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Immunomodulatory and anti-oxidant mechanisms of plant-derived bioactive scaffolds in diabetic wound healing: Molecular pathways and therapeutic implications

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ABSTRACT

Diabetic wound healing remains challenging due to persistent inflammation, oxidative stress, and impaired angiogenesis. Plant-derived bioactive scaffolds address multiple pathophysiological mechanisms simultaneously through inherent immunomodulatory and anti-oxidant properties. This review critically analyzes recent advances in plant-derived scaffolds for diabetic wound healing, focusing on molecular mechanisms. A systematic literature search was conducted in PubMed, Scopus, and Web of Science using terms such as "plant-derived scaffolds," "decellularized scaffolds," "diabetic wound healing," "immunomodulation," "anti-oxidant," and "angiogenesis." Studies published primarily between 2019 and 2026 that reported in vitro, in vivo, or ex vivo data on plant scaffold performance in diabetic wound models were prioritized; mechanistically relevant phytochemical studies were included where direct scaffold-level evidence was limited. The analysis emphasizes immunomodulatory, anti-oxidant, and angiogenic effects in experimental models. Plant-derived scaffolds from kelp, spinach, pomelo peel, walnut leaves, and mushrooms demonstrate therapeutic potential through multiple mechanisms. They promote macrophage polarization from pro-inflammatory M1 to regenerative M2 phenotypes, reduce reactive oxygen species via polyphenolic and flavonoid compounds, and enhance angiogenesis through VEGF up-regulation. Bioactive components, including fucoidan, gallic acid, carotenoids, and p-coumaric acid, reduce pro-inflammatory cytokines, enhance collagen deposition, and accelerate wound closure, exceeding 90% by day 14 in diabetic animal models, compared with approximately 70% in untreated controls. Plant-derived bioactive scaffolds represent a paradigm shift in diabetic wound management by simultaneously targeting inflammation, oxidative stress, and impaired regeneration through naturally occurring bioactive compounds while preserving extracellular matrix architecture.

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Introduction

Diabetes mellitus affects approximately 537 million adults globally, with diabetic foot ulcers developing in 19-34% of patients during their lifetime, representing one of the most severe complications of this metabolic disorder (1). The pathophysiology of diabetic wound healing is characterized by a complex interplay of cellular and molecular dysfunctions, including prolonged inflammatory responses, excessive oxidative stress, impaired angiogenesis, reduced growth factor availability, and compromised extracellular matrix remodeling. These interconnected pathological processes create a hostile microenvironment

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that fundamentally impairs the body's natural healing capacity, leading to chronic non-healing wounds with devastating consequences, including amputation, sepsis, and mortality. Traditional wound management strategies often fail to address the multifactorial nature of diabetic wounds, underscoring the urgent need for innovative therapeutic approaches that simultaneously target multiple pathophysiological mechanisms (2).

The excessive and prolonged inflammatory response in diabetic wounds is a critical barrier to healing. Unlike acute wounds, where inflammation resolves within days, diabetic wounds remain trapped in a persistent inflammatory state marked by sustained infiltration of pro-inflammatory M1 macrophages and neutrophils (2, 3). These immune cells continuously release pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6), thereby perpetuating tissue damage and preventing the transition to the proliferative phase of healing. Simultaneously, the hyperglycemic environment generates excessive reactive oxygen species (ROS) through multiple mechanisms, including glucose auto-oxidation, protein glycation, and mitochondrial dysfunction (4). This oxidative stress overwhelms endogenous anti-oxidant defenses, leading to lipid peroxidation, protein oxidation, DNA damage, and cellular dysfunction that further impair wound healing. The combination of chronic inflammation and oxidative stress creates a vicious cycle that degrades growth factors, disrupts cell signaling pathways, and maintains the wound in a non-healing state (5).

Furthermore, diabetic wounds exhibit profoundly impaired angiogenesis despite the hypoxic environment that normally stimulates new blood vessel formation (6). The expression and bioavailability of vascular endothelial growth factor (VEGF), a critical mediator of angiogenesis, are significantly reduced in diabetic tissues due to advanced glycation end-products, oxidative stress, and inflammatory cytokines (7). This angiogenic insufficiency results in inadequate tissue perfusion, limited oxygen and nutrient delivery, and accumulation of metabolic waste products, all of which severely compromise cellular function and tissue regeneration. Impaired microcirculation also reduces recruitment of progenitor cells and therapeutic agents to the wound site, further hampering the healing process. Additionally, the extracellular matrix in diabetic wounds shows abnormal composition and organization, with reduced deposition of functional collagen and increased accumulation of degraded matrix components that fail to provide adequate structural support for cellular activities (8).

In response to these challenges, researchers have explored various biomaterial-based approaches to promote diabetic wound healing. Among these, plant-derived scaffolds have emerged as particularly promising therapeutic platforms due to their unique combination of structural, biochemical, and biological properties (9-12). Unlike synthetic biomaterials that primarily provide passive structural support, plant-derived scaffolds offer intrinsic bioactive compounds, including polyphenols, flavonoids, terpenoids, and polysaccharides, which possess documented anti-inflammatory, anti-oxidant, and pro-angiogenic activities. These natural bioactive molecules, accumulated by plants as secondary metabolites for their own defense and growth, can be strategically harnessed for therapeutic purposes in wound healing (13, 14). The preserved plant extracellular matrix, composed primarily of cellulose microfibrils, hemicelluloses, and pectins, provides a three-dimensional architectural framework that closely mimics aspects of mammalian extracellular matrix, facilitating cell adhesion, migration, and proliferation (15, 16).

Recent advances in decellularization techniques have enabled the removal of plant cellular components while preserving both the structural integrity of the extracellular matrix and the bioactive compounds embedded within it (17). This preservation is crucial because many bioactive molecules are naturally associated with the cell wall structure and remain functionally active even after decellularization. The resulting acellular scaffolds retain their inherent biocompatibility, biodegradability, and mechanical properties while offering sustained release of therapeutic compounds directly at the wound site (18). Moreover, the hierarchical porosity of plant tissues, originally evolved for efficient nutrient and water transport, provides excellent permeability for wound exudate management and allows cellular infiltration, which is essential for tissue regeneration. The vascular architecture in plant leaves and stems, when preserved through careful decellularization, can guide the formation of new blood vessels in healing tissue (19).

The therapeutic potential of plant-derived scaffolds extends beyond their passive structural role to include active modulation of the wound-healing environment through multiple molecular mechanisms (20). These scaffolds have demonstrated the ability to reprogram the inflammatory response by promoting the phenotypic switch of macrophages from the pro-inflammatory M1 state to the anti-inflammatory, pro-regenerative M2 state (21). This immunomodulatory effect is mediated through bioactive compounds that influence key signaling pathways, including nuclear factor kappa B (NF-κB), mitogen-activated protein kinases (MAPK), and signal transducer and activator of transcription (STAT) pathways (22). Simultaneously, the anti-oxidant compounds in these scaffolds directly scavenge reactive oxygen species and increase the expression of endogenous anti-oxidant enzymes, including superoxide dismutase, catalase, and glutathione peroxidase, thereby reducing oxidative damage to cellular components and supporting metabolic function. The pro-angiogenic effects are mediated through up-regulation of VEGF and other growth factors, as well as direct stimulation of endothelial cell proliferation and migration (23).

Different plant sources offer distinct profiles of bioactive compounds and structural characteristics, allowing for tailored therapeutic approaches. Marine plants, such as kelp, provide unique sulfated polysaccharides, including fucoidan, with potent immunomodulatory properties. In contrast, terrestrial plants such as spinach exhibit high concentrations of phenolic compounds and well-preserved vascular networks (24). Tree-derived materials from walnut leaves and citrus peels contain specific tannins and flavonoids with strong anti-oxidant activity. At the same time, fungal sources, such as mushroom stems, provide polysaccharides with immune-enhancing properties (25, 26). This diversity in botanical sources enables the development of scaffolds optimized for specific aspects of diabetic wound healing, whether prioritizing anti-inflammatory effects, anti-oxidant capacity, or angiogenic stimulation.

The integration of additional functional components with plant-derived scaffolds has further enhanced their therapeutic efficacy. Incorporation of pro-angiogenic molecules such as 2-deoxy-D-ribose, anti-oxidant vitamins like ascorbic acid derivatives, antimicrobial metal-organic frameworks, and photothermal agents has created multifunctional platforms that address the complex pathophysiology of diabetic wounds more comprehensively. These hybrid approaches leverage both the intrinsic benefits of plant-derived matrices and the targeted actions of incorporated bioactive agents, resulting in synergistic therapeutic effects (27, 28). The controlled-release kinetics of these molecules incorporated into the plant matrix ensure sustained therapeutic levels at the wound site, thereby avoiding the rapid clearance that limits the efficacy of topically applied agents (29).

Despite the growing body of evidence supporting the therapeutic potential of plant-derived scaffolds in diabetic wound healing, the field remains characterized by fragmented knowledge regarding the precise molecular mechanisms underlying their beneficial effects (30). While individual studies have demonstrated various aspects of their activity, a comprehensive understanding of how different plant-derived scaffolds modulate specific signaling pathways, alter gene expression patterns, and coordinate multiple cellular responses is still emerging. Furthermore, the relationships among scaffold structural properties, bioactive compound profiles, and therapeutic outcomes require systematic analysis to guide the rational design of optimized wound-healing platforms (31). The translation of these promising materials from laboratory research to clinical application requires deeper mechanistic insights to inform the standardization of preparation methods, quality control parameters, and treatment protocols.

This review aims to provide a critical, comprehensive analysis of the immunomodulatory and anti-oxidant mechanisms by which plant-derived bioactive scaffolds promote diabetic wound healing. By synthesizing evidence from recent research on diverse botanical sources including marine algae, leafy vegetables, fruit peels, tree leaves, and fungal materials, we examine the molecular pathways activated by these scaffolds and their effects on key cellular processes, including macrophage polarization, oxidative stress reduction, angiogenesis, and tissue remodeling. Particular emphasis is placed on understanding how the intrinsic bioactive compounds in different plant sources contribute to therapeutic efficacy, how scaffold structural properties influence cellular responses, and how these materials can be optimized or functionalized to enhance their wound-healing potential. Through this analysis, we seek to establish a mechanistic framework that connects botanical source selection, bioactive compound profiles, cellular and molecular effects, and ultimately clinical outcomes in diabetic wound healing.

Scaffold classification

The plant-derived scaffolds discussed in this review can be categorized into three principal types that differ meaningfully in their construction, bioactive release mechanisms, and expected therapeutic profiles. Type I scaffolds are purely decellularized plant matrices in which the native botanical architecture is preserved, and the inherent bioactive compounds (polyphenols, polysaccharides, carotenoids) remain embedded within the cellulosic structure following removal of plant cellular material; examples include the deep-eutectic-solvent-decellularized kelp scaffold (32) and Tween-20-decellularized spinach (33). In these systems, bioactive release is governed primarily by matrix hydration and biodegradation kinetics, producing a prolonged, low-level release profile. Type II scaffolds are hybrid platforms in which a plant-derived matrix serves as the structural carrier for exogenously incorporated therapeutic agents—such as 2-deoxy-D-ribose, ascorbic acid-2-phosphate, or metal-organic frameworks—that are not native to the plant; examples include 2dDR-loaded spinach scaffolds (34) and Cu/GA MOF-functionalized pomelo peel sponges (35). In these systems, release kinetics are biphasic: an initial burst phase corresponding to the surface-adsorbed agent is followed by sustained diffusion of the matrix-embedded compound, and the total bioactive profile is the sum of the exogenous agent and residual plant compounds. Type III scaffolds combine plant matrices with secondary biological matrices or proteins, such as the kelp–liver extracellular matrix composite (36), producing hybrid mechanical and bioactive properties that reflect both components. Recognizing these distinctions is essential when interpreting mechanistic data because attributing observed cellular effects to a specific compound or structural feature requires knowledge of which scaffold type was studied.

