
		Regulatory categorization: The regulatory categorization of a bioactive can change based on its intended usage. Certain formulations based on bioactive ingredients can be designated as pharmaceuticals or cosmetics, while others might be considered medical devices. For example, peptides and growth factors may be categorized as drugs, but honey-based wound care treatments may be categorized as medical devices. This categorization disparity may lead to misunderstandings and make the regulatory clearance process more difficult, which might result in higher expenses and a longer time to market (82)
		Standardization: Because bioactives, such as natural oils or plant extracts, have different chemical compositions, it can be challenging to create standardized formulations. Consistent effectiveness and quality data are required by regulatory bodies, yet the inherent diversity of plant-based bioactives complicates the formulation process. Large-scale manufacture and approval may be hampered by this unpredictability, which may also have an impact on repeatability in clinical settings (83)
		Toxicological Issues: Bioactives, especially those derived from plants, may have intricate pharmacological profiles that call for a thorough toxicological evaluation. To guarantee their safety in human usage, some bioactives must undergo extensive testing in preclinical studies to rule out the possibility of allergic responses, skin irritation, or similar adverse consequences. The toxicological safety evaluation thus turns into a major approval procedure bottleneck (84)

Table 6. Emerging technologies and bioactive carriers in wound healing

Technology	Bioactive Carrier	Functionality	Example Bioactives	Application Area	References
Nanotechnology	Liposomes, nanoparticles	Enhance penetration, protect bioactives, enable sustained/ controlled release	Curcumin, Quercetin, Growth factors	Diabetic foot ulcers, chronic wounds	(45)
Smart Dressings	Hydrogels, films	Responsive to stimuli (pH, temperature, enzymes); release actives accordingly	Antimicrobial peptides, Flavonoids	Infected or inflammatory wounds	(46)
3D Bioprinting	Scaffolds, hydrogel inks	Enable spatial delivery of bioactives and cells, tissue regeneration scaffolding	Stem cells, VEGF	Deep tissue injuries, burn wounds	(47)
Gene Therapy	Viral/non-viral vectors	Promote expression of healing -related genes	VEGF, EGF genes	Non-healing ulcers	(48)
Microneedles	Polymer/drug-loaded microneedles	Minimally invasive, localized, precise delivery	Growth factors, anti-inflammatories	Pressure ulcers, ischemic wounds	(49)
Electrospun Fibers	Nanofiber mats	Mimic ECM structure, allow drug loading and sustained release	Antibiotics, antioxidants	Surgical wounds, trauma wounds	(50)

types. Personalized wound care, considering genetic and comorbid factors, is crucial for improving therapeutic outcomes, reducing chronic wound prevalence and enhancing patient quality of life (50).

Despite their promise in wound healing, bioactive compounds face key clinical translation challenges. These include the lack of targeted delivery systems for chronic wounds like diabetic foot ulcers, poor stability and bioavailability of natural bioactives and the absence of robust long-term clinical trials. Regulatory inconsistencies and the lack of standardized formulations further hinder adoption. Additionally, limited integration with clinical workflows and monitoring tools delays their practical implementation (46). Personalized wound care leverages genetic, physiological and lifestyle data to tailor bioactive therapies. Advances in bioinformatics, wearable sensors and 3D printing enable customized delivery systems. For example, gene profiling can guide targeted therapies, while 3D-printed scaffolds can deliver patient-specific bioactives based on wound characteristics. AI-integrated smart dressings offer real-time monitoring and adaptive treatment (45).

Conclusion

Bioactives, derived from natural and synthetic sources including microorganisms, plants and animals, play a pivotal role in the wound healing process. They contribute by lowering inflammation, reducing oxidative stress, promoting angiogenesis and accelerating cell migration and proliferation. These compounds have shown considerable promise in aiding the healing of both acute and chronic wounds. When incorporated into conventional and advanced treatment systems such as creams, gels and bioactive dressings, they have demonstrated notable improvements in tissue repair, as well as in minimizing complications such as infection and scarring.

Despite encouraging preclinical results and some emerging clinical applications, several barriers hinder the routine clinical use of bioactive-based therapies. Key challenges include issues with the stability and bioavailability of bioactives, along with the need for controlled release mechanisms to ensure effective delivery to wound sites. Furthermore, regulatory hurdles, safety concerns and the lack of comprehensive, long-term clinical trials continue to impede widespread adoption. These limitations underscore the need for improved delivery systems and thorough evaluation of safety and efficacy across diverse patient populations.

To unlock the full therapeutic potential of bioactives in wound care, intensified research and development efforts are essential. Future work should focus on enhancing delivery technologies-leveraging innovations such as nanotechnology, gene therapy and smart wound dressings-to ensure targeted, sustained and safe release of bioactives. Moreover, comprehensive clinical studies and personalized medicine approaches are crucial to establish efficacy, safety and cost-effectiveness. With continued scientific and technological advancements, bioactive-based therapies hold great promise for transforming wound management and improving patient outcomes in the years to come.

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Authors' contributions

UT drafted the manuscript; AR and RM participated in the study design; and RM checked the manuscript.

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