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Review Article

Plant-Derived Phytotherapeutics in Cutaneous Wound Healing: Mechanistic Insights, Translational Evidence, and Clinical Perspectives

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ABSTRACT

Cutaneous wound healing is a complex, tightly regulated, and highly dynamic physiological process involving the coordinated interaction of multiple cell types, extracellular matrix components, and signaling pathways that collectively restore tissue integrity following injury. This process proceeds through four temporally overlapping phases—hemostasis, inflammation, proliferation, and remodeling—each governed by intricate molecular networks including cytokines, chemokines, growth factors, and transcriptional regulators such as nuclear factor-kappa B (NF- κ B), mitogen-activated protein kinases (MAPKs), transforming growth factor-beta (TGF- β), and hypoxia-inducible factor-1 alpha (HIF-1 α) [1,2]. While acute wounds typically follow an orderly and self-limiting healing trajectory, pathological conditions such as diabetes mellitus, vascular insufficiency, aging, and chronic infection disrupt this finely tuned cascade, resulting in impaired healing characterized by persistent inflammation, excessive oxidative stress, defective angiogenesis, and dysregulated extracellular matrix remodeling [3–5]. Chronic wounds, including diabetic foot ulcers, venous leg ulcers, and pressure ulcers, therefore represent a significant global healthcare burden, associated with increased morbidity, risk of infection, limb amputation, and substantial economic costs [6]. Despite advances in conventional wound care strategies—including antimicrobial therapy, advanced dressings, growth factor-based treatments, and surgical interventions—the clinical management of chronic wounds remains suboptimal. These approaches often fail to address the multifactorial pathophysiology underlying impaired healing, particularly the interplay between inflammation, oxidative stress, microbial burden, and cellular dysfunction [7]. Furthermore, challenges such as antimicrobial resistance, high treatment costs, limited accessibility, and adverse effects associated with synthetic agents necessitate the exploration of alternative and complementary therapeutic strategies that can target multiple biological pathways simultaneously [8].

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In this context, plant-derived phytotherapeutics have emerged as promising candidates for wound management, owing to their rich diversity of bioactive compounds and long-standing use in traditional medical systems. Medicinal plants synthesize a wide array of secondary metabolites, including flavonoids, tannins, alkaloids, saponins, and terpenoids, which exhibit diverse pharmacological properties relevant to wound healing [9]. Unlike conventional single-target drugs, these phytochemicals demonstrate pleiotropic mechanisms of action, enabling them to modulate several critical aspects of the wound healing process simultaneously, including inflammation, oxidative stress, microbial proliferation, angiogenesis, and extracellular matrix synthesis [10]. Flavonoids and other polyphenolic compounds, for instance, exert potent antioxidant effects by scavenging reactive oxygen species and upregulating endogenous antioxidant defense systems such as superoxide dismutase (SOD), catalase, and glutathione peroxidase, thereby mitigating oxidative damage within the wound microenvironment [11]. In addition, these compounds inhibit pro-inflammatory signaling pathways, including NF- κ B and cyclooxygenase-2 (COX-2), resulting in reduced expression of key inflammatory mediators such as tumor necrosis factor- α (TNF- α) and interleukin-1 beta (IL-1 β) [12]. Tannins contribute to wound healing through their astringent properties, promoting protein precipitation, wound contraction, and microbial inhibition, while also enhancing tissue resistance to oxidative stress [13]. Saponins and terpenoids play a critical role in stimulating angiogenesis and collagen synthesis by modulating signaling pathways involving vascular endothelial growth factor (VEGF) and TGF- β , thereby facilitating granulation tissue formation and tissue regeneration [14]. Alkaloids further complement these effects through their anti-inflammatory and antimicrobial properties, contributing to reduced infection and improved healing outcomes [15]. A growing body of experimental evidence supports the wound-healing efficacy of numerous medicinal plants. Botanicals such as *Aloe vera*, *Centella asiatica*, *Curcuma longa*, *Azadirachta indica*, *Ocimum sanctum*, *Calendula officinalis*, *Moringa oleifera*, *Camellia sinensis*, and *Panax ginseng* have been extensively investigated in *in vitro* and *in vivo* models, demonstrating significant improvements in wound contraction, re-epithelialization, collagen deposition, tensile strength, and angiogenesis [16–19]. Key bioactive compounds such as asiaticoside, curcumin, epigallocatechin gallate (EGCG), and ginsenosides have been identified as major contributors to these therapeutic effects through their ability to modulate multiple molecular pathways involved in wound repair

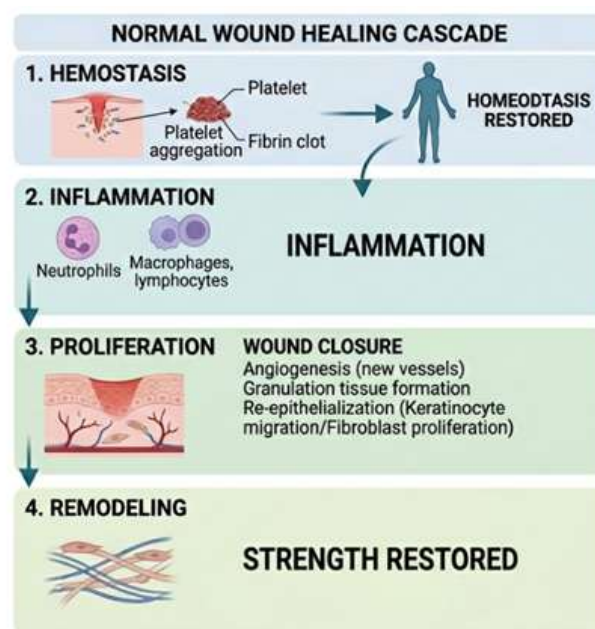
[17,18]. However, while preclinical data are abundant and promising, clinical validation remains limited, with relatively few well-designed randomized controlled trials evaluating the efficacy and safety of plant-based formulations in human populations [20]. Despite their therapeutic potential, several challenges hinder the translation of plant-derived therapeutics into clinical practice. One of the *प्रमुख* limitations is the inherent variability in phytochemical composition, which can be influenced by factors such as plant species, geographical origin, harvesting conditions, and extraction methods [21]. This variability complicates standardization, quality control, and reproducibility of results, posing significant barriers to regulatory approval and clinical adoption. Additionally, many phytochemicals exhibit poor solubility, stability, and bioavailability, limiting their therapeutic efficacy when administered in conventional formulations [22]. Advances in drug delivery systems, including nanoformulations, hydrogels, and biomaterial-based scaffolds, have shown promise in overcoming these limitations; however, further research is required to optimize these approaches for clinical use [23]. Safety considerations also warrant careful attention, as plant-based products may be associated with allergic reactions, cytotoxicity at higher concentrations, and contamination with heavy metals or pesticides if not properly processed and standardized [24]. Moreover, interactions between phytochemicals and conventional medications remain poorly understood and require systematic investigation. From a regulatory perspective, the classification of herbal products varies across regions, further complicating their clinical integration. In summary, plant-derived phytotherapeutics represent a promising and multifaceted approach to enhancing cutaneous wound healing through their ability to target multiple biological pathways simultaneously. Their anti-inflammatory, antioxidant, antimicrobial, and regenerative properties position them as valuable adjuncts or alternatives to conventional wound care strategies. However, the successful translation of these therapies into evidence-based clinical practice requires rigorous standardization of extracts, comprehensive pharmacokinetic and toxicological evaluation, and well-designed large-scale clinical trials. Future research should focus on elucidating molecular mechanisms, optimizing delivery systems, and integrating advanced technologies such as omics-based approaches and computational modeling to fully harness the therapeutic potential of plant-derived compounds in wound management [25].

INTRODUCTION

Cutaneous wound healing is a fundamental physiological process that restores the structural and functional integrity of the skin following injury and represents a highly coordinated interplay of cellular, molecular, and biochemical events regulated in a precise spatiotemporal manner. The skin, as the largest organ of the human body, serves as the first line of defense against environmental insults, microbial invasion, and physical trauma; therefore, any disruption to its integrity necessitates rapid and efficient repair mechanisms to maintain homeostasis and prevent systemic complications [1]. Under normal physiological conditions, wound healing proceeds through a tightly regulated cascade comprising hemostasis, inflammation, proliferation, and remodeling phases, each governed by a complex network of cytokines, chemokines, growth factors, and intracellular signaling pathways such as nuclear factor-kappa B (NF- κ B), mitogen-activated protein kinases (MAPKs), phosphoinositide 3-kinase/protein kinase B (PI3K/Akt), and transforming growth factor-beta (TGF- β)/Smad signaling [2,3]. The successful progression through these stages ensures timely wound closure and restoration of tissue function; however, disruption of this finely tuned process can result in delayed healing, chronic wound formation, or pathological scarring [4].