Literature selection

Eligible publications were identified through searches of PubMed, Scopus, and Web of Science conducted in early 2026. Search terms were combined using Boolean operators and included "plant scaffold," "decellularized plant," "botanical scaffold," "diabetic wound," "diabetic ulcer," "macrophage polarization," "NF-κB wound," "Nrf2 wound," "angiogenesis scaffold," "fucoidan wound," and names of specific plant sources. Original research articles, systematic reviews, and relevant mechanistic studies published in English between January 2019 and March 2026 were considered. Studies were included if they reported data from diabetic wound models (*in vivo* or *in vitro* under high-glucose conditions), characterized the scaffold's bioactive content, and assessed at least one molecular or cellular outcome. Studies using non-diabetic wound models were included selectively when they provided mechanistic insights not available in the diabetic-specific literature. Given these criteria, the included studies reflect the current state of an actively growing field; publication bias cannot be excluded, as discussed in the Challenges section.

Immunomodulatory mechanisms of plant-derived scaffolds in diabetic wounds

The dysregulated immune response in diabetic wounds is a fundamental obstacle to healing, characterized by excessive, prolonged inflammation that impedes progression through the normal healing phases (37). Plant-derived scaffolds have demonstrated a remarkable capacity to modulate this aberrant immune response through multiple interconnected mechanisms, with macrophage polarization emerging as a central therapeutic target. Macrophages exist along a spectrum of activation states, with the classically activated M1 phenotype promoting inflammation and pathogen clearance. In contrast, the alternatively activated M2 phenotype supports tissue repair, angiogenesis, and

resolution of inflammation (38). In diabetic wounds, macrophages remain predominantly trapped in the M1 state, continuously secreting pro-inflammatory mediators that sustain tissue damage. Plant-derived scaffolds, particularly those containing specific bioactive polysaccharides and phenolic compounds, actively reprogram this macrophage phenotype, shifting the balance toward the regenerative M2 state and thereby fundamentally altering the wound microenvironment (39).

Kelp-derived scaffolds have emerged as particularly potent immunomodulators, with their effects largely attributed to the presence of fucoidan, a sulfated polysaccharide unique to brown algae. Research using kelp scaffolds prepared via deep eutectic solvent decellularization demonstrated significant effects on macrophage polarization in diabetic mouse models (32). The scaffolds induced substantial increases in M2 marker expression, particularly CD206 (mannose receptor), while simultaneously reducing M1 markers, including inducible nitric oxide synthase. This phenotypic shift was accompanied by profound changes in cytokine profiles, with a marked elevation of the anti-inflammatory cytokine interleukin-10 (IL-10) and a significant reduction in pro-inflammatory mediators, including TNF-α and IL-1β. It is important to note that while these cytokine and surface-marker changes are directly demonstrated in the scaffold-based diabetic wound model (36, 40), the specific intracellular mechanisms—particularly IKK phosphorylation, IκB stabilization, and NF-κB nuclear exclusion—are primarily inferred from the established phytochemical literature on isolated fucoidan and polyphenol preparations rather than from phosphorylation assays performed within the scaffold model itself. Future studies should directly verify these pathway interventions at the protein level using immunoblotting or proximity ligation assays in scaffold-treated wound tissue. The molecular mechanisms underlying these effects involve fucoidan binding to specific cell surface receptors on macrophages, triggering intracellular signaling cascades that alter gene transcription patterns. Fucoidan has been shown to inhibit the nuclear factor kappa B (NF-κB) pathway, a master regulator of inflammatory gene expression, while simultaneously activating pathways associated with tissue repair and regeneration. The preserved polyphenolic compounds in kelp scaffolds further contribute to immunomodulation by scavenging reactive oxygen species that would otherwise sustain M1 activation and inflammatory signaling.

The immunomodulatory effects of kelp scaffolds extend beyond simple M1-to-M2 conversion, encompassing broader effects on immune cell recruitment and function. Studies incorporating p-coumaric acid into kelp-liver extracellular matrix hybrid scaffolds revealed enhanced control over the inflammatory cascade in diabetic rat wounds (36). p-coumaric acid, a hydroxycinnamic acid derivative with established anti-inflammatory properties, acted synergistically with kelp-derived bioactives to suppress early inflammatory responses and promote timely resolution of inflammation. Immunohistochemical analysis of treated wounds showed reduced neutrophil infiltration during early healing phases and increased M2 macrophage presence during later regenerative phases, indicating a temporal optimization of the immune response. The molecular basis for p-coumaric acid's anti-inflammatory effects involves multiple mechanisms, including direct inhibition of cyclooxygenase enzymes responsible for prostaglandin synthesis, suppression of NF-κB activation, and modulation of mitogen-activated protein kinase signaling pathways. These effects collectively reduced the production of inflammatory mediators while preserving beneficial immune responses necessary for infection control and debris clearance.

Plant-derived scaffolds from terrestrial sources have also demonstrated significant immunomodulatory capabilities, though with somewhat different molecular profiles than those of marine sources. Pomelo peel scaffolds functionalized with copper-gallic acid metal-organic frameworks exhibited potent effects on macrophage polarization in infected diabetic wound models (35). The combination of inherent pomelo bioactives, including flavonoids and coumarins, with the controlled release of copper ions and gallic acid created a multifaceted immunomodulatory environment. Copper ions, released in response to the acidic pH typical of infected diabetic wounds, possess well-documented anti-inflammatory properties mediated through effects on immune cell signaling. Gallic acid, a trihydroxybenzoic acid abundant in many plant sources, exhibits strong anti-inflammatory activity through multiple mechanisms, including inhibition of pro-inflammatory transcription factors, suppression of inflammatory enzyme activity, and direct anti-oxidant effects that prevent oxidative activation of inflammatory pathways. The scaffold-treated wounds showed dramatic shifts in macrophage phenotype, with immunofluorescence revealing decreased expression of M1 marker iNOS and increased expression of M2 markers CD206 and arginase-1. Gene expression analysis confirmed these phenotypic changes, showing up-regulation of genes associated with tissue remodeling and down-regulation of pro-inflammatory gene signatures.

The molecular mechanisms underlying gallic acid's immunomodulatory effects have been increasingly elucidated through studies of plant-derived scaffolds. Gallic acid directly inhibits the activation of NF-κB by preventing the degradation of its inhibitor protein IκB, thereby blocking the nuclear translocation of NF-κB subunits and subsequent transcription of inflammatory genes. Additionally, gallic acid modulates the MAPK signaling pathways, particularly the p38 and JNK pathways that mediate inflammatory cytokine production in response to cellular stress and pathogen-associated molecular patterns. By interfering with these key signaling cascades, gallic acid-containing scaffolds fundamentally alter the transcriptional program of immune cells within the wound, shifting gene expression away from inflammation and toward tissue repair. The sustained release of gallic acid from scaffold matrices ensures prolonged immunomodulatory effects throughout the healing process, avoiding the rapid clearance that limits the efficacy of topically applied anti-inflammatory agents (41, 42).

Walnut leaf-derived scaffolds represent another terrestrial plant source with demonstrated immunomodulatory properties, attributed to their rich content of hydrolyzable tannins and polyphenolic compounds (43). While detailed molecular mechanism studies are still emerging for this specific source, histological analysis of diabetic wounds treated with walnut leaf scaffolds revealed reduced inflammatory cell infiltration and improved tissue organization compared to controls. The tannins present

in walnut leaves possess multiple anti-inflammatory mechanisms, including protein binding that may sequester pro-inflammatory mediators, direct free-radical scavenging that prevents oxidative activation of inflammatory pathways, and modulation of immune cell function through effects on cell-surface receptors and signaling molecules. The preserved carotenoid content in these scaffolds may also contribute to immunomodulation by modulating inflammatory gene expression and immune cell differentiation.

The immunomodulatory effects of plant-derived scaffolds are not limited to macrophages but also extend to other immune cell populations relevant to wound healing. Mushroom-derived scaffolds modified with graphene oxide and polydopamine demonstrated broad anti-inflammatory effects in infected diabetic wounds (44). Beyond promoting M2 macrophage polarization, these scaffolds reduced overall inflammatory cytokine levels in wound tissue, indicating effects on multiple immune cell types, including neutrophils, dendritic cells, and lymphocytes. The reduction in TNF-α and IL-6 levels was particularly significant, as these cytokines play central roles in perpetuating chronic inflammation in diabetic wounds. The molecular mechanisms likely involve multiple pathways, as the mushroom-derived polysaccharides, particularly β-glucans, are known to modulate immune function through binding to pattern recognition receptors on various immune cells. Graphene oxide and polydopamine components may contribute additional immunomodulatory effects through their anti-oxidant properties and ability to adsorb inflammatory mediators.

An important aspect of the immunomodulatory activity of plant-derived scaffolds is their ability to influence the resolution phase of inflammation, a critical process often impaired in diabetic wounds. Resolution of inflammation is not simply the passive cessation of inflammatory signals but rather an active process mediated by specialized pro-resolving lipid mediators, anti-inflammatory cytokines, and phenotypically switched immune cells (45). Plant bioactives, including omega-3 fatty acids present in some plant sources, specialized polyphenols, and specific polysaccharides, can promote this resolution process by enhancing macrophage phagocytosis of apoptotic cells, stimulating the production of pro-resolving mediators, and preventing the chronic persistence of inflammatory stimuli. The temporal dynamics of cytokine expression in scaffold-treated wounds, showing early suppression of pro-inflammatory signals followed by elevation of anti-inflammatory and pro-regenerative mediators, suggest that these materials actively promote inflammatory resolution rather than simply suppressing inflammation (46).

The structural properties of plant-derived scaffolds also contribute to their immunomodulatory effects beyond the actions of soluble bioactive compounds. The three-dimensional architecture of decellularized plant matrices influences immune cell behavior through physical and mechanical cues that affect cell adhesion, migration, and activation state. The porous structure of plant scaffolds allows infiltration by immune cells, while their mechanical properties influence mechanotransduction pathways that regulate immune cell function. Studies have shown that substrate stiffness, pore size, and surface topography can all influence macrophage polarization, with certain physical parameters favoring M2 over M1 activation (47). Plant-derived scaffolds, with their inherently compliant mechanical properties and hierarchical porous structure, may provide physical cues that synergize with the effects of bioactive compounds to promote anti-inflammatory immune responses. The cellulose-based structure of plant cell walls may also interact with immune cell receptors in ways that influence activation state, though this area requires further investigation (13).

The integration of additional immunomodulatory agents with plant-derived scaffolds has demonstrated synergistic effects on immune modulation in diabetic wounds. The combination of intrinsic plant bioactives with incorporated molecules such as p-coumaric acid, copper ions, or other anti-inflammatory compounds creates multifaceted therapeutic platforms with enhanced and sustained immunomodulatory activity. These combination approaches allow simultaneous targeting of multiple inflammatory pathways, potentially overcoming compensatory mechanisms that might limit the efficacy of single-agent approaches (48, 49). The sustained-release kinetics of plant matrices ensure prolonged therapeutic effects, maintaining anti-inflammatory conditions throughout the extended healing timeline typical of diabetic wounds.

Understanding the precise molecular mechanisms through which different plant-derived bioactives modulate immune responses remains an active area of investigation. While the inhibition of NF-κB and MAPK pathways is a common mechanism in many plant compounds, additional pathways, including JAK-STAT signaling, PI3K-Akt pathways, and Nrf2-mediated anti-oxidant responses, may also contribute to immunomodulatory effects (50). The complexity of plant extracts, containing multiple bioactive compounds with potentially synergistic or complementary mechanisms, presents both opportunities and challenges for mechanistic understanding. Systems biology approaches, including transcriptomics, proteomics, and metabolomics, are increasingly being used to comprehensively characterize the molecular changes induced by plant-derived scaffolds in immune cells and wound tissue, providing insights to guide the optimization of therapeutic formulations (51, 52).

The immunomodulatory mechanisms of plant-derived scaffolds in diabetic wound healing represent a promising therapeutic approach that addresses a fundamental pathophysiological defect in these chronic wounds. By reprogramming the immune response away from destructive chronic inflammation and toward constructive tissue regeneration, these scaffolds create a permissive environment for the other cellular processes essential to healing, including angiogenesis, fibroblast proliferation, and epithelialization. The diversity of bioactive compounds from different plant sources provides opportunities to tailor immunomodulatory profiles to specific wound characteristics, while combining multiple mechanisms within single scaffold platforms offers the potential for superior efficacy compared to conventional anti-inflammatory approaches (53).

Anti-oxidant mechanisms and oxidative stress reduction

Oxidative stress represents a critical pathophysiological mechanism in diabetic wound healing, fundamentally disrupting cellular function and perpetuating the chronic non-healing state. The hyperglycemic environment characteristic of diabetes generates excessive reactive oxygen

species through multiple pathways, including enhanced glucose auto-oxidation, increased polyol pathway flux, elevated formation of advanced glycation end-products, and mitochondrial dysfunction (54). These processes overwhelm the endogenous anti-oxidant defense systems in diabetic tissues, resulting in accumulation of superoxide radicals, hydrogen peroxide, hydroxyl radicals, and other reactive species that damage cellular macromolecules, including lipids, proteins, and nucleic acids. The oxidative damage extends to growth factors, extracellular matrix components, and cell signaling molecules, profoundly impairing the cellular and molecular processes essential for wound healing. Plant-derived scaffolds, rich in natural anti-oxidant compounds evolved for plant defense against environmental stressors, offer potent mechanisms to counteract this oxidative burden and restore redox balance in diabetic wounds (55).

The anti-oxidant capacity of kelp-derived scaffolds has been extensively characterized, revealing multiple mechanisms through which these marine plant materials reduce oxidative stress in diabetic wounds. Kelp scaffolds prepared using deep eutectic solvents and functionalized with p-coumaric acid demonstrated exceptional free-radical scavenging activity, as measured by standard anti-oxidant assays, including DPPH and ABTS radical-scavenging tests (32, 36). The primary anti-oxidant compounds in kelp include polyphenols, particularly phlorotannins, which are unique to brown algae, and flavonoids, including quercetin derivatives and catechins. These compounds possess multiple hydroxyl groups that can donate hydrogen atoms to neutralize free radicals, thereby interrupting radical chain reactions that propagate oxidative damage. The phenolic hydroxyl groups are particularly effective at scavenging lipid peroxyl radicals, preventing the oxidative degradation of cell membrane lipids that compromises cellular integrity. *In vitro* studies using diabetic wound models showed that kelp scaffold extracts significantly reduced malondialdehyde levels, a marker of lipid peroxidation, indicating effective protection against oxidative membrane damage.

The molecular mechanisms underlying the anti-oxidant effects of kelp-derived compounds extend beyond direct radical scavenging to include modulation of cellular anti-oxidant enzyme systems. Studies of kelp scaffolds in diabetic wound models revealed up-regulation of superoxide dismutase (SOD). This enzyme catalyzes the conversion of superoxide radicals to hydrogen peroxide, representing the first line of enzymatic defense against oxidative stress (32). The polyphenolic compounds in kelp activate the nuclear factor erythroid 2-related factor 2 (Nrf2) transcription factor, a master regulator of anti-oxidant gene expression. Upon activation, Nrf2 translocates to the nucleus and binds to anti-oxidant response elements in the promoter regions of genes encoding anti-oxidant enzymes, including SOD, catalase, glutathione peroxidase, and heme oxygenase-1. This coordinated up-regulation of anti-oxidant enzymes provides sustained protection against oxidative stress, complementing the direct radical scavenging effects of the polyphenolic compounds. The dual mechanism of immediate radical neutralization coupled with enhanced endogenous anti-oxidant capacity creates a robust defense system that effectively reduces oxidative damage in the harsh environment of diabetic wounds.

Fucoidan, the sulfated polysaccharide abundant in kelp, contributes additional anti-oxidant mechanisms beyond those of phenolic compounds. Research has demonstrated that fucoidan exhibits metal-chelating activity, binding transition-metal ions such as iron and copper that catalyze the generation of highly reactive hydroxyl radicals via Fenton chemistry (56). By sequestering these catalytic metals, fucoidan prevents the amplification of oxidative stress that occurs when metals facilitate the conversion of relatively stable hydrogen peroxide into extremely damaging hydroxyl radicals. Furthermore, fucoidan has been shown to enhance cellular glutathione levels, the primary intracellular anti-oxidant that donates electrons to reduce reactive species and peroxides. The mechanism appears to involve up-regulation of enzymes in the glutathione synthesis pathway, increasing the cellular capacity for anti-oxidant defense (57). The combination of metal chelation, glutathione enhancement, and the direct radical scavenging effects of co-present phenolic compounds creates a comprehensive anti-oxidant profile that addresses multiple sources and types of oxidative stress in diabetic wounds (58).

Terrestrial plant-derived scaffolds offer distinct anti-oxidant profiles compared to marine sources, with specific components that contribute to unique mechanisms of oxidative stress reduction. Walnut leaf scaffolds contain exceptionally high levels of hydrolyzable tannins, including ellagitannins and gallotannins, which exhibit potent anti-oxidant activity through multiple mechanisms (43). These tannins possess numerous phenolic hydroxyl groups that confer strong radical-scavenging capacity, with studies showing their anti-oxidant activity surpasses that of many conventional anti-oxidants in certain assay systems. The tannins also exhibit protein-binding properties that may protect proteins from oxidative modification, preserving the function of enzymes, growth factors, and structural proteins in the wound environment. Carotenoids present in walnut leaves, including beta-carotene and lutein, provide additional anti-oxidant mechanisms through their ability to quench singlet oxygen, a particularly reactive form of oxygen generated under conditions of oxidative stress. The polyunsaturated structure of carotenoids allows them to absorb excess energy from singlet oxygen, converting it to the less reactive triplet state and thereby preventing oxidative damage to cellular components.

Pomelo peel scaffolds functionalized with gallic acid metal-organic frameworks demonstrated exceptional anti-oxidant capacity attributed to the combined effects of inherent citrus bioactives and the controlled release of gallic acid (35). Gallic acid ranks among the most potent natural anti-oxidants, with particularly strong activity in scavenging hydroxyl radicals, the most reactive and damaging of the reactive oxygen species. The trihydroxy substitution pattern on the benzoic acid structure provides optimal geometry for hydrogen donation and radical stabilization. Beyond direct radical scavenging, gallic acid exhibits anti-inflammatory effects that indirectly reduce oxidative stress by suppressing inflammatory enzymes, including cyclooxygenases and lipoxygenases, which generate reactive species as byproducts of their catalytic activity. The flavonoids present in pomelo peel, including naringin and hesperidin, contribute additional anti-oxidant mechanisms through their ability to scavenge multiple types of radicals and to chelate pro-oxidant metal ions. The synergistic interaction between gallic acid and citrus flavonoids creates an anti-oxidant

system with broad-spectrum activity against various reactive species.

The controlled-release characteristics of anti-oxidant compounds from plant-derived scaffold matrices represent a critical advantage in managing oxidative stress in diabetic wounds. Unlike bolus administration of anti-oxidants, which results in transient elevation followed by rapid clearance, the sustained release from scaffold matrices maintains therapeutic anti-oxidant levels throughout the extended healing period. Studies of kelp and pomelo peel scaffolds demonstrated release kinetics with an initial burst during the first hours, corresponding to superficially associated compounds, followed by sustained release over days to weeks as deeper matrix-embedded compounds gradually diffuse out (35, 36). This release profile aligns well with the temporal dynamics of oxidative stress in diabetic wounds, providing high anti-oxidant activity during the acute inflammatory phase, when the oxidative burst from neutrophils and macrophages is most intense, while maintaining protective levels during subsequent healing phases. The matrix association also protects anti-oxidant compounds from premature degradation, preserving their activity until release into the wound environment.

Spinach-derived scaffolds functionalized with ascorbic acid-2-phosphate (AA2P) exemplify a strategy for enhancing natural plant anti-oxidants by incorporating additional vitamin-based anti-oxidant systems (59). Ascorbic acid serves as a crucial cofactor for enzymes involved in collagen synthesis and provides potent anti-oxidant activity by donating electrons to neutralize reactive species. The phosphorylated derivative AA2P offers superior stability compared to ascorbic acid, resisting oxidative degradation until dephosphorylation by cellular phosphatases releases the active ascorbic acid. This pro-drug approach ensures delivery of functional anti-oxidant vitamins rather than oxidized, inactive forms. The spinach scaffold matrix itself contributes phenolic anti-oxidants, and the preserved cellulosic structure may provide some physical protection against oxidative damage. Studies demonstrated that AA2P-loaded spinach scaffolds significantly enhanced fibroblast metabolic activity and collagen synthesis over extended culture periods, effects attributed in part to reduced oxidative stress, which otherwise impairs these cellular functions under high-glucose conditions.

The relationship between anti-oxidant activity and other beneficial effects of plant-derived scaffolds reveals important mechanistic connections. Oxidative stress directly impairs angiogenesis by oxidatively modifying VEGF and its receptors, reducing their expression and function. By reducing oxidative damage, plant-derived anti-oxidants preserve VEGF bioactivity and enhance angiogenic signaling (60). Similarly, oxidative stress impairs fibroblast function and collagen synthesis through multiple mechanisms, including oxidative damage to fibroblast growth factor receptors, direct inhibition of collagen-synthesizing enzymes, and oxidative modification of newly synthesized collagen that impairs its proper assembly into functional fibrils. The anti-oxidant protection provided by plant scaffolds thus indirectly enhances these critical healing processes by creating a redox environment permissive for their function (61). The interplay between anti-oxidant effects and immunomodulation is particularly important, as reactive oxygen species act as signaling molecules that activate inflammatory pathways, including the NF-κB pathway. By scavenging these reactive species, plant-derived anti-oxidants interrupt inflammatory signaling cascades, complementing their direct anti-inflammatory mechanisms (62).