Chronic wounds constitute a major global health burden, affecting millions of individuals worldwide and significantly impacting healthcare systems due to prolonged treatment durations, high costs, and increased risk of complications such as infection and limb amputation [5]. Conditions such as diabetic foot ulcers, venous leg ulcers, and pressure ulcers are particularly challenging to manage, as they are often characterized by persistent inflammation,

impaired angiogenesis, excessive protease activity, and elevated oxidative stress, all of which contribute to a hostile wound microenvironment that inhibits normal healing processes [6,7]. Among these, diabetic wounds are especially problematic due to hyperglycemia-induced alterations in cellular function, including reduced fibroblast proliferation, impaired keratinocyte migration, and diminished endothelial cell activity, which collectively compromise tissue repair [8]. Furthermore, the presence of microbial biofilms in chronic wounds exacerbates inflammation and confers resistance to antimicrobial therapies, thereby prolonging the inflammatory phase and preventing progression to subsequent healing stages [9].



Despite significant advances in modern wound care, including the development of advanced dressings, antimicrobial agents, growth factor therapies, and surgical interventions, the clinical management of chronic wounds remains suboptimal [10]. Conventional treatments often target single aspects of wound pathology and may fail to address the multifactorial nature of impaired healing. For instance, while antibiotics can

effectively reduce microbial load, their overuse has led to the emergence of antimicrobial resistance, posing a significant challenge in clinical practice [11]. Similarly, growth factor-based therapies, although promising, are limited by issues such as high cost, short half-life, and potential adverse effects [12]. These limitations underscore the need for alternative or adjunctive therapeutic approaches that can simultaneously modulate multiple biological pathways involved in wound healing.

In recent years, there has been growing interest in plant-derived phytotherapeutics as potential candidates for wound management, driven by their rich diversity of bioactive compounds and long-standing use in traditional medicine systems such as Ayurveda, Traditional Chinese Medicine, and Unani medicine [13]. Medicinal plants have been employed for centuries in the treatment of wounds and skin disorders, with empirical evidence supporting their efficacy in promoting tissue repair and preventing infection. Advances in phytochemistry and pharmacology have enabled the identification and characterization of numerous plant-derived compounds that exhibit significant wound-healing properties [14]. These compounds, collectively referred to as phytochemicals, include flavonoids, tannins, alkaloids, saponins, and terpenoids, each of which contributes to wound healing through distinct yet often overlapping mechanisms of action [15].

A key advantage of plant-derived therapeutics lies in their pleiotropic nature, allowing them to target multiple pathways simultaneously. For example, flavonoids and other polyphenolic compounds possess potent antioxidant properties, enabling them to scavenge reactive oxygen species (ROS) and reduce oxidative stress within the wound microenvironment [16]. In addition, these compounds exhibit anti-inflammatory effects by

inhibiting key signaling pathways such as NF- κ B and reducing the production of pro-inflammatory cytokines, including tumor necrosis factor- α (TNF- α) and interleukin-1 beta (IL-1 β) [17]. Tannins contribute to wound healing through their astringent properties, promoting protein precipitation and wound contraction while also exerting antimicrobial effects [18]. Saponins and terpenoids play a critical role in stimulating angiogenesis and collagen synthesis, processes that are essential for the formation of granulation tissue and restoration of tissue integrity [19]. Alkaloids further enhance wound healing by modulating inflammatory responses and providing antimicrobial protection, thereby reducing the risk of infection [20].

Experimental studies have provided substantial evidence supporting the wound-healing potential of various medicinal plants. For instance, triterpenoids derived from *Centella asiatica* have been shown to enhance collagen synthesis and extracellular matrix remodeling through activation of TGF- β signaling pathways [21]. Similarly, curcumin, the main bioactive compound of *Curcuma longa*, exhibits potent anti-inflammatory and antioxidant effects by modulating NF- κ B signaling and reducing ROS levels, thereby accelerating wound closure [22]. Extracts from *Aloe vera* have demonstrated the ability to promote fibroblast proliferation and collagen deposition, while also enhancing re-epithelialization [23]. Additionally, ginsenosides from *Panax ginseng* have been reported to stimulate angiogenesis by upregulating vascular endothelial growth factor (VEGF), highlighting their role in improving tissue perfusion and facilitating wound repair [24]. These findings underscore the therapeutic potential of plant-derived compounds as multi-functional agents capable of addressing the complex pathophysiology of wound healing.



Despite these promising findings, several challenges must be addressed to facilitate the clinical translation of plant-based therapies. One of the primary limitations is the variability in phytochemical composition, which can be influenced by factors such as plant species, geographical origin, cultivation conditions, harvesting time, and extraction methods [25]. This variability poses significant challenges in ensuring consistency, reproducibility, and efficacy of plant-derived formulations. Furthermore, the lack of standardized extraction protocols and quality control measures complicates the comparison of results across studies and hinders regulatory approval [26]. In addition, while numerous *in vitro* and animal studies have demonstrated the wound-healing potential of plant extracts, high-quality clinical trials in human populations remain limited, thereby restricting the evidence base required for widespread clinical adoption [27].

Another critical consideration is the pharmacokinetics and bioavailability of phytochemicals, which are often poorly understood. Many plant-derived compounds exhibit low solubility, poor stability, and limited permeability, which can reduce their therapeutic efficacy when administered in conventional formulations [28]. Advances in drug delivery systems, including nanoparticles, liposomes, hydrogels, and nanoemulsions, have shown promise in enhancing the stability, bioavailability, and targeted delivery of these compounds; however, further research is needed to optimize these technologies for clinical application [29]. Additionally, safety concerns, including potential allergic reactions, cytotoxic effects at higher concentrations, and contamination with heavy metals or pesticides, must be carefully evaluated through rigorous toxicological studies [30].

Given the increasing burden of chronic wounds and the limitations of existing therapeutic strategies, there is a pressing need for comprehensive and mechanistically informed approaches to wound management. Plant-derived phytotherapeutics, with their diverse bioactive compounds and multi-target mechanisms of action, offer a promising avenue for addressing the complex challenges associated with wound healing. However, the successful integration of these therapies into clinical practice requires a thorough understanding of their molecular mechanisms, standardized formulation approaches, and robust clinical validation.

BIOLOGY OF CUTANEOUS WOUND HEALING: CELLULAR, MOLECULAR, AND SYSTEMS-LEVEL INTEGRATION

Cutaneous wound healing is a complex, highly coordinated biological process that restores tissue integrity through the synchronized activity of multiple cell types, extracellular matrix (ECM) components, and signaling networks. This process is classically divided into four overlapping phases—hemostasis, inflammation, proliferation, and remodeling—each regulated by tightly controlled molecular pathways involving cytokines, chemokines, growth factors, and transcriptional regulators. Central signaling axes include nuclear factor-kappa B (NF- κ B), mitogen-activated protein kinases (MAPKs), phosphoinositide 3-kinase/protein kinase B (PI3K/Akt), transforming growth factor-beta (TGF- β)/Smad, and hypoxia-inducible factor-1 alpha (HIF-1 α), which collectively orchestrate cellular recruitment, activation, differentiation, and matrix dynamics [1–3]. The temporal and spatial precision of these pathways is critical; even subtle dysregulation—driven by metabolic disease, hypoxia, infection, or aging—can derail the healing trajectory and result in chronic, non-



resolving wounds [4,5]. Importantly, these phases are not discrete compartments but exist along a continuum with substantial overlap, feedback regulation, and cross-talk among cell populations and signaling cascades.

Hemostasis: Coagulation, Platelet-Derived Signaling, and Provisional Matrix Assembly

The hemostatic phase is initiated within seconds following tissue injury and serves dual roles: rapid cessation of bleeding and establishment of a provisional matrix that scaffolds subsequent cellular infiltration. Vascular injury induces immediate vasoconstriction mediated by endothelin-1 and neurogenic reflexes, followed by platelet adhesion to exposed subendothelial collagen and von Willebrand factor via glycoprotein receptors (GPIb-IX-V complex, GPVI) and integrins (α IIb β 3) [6,7]. Platelet activation triggers a conformational shift that promotes aggregation and degranulation, releasing dense granule contents (ADP, serotonin, calcium) and α -granule-derived growth factors, including platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF- β), epidermal growth factor (EGF), and vascular endothelial growth factor (VEGF) [8,9].

Concurrently, the coagulation cascade is activated through intrinsic (contact activation) and extrinsic (tissue factor-mediated) pathways, converging on thrombin generation. Thrombin catalyzes the conversion of fibrinogen to fibrin, producing an insoluble fibrin network stabilized by factor XIIIa-mediated crosslinking. This fibrin clot, interlaced with fibronectin, vitronectin, and thrombospondin, constitutes a biologically active provisional ECM that supports integrin-mediated adhesion and migration of inflammatory cells [10,11]. Beyond structural support, the clot functions as a reservoir for growth factors and cytokines, establishing

concentration gradients that guide leukocyte chemotaxis and early reparative signaling.

Platelets further secrete chemokines such as CXCL4 (platelet factor 4) and CCL5 (RANTES), which recruit neutrophils and monocytes, thereby coupling hemostasis to the inflammatory phase [12]. The architecture and porosity of the fibrin matrix influence oxygen diffusion, cell migration, and subsequent angiogenesis; thus, both insufficient clot formation (e.g., coagulopathy, anticoagulant therapy) and excessive fibrin deposition can impair healing dynamics [13]. Resolution of the clot is mediated by the fibrinolytic system, primarily via plasmin, regulated by tissue plasminogen activator (tPA) and plasminogen activator inhibitor-1 (PAI-1), ensuring timely transition to tissue formation [14].