The diversity of anti-oxidant compounds present in plant-derived scaffolds, each with distinct chemical structures and mechanisms, provides comprehensive protection against the various types of oxidative damage that occur in diabetic wounds. Phenolic compounds primarily scavenge lipid radicals and protect membranes; carotenoids specialize in singlet oxygen quenching; ascorbic acid functions in aqueous environments and regenerates other anti-oxidants; while polysaccharides like fucoidan chelate pro-oxidant metals and enhance endogenous anti-oxidant systems (63). This multi-mechanistic approach addresses the complexity of oxidative stress in diabetic wounds more effectively than single-compound anti-oxidant therapies. Furthermore, the natural co-occurrence of these compounds in plant tissues suggests evolutionary optimization of their synergistic interactions, with certain combinations exhibiting enhanced total anti-oxidant capacity relative to the sum of their individual activities (64).

Recent investigations employing advanced analytical techniques have begun to elucidate the molecular mechanisms by which plant-derived anti-oxidants interact with specific reactive species and cellular targets in diabetic wound environments. Studies using electron paramagnetic resonance spectroscopy have directly demonstrated radical scavenging by plant scaffold extracts in wound tissue homogenates. Proteomic analyses have revealed that plant scaffold treatment reduces oxidative modifications of specific proteins critical for wound healing, including matrix metalloproteinases, growth factors, and cell adhesion molecules (65). These molecular-level insights confirm that the anti-oxidant effects of plant scaffolds translate to preservation of functionally important biomolecules in the wound. Gene expression profiling has shown up-regulation of Nrf2 target genes in scaffold-treated wounds, confirming activation of endogenous anti-oxidant defense pathways (66).

The anti-oxidant mechanisms of plant-derived scaffolds represent a crucial component of their therapeutic activity in diabetic wounds, addressing a fundamental pathophysiological defect that conventional wound treatments often neglect. By simultaneously providing exogenous anti-oxidant compounds and enhancing endogenous anti-oxidant capacity, these scaffolds create a redox environment conducive to the cellular and molecular processes required for healing (67). The sustained delivery of anti-oxidants from scaffold matrices ensures prolonged protection throughout the healing timeline. In contrast, the diversity of anti-oxidant mechanisms provides comprehensive defense against the multiple forms of oxidative stress present in diabetic wounds. Integration of anti-oxidant activity with the immunomodulatory and pro-angiogenic effects of these scaffolds creates multifunctional therapeutic platforms that address the complex, interconnected pathophysiology of diabetic wound healing (13)(Figure 1).

Pro-angiogenic effects and vascular regeneration

Impaired angiogenesis represents one of the most

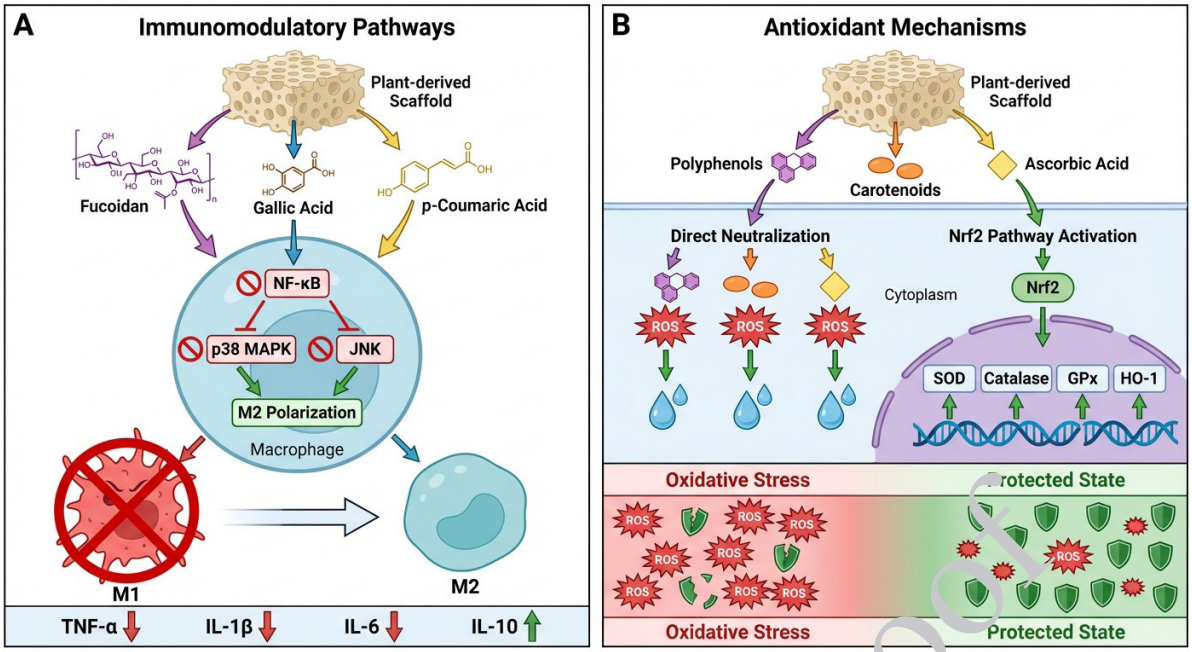

Figure 1. Molecular mechanisms of immunomodulation and oxidative stress reduction by plant-d ved scaffolds
(A) Immunomodulatory Pathways: Plant scaffold-released bioactive compounds, including fucoidan, galli acid, nd p-c maric acid, modulate inflammatory signaling in macrophages by inhibiting the NF-κB, p38 MAPK, and JNK pathways. These molecular interventions promote macrophage phenotypic switching from the pro-inflammatory M1 phenotype (characterized by irregular morphology and high inflammatory cytokine production) to the anti-inflammatory M2 phenotype (characterized by rounded morphology and tissue-reparative functions). The polarization shift results in decreased secretion of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) and increased production of anti-inflammatory IL-10, creating a permissive microenvironment for wound healing. (B) Antioxidant Mechanisms: Plant-derived antioxidant compounds including polyphenols, carotenoids, and ascorbic acid reduce oxidative stress through dual mechanisms: (Left pathway) Direct scavenging of reactive oxygen species (ROS), neutralizing free radicals and preventing oxidative damage to cellular components; (Right pathway) Activation of the Nrf2 transcription factor pathway, leading to nuclear translocation of Nrf2 and subsequent up-regulation of endogenous antioxidant enzymes including superoxide dismutase (SOD), catalase (Cat), glutathione peroxidase (GPx), and heme oxygenase-1 (HO-1). The combined effects create a protected cellular state with reduced oxidative burden, supporting cellular functions essential for tissue regeneration. Red arrows/symbols indicate inhibition or down-regulation; green arrows indicate activation or up-regulation
NF-κB, nuclear factor kappa B; MAPK, mitogen-activated protein kinase; JNK, c-Jun N-terminal kinase; M1, classically activated macrophage phenotype; M2, alternatively activated macrophage phenotype; TNF-α, tumor necrosis factor-alpha; IL, interleukin; ROS, reactive oxygen species; Nrf2, nuclear factor erythroid 2-related factor 2; SOD, superoxide dismutase; Cat, catalase; GPx, glutathione peroxidase; HO-1, heme oxygenase-1

critical pathophysiological defects in diabetic wound healing, fundamentally limiting tissue regeneration through inadequate delivery of oxygen, nutrients, and cellular building blocks to the healing tissue. Despite the hypoxic conditions that normally trigger robust angiogenic responses, diabetic wounds exhibit paradoxically reduced new blood vessel formation due to multiple molecular abnormalities, including decreased expression and bioavailability of vascular endothelial growth factor, impaired function of endothelial progenitor cells, reduced responsiveness of endothelial cells to angiogenic stimuli, and hostile microenvironment conditions, including oxidative stress and inflammation that actively inhibit vascular growth (68). The resulting vascular insufficiency creates a vicious cycle in which tissue hypoxia generates additional oxidative stress and inflammation, which in turn impair angiogenesis. Plant-derived scaffolds have demonstrated a remarkable capacity to restore angiogenic function in diabetic wounds through multiple mechanisms, including direct stimulation of endothelial cell function, up-regulation of angiogenic growth factors, provision of structural guidance for vessel formation, and creation of a permissive microenvironment through their anti-oxidant and anti-inflammatory effects (69).

The structural features of certain plant-derived scaffolds provide inherent advantages in promoting angiogenesis by preserving natural vascular architecture. Spinach leaf scaffolds retain the complex three-dimensional vascular network originally present in the plant tissue, consisting of interconnected channels that served to transport nutrients and water in the living plant (33, 34). This preserved vascular architecture, visualized through microscopy techniques showing patent tubular structures extending throughout the scaffold, provides physical templates that guide the formation of new blood vessels in the healing tissue. Studies using spinach scaffolds demonstrated that endothelial cells seeded onto these scaffolds preferentially migrated along the preserved vascular channels, using them as guidance structures for organizing into vessel-like formations. The dimensions of these plant vascular channels, ranging from micrometers to hundreds of micrometers, appropriately match the size range of capillaries and small vessels required for effective tissue perfusion. The hierarchical organization of plant vasculature, with progressively branching vessels connecting larger “veins” to smaller “capillaries,” mirrors the organization required in healing tissue and may facilitate the formation of functionally connected vascular networks.

Beyond structural guidance, plant-derived scaffolds actively stimulate angiogenesis through bioactive compounds that influence endothelial cell behavior and angiogenic signaling pathways. Kelp-derived scaffolds demonstrated potent pro-angiogenic effects attributed primarily to fucoidan, which has been extensively studied for its ability to promote blood vessel formation (32). Fucoidan stimulates endothelial cell proliferation and migration, the fundamental cellular processes underlying angiogenesis,

through mechanisms involving binding to growth factor receptors and activation of intracellular signaling cascades including the phosphatidylinositol 3-kinase (PI3K)-Akt and extracellular signal-regulated kinase (ERK) pathways. These pathways regulate endothelial cell survival, proliferation, and migration, and their activation by fucoidan provides a direct pro-angiogenic stimulus. Furthermore, fucoidan enhances the expression and secretion of vascular endothelial growth factor from various cell types present in wounds, including fibroblasts, keratinocytes, and immune cells. This paracrine VEGF production supplements any direct effects on endothelial cells, amplifying the angiogenic response. Studies of kelp scaffold-treated diabetic wounds confirmed significant increases in VEGF protein levels and VEGF gene expression compared to control wounds.

The synergistic interaction between the angiogenic effects of bioactive compounds and the permissive effects of oxidative stress reduction creates particularly favorable conditions for vascular regeneration. Oxidative stress directly impairs endothelial cell function through multiple mechanisms, including oxidative modification of VEGF, which reduces its receptor-binding affinity; oxidative damage to endothelial cell membranes, which impairs migration; and activation of apoptotic pathways, which reduce endothelial cell survival. The anti-oxidant compounds present in plant scaffolds protect endothelial cells from these oxidative insults, preserving their capacity to respond to angiogenic signals. Kelp scaffolds demonstrated this protective effect, with *in vitro* studies showing that scaffold extracts preserved endothelial cell viability and function under high-glucose conditions that typically induce oxidative stress and endothelial dysfunction (32). The reduction in reactive oxygen species in scaffold-treated wounds, measured *in vivo*, correlated with increased vascular density, supporting a mechanistic link between anti-oxidant activity and enhanced angiogenesis.

Functionalization of plant scaffolds with specific pro-angiogenic molecules has yielded enhanced vascular regeneration beyond that achieved with native plant bioactives alone. Spinach scaffolds loaded with 2-deoxy-D-ribose (2dDR), a sugar molecule with documented pro-angiogenic properties, demonstrated superior angiogenic effects compared to unmodified scaffolds (34). The 2dDR released from the scaffold stimulates endothelial cells through mechanisms that remain under investigation but appear to involve enhanced cellular metabolism and up-regulation of angiogenic gene expression. *In vitro* tube formation assays, which model the cellular organization processes of angiogenesis, showed that human umbilical vein endothelial cells exposed to 2dDR-loaded spinach scaffolds formed significantly more complex tubular networks compared to cells on control scaffolds. The sustained release of 2dDR from the spinach matrix over 48 hours provided prolonged angiogenic stimulus, avoiding the rapid clearance that limits the efficacy of bolus 2dDR administration. Ex vivo chorioallantoic membrane assays and *in vivo* wound models confirmed the translation of these *in vitro* effects to enhanced neovascularization in tissue environments.

The temporal dynamics of VEGF expression and release from plant-derived scaffolds correlate with the time course of angiogenic requirements during wound healing. Studies of kelp and pomelo peel scaffolds showed that VEGF up-regulation occurred predominantly during the first week after scaffold application, corresponding to the proliferative phase of healing when angiogenesis is most critical (32, 35). Immunohistochemical staining for CD31, an endothelial cell marker used to identify blood vessels, revealed progressive increases in vascular density in scaffold-treated wounds, with maximum effects observed during the second week of healing. This timing suggests that plant scaffold-induced angiogenesis provides functional blood vessels during the period when the metabolic demands of proliferating cells are highest. The enhanced tissue perfusion resulting from this neovascularization supports the increased cellular activity required for tissue regeneration, creating a positive feedback loop where improved vascular supply enables better tissue healing.

The mechanisms through which plant-derived bioactives enhance VEGF expression involve transcriptional regulation through multiple signaling pathways. Hypoxia-inducible factor 1 (HIF-1α), the primary transcription factor regulating VEGF expression under hypoxic conditions, appears to be stabilized by certain plant compounds even under normoxic conditions, thereby enhancing VEGF transcription (70). Additionally, plant polyphenols and polysaccharides activate signaling pathways, including the PI3K-Akt and MAPK cascades, that converge on transcription factors regulating VEGF gene expression. Studies examining VEGF mRNA levels in scaffold-treated wounds confirmed transcriptional up-regulation rather than merely post-translational stabilization of VEGF protein. The sustained elevation of VEGF mRNA over multiple days indicates ongoing transcriptional activation rather than transient signaling, consistent with the sustained release of bioactive compounds from scaffold matrices (71).

Pomelo peel scaffolds demonstrated that angiogenic effects can be significantly enhanced by optimizing the wound microenvironment to address multiple barriers to vessel formation (35). The combination of inherent pro-angiogenic flavonoids with the anti-inflammatory and antimicrobial effects of copper-gallic acid metal-organic frameworks created conditions particularly conducive to angiogenesis. Infection and inflammation actively suppress angiogenesis through multiple mechanisms, including the sequestration of angiogenic growth factors by inflammatory proteases, the production of anti-angiogenic factors by inflammatory cells, and the direct toxic effects on endothelial cells. By controlling infection through antimicrobial copper ion release and modulating inflammation through gallic acid and intrinsic anti-inflammatory compounds, the scaffolds removed these barriers to angiogenesis. Histological analysis showed that vascular density in pomelo scaffold-treated infected diabetic wounds approached that of non-infected wounds, suggesting restoration of near-normal angiogenic capacity despite the challenging infected environment.

The molecular signaling pathways activated by plant-derived scaffolds to promote angiogenesis extend beyond VEGF-mediated mechanisms to include other important angiogenic factors. Transforming growth factor-beta (TGF-β), which regulates endothelial cell differentiation and vessel maturation, showed elevated expression in kelp scaffold-treated wounds (32). TGF-β is essential for the later stages of angiogenesis, in which newly formed vessels stabilize and mature through the recruitment of pericytes and smooth muscle cells, ensuring that the new vasculature persists and functions properly. The coordinated up-

regulation of both VEGF and TGF-β suggests that plant scaffolds promote complete angiogenic programs encompassing initial vessel sprouting, proliferation, and maturation. Basic fibroblast growth factor (bFGF), another important angiogenic mediator, may also be up-regulated by certain plant bioactives, though this requires further investigation in scaffold-specific contexts.

The direct effects of plant-derived compounds on endothelial cell behavior have been characterized through *in vitro* studies examining specific cellular processes underlying angiogenesis. Migration assays demonstrated that fucoidan and other plant polysaccharides significantly enhance endothelial cell migration toward chemoattractant gradients, a process essential for vessel sprouting and extension (32). The enhanced migration appears to involve modulation of focal adhesion dynamics and cytoskeletal reorganization, cellular processes that control cell movement. Proliferation assays showed that plant scaffold extracts increase endothelial cell proliferation rates, providing the additional cells needed to form new vessel structures. Importantly, these proliferative effects occurred without inducing abnormal cellular transformation, as evidenced by normal cell morphology and contact inhibition patterns. Tube formation assays, which assess the ability of endothelial cells to organize into three-dimensional capillary-like structures, demonstrated that plant bioactives promote this complex organizational behavior that represents the culmination of the angiogenic process.

The preservation of bioactive compound gradients within plant scaffold matrices may create microenvironmental cues that guide organized angiogenesis rather than chaotic vessel growth. The non-uniform distribution of bioactives within the hierarchical plant structure could establish concentration gradients that direct endothelial cell migration in organized patterns, similar to the chemotactic gradients that guide physiological angiogenesis. This concept requires further investigation, but could explain the organized, functional vascular networks observed in scaffold-treated wounds rather than disorganized vessel proliferation. The mechanical properties of plant scaffolds may also influence angiogenesis, as endothelial cells respond to substrate stiffness and structure via mechanotransduction pathways that modulate their angiogenic behavior (72).

Integration of pro-angiogenic mechanisms with the immunomodulatory effects of plant scaffolds creates particularly favorable conditions for vascular regeneration. M2 macrophages, which are promoted by plant scaffold immunomodulatory activity, secrete pro-angiogenic factors including VEGF, bFGF, and platelet-derived growth factor, amplifying the direct angiogenic effects of plant bioactives. The anti-inflammatory microenvironment created by scaffold-induced M2 polarization removes the active suppression of angiogenesis that occurs in inflammatory conditions. This integration of multiple mechanisms—direct stimulation of endothelial cells, up-regulation of growth factors, structural guidance, anti-oxidant protection, and immunomodulatory optimization of the microenvironment—produces comprehensive pro-angiogenic effects that address the multifactorial angiogenic impairment in diabetic wounds (73).

The clinical significance of enhanced angiogenesis in diabetic wound healing extends beyond simply increasing blood vessel numbers to encompass improvements in tissue oxygenation, metabolic support, and cellular function, collectively accelerating healing. Studies correlating vascular density with wound closure rates in plant scaffold-treated diabetic wounds showed strong positive associations, confirming the functional importance of the angiogenic effects (32, 35). Improved tissue perfusion enables sustained fibroblast proliferation and collagen synthesis, supports keratinocyte migration and epithelialization, and facilitates immune cell function, including bacterial clearance and debris removal. The restoration of more normal vascular architecture in scaffold-treated wounds, with organized networks rather than chaotic vessel patterns, suggests the formation of functionally competent vasculature that will persist and support the healed tissue long term (Figure 2).

Wound healing outcomes in diabetic models

The translation of molecular mechanisms into measurable therapeutic outcomes is the ultimate test of any wound-healing intervention, and plant-derived scaffolds have demonstrated impressive efficacy across multiple diabetic wound models. These outcomes include accelerated wound closure kinetics, enhanced tissue quality parameters, including collagen organization and epithelialization, reduced scar formation, and restoration of more normal tissue architecture compared with control treatments. The consistency of positive outcomes across diverse plant sources, scaffold preparation methods, and animal models strengthens the evidence for clinical potential. It reveals important patterns in which scaffold characteristics correlate with superior healing outcomes.

Kelp-derived scaffolds have consistently demonstrated exceptional wound-healing outcomes in diabetic models, with closure rates that significantly exceed those of control wounds. Studies using kelp scaffolds prepared via deep eutectic solvent decellularization reported wound closure approaching 94% by day 14 in diabetic C57BL/6 mice, compared with approximately 70% in untreated controls. In comparison, commercial collagen dressings achieved intermediate closure (~82%) in the same model (32). The accelerated closure kinetics were evident at early time points, with scaffold-treated wounds showing significantly greater closure by day 7, indicating that the therapeutic effects manifested rapidly rather than requiring extended treatment. Macroscopic examination revealed that scaffold-treated wounds progressed through the healing phases more rapidly, with an earlier transition from the inflammatory to the proliferative phase and an earlier onset of remodeling. The wound beds in treated animals appeared healthier, with robust granulation tissue formation, reduced exudate, and earlier re-epithelialization, compared with controls that remained in inflamed, non-granulating states for extended periods.