Inflammation: Innate Immune Recruitment, Cytokine Networks, and Resolution Programming

The inflammatory phase is characterized by rapid recruitment and activation of innate immune cells responsible for debridement, antimicrobial defense, and initiation of tissue repair. Neutrophils are the earliest infiltrating leukocytes, guided by chemotactic gradients of interleukin-8 (IL-8/CXCL8), complement fragments (C3a, C5a), and damage-associated molecular patterns (DAMPs) released from injured cells [15]. Neutrophils execute phagocytosis and deploy antimicrobial mechanisms, including reactive oxygen species (ROS) generation via NADPH oxidase, release of proteases (elastase, cathepsins), and formation of neutrophil extracellular traps (NETs) [16,17]. While essential for microbial clearance, excessive neutrophil persistence amplifies tissue injury through oxidative stress and proteolytic degradation of ECM components [18].

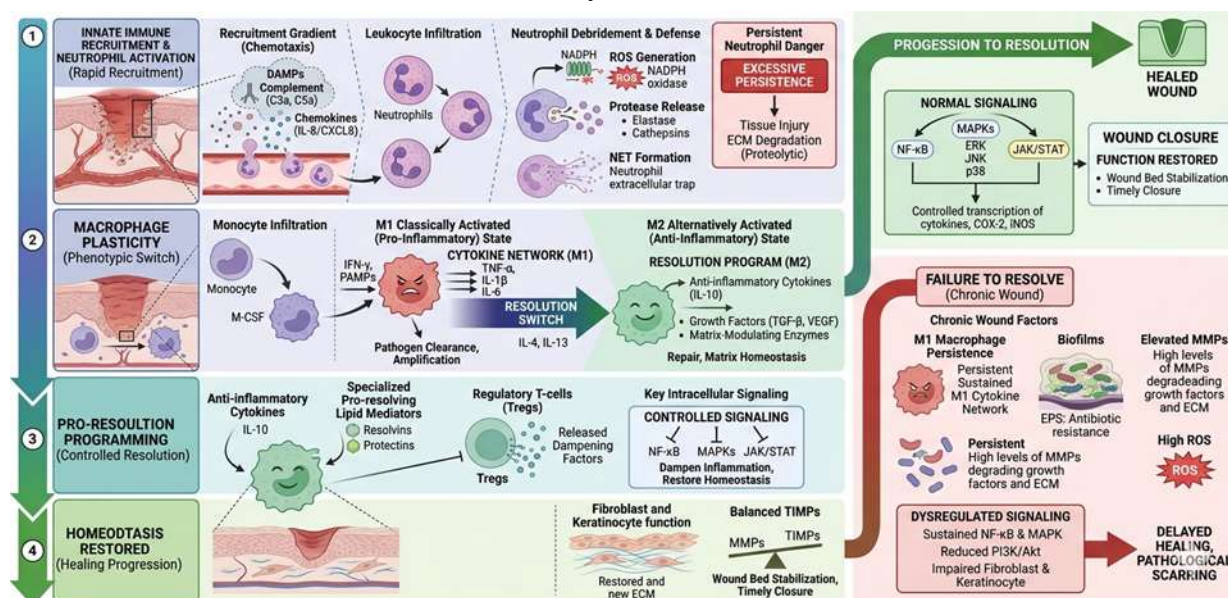


Monocytes subsequently infiltrate the wound and differentiate into macrophages under the influence of macrophage colony-stimulating factor (M-CSF). Macrophages are central regulators of wound healing, exhibiting phenotypic plasticity along a spectrum from classically activated (M1) to alternatively activated (M2) states [19]. M1 macrophages, induced by interferon-gamma (IFN- γ) and pathogen-associated molecular patterns (PAMPs), produce pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF- α), interleukin-1 beta (IL-1 β), and interleukin-6 (IL-6), amplifying inflammation and facilitating pathogen clearance [20]. Transition to the M2 phenotype, driven by interleukins IL-4 and IL-13, marks a critical switch toward resolution and repair, with secretion of anti-inflammatory cytokines (IL-10), growth factors (TGF- β , VEGF), and matrix-modulating enzymes [21].

This M1-to-M2 transition is a pivotal determinant of healing progression. Failure to resolve inflammation—commonly observed in chronic wounds—results in sustained activation of NF- κ B and MAPK pathways, persistent cytokine production, and elevated ROS levels, collectively

degrading growth factors and impairing fibroblast and keratinocyte function [22,23]. Chronic wounds also exhibit increased matrix metalloproteinase (MMP) activity relative to tissue inhibitors of metalloproteinases (TIMPs), leading to excessive ECM degradation and destabilization of the wound bed [24]. Additionally, bacterial biofilms—structured microbial communities encased in extracellular polymeric substances—protect pathogens from host immunity and antimicrobial agents, perpetuating inflammation and delaying healing [25].

At the signaling level, inflammatory responses are governed by NF- κ B, MAPKs (ERK, JNK, p38), and JAK/STAT pathways, which regulate transcription of cytokines, adhesion molecules, and enzymes such as cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) [26]. Controlled resolution involves anti-inflammatory mediators, specialized pro-resolving lipid mediators (resolvins, protectins), and regulatory T cells, which collectively dampen inflammation and restore tissue homeostasis [27].



Proliferation: Fibroblast Activation, Angiogenesis, and Re-epithelialization

The proliferative phase is characterized by the formation of granulation tissue, restoration of vascular networks, and re-establishment of the epidermal barrier. Fibroblasts are the principal effector cells during this phase, migrating into the wound under the influence of PDGF, TGF- β , and fibroblast growth factor (FGF) gradients [28]. Activated fibroblasts proliferate and synthesize ECM components, including collagen type III, fibronectin, and proteoglycans, which provide structural integrity and a scaffold for cellular interactions [29]. Gene expression of collagen isoforms (COL3A1 initially, followed by COL1A1) is tightly regulated by TGF- β /Smad signaling, while PI3K/Akt and MAPK pathways support fibroblast survival and proliferation [30].

A subset of fibroblasts differentiates into myofibroblasts, characterized by expression of alpha-smooth muscle actin (α -SMA) and enhanced contractile capacity. Myofibroblast differentiation is driven by TGF- β , mechanical tension, and ECM stiffness, enabling wound contraction and reduction of wound area [31]. Dysregulation of this process can contribute to fibrosis and pathological scarring.

Angiogenesis is a central component of the proliferative phase, ensuring adequate oxygenation and nutrient delivery. Hypoxia within the wound microenvironment stabilizes hypoxia-inducible factor-1 alpha (HIF-1 α), which upregulates VEGF expression, promoting endothelial cell proliferation, migration, and capillary tube formation [32]. Additional regulators include angiopoietins (Ang-1, Ang-2), platelet-derived growth factors, and nitric oxide (NO), which collectively coordinate vascular maturation and permeability [33]. Newly formed vessels are initially immature and leaky, but

gradually stabilize through pericyte recruitment and basement membrane deposition.

Re-epithelialization involves keratinocyte activation, migration, proliferation, and differentiation to restore the epidermal barrier. Keratinocytes at the wound edge undergo phenotypic changes, reducing cell-cell adhesion and increasing motility under the influence of EGF, keratinocyte growth factor (KGF/FGF-7), and TGF- α [34]. Integrins (e.g., α 5 β 1, α v β 6) mediate keratinocyte interaction with the provisional ECM, facilitating directed migration across the wound bed [35]. Matrix metalloproteinases assist in remodeling ECM to allow cell movement, while tight regulation prevents excessive degradation.

Impairment of the proliferative phase is a defining feature of chronic wounds. In diabetes, hyperglycemia induces formation of advanced glycation end-products (AGEs), which interfere with fibroblast function, reduce collagen synthesis, and impair angiogenic signaling [36]. Endothelial dysfunction, reduced nitric oxide bioavailability, and diminished VEGF expression further compromise neovascularization, while persistent inflammation continues to degrade newly formed matrix [37].

Remodeling: Matrix Reorganization, Mechanical Strength Acquisition, and Scar Maturation

The remodeling phase represents the final stage of wound healing, during which the initially disorganized granulation tissue is transformed into a structurally organized and mechanically competent scar. This phase may extend from weeks to months and involves dynamic ECM turnover regulated by a balance between matrix metalloproteinases (MMPs) and their endogenous inhibitors (TIMPs) [38]. Collagen type III,



predominant in early granulation tissue, is gradually replaced by collagen type I, resulting in increased tensile strength and improved structural organization [39]. Collagen fibers undergo reorientation along lines of mechanical stress, enhancing functional resilience.

Myofibroblasts play a transient but critical role in matrix contraction and alignment; however, they undergo apoptosis upon completion of their function to prevent excessive fibrosis [40]. Persistence of myofibroblasts is associated with pathological scarring, including hypertrophic scars and keloids, which are characterized by excessive collagen deposition and dysregulated TGF- β signaling [41]. Angiogenesis is progressively downregulated during remodeling, leading to reduced vascular density and formation of relatively avascular scar tissue.

Despite these maturation processes, the regenerated tissue rarely achieves the full functional and mechanical properties of uninjured skin, typically reaching approximately 70–80% of original tensile strength [42]. Alterations in pigmentation, elasticity, and adnexal structures are common, reflecting incomplete restoration of normal tissue architecture. Chronic wounds often fail to progress to this phase due to persistent inflammation, protease imbalance, and defective cellular responses.

PHYTOCHEMICAL CLASSES AND THEIR MECHANISTIC ROLES IN CUTANEOUS WOUND HEALING

Plant-derived phytochemicals comprise a structurally diverse repertoire of secondary metabolites that exert pleiotropic effects across the wound healing continuum. Their therapeutic value in cutaneous repair derives from the capacity to modulate interconnected biological processes—namely inflammation, oxidative stress, microbial

burden, angiogenesis, and extracellular matrix (ECM) remodeling—through coordinated regulation of signaling pathways such as nuclear factor-kappa B (NF- κ B), mitogen-activated protein kinases (MAPKs), phosphoinositide 3-kinase/protein kinase B (PI3K/Akt), transforming growth factor-beta (TGF- β)/Smad, and nuclear factor erythroid 2-related factor 2 (Nrf2). In contrast to single-target pharmacotherapies, phytochemicals act on multiple molecular nodes, producing system-level effects that are particularly relevant in complex or chronic wounds characterized by dysregulated inflammation, excessive reactive oxygen species (ROS), impaired angiogenesis, and defective fibroblast function [1–3]. The principal phytochemical classes implicated in wound repair include flavonoids, tannins, saponins, alkaloids, and terpenoids. Although these classes are discussed discretely for clarity, their mechanisms are highly interconnected and often synergistic within whole-plant extracts or polyherbal formulations.

Flavonoids: Redox Modulation, Anti-inflammatory Signaling, and Cellular Proliferation

Flavonoids are polyphenolic compounds with a C6–C3–C6 backbone, encompassing subclasses such as flavonols (quercetin, kaempferol), flavones (luteolin), flavan-3-ols (catechins), and anthocyanins. Their role in wound healing is primarily mediated through robust antioxidant and anti-inflammatory activities coupled with pro-regenerative signaling. At the biochemical level, flavonoids neutralize ROS via electron donation and metal ion chelation, thereby preventing lipid peroxidation and oxidative damage to proteins and nucleic acids within the wound microenvironment [4]. Beyond direct scavenging, flavonoids activate the Nrf2/antioxidant response element (ARE) pathway, resulting in transcriptional upregulation

of cytoprotective enzymes including superoxide dismutase, catalase, glutathione peroxidase, and heme oxygenase-1 [5]. This dual antioxidant action is critical in limiting oxidative stress–induced impairment of growth factors and cellular function during early healing phases.

Concomitantly, flavonoids suppress inflammatory signaling through inhibition of NF- κ B translocation and attenuation of MAPK cascades (ERK1/2, JNK, and p38), leading to reduced transcription of pro-inflammatory mediators such as TNF- α , IL-1 β , IL-6, COX-2, and inducible nitric oxide synthase (iNOS) [6]. This modulation facilitates the transition from the inflammatory to proliferative phase. Flavonoids also influence cellular dynamics by promoting fibroblast proliferation, collagen synthesis, and keratinocyte migration. Mechanistically, these effects are mediated via PI3K/Akt and ERK signaling, which regulate cell survival, cytoskeletal reorganization, and gene expression associated with ECM production [7]. Additionally, certain flavonoids enhance angiogenesis by upregulating vascular endothelial growth factor (VEGF) under hypoxic conditions, thereby supporting neovascularization and nutrient delivery to regenerating tissue.

Tannins: Astringency, Protein Interactions, and Antimicrobial Defense

Tannins are high-molecular-weight polyphenols broadly classified into hydrolyzable tannins (gallotannins, ellagitannins) and condensed tannins (proanthocyanidins). Their wound-healing activity is strongly associated with their astringent properties and ability to form stable complexes with proteins. Upon topical application, tannins precipitate proteins at the wound surface, generating a protective layer that reduces capillary permeability, limits exudation, and provides a physical barrier against microbial invasion [8]. This effect is particularly beneficial during the

early phases of wound healing, where control of fluid loss and microbial contamination is essential.

At the molecular level, tannins exhibit potent antioxidant activity attributable to their multiple hydroxyl groups, which facilitate free radical scavenging and metal ion chelation [9]. By mitigating oxidative stress, tannins preserve cellular integrity and maintain the functional activity of growth factors and enzymes involved in tissue repair. In addition, tannins possess significant antimicrobial activity, achieved through binding to bacterial cell walls, membrane proteins, and extracellular enzymes, leading to structural disruption and inhibition of microbial metabolism [10]. Tannins can also interfere with quorum sensing mechanisms, thereby reducing biofilm formation—a critical factor in chronic wound persistence.

Tannins further contribute to inflammation control by modulating cytokine release and inhibiting leukocyte infiltration. Their ability to stabilize collagen fibers and inhibit proteolytic enzymes, including matrix metalloproteinases (MMPs), supports ECM integrity and prevents excessive matrix degradation [11]. Collectively, these actions facilitate wound contraction, reduce infection risk, and enhance structural stability during tissue repair.

Saponins: Angiogenesis, Fibroblast Activation, and ECM Synthesis

Saponins are amphiphilic glycosides characterized by a hydrophobic aglycone (sapogenin) linked to one or more hydrophilic sugar moieties. This unique structure enables interaction with lipid membranes and modulation of cellular signaling pathways. In wound healing, saponins are particularly important for their pro-angiogenic and pro-fibrotic activities. Mechanistically, saponins upregulate the expression of VEGF and other



angiogenic mediators through activation of hypoxia-inducible pathways and PI3K/Akt signaling, thereby promoting endothelial cell proliferation, migration, and capillary tube formation [12]. Enhanced angiogenesis improves oxygenation and nutrient supply, which are critical for granulation tissue formation.

Saponins also stimulate fibroblast proliferation and collagen synthesis via activation of TGF- β /Smad signaling, leading to increased deposition of collagen types I and III and other ECM components [13]. This results in improved tensile strength and structural organization of the healing tissue. Additionally, saponins have been shown to enhance keratinocyte migration and re-epithelialization, contributing to restoration of the epidermal barrier.

From an immunological perspective, saponins exhibit moderate anti-inflammatory effects by inhibiting pro-inflammatory cytokine production and reducing oxidative stress. Their surfactant properties may also facilitate penetration of other bioactive compounds into the wound bed, potentially enhancing the efficacy of combined phytochemical formulations. Furthermore, saponins demonstrate antimicrobial activity against a range of pathogens, supporting infection control in wound environments.

Alkaloids: Immunomodulation, Antimicrobial Activity, and Cytokine Regulation

Alkaloids are a diverse class of nitrogen-containing compounds with significant pharmacological activity. In the context of wound healing, alkaloids contribute primarily through immunomodulatory and antimicrobial mechanisms. Many alkaloids inhibit the production of pro-inflammatory cytokines by suppressing NF- κ B and MAPK signaling pathways, thereby reducing inflammation and

associated tissue damage [14]. This regulatory effect is crucial in preventing prolonged inflammatory responses that can impair healing progression.

Alkaloids also exhibit potent antimicrobial activity, targeting bacterial, fungal, and, in some cases, viral pathogens. Their mechanisms of action include disruption of cell membrane integrity, inhibition of nucleic acid synthesis, and interference with essential metabolic pathways [15]. This antimicrobial property is particularly important in preventing wound infection and biofilm formation, which are major contributors to chronic wound pathology.

Emerging evidence suggests that certain alkaloids may influence cellular proliferation and differentiation, potentially enhancing fibroblast activity and keratinocyte function. Additionally, some alkaloids possess analgesic properties, which may indirectly support wound healing by reducing pain-induced stress responses and improving patient compliance with treatment. However, the therapeutic window of alkaloids must be carefully considered, as some compounds may exhibit cytotoxicity at higher concentrations.

Terpenoids: Anti-inflammatory Enzyme Inhibition, ECM Remodeling, and Antimicrobial Effects

Terpenoids, derived from isoprene units, encompass a broad range of compounds including monoterpenes, sesquiterpenes, diterpenes, and triterpenes. These compounds exhibit extensive biological activity relevant to wound healing, particularly in the modulation of inflammation and ECM dynamics. Terpenoids inhibit key inflammatory enzymes such as cyclooxygenase-2 (COX-2) and lipoxygenase (LOX), thereby reducing the synthesis of pro-inflammatory eicosanoids, including prostaglandins and



leukotrienes [16]. They also suppress NF- κ B and MAPK signaling pathways, leading to decreased expression of inflammatory cytokines and mediators.

In addition to their anti-inflammatory effects, terpenoids promote ECM synthesis and remodeling by activating TGF- β signaling pathways, which regulate fibroblast proliferation and collagen deposition [17]. This contributes to the formation of a stable and functional tissue matrix. Certain terpenoids also enhance angiogenesis by modulating VEGF expression and endothelial cell activity.

Terpenoids possess strong antimicrobial properties, often acting through disruption of microbial cell membranes and inhibition of biofilm formation. Essential oils rich in terpenoids have demonstrated efficacy against a wide spectrum of wound-associated pathogens. Furthermore, their lipophilic nature facilitates penetration into the skin, enhancing their therapeutic effectiveness in topical applications.

Integrated Mechanistic Perspective

The wound-healing efficacy of phytochemicals is not attributable to isolated mechanisms but rather to their integrated and synergistic effects on multiple biological pathways. By concurrently reducing inflammation, neutralizing oxidative stress, inhibiting microbial growth, promoting angiogenesis, and stimulating ECM synthesis, these compounds create a favorable microenvironment for tissue repair. Importantly, their multi-target nature aligns with the complex pathophysiology of chronic wounds, where dysregulation occurs across several interconnected processes.

However, despite their therapeutic potential, challenges remain in translating phytochemicals

into standardized clinical interventions. Variability in chemical composition, limited pharmacokinetic data, and insufficient clinical validation highlight the need for rigorous research and development. Advances in analytical techniques, molecular biology, and drug delivery systems are expected to play a critical role in overcoming these limitations and enabling the integration of phytochemical-based therapies into modern wound care.

EVIDENCE-BASED MEDICINAL PLANTS IN CUTANEOUS WOUND HEALING: PHYTOCHEMISTRY, MECHANISMS, AND EXPERIMENTAL EVIDENCE

Medicinal plants represent a critical source of bioactive compounds with demonstrated efficacy in modulating multiple phases of the wound healing cascade. Their therapeutic potential is primarily attributed to complex phytochemical compositions that exert synergistic effects on inflammation, oxidative stress, microbial burden, angiogenesis, and extracellular matrix (ECM) remodeling. Unlike synthetic drugs that often target a single molecular pathway, plant-derived extracts act on interconnected biological systems, thereby addressing the multifactorial nature of impaired wound healing. A growing body of experimental and clinical evidence supports the use of several botanicals in enhancing wound repair, particularly through mechanisms involving cytokine modulation, growth factor regulation, fibroblast activation, and collagen synthesis. The following section provides a detailed, evidence-based analysis of key medicinal plants widely studied for their wound-healing properties, along with a structured summary table.



Botanical Name (Family)	Common Name	Major Bioactive Compounds	Mechanisms of Action	Evidence Summary
<i>Aloe vera</i> (Asphodelaceae)	Aloe	Acemannan, glucomannan, flavonoids	Fibroblast proliferation, collagen synthesis, anti-inflammatory, re-epithelialization	Accelerated wound contraction and epithelialization in burn and excision models; clinical support in superficial wounds
<i>Centella asiatica</i> (Apiaceae)	Gotu kola	Asiaticoside, madecassoside	TGF- β activation, collagen synthesis, angiogenesis	Enhanced collagen deposition, improved tensile strength, effective in diabetic wounds
<i>Curcuma longa</i> (Zingiberaceae)	Turmeric	Curcumin	NF- κ B inhibition, antioxidant, angiogenesis	Reduced inflammation, improved granulation and re-epithelialization
<i>Azadirachta indica</i> (Meliaceae)	Neem	Nimbidin, azadirachtin	Antimicrobial, anti-inflammatory, collagen promotion	Effective against wound pathogens, improved wound contraction
<i>Ocimum tenuiflorum</i> (Lamiaceae)	Holy basil	Eugenol, ursolic acid	Antioxidant, anti-inflammatory, collagen stabilization	Increased hydroxyproline content and tensile strength
<i>Calendula officinalis</i> (Asteraceae)	Marigold	Flavonoids, triterpenoids	Anti-inflammatory, angiogenic, antimicrobial	Faster wound contraction and reduced inflammation
<i>Moringa oleifera</i> (Moringaceae)	Drumstick tree	Quercetin, kaempferol	Antioxidant, anti-inflammatory, collagen synthesis	Enhanced wound closure and epithelialization
<i>Camellia sinensis</i> (Theaceae)	Green tea	EGCG, catechins	Antioxidant, anti-biofilm, anti-inflammatory	Reduced bacterial load, improved tensile strength
<i>Panax ginseng</i> (Araliaceae)	Ginseng	Ginsenosides	VEGF upregulation, angiogenesis, collagen synthesis	Increased vascularization and epithelial regeneration
<i>Commiphora myrrha</i> (Burseraceae)	Myrrh	Sesquiterpenes	Anti-inflammatory, antimicrobial	Promotes granulation and reduces infection
<i>Hibiscus rosa-sinensis</i> (Malvaceae)	Hibiscus	Anthocyanins, flavonoids	Antioxidant, collagen synthesis, angiogenesis	Increased fibroblast activity and collagen content
<i>Ganoderma lucidum</i> (Ganodermataceae)	Reishi mushroom	β -glucans	Immunomodulation, antioxidant, angiogenesis	Improved healing in diabetic wound models

Detailed Mechanistic Analysis of Individual Medicinal Plants

Aloe vera has been extensively studied for its wound-healing efficacy, particularly due to its polysaccharide-rich composition. Acemannan, a key bioactive component, plays a central role in

stimulating macrophage activation, which leads to increased production of growth factors such as transforming growth factor-beta (TGF- β) and vascular endothelial growth factor (VEGF). These growth factors are essential for fibroblast proliferation, collagen synthesis, and angiogenesis. Additionally, *Aloe vera* enhances



keratinocyte migration, thereby promoting re-epithelialization. Its anti-inflammatory effects are mediated through inhibition of cyclooxygenase pathways and reduction of prostaglandin synthesis, while its antioxidant properties protect tissues from oxidative damage. Experimental models consistently demonstrate accelerated wound contraction, improved tensile strength, and enhanced collagen deposition, supporting its widespread use in topical wound formulations.

Centella asiatica is characterized by its triterpenoid compounds, particularly asiaticoside and madecassoside, which have a pronounced effect on extracellular matrix remodeling. These compounds activate TGF- β /Smad signaling pathways, leading to increased synthesis of collagen types I and III, fibronectin, and glycosaminoglycans. This results in improved structural integrity and tensile strength of the healed tissue. Additionally, *Centella asiatica* enhances keratinocyte proliferation and migration, facilitating rapid re-epithelialization. Its anti-inflammatory effects further contribute to wound healing by reducing cytokine-mediated tissue damage. Evidence from diabetic wound models indicates significant improvements in healing outcomes, highlighting its therapeutic potential in chronic wounds.

Curcuma longa exerts its wound-healing effects primarily through curcumin, a polyphenolic compound with potent anti-inflammatory and antioxidant properties. Curcumin inhibits NF- κ B signaling, thereby reducing the expression of pro-inflammatory cytokines such as TNF- α and IL-1 β . Simultaneously, it activates the Nrf2 pathway, enhancing the expression of antioxidant enzymes and reducing oxidative stress. These combined effects facilitate the transition from the inflammatory to the proliferative phase of healing. Curcumin also promotes fibroblast proliferation,

collagen synthesis, and angiogenesis through modulation of TGF- β and VEGF signaling pathways. Despite its strong pharmacological activity, its clinical application is limited by poor bioavailability, necessitating the development of advanced delivery systems.

Azadirachta indica demonstrates significant antimicrobial activity, making it particularly valuable in preventing wound infections. Its bioactive compounds disrupt microbial cell membranes and inhibit enzymatic processes essential for pathogen survival. In addition to its antimicrobial effects, neem exhibits anti-inflammatory properties by suppressing NF- κ B signaling and reducing cytokine production. These actions contribute to reduced inflammation and enhanced tissue repair. Preclinical studies show improved wound contraction, increased collagen synthesis, and accelerated epithelialization.

Ocimum tenuiflorum contains bioactive compounds such as eugenol and ursolic acid, which contribute to its antioxidant and anti-inflammatory effects. These compounds reduce oxidative stress and inhibit inflammatory pathways, thereby protecting tissues from damage. Experimental studies demonstrate increased collagen content, as indicated by elevated hydroxyproline levels, and improved tensile strength of healed tissue. These findings suggest a significant role for *Ocimum* in enhancing structural integrity during wound healing.

Calendula officinalis is widely used in topical applications due to its anti-inflammatory and antimicrobial properties. Its flavonoids and triterpenoids inhibit pro-inflammatory mediators and promote angiogenesis, facilitating granulation tissue formation. Clinical and experimental studies report faster wound contraction, reduced edema, and improved epithelialization, supporting its therapeutic use.



Moringa oleifera is rich in polyphenols and antioxidants that protect tissues from oxidative damage. Its extracts enhance collagen synthesis and promote epithelialization, resulting in faster wound closure. Anti-inflammatory effects further contribute to improved healing outcomes.

Camellia sinensis contains catechins such as epigallocatechin gallate (EGCG), which exhibit strong antioxidant and antimicrobial activity. EGCG disrupts bacterial biofilms and reduces inflammation, thereby creating a favorable environment for healing. Experimental studies demonstrate improved collagen synthesis and tensile strength.

Panax ginseng enhances wound healing through its ginsenosides, which stimulate angiogenesis by upregulating VEGF expression. Increased vascularization improves nutrient and oxygen supply, facilitating tissue repair. Additionally, ginsenosides promote collagen synthesis and epithelial regeneration.

Commiphora myrrha, *Hibiscus rosa-sinensis*, and *Ganoderma lucidum* further contribute to wound healing through their combined anti-inflammatory, antioxidant, and immunomodulatory effects, supporting fibroblast activity, angiogenesis, and tissue regeneration.

FORMULATION STRATEGIES AND ADVANCED DRUG DELIVERY SYSTEMS FOR PLANT-DERIVED WOUND THERAPEUTICS

The clinical utilization of plant-derived bioactive compounds in wound healing is substantially limited by formulation-associated constraints, despite extensive experimental evidence demonstrating their therapeutic efficacy across multiple biological pathways. A primary challenge arises from the poor aqueous solubility of many

phytochemicals, which significantly restricts their dissolution and bioavailability at the wound site [12]. In addition to solubility limitations, the lipophilic nature of numerous plant-derived compounds leads to uneven distribution in conventional hydrophilic delivery systems, thereby compromising therapeutic consistency [27]. Chemical instability further complicates their application, as exposure to oxygen, light, and enzymatic activity within the wound environment can result in rapid degradation and loss of biological activity [41]. Traditional topical formulations such as ointments, creams, and gels are widely used due to their simplicity and accessibility; however, these systems lack the capacity for controlled drug release, resulting in an initial burst release followed by rapid depletion of active constituents [5]. Ointment-based systems, while effective in maintaining occlusion and hydration, often impede the release of hydrophilic phytoconstituents and limit their penetration into deeper tissue layers [22]. Cream formulations, although more acceptable from a patient compliance perspective, are prone to physical instability, including phase separation and inconsistent distribution of active compounds over time [14]. Gel-based systems, despite their advantages in maintaining a moist wound environment, frequently exhibit poor mechanical strength and bioadhesive properties, leading to premature removal from the wound surface, particularly in highly exudative wounds [9]. Moreover, these conventional delivery systems fail to account for the dynamic and pathophysiological complexity of the wound microenvironment, which is characterized by fluctuations in pH, elevated proteolytic activity, hypoxia, and microbial colonization that can directly influence drug stability and therapeutic performance [18]. The inability to sustain therapeutic concentrations at the wound site necessitates repeated application, thereby

increasing the likelihood of non-compliance and inconsistent treatment outcomes [29]. Additionally, variability in phytochemical composition resulting from differences in plant source, harvesting conditions, extraction methods, and storage further complicates formulation reproducibility and standardization, posing significant challenges for regulatory approval and clinical translation [11].

Hydrogel-based delivery systems

Hydrogel-based delivery systems have emerged as one of the most promising platforms for the administration of plant-derived therapeutics in wound healing due to their unique ability to provide a hydrated, biocompatible, and structurally supportive environment that closely mimics the extracellular matrix. These three-dimensional polymeric networks are capable of retaining large volumes of water, thereby maintaining a moist wound environment that is essential for facilitating keratinocyte migration, fibroblast proliferation, angiogenesis, and enzymatic activity associated with tissue regeneration [6]. The incorporation of phytochemicals into hydrogel matrices enables sustained and controlled release of bioactive compounds, ensuring prolonged therapeutic action and reducing the frequency of application required for effective treatment [42]. Natural polymers such as chitosan, alginate, gelatin, and hyaluronic acid are widely utilized in hydrogel formulations due to their inherent biocompatibility, biodegradability, and biological activity, including antimicrobial and hemostatic effects that further enhance wound healing [21]. Synthetic polymers, including polyethylene glycol and polyvinyl alcohol, offer additional advantages by providing precise control over mechanical strength, elasticity, and degradation kinetics, thereby enabling customization for different wound types and

clinical conditions [8]. Advanced hydrogel systems can be engineered to exhibit stimuli-responsive behavior, allowing for the release of encapsulated phytochemicals in response to environmental triggers such as pH changes, temperature variations, or enzymatic activity within the wound microenvironment [17]. This is particularly advantageous in infected wounds, where acidic pH conditions can trigger the release of antimicrobial agents, thereby enhancing therapeutic specificity and reducing systemic exposure [13]. Furthermore, hydrogels can function as multifunctional delivery platforms capable of incorporating multiple bioactive agents, including phytochemicals, growth factors, and antimicrobial compounds, thereby promoting synergistic interactions that accelerate wound healing processes [20]. The tunability of hydrogel properties, including porosity, crosslinking density, and degradation rate, allows for precise modulation of drug release kinetics and mechanical stability, making them highly adaptable for both acute and chronic wound management [47].

Nanotechnology-based delivery systems

Nanotechnology-based delivery systems represent a significant advancement in the formulation of plant-derived therapeutics, offering solutions to key limitations related to solubility, stability, and bioavailability. Many phytochemicals, including curcumin and various flavonoids, exhibit poor aqueous solubility and limited permeability across biological membranes, which restricts their therapeutic potential when delivered through conventional formulations [33]. Nanocarriers, such as polymeric nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, and nanoemulsions, enable the encapsulation of these compounds, thereby enhancing their stability and protecting them from degradation within the

wound environment [48]. The nanoscale size of these carriers increases surface area and facilitates enhanced interaction with cellular membranes, improving cellular uptake and tissue penetration [24]. Polymeric nanoparticles composed of biodegradable materials allow for controlled release through gradual polymer degradation, ensuring sustained delivery of bioactive compounds at the wound site [36]. Lipid-based nanocarriers provide additional advantages, including enhanced biocompatibility and improved permeability across the stratum corneum due to their affinity for lipid-rich biological membranes [34]. Surface modification of nanocarriers with targeting ligands enables selective delivery to specific cell types involved in wound healing, such as fibroblasts and endothelial cells, thereby improving therapeutic precision and reducing off-target effects [40]. Furthermore, nanotechnology facilitates the co-delivery of multiple phytochemicals, enabling synergistic interactions that enhance overall therapeutic efficacy [52]. Despite these advantages, challenges such as potential cytotoxicity, large-scale manufacturing constraints, and regulatory considerations must be addressed to ensure safe and effective clinical application [53].

Liposomal and Vesicular Delivery Systems

Liposomal and vesicular delivery systems, including niosomes, transferosomes, and ethosomes, have gained considerable attention as effective carriers for plant-derived phytochemicals due to their ability to enhance drug stability, improve skin penetration, and enable controlled release. These systems are composed of lipid bilayers that encapsulate bioactive compounds, protecting them from degradation and facilitating their transport across the stratum corneum [16]. Liposomes, in particular, are highly biocompatible and capable of encapsulating both hydrophilic and

lipophilic compounds, making them suitable for delivering complex plant extracts [25]. Transferosomes and ethosomes, which are modified vesicular systems with enhanced deformability and ethanol content, respectively, exhibit superior penetration capabilities, allowing them to deliver phytochemicals to deeper layers of the skin [31]. This enhanced penetration is particularly beneficial in chronic wounds, where effective delivery to underlying tissues is required for optimal therapeutic outcomes [45]. Additionally, vesicular systems can be engineered to provide sustained release, thereby maintaining therapeutic concentrations of bioactive compounds over extended periods [28]. The ability to co-encapsulate multiple phytochemicals further enhances their utility, enabling synergistic interactions that improve wound healing efficacy [35]. These systems also reduce irritation and improve patient compliance by minimizing direct exposure of the skin to potentially reactive compounds [43].

Scaffold-Based and Tissue Engineering Approaches

Scaffold-based delivery systems represent an advanced approach in wound healing, integrating principles of tissue engineering to provide structural support for tissue regeneration while simultaneously delivering plant-derived bioactive compounds. These scaffolds are designed to mimic the extracellular matrix, providing a three-dimensional framework that supports cell adhesion, proliferation, and differentiation [30]. Natural biomaterials such as collagen, chitosan, and silk fibroin are commonly used due to their biocompatibility and biodegradability, while synthetic polymers offer greater control over mechanical properties and degradation rates [38]. The incorporation of phytochemicals into scaffold systems enables localized and sustained delivery,

enhancing therapeutic efficacy while minimizing systemic exposure [46]. Electrospun nanofiber scaffolds, in particular, offer high surface area and porosity, facilitating efficient drug loading and controlled release [50]. These systems promote angiogenesis, collagen synthesis, and epithelialization, thereby accelerating tissue regeneration [54]. Additionally, scaffold-based systems can be functionalized with growth factors, antimicrobial agents, or stem cells, creating multifunctional platforms capable of addressing multiple aspects of wound healing simultaneously [49].

Stimuli-responsive delivery systems

Stimuli-responsive delivery systems represent a cutting-edge advancement in wound therapeutics, enabling precise control over drug release in response to specific environmental cues within the wound microenvironment. These systems are designed to respond to factors such as pH, temperature, redox conditions, or enzymatic activity, which are often altered in pathological wounds [26]. For example, infected wounds typically exhibit acidic pH and elevated levels of proteolytic enzymes, which can be exploited to trigger the release of antimicrobial and anti-inflammatory phytochemicals from smart delivery systems [37]. Temperature-sensitive hydrogels can undergo phase transitions in response to body temperature, allowing for controlled drug release upon application [44]. Redox-responsive nanoparticles release their payload in response to oxidative stress conditions, which are commonly observed in chronic wounds [51]. These systems offer significant advantages in terms of therapeutic precision, ensuring that bioactive compounds are released only when and where they are needed, thereby maximizing efficacy and minimizing potential side effects [32]. Furthermore, integration with biosensing technologies enables

real-time monitoring of wound conditions and adaptive drug release, representing a promising direction for personalized wound care [55].

SAFETY, TOXICOLOGY, AND STANDARDIZATION CHALLENGES IN PLANT-DERIVED WOUND THERAPEUTICS

The perception that plant-derived therapeutics are inherently safe due to their natural origin remains a persistent but scientifically oversimplified assumption, particularly in the context of cutaneous wound healing where compromised skin integrity can significantly alter absorption kinetics and systemic exposure. While many phytochemicals, including flavonoids and polysaccharides, demonstrate favorable safety profiles at therapeutic concentrations, their dermal tolerability is highly dependent on formulation, concentration, duration of exposure, and the physiological status of the wound bed [56]. The disruption of the epidermal barrier in acute and chronic wounds facilitates enhanced penetration of bioactive compounds, which may lead to localized or systemic adverse effects if not carefully controlled. Contact dermatitis represents one of the most frequently reported adverse reactions associated with topical botanical preparations, particularly those containing sensitizing constituents such as sesquiterpene lactones, phenolic compounds, or essential oil components [63]. These reactions are typically mediated through delayed-type hypersensitivity mechanisms involving T-cell activation and cytokine release, leading to erythema, edema, and pruritus that can further delay wound healing. In addition to hypersensitivity reactions, certain phytochemicals may exhibit direct cytotoxic effects on keratinocytes and fibroblasts at elevated concentrations, thereby impairing critical processes such as re-epithelialization and

extracellular matrix deposition [59]. Furthermore, the presence of bioactive alkaloids in some plant extracts introduces additional safety concerns, as these compounds may interfere with cellular proliferation and mitochondrial function under specific conditions. The potential for systemic absorption, particularly in large or chronic wounds, necessitates careful evaluation of pharmacokinetic parameters and dose-dependent toxicity, especially in vulnerable populations such as pediatric, geriatric, or immunocompromised patients [61]. Therefore, comprehensive safety assessment, including *in vitro* cytotoxicity assays, *in vivo* dermal irritation studies, and controlled clinical evaluations, is essential to establish safe therapeutic windows and ensure compatibility with human tissue.

Toxicological Considerations and Dose-Response Relationships

The toxicological evaluation of plant-derived therapeutics in wound healing must account for the complex interplay between dose, exposure duration, and the multifaceted biological activities of phytochemicals. While low concentrations of plant-derived compounds often exert beneficial effects through anti-inflammatory, antioxidant, and antimicrobial mechanisms, higher concentrations may produce paradoxical or deleterious effects, including cytotoxicity, oxidative imbalance, and inhibition of cellular proliferation [58]. This biphasic dose-response relationship, commonly referred to as hormesis, underscores the importance of precise dose optimization in phytotherapeutic formulations. Excessive antioxidant activity, for instance, may disrupt physiological redox signaling pathways that are essential for normal wound healing processes, including cell migration and angiogenesis [64]. Similarly, high concentrations of polyphenols have been shown to inhibit

fibroblast proliferation and collagen synthesis, thereby delaying tissue repair. Alkaloids, known for their potent pharmacological activity, require particularly careful evaluation due to their potential to interfere with DNA replication and induce apoptosis in rapidly dividing cells [60]. Essential oils, which are rich in terpenoids, may cause skin irritation, neurotoxicity, or systemic toxicity if not properly diluted, especially when applied to large wound areas [62]. Moreover, the cumulative effects of prolonged exposure to phytochemicals must be considered, as chronic application may lead to bioaccumulation or delayed adverse effects. Another critical aspect is the potential for herb-drug interactions, particularly in patients receiving concurrent pharmacological treatments such as antibiotics, anti-inflammatory agents, or anticoagulants, as phytochemicals may modulate metabolic enzymes and alter drug pharmacokinetics [57]. These complexities necessitate comprehensive toxicological studies that evaluate acute, sub-chronic, and chronic toxicity, as well as pharmacokinetic and pharmacodynamic interactions, to ensure safe and effective clinical application.

Standardization and quality control

One of the most significant barriers to the clinical translation of plant-derived wound therapeutics is the lack of standardization and quality control in the preparation and characterization of botanical extracts. Unlike synthetic pharmaceuticals, which are composed of well-defined chemical entities, plant extracts are inherently complex mixtures containing multiple bioactive constituents whose composition can vary widely depending on factors such as plant species, geographical origin, cultivation practices, harvesting time, and extraction methods [65]. This variability can lead to significant differences in pharmacological



activity, thereby compromising reproducibility and reliability of therapeutic outcomes. Standardization involves the identification and quantification of key bioactive markers, ensuring that each batch of extract contains consistent concentrations of these compounds [68]. Advanced analytical techniques such as high-performance liquid chromatography, gas chromatography, and mass spectrometry are essential for establishing chemical fingerprints and detecting potential contaminants, including heavy metals, pesticides, and microbial impurities [66]. In addition to chemical standardization, biological standardization based on pharmacological activity may be necessary to ensure functional consistency across batches. The use of authenticated plant materials, supported by botanical identification and voucher specimens, is critical to prevent misidentification and adulteration, which can significantly impact both safety and efficacy [67]. Furthermore, adherence to Good Agricultural and Collection Practices (GACP) and Good Manufacturing Practices (GMP) is essential to maintain quality throughout the production process and ensure compliance with regulatory requirements [69]. Without rigorous standardization and quality control measures, the clinical application of plant-derived therapeutics remains limited by variability and lack of reproducibility.

Regulatory Challenges and Clinical Translation Barriers

The regulatory framework governing plant-derived therapeutics presents unique challenges that can impede their clinical translation and widespread adoption in wound care. Unlike conventional pharmaceuticals, botanical products are often classified under diverse regulatory categories, including herbal medicines, dietary supplements, or traditional remedies, depending

on jurisdiction, each with distinct requirements for safety, efficacy, and quality evaluation [70]. One of the primary challenges is the limited availability of high-quality clinical evidence supporting the efficacy of many plant-derived wound healing agents. While numerous preclinical studies demonstrate promising results, the lack of large-scale randomized controlled trials limits the ability to establish standardized dosing regimens and validate therapeutic outcomes in diverse patient populations [71]. Additionally, regulatory agencies require detailed characterization of active constituents, mechanisms of action, and pharmacokinetic profiles, which can be difficult to achieve given the complexity of plant extracts. The absence of standardized formulations further complicates regulatory approval, as variability in composition can lead to inconsistent therapeutic effects [72]. Furthermore, intellectual property challenges associated with natural products may reduce commercial incentives for large-scale clinical trials, thereby limiting investment in research and development. The integration of pharmacovigilance systems to monitor adverse effects and ensure post-market safety is also essential for building confidence in plant-based therapeutics and facilitating their acceptance in clinical practice.

Knowledge Gaps and Future Research Directions

Despite significant progress in the field of phytotherapeutic wound healing, several critical knowledge gaps remain that must be addressed to fully realize the clinical potential of plant-derived therapeutics. One major limitation is the incomplete understanding of the molecular mechanisms underlying the effects of many phytochemicals, particularly in complex wound environments where multiple signaling pathways interact simultaneously [73]. Advances in omics



technologies, including genomics, proteomics, and metabolomics, offer promising tools for elucidating these mechanisms and identifying novel therapeutic targets. Another important area of research is the development of optimized delivery systems that can enhance the stability, bioavailability, and targeted delivery of phytochemicals, thereby improving therapeutic efficacy [74]. Large-scale, well-designed clinical trials are essential to validate the safety and efficacy of plant-based therapies and to establish standardized treatment protocols for different types of wounds [75]. The exploration of synergistic interactions between different phytochemicals, as well as between phytochemicals and conventional drugs, represents another promising avenue for enhancing therapeutic outcomes. Additionally, the integration of interdisciplinary approaches, combining expertise from pharmacology, material science, molecular biology, and clinical medicine, will be essential to overcome existing challenges and advance the field toward evidence-based clinical application.

CLINICAL EVIDENCE, HUMAN TRIALS, AND TRANSLATIONAL VALIDATION OF PLANT-DERIVED WOUND THERAPEUTICS

The clinical translation of plant-derived therapeutics for wound healing has gained increasing attention over the past two decades, driven by extensive preclinical evidence demonstrating their multifaceted biological activity; however, the body of human clinical evidence remains comparatively limited, heterogeneous, and often methodologically constrained. While numerous *in vitro* and *in vivo* studies have consistently demonstrated that phytochemicals exert anti-inflammatory, antimicrobial, antioxidant, and pro-regenerative

effects, the extrapolation of these findings into clinical practice requires rigorous validation through well-designed human trials [76]. Existing clinical studies, although promising, often vary significantly in terms of study design, sample size, formulation type, and outcome measures, thereby complicating direct comparison and synthesis of results. In many cases, plant-derived interventions have been evaluated as adjunct therapies rather than standalone treatments, which further limits the ability to isolate their specific therapeutic contributions. Despite these limitations, emerging clinical evidence suggests that botanical formulations can significantly enhance wound healing outcomes by accelerating re-epithelialization, reducing infection rates, and improving overall tissue quality, particularly in chronic and non-healing wounds where conventional therapies often fail [77]. The translational relevance of these findings is particularly pronounced in resource-limited settings, where plant-based therapies offer cost-effective and accessible alternatives to synthetic drugs, thereby addressing significant gaps in global wound care management [78]. However, the lack of standardized protocols, inconsistent phytochemical composition, and limited regulatory oversight remain major barriers to widespread clinical adoption, necessitating further high-quality research to establish robust evidence-based guidelines.

Clinics

Several plant-derived therapeutics have been investigated in clinical settings, with varying degrees of success, highlighting both the potential and limitations of phytotherapy in wound management. Among the most extensively studied botanicals is *Aloe vera*, which has demonstrated significant efficacy in the treatment of burn wounds, surgical incisions, and chronic ulcers,



primarily through its ability to enhance fibroblast proliferation, collagen synthesis, and angiogenesis [79]. Clinical trials evaluating *ThishaCurcuma longa* (curcumin)*Calendar* preparations have also been assessed in clinical studies, demonstrating anti-inflammatory and antimicrobial effects that contribute to faster wound closure and reduced infection rates [82]. In addition, *Azadirachta indica*.

Methodology

A critical evaluation of existing clinical studies on plant-derived wound therapeutics reveals several methodological limitations that hinder the generation of high-quality evidence and impede regulatory approval. One of the most significant challenges is the lack of standardization in phytochemical composition, as variations in plant source, extraction methods, and formulation processes can lead to substantial differences in the concentration and activity of bioactive compounds [84]. This variability complicates reproducibility and limits the ability to compare results across studies. Additionally, many clinical trials lack adequate randomization and blinding, increasing the risk of bias and reducing the reliability of reported outcomes. The use of subjective endpoints, such as visual assessment of wound healing, further introduces variability and limits the precision of outcome measurement [85]. Moreover, the relatively short duration of many studies fails to capture long-term outcomes, including scar formation and tissue remodeling, which are critical components of wound healing. Another limitation is the underrepresentation of diverse patient populations, including individuals with comorbid conditions such as diabetes, which significantly influence wound healing dynamics [86]. The absence of standardized dosing regimens and formulation protocols further complicates the interpretation of clinical data, as differences in

dosage and delivery methods can significantly impact therapeutic efficacy. These methodological challenges underscore the need for rigorous clinical trial design, including standardized protocols, objective outcome measures, and long-term follow-up, to establish reliable evidence for the clinical use of plant-derived therapeutics.

Comparative Efficacy with Conventional Therapies

Comparative studies evaluating plant-derived therapeutics against conventional wound care treatments have provided valuable insights into their relative efficacy and potential role in clinical practice. In several clinical trials, botanical formulations have demonstrated comparable or superior outcomes in terms of wound closure rate, reduction of inflammation, and infection control when compared to standard treatments such as silver sulfadiazine and antibiotic ointments [87]. The multifunctional nature of phytochemicals, which allows them to simultaneously target multiple aspects of the wound healing process, provides a distinct advantage over single-target synthetic drugs. For instance, while conventional antimicrobials primarily focus on infection control, plant-derived compounds often exhibit additional anti-inflammatory and antioxidant effects, thereby addressing multiple pathological factors simultaneously [88]. Furthermore, plant-based therapies are generally associated with fewer adverse effects, particularly in terms of cytotoxicity and delayed healing, which are commonly observed with certain synthetic agents [89]. However, it is important to note that the efficacy of plant-derived therapeutics is highly dependent on formulation quality, dosage, and application protocol, and inconsistent results have been reported in studies lacking standardized methodologies. As such, while botanical therapies hold significant promise as either standalone or



adjunct treatments, further comparative studies with robust design are required to establish their definitive clinical value.

Emerging Clinic

The future of plant-derived wound therapeutics lies in the integration of traditional knowledge with modern scientific approaches, including advanced drug delivery systems, molecular biology, and personalized medicine. Recent clinical trends indicate a growing interest in the use of phytochemical-loaded nanocarriers, hydrogels, and scaffold-based systems, which enhance the stability, bioavailability, and targeted delivery of bioactive compounds, thereby improving clinical outcomes [90]. The incorporation of biomarkers and omics-based approaches into clinical research is expected to provide deeper insights into the molecular mechanisms underlying the therapeutic effects of phytochemicals, enabling the development of more precise and effective treatment strategies [91]. Additionally, the exploration of synergistic interactions between multiple phytochemicals and between phytochemicals and conventional drugs represents a promising avenue for enhancing therapeutic efficacy and overcoming resistance mechanisms [92]. Large-scale, multicenter randomized controlled trials are essential to validate the safety and efficacy of plant-derived therapeutics and to establish standardized treatment protocols for different types of wounds. Furthermore, the development of regulatory frameworks that accommodate the complexity of botanical products while ensuring safety and efficacy will be critical for facilitating their integration into mainstream clinical practice [93]. As research in this field continues to evolve, plant-derived therapeutics are poised to play an increasingly important role in the future of wound

care, offering a holistic and multifaceted approach to tissue repair and regeneration.

CONCLUSION AND FUTURE PERSPECTIVES

The present review underscores the significant therapeutic potential of plant-derived bioactive compounds in the management of cutaneous wound healing, emphasizing their capacity to modulate multiple interconnected biological processes that govern tissue repair. Unlike conventional single-target pharmacological agents, phytochemicals exhibit a pleiotropic mode of action, simultaneously influencing inflammatory signaling pathways, oxidative stress responses, microbial colonization, and extracellular matrix remodeling. This multi-mechanistic profile is particularly advantageous in complex wound environments, such as chronic and non-healing wounds, where dysregulation of cytokine networks, excessive reactive oxygen species generation, and persistent infection collectively impair the normal progression of healing. Compounds such as flavonoids, terpenoids, and polyphenols have been shown to enhance fibroblast proliferation, stimulate collagen synthesis, promote angiogenesis, and accelerate re-epithelialization, thereby improving both the rate and structural quality of wound closure [94]. Furthermore, the intrinsic antimicrobial properties of several plant-derived constituents provide an additional layer of therapeutic benefit by reducing microbial load and preventing biofilm formation, which is a major barrier to healing in chronic wounds [95]. These combined effects position plant-based therapeutics as a biologically comprehensive and clinically relevant strategy for wound management.

Despite these promising attributes, the translation of plant-derived therapeutics into standardized clinical practice remains constrained by several



critical challenges that must be addressed to achieve broader acceptance within evidence-based medicine. One of the most significant limitations is the inherent variability in phytochemical composition, which arises from differences in plant species, geographical origin, cultivation conditions, harvesting time, and extraction methodologies. This variability directly impacts the reproducibility, efficacy, and safety of botanical formulations, thereby complicating their clinical validation and regulatory approval [96]. In addition, the current body of clinical evidence is limited by small sample sizes, lack of rigorous randomized controlled trials, and inconsistencies in study design and outcome measures, which collectively weaken the strength of evidence required for integration into clinical guidelines [97]. The absence of standardized dosing regimens and formulation protocols further exacerbates this issue, as variations in concentration and delivery systems can significantly influence therapeutic outcomes. Moreover, the complex pathophysiology of chronic wounds, characterized by persistent inflammation, impaired angiogenesis, hypoxia, and microbial biofilm formation, necessitates advanced and precisely targeted therapeutic approaches that conventional botanical preparations may not adequately provide [98].

In this context, the integration of plant-derived bioactive compounds with advanced drug delivery systems represents a critical avenue for enhancing their clinical utility and overcoming existing limitations. Emerging technologies such as hydrogel-based systems, nanocarriers, liposomal formulations, and bioengineered scaffolds offer the potential to improve the stability, bioavailability, and targeted delivery of phytochemicals within the wound microenvironment. These systems enable controlled and sustained release of bioactive

compounds, thereby maintaining therapeutic concentrations over extended periods and reducing the frequency of application [99]. Additionally, the incorporation of stimuli-responsive and smart delivery platforms allows for the precise modulation of drug release in response to specific wound conditions, such as changes in pH, temperature, or enzymatic activity, thereby enhancing therapeutic specificity and minimizing off-target effects. The convergence of phytotherapy with material science and nanotechnology thus represents a promising strategy for optimizing the clinical performance of plant-derived therapeutics.

Future research should prioritize the development of standardized and well-characterized phytopharmaceutical formulations, supported by rigorous analytical validation and quality control frameworks to ensure consistency and reproducibility. The application of advanced analytical techniques, including chromatographic and spectrometric methods, will be essential for identifying and quantifying active constituents and establishing reliable chemical fingerprints for botanical extracts. Furthermore, large-scale, multicenter randomized controlled trials with standardized endpoints and long-term follow-up are imperative to establish definitive evidence regarding the safety, efficacy, and optimal dosing of plant-based wound therapies. The integration of systems biology approaches, including genomics, proteomics, and metabolomics, may provide deeper insights into the molecular mechanisms underlying phytochemical-mediated wound healing, thereby facilitating the development of precision-based therapeutic strategies tailored to individual patient profiles [100]. Additionally, the exploration of synergistic interactions between different phytochemicals, as well as between phytochemicals and conventional pharmacological agents, represents a promising



area for enhancing therapeutic outcomes and overcoming resistance mechanisms.

In conclusion, plant-derived wound therapeutics offer a scientifically robust and clinically promising approach to tissue repair, characterized by their multifunctional mechanisms, relative safety, and potential cost-effectiveness. However, their successful translation into mainstream clinical practice will depend on overcoming key challenges related to standardization, formulation, and clinical validation. Through continued interdisciplinary research and technological innovation, these natural bioactive compounds have the potential to evolve into evidence-based, globally accessible therapeutic solutions for both acute and chronic wound management.

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