The enhanced wound closure associated with kelp scaffolds was strongly correlated with the immunomodulatory and angiogenic effects observed in molecular and cellular analyses. Histological examination of wounds at sequential time points revealed that accelerated healing in scaffold-treated groups was accompanied by earlier M2 macrophage polarization, reduced neutrophil infiltration duration, enhanced neovascularization, and increased fibroblast proliferation (32, 36). These cellular and structural changes represent the tissue-level manifestations of the molecular mechanisms activated by scaffold bioactives. The timing

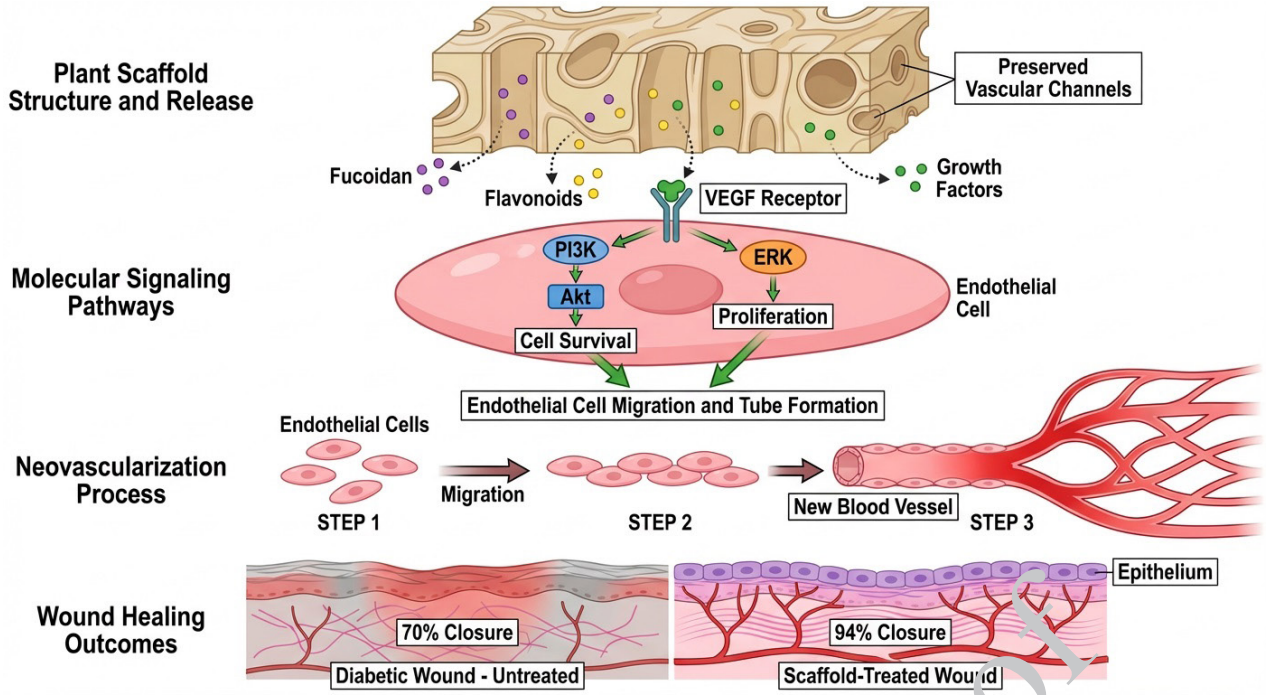

Figure 2. Pro-angiogenic effects and wound healing outcomes of plant-derived scaffolds
(Top) Scaffold Structure and Bioactive Release: Plant-derived scaffolds retain their native vascular channel architecture, providing structural guidance for neovascularization while enabling the sustained release of pro-angiogenic bioactive compounds, such as fucoidan, flavonoids, and growth factors from the porous scaffold matrix. (Middle) Molecular Signaling Pathways: Released bioactive molecules interact with endothelial cell surface receptors and trigger intracellular signaling pathways that regulate angiogenic responses. Activation of survival- and proliferation-associated signaling cascades enhances endothelial cell viability, metabolic activity, and proliferative capacity. These coordinated molecular events promote endothelial cell migration, alignment, and assembly into nascent vascular structures. (Lower) Neovascularization Process: Angiogenesis is illustrated as a sequential process in which endothelial cells initially respond to chemotactic stimuli (Step 1), subsequently migrate and align along scaffold-guided vascular channels (Step 2), and ultimately form mature tubular blood vessels with distinct luminal structures that establish functional vascular networks (Step 3). (Bottom) Wound Healing Outcomes—Comparative Analysis: Untreated diabetic wounds are characterized by sparse and disorganized vascularization, irregular collagen deposition, limited epithelial coverage, and incomplete wound closure by day 14. In contrast, wounds treated with plant-derived scaffolds demonstrate dense and well-organized vascular networks, physiologically aligned collagen fibers resembling native dermal architecture, complete re-epithelialization, and markedly improved wound closure. Enhanced angiogenesis contributes to improved tissue perfusion, thereby supporting cellular proliferation, extracellular matrix deposition, and coordinated tissue regeneration
VEGF, vascular endothelial growth factor; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; ERK, extracellular signal-regulated kinase

relationships, with immunomodulation evident by day 3–5, angiogenesis prominent by day 7-10, and peak tissue regeneration occurring around day 10-14, suggest a logical mechanistic cascade in which early anti-inflammatory effects create conditions that permit angiogenesis, which in turn enables robust tissue proliferation and regeneration.

Collagen deposition and organization are critical determinants of wound-healing quality distinguishing functional tissue repair from scar formation. Kelp scaffold-treated diabetic wounds demonstrated enhanced collagen deposition, as quantified by Masson's trichrome staining and biochemical collagen assays (32). Beyond mere quantity, the organizational pattern of collagen differed between treated and control wounds, with scaffold-treated tissues showing more organized, basket-weave collagen architecture resembling normal dermis rather than the parallel, scar-like collagen bundles typical of diabetic wound healing. This improved organization likely reflects the combined effects of controlled inflammation, which prevents excessive matrix degradation; enhanced fibroblast function, which supports proper collagen synthesis; and an appropriate mechanical environment provided by the scaffold matrix. Scar formation was notably reduced in scaffold-treated wounds, with quantitative scar assessment showing smaller scar areas and better cosmetic appearance compared to controls. The mechanisms underlying reduced scarring likely involve anti-inflammatory effects that prevent excessive fibrosis-promoting cytokine production and enhanced angiogenesis that improves tissue perfusion, supporting organized rather than chaotic repair (74).

Pomelo peel scaffolds demonstrated particularly impressive outcomes in the challenging context of infected diabetic wounds, where bacterial contamination further complicates already impaired healing (35). Treatment with pomelo peel scaffolds functionalized with copper-gallic acid metal-organic frameworks achieved wound closure rates comparable to those of kelp scaffolds in non-infected diabetic wounds, despite significant bacterial loads on initial wound assessments. The bacterial counts in scaffold-treated wounds decreased dramatically within the first 3–5 days, with quantitative microbiology showing a reduction of more than 99% in viable bacteria compared to baseline. This antimicrobial efficacy translated directly into improved healing outcomes, as the removal of bacterial burden eliminated the ongoing inflammatory stimulus and tissue damage caused by bacteria. Histological analysis revealed that by day 14, scaffold-treated infected wounds had tissue architecture closely resembling that of non-infected wounds, with well-organized granulation tissue, abundant neovascularization, and progressive re-epithelialization. This restoration of near-normal healing despite infection represents a significant therapeutic achievement, as infected diabetic wounds typically show severely delayed or absent healing.

The quality of healing in pomelo scaffold-treated wounds extended beyond simple closure to encompass restoration

of tissue function and structure. Immunohistochemical analysis of tissue regeneration markers showed that scaffold-treated wounds exhibited higher expression of markers associated with mature, functional tissue, including specific cytokeratins in the epithelium and appropriate collagen subtypes in the dermis (35). The vascular networks in healed tissue appeared morphologically normal with appropriate vessel caliber, organization, and distribution rather than the dilated, tortuous vessels often seen in pathological healing. Assessment of inflammatory markers in healed tissue showed resolution to near-baseline levels in scaffold-treated wounds. In contrast, control wounds maintained elevated inflammatory markers even after apparent closure, suggesting that scaffold treatment promoted true resolution rather than merely superficial coverage of persistent pathology.

Spinach-derived scaffolds, particularly those functionalized with pro-angiogenic or pro-collagen-synthesis agents, demonstrated distinct outcome patterns that reflect their specific mechanisms of action. Scaffolds loaded with 2-deoxy-D-ribose showed particularly pronounced effects on vascular density, with quantitative analysis revealing 2–3 fold increases in vessel numbers compared to control wounds (34). This robust angiogenesis translated into improved tissue oxygenation, as measured by oxygen electrodes, confirming functional blood flow through the newly formed vessels rather than merely anatomical vessel presence. The enhanced perfusion supported vigorous fibroblast activity, with immunostaining showing dense populations of proliferating fibroblasts in scaffold-treated wounds during the proliferative phase. Collagen synthesis rates, assessed through incorporation of radiolabeled proline or through gene expression of collagen subunits, were significantly elevated in 2dDR-loaded spinach scaffold-treated wounds compared to control.

Spinach scaffolds functionalized with ascorbic acid-2-phosphate demonstrated particularly strong effects on collagen quality and epithelial regeneration (59). The ascorbic acid released from these scaffolds serves as an essential cofactor for prolyl and lysyl hydroxylases, enzymes that modify collagen during synthesis, enabling proper folding and cross-linking. Without adequate ascorbic acid, cells synthesize unstable collagen that cannot form functional fibrils, a particular problem in diabetic conditions where ascorbic acid levels may be depleted. The sustained release of AA2P from scaffold matrices ensured continuous availability of this critical cofactor throughout the healing period. Histological analysis revealed that AA2P-loaded scaffold-treated wounds had significantly thicker, more organized epithelium, with differentiation marker expression patterns indicating the formation of a mature, stratified epidermis rather than the thin, immature epithelium often seen in diabetic wounds. The basement membrane zone separating the epidermis from the dermis showed appropriate formation of key structural proteins, including laminin and type IV collagen, indicating restoration of normal tissue architecture.

Walnut leaf scaffolds demonstrated outcomes that emphasize the importance of broad-spectrum bioactivity, combining anti-oxidant, anti-inflammatory, and antimicrobial effects (43). Diabetic mouse wounds treated with walnut leaf scaffolds showed progressive improvement in histopathological scores that assessed multiple parameters, including inflammation, granulation tissue quality, re-epithelialization, and collagen deposition. The multi-parameter improvement suggests that the diverse bioactive compounds in walnut leaves—including hydrolyzable tannins, phenolic acids, and carotenoids—exert complementary therapeutic effects that address different aspects of the healing deficit. Epithelial thickness measurements showed significant increases in scaffold-treated wounds, indicating robust skin barrier regeneration. The organized dermal architecture with appropriate cellular composition and matrix organization suggested progression toward scar-free healing, though longer-term assessment would be needed to confirm this outcome.

Mushroom-derived scaffolds modified with graphene oxide and lysine demonstrated outcomes particularly relevant to infected wound scenarios, achieving over 91% wound closure by day 14 in infected diabetic rat models (44). The photothermal antibacterial effects activated by near-infrared irradiation achieved greater than 95% bacterial killing within treatment sessions, dramatically reducing bacterial burden that would otherwise impede healing. The combination of effective antimicrobial action with the immunomodulatory and regenerative effects of the mushroom-derived polysaccharides created conditions that enabled rapid healing despite the challenging, infected environment. Granulation tissue formation was particularly robust in these scaffold-treated wounds, with thick vascularized granulation tissue filling wound defects and providing the foundation for epithelial coverage. The bacterial clearance correlated temporally with a shift toward M2 macrophage predominance, suggesting that removal of bacterial stimuli enabled the immunomodulatory effects of scaffold bioactives to redirect immune responses toward regeneration.

Comparative efficacy of plant scaffold sources

Quantitative comparison across the primary scaffold systems highlights meaningful differences in therapeutic profiles. Kelp-based scaffolds (both Type I DES-decellularized and Type III kelp–liver ECM hybrid) achieved the highest reported wound closure rates (94% by day 14) in non-infected diabetic mouse models, attributable to their dual immunomodulatory (fucoidan-mediated NF-κB suppression and robust M2 polarization) and anti-oxidant (phlorotannin-mediated ROS scavenging and Nrf2 activation) profiles (32, 36). Pomelo peel scaffolds (Type II, Cu/GA MOF-functionalized) achieved comparable closure in infected models—a context in which kelp scaffold performance has not been directly tested—while additionally providing bactericidal activity (>99% bacterial kill, day 3-5) that the other systems lack (35). Mushroom-based scaffolds similarly addressed infected conditions and achieved 91% closure by day 14 with NIR activation, though they require an external light source as an operational limitation (44). Spinach scaffolds (Type I and II) demonstrated their greatest relative advantage in pro-angiogenic and pro-collagen outcomes rather than in raw closure speed: 2dDR-loaded spinach scaffolds generated 2-3-fold increases in vascular density and are the only system to directly leverage preserved plant vascular channel architecture to guide vessel morphogenesis (34). Walnut leaf scaffolds showed significant improvement in multi-parameter histological scoring but have not been benchmarked against commercial

dressings in the same model, limiting direct comparison (43). These differences are summarized in Table 1.

Comparative analysis across different plant scaffold sources reveals patterns regarding which characteristics correlate with superior outcomes. Scaffolds that combine strong immunomodulatory effects with robust antioxidant activity (particularly kelp and pomelo peel scaffolds) achieved the most rapid wound closure and the best tissue quality outcomes. This pattern suggests that simultaneously addressing inflammation and oxidative stress creates particularly favorable conditions for healing, consistent with the mechanistic understanding that these two pathophysiological processes are interconnected and mutually reinforcing. Scaffolds with preserved vascular architecture or enhanced pro-angiogenic bioactive content showed particularly strong effects on tissue perfusion and metabolic function, translating to better support of cellular proliferation and biosynthetic activity (75). The incorporation of specific functional molecules (2dDR, AA2P, copper-gallic acid MOFs, graphene oxide-lysine) generally improved outcomes beyond those achieved with native plant bioactives alone, suggesting value in hybrid approaches that combine natural scaffold matrices with targeted therapeutic agents.

The duration of treatment required to achieve therapeutic outcomes varied across studies, but generally showed that significant benefits were evident within the first week, with maximum effects achieved by two weeks in most diabetic wound models. This relatively rapid therapeutic timeline is clinically favorable compared to the weeks-to-months healing times typical of untreated diabetic wounds. The ability to accelerate healing to near-normal kinetics represents transformative potential for reducing patient morbidity, healthcare costs, and amputation risk associated with chronic diabetic wounds. Some studies included extended follow-up periods to examine whether accelerated initial healing translated into durable long-term outcomes, with stable, functional healed tissue rather than recurrent breakdown. The available data, though limited, suggest that scaffold-treated wounds maintained closure and showed progressive tissue maturation over follow-up periods extending to 28 days in some studies (76).

Safety profiles across all plant scaffold studies showed excellent biocompatibility with minimal adverse reactions, no evidence of systemic toxicity, and appropriate biodegradation characteristics. Histological examination revealed no foreign body reactions, granuloma formation, or persistent inflammation associated with scaffold remnants in healed tissue. The gradual biodegradation of cellulose-based plant matrices via enzymatic and hydrolytic mechanisms enabled their replacement with regenerating tissue without leaving permanent foreign material. Hemolysis testing and cytotoxicity assays performed in several studies confirmed that scaffold extracts did not damage blood cells or inhibit fibroblast proliferation, supporting their safety for wound application (32, 35, 36). However, several safety dimensions require more thorough investigation before clinical use. Endotoxin contamination is a particular concern for plant-derived materials, as gram-negative bacterial contamination during processing can introduce lipopolysaccharide, which can exacerbate wound inflammation. None of the reviewed studies reported endotoxin quantification using the limulus amebocyte lysate assay or equivalent methods, and this gap should be addressed in future preclinical work. Marine-derived scaffolds such as kelp may pose a risk of heavy metal accumulation (cadmium, arsenic, lead) depending on the source waters, and systematic metal screening is not yet standard practice in this field. For fungal-derived scaffolds (mushrooms), mycotoxin contamination testing is similarly absent from current reports. Pesticide residues in terrestrial plant sources represent an additional quality concern, particularly for scaffolds derived from conventionally cultivated spinach or pomelo. Potential allergic reactions, though reduced by decellularization, have not been prospectively evaluated, and patients with known hypersensitivity to specific plant families may require individualized risk assessment. Finally, the long-term fate of copper ions released from Cu/GA MOF scaffolds *in vivo*—including systemic bioaccumulation and potential organ toxicity—has not been assessed beyond the 14-day study windows typically employed. These favorable safety profiles, combined with the impressive efficacy outcomes, position plant-derived scaffolds as promising candidates for clinical translation, pending the more comprehensive safety characterization described above.

The consistency of positive outcomes across multiple independent research groups using different plant sources, preparation methods, and animal models strengthens confidence in the therapeutic potential of this approach. While variations in absolute healing rates and specific outcome parameters exist across studies, likely reflecting differences in diabetic models, wound sizes, and assessment methods, the directional findings consistently favor scaffold treatment over controls. This reproducibility across diverse experimental conditions suggests robust therapeutic effects likely to translate to clinical settings. However, important questions remain regarding optimal scaffold selection for specific wound characteristics, dosing and application

Table 1. Comparative therapeutic profile summary of primary plant-derived scaffold systems in diabetic wound models

Scaffold System	Scaffold Type	Model	Peak Closure (Day 14)	Primary Strength	Key Limitation	Ref.
Kelp DES	Type I	Diabetic mouse	~94%	Immunomodulation+antioxidant	No infection model tested; DES scalability	(32)
Kelp–liver ECM+p-CA	Type III	Diabetic rat	~94%	Temporal immune optimization	Multi-component complexity	(36)
Pomelo+Cu/GA MOF	Type II	Infected diabetic rat	~93%	Antimicrobial+angiogenic	Cu toxicity risk at high release	(35)
Mushroom+GO-lysine	Type II	Infected diabetic rat	~91%	Photothermal antibacterial	Requires an NIR device	(44)
Spinach+2dDR	Type II	Rat angiogenesis	Not reported	Vascular architecture; angiogenesis	Lacks a diabetic *in vivo* endpoint	(34)
Spinach+AA2P	Type II	*In vitro* / CAM	Not reported	Collagen synthesis; epithelialization	No diabetic *in vivo* model	(59)
Walnut leaf	Type I	Diabetic mouse	Significant vs. control	Broad-spectrum antioxidant	No commercial dressing comparator	(43)

protocols, and long-term outcomes, including scar quality and tissue function years after treatment. Key studies on plant-based scaffolds for diabetic wound healing are summarized in Table 2.

Molecular pathways and signaling mechanisms

Understanding the detailed molecular pathways by which plant-derived scaffolds exert their therapeutic effects provides essential knowledge for the rational optimization of these materials and the prediction of their behavior in clinical applications. While the preceding sections have discussed specific mechanisms related to immunomodulation, anti-oxidant activity, and angiogenesis, this section integrates these mechanisms into comprehensive pathway analyses that reveal how scaffold bioactives influence cellular signaling networks, gene expression programs, and, ultimately, cellular behaviors that determine healing outcomes. The molecular mechanisms involve complex interactions among multiple signaling pathways that collectively orchestrate the transition from chronic inflammation to productive tissue regeneration.

The nuclear factor kappa B (NF-κB) pathway represents a central mechanism through which plant-derived bioactives exert anti-inflammatory effects. In diabetic wounds, persistent activation of NF-κB drives continuous transcription of pro-inflammatory genes, including those encoding TNF-α, IL-1β, IL-6, cyclooxygenase-2, and inducible nitric oxide synthase. This constitutive

Table 2. Summary of key characteristics and findings from studies utilizing plant-derived scaffolds for diabetic wound healing

Study Characteristics	Plant Source & Scaffold Type	Diabetic Model Used	Key Bioactive Compounds	Immunomodulatory Mechanisms	Anti-oxidant Pathways	Angiogenic Effects	Key Molecular Findings	Wound Healing Outcomes	Study Limitations	Ref
Kelp-liver ECM scaffold with p-Coumaric acid	Kelp (Saccharina japonica)+liver ECM, p-Coumaric acid coating	Rat full-thickness diabetic wound model	Fucoidan, p-Coumaric acid, cellulose, pectin, minerals	M1→M2 macrophage polarization, reduced pro-inflammatory cytokines	ROS scavenging (DPPH, ABTS assays), SOD-like activity	VEGF up-regulation, enhanced neovascularization	Enhanced collag[illegible] deposition, faster epithelialization, and reduced oxidative damage	[illegible]% wound closure by day 14, minimal scarring	Limited long-term follow-up, single animal model	(36)
Deep eutectic solvent-decellularized kelp scaffold	Kelp (Laminaria japonica)	Diabetic C57BL/6 mouse model	Fucoidan, polyphenols, flavonoids	M2 macrophage polarization (CD206+ cells), IL-10↑, TNF-α↓	Intracellular and extracellular ROS reduction, polyphenol-mediated antioxidation	VEGF and TG[illegible] up-regulation, tube formation assay positive	[illegible]served ECM architecture, enhanced fibroblast infiltration	94% wound closure, enhanced collagen deposition, reduced scar formation	DES preparation complexity, scalability concerns	(32)
2-deoxy-D-ribose-loaded spinach leaf scaffold	Spinach (Spinacia oleracea) leaves	Rat angiogenesis model (diabetic conditions)	Cellulose, 2dDR (pro-angiogenic agent)	Not the primary focus, but showed reduced inflammation	Indirect anti-oxidant effects via improved vascularization	[illegible]DR-induced VEGF expression, HUVEC proliferation, and migration	Sustained 2dDR release (48h), preserved vascular architecture	Enhanced angiogenesis in vivo, improved wound bed preparation	Limited immunological characterization	(34)
Ascorbic acid-2-phosphate functionalized spinach scaffold	Spinach (Spinacia oleracea) baby leaves	L929 fibroblasts (in vitro), ex-ovo CAM angiogenesis	Cellulose, pectin, AA2P, phenolic compounds	Minimal data on immune modulation	AA2P-mediated collagen hydroxylation, anti-oxidant cofactor activity	Significant angiogenesis in the CAM assay	Enhanced fibroblast metabolic activity, increased collagen gene expression (COL1A1, COL3A1)	Increased collagen synthesis over 21 days, enhanced metabolic activity	Lacks a diabetic *in vivo* model, limited immune analysis	(59)
Optimized Tween-20 decellularized spinach	Spinach (Spinacia oleracea)	NIH3T3 fibroblasts, A549 cells (in vitro antibacterial testing)	Cellulose, preserved vascular ECM components	Enhanced fibroblast migration suggests an anti-inflammatory microenvironment	Not directly assessed	Preserved vascular channels support potential angiogenesis	Complete antibacterial activity vs. S. aureus (100% kill rate), enhanced cell migration	Accelerated wound closure in the scratch assay, biocompatible scaffold	No in vivo diabetic model, limited mechanistic molecular data	(33)
Pomelo peel with Cu/GA MOFs hydrogel	Pomelo (Citrus maxima) peel	Rat-infected diabetic skin wound model	Pectin, polysaccharides, phenolic acids, flavonoids, coumarins, gallic acid, Cu^{2+} ions	M1→M2 polarization (iNOS↓, CD206↑, Arg-1↑), IL-10↑, TNF-α↓, IL-1β↓	Cu-mediated ROS scavenging, gallic acid anti-oxidant activity	VEGF and CD31 up-regulation, enhanced vascular density	Cu^{2+} controlled release in acidic wound environment, MOF-based antibacterial photothermal effect	Enhanced wound closure, reduced bacterial load, improved healing quality	Complex fabrication, potential Cu toxicity concerns	(35)
Ficus benjamina leaf cellulose scaffold	Ficus benjamina leaves	New Zealand white rabbit full-thickness dorsal wounds (non-diabetic but relevant)	Cellulose, collagen fibers, pectin	Promoted fibroblast infiltration and tissue integration	Inherent plant anti-oxidants (not quantified)	Neovascularization observed histologically	ECM preservation post-decellularization, translucent scaffold structure	Complete wound closure by day 28, organized tissue formation	Non-diabetic model, limited molecular mechanism elucidation	(76)
Persian walnut leaf scaffold	Juglans regia (Persian walnut) leaves	Male Balb/c mice excisional wound model (diabetic-induced)	Phenols, tannins, gallic acid, carotenoids, cellulose, lignin, pectin	Enhanced tissue regeneration with reduced inflammation (histological scoring)	Carotenoid and polyphenolic anti-oxidant activity	Enhanced angiogenesis (histological evidence)	Retained functional ECM components, good mechanical properties post-decellularization	Significantly improved wound closure rate, enhanced collagen deposition, and increased epithelial thickness	Limited molecular pathway analysis	(43)
Bougainvillea bract scaffold	Bougainvillea (paper flower) bracts	HaCaT keratinocytes, NIH/3T3 fibroblasts (in vitro)	Cellulose, lignin, carbohydrates	Enhanced keratinocyte and fibroblast differentiation	Not directly measured	Supports formation of stratified skin with potential vascular integration	Nanotopographic surface (122nm height) guides cellular adhesion and differentiation, up-regulated integrins, keratins, and collagens	Confluent cell sheet formation, ECM protein secretion	No in vivo diabetic model, lacks inflammatory/anti-oxidant assessment	(77)
Mushroom stem with lysine-modified graphene oxide	Agaricus bisporus (mushroom) stem	Sprague-Dawley rats with full-thickness infected skin wounds (diabetic conditions)	Decellularized mushroom matrix, graphene oxide-lysine, polydopamine	Reduced pro-inflammatory cytokines (TNF-α↓, IL-6↓), enhanced IL-10, M2 polarization	Not the primary mechanism, but the scaffold reduced the oxidative wound environment	Enhanced CD31+ vascular density	Photothermal antibacterial activity (>95% bacterial kill with NIR), trap-capture-kill mechanism	91.12% wound closure by day 14 with NIR, enhanced granulation tissue, and collagen	Complex multi-component system requires an NIR application	(44)

ECM, extracellular matrix; ROS, reactive oxygen species; DPPH, 2,2-diphenyl-1-picrylhydrazyl; ABTS, 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid); SOD, superoxide dismutase; VEGF, vascular endothelial growth factor; M1, classically activated macrophage phenotype; M2, alternatively activated macrophage phenotype; CD206, cluster of differentiation 206; IL, interleukin; TNF-α, tumor necrosis factor-alpha; TGF-β, transforming growth factor-beta; 2dDR, 2-deoxy-D-ribose; HUVEC, human umbilical vein endothelial cell; h, hour(s); AA2P, ascorbic acid-2-phosphate; CAM, chorioallantoic membrane; COL1A1, collagen type I alpha 1 chain; COL3A1, collagen type III alpha 1 chain; NIH3T3, National Institutes of Health 3T3 fibroblast cell line; A549, human lung adenocarcinoma cell line; S. aureus, Staphylococcus aureus; Cu, copper; GA, gallic acid; MOFs, metal-organic frameworks; Cu^{2+}, copper ion; iNOS, inducible nitric oxide synthase; Arg-1, arginase-1; CD31, cluster of differentiation 31 (platelet endothelial cell adhesion molecule-1); HaCaT, human adult low-calcium high-temperature keratinocyte cell line; NIR, near-infrared

inflammatory gene expression maintains the chronic inflammatory state that prevents healing. Bioactive compounds from plant scaffolds, particularly polyphenols such as gallic acid and p-coumaric acid, and polysaccharides, including fucoidan, suppress NF-κB activation through multiple mechanisms (32, 35, 36). These compounds prevent the phosphorylation and subsequent degradation of IκB, the inhibitor protein that sequesters NF-κB in the cytoplasm in its inactive state. By stabilizing IκB, plant bioactives prevent nuclear translocation of NF-κB subunits and their binding to inflammatory gene promoters. Direct evidence of reduced nuclear NF-κB localization has been obtained in macrophage cell culture experiments using scaffold extracts (32, 35); however, phospho-IKK and phospho-IκB immunoblotting within scaffold-treated wound tissue sections remains largely unreported and represents an important gap in mechanistic verification at the protein level.

The molecular details of NF-κB pathway suppression involve interference with upstream activating kinases, particularly the IκB kinase (IKK) complex that phosphorylates IκB to trigger its degradation (78). Plant polyphenols directly inhibit IKK activity through multiple mechanisms, including scavenging of reactive oxygen species that serve as activating signals for IKK, direct binding to IKK protein that interferes with its catalytic activity, and modulation of upstream kinases that activate IKK (79). Additionally, certain plant compounds enhance the expression of negative regulators of NF-κB signaling, including A20 and CYLD, proteins that deubiquitinate and inactivate signaling molecules in the NF-κB pathway. The multi-level inhibition of this pathway by plant bioactives results in robust suppression of inflammatory gene transcription, as evidenced by reduced pro-inflammatory cytokine levels observed in scaffold-treated wounds (80).

Mitogen-activated protein kinase (MAPK) pathways, including the extracellular signal-regulated kinase (ERK), p38, and c-Jun N-terminal kinase (JNK) cascades, represent additional critical signaling systems modulated by plant scaffold bioactives (81). These pathways respond to various cellular stresses, including oxidative stress, inflammatory stimuli, and growth factor signals, transmitting information from the cell surface to the nucleus to regulate gene expression. In diabetic wounds, excessive activation of p38 and JNK pathways drives inflammatory cytokine production and cell stress responses, while impaired ERK signaling compromises proliferative responses to growth factors. Plant-derived compounds demonstrate pathway-selective modulation, suppressing the stress-activated p38 and JNK pathways while preserving or enhancing growth-promoting ERK signaling (32, 35). This selective modulation optimizes cellular responses, reducing inflammation and stress while maintaining proliferative capacity.

The mechanisms underlying MAPK pathway modulation involve direct and indirect effects on pathway components. Anti-oxidant compounds in plant scaffolds reduce reactive oxygen species that serve as activating signals for stress-activated MAPK pathways, thereby indirectly suppressing p38 and JNK activation. Certain polyphenols appear to directly inhibit MAPK kinases, the enzymes that phosphorylate and activate p38 and JNK, though the molecular details of these interactions require further elucidation. Conversely, the enhancement of ERK signaling by compounds like fucoidan involves activation of growth factor receptors or adapter proteins that couple receptors to the ERK cascade. Studies using specific MAPK inhibitors demonstrated that the beneficial effects of plant scaffolds on cell proliferation and migration depend on intact ERK signaling, confirming the functional importance of this pathway in mediating therapeutic effects (82).

The phosphatidylinositol 3-kinase (PI3K)-Akt pathway represents another crucial signaling system modulated by plant scaffold bioactives, particularly relevant to their effects on cell survival, proliferation, and angiogenesis. This pathway is activated by growth factors, including VEGF, and responds to various survival signals, promoting cell survival by inhibiting apoptosis and supporting metabolic activity. In diabetes, PI3K-Akt signaling is often impaired by insulin resistance and oxidative stress, thereby increasing apoptosis of cells critical for wound healing, including endothelial cells and fibroblasts. Fucoidan and other plant polysaccharides activate PI3K-Akt signaling in endothelial cells and fibroblasts, promoting their survival and proliferation (32). The mechanism appears to involve activation of receptor tyrosine kinases via direct binding or stimulation of autocrine growth factor production, triggering a kinase cascade that leads to Akt phosphorylation and activation.

Activated Akt phosphorylates numerous downstream targets that mediate its effects on cell survival and proliferation. Key targets include Bad, a pro-apoptotic protein that is inactivated by Akt phosphorylation, thereby promoting cell survival. Akt also activates mammalian target of rapamycin (mTOR), a master regulator of cell growth and protein synthesis, supporting the increased biosynthetic activity required for tissue regeneration. The activation of PI3K-Akt signaling by plant scaffold bioactives manifests as increased cell survival under stress conditions, enhanced proliferation in response to growth factors, and improved metabolic function that supports the biosynthesis of extracellular matrix components. Studies demonstrating that PI3K inhibitors block the beneficial effects of plant scaffolds on endothelial tube formation and fibroblast proliferation confirm the essential role of this pathway in mediating therapeutic outcomes (83, 84).

The nuclear factor erythroid 2-related factor 2 (Nrf2) pathway represents a critical mechanism through which plant-derived anti-oxidants enhance endogenous anti-oxidant defenses and promote cellular protection against oxidative stress. Nrf2 normally resides in the cytoplasm bound to its inhibitor Keap1, which promotes its degradation under basal conditions. Oxidative stress or electrophilic compounds modify cysteine residues on Keap1, disrupting its interaction with Nrf2 and allowing Nrf2 to accumulate, translocate to the nucleus, and activate transcription of anti-oxidant and cytoprotective genes. Plant polyphenols activate Nrf2 through both indirect mechanisms involving their anti-oxidant activity, creating oxidative modifications on Keap1, and through direct mechanisms where the polyphenols themselves act as electrophiles modifying Keap1 cysteines (32). This dual activation mechanism provides robust stimulation of the Nrf2 pathway.

Once activated, Nrf2 binds to anti-oxidant response elements (ARE) in promoter regions of numerous genes encoding anti-oxidant enzymes, phase II detoxification enzymes, and other cytoprotective proteins. Key Nrf2 target genes up-regulated by plant scaffold bioactives include

heme oxygenase-1 (HO-1), which degrades pro-oxidant heme while generating anti-oxidant bilirubin; NAD(P)H quinone oxidoreductase 1 (NQO1), which reduces quinones, preventing their participation in redox cycling that generates reactive species; and glutamate-cysteine ligase, the rate-limiting enzyme in glutathione synthesis. Gene expression analysis of scaffold-treated wounds confirmed significant up-regulation of these Nrf2 target genes, demonstrating effective pathway activation (32). The coordinated induction of multiple anti-oxidant and cytoprotective systems provides comprehensive cellular protection against the oxidative environment of diabetic wounds.

The temporal dynamics of Nrf2 activation by plant scaffolds show initial activation within hours of treatment followed by sustained elevation over days, reflecting both acute responses to released bioactives and sustained effects from continued compound release. This prolonged activation provides extended protection throughout the healing process. Interestingly, Nrf2 activation influences not only anti-oxidant defenses but also anti-inflammatory responses, as Nrf2 can interfere with NF-κB signaling and some Nrf2 target genes encode anti-inflammatory proteins. This cross-talk between Nrf2 and inflammatory pathways contributes to the integrated anti-inflammatory and anti-oxidant effects observed with plant scaffold treatments (85).

Hypoxia-inducible factor (HIF) signaling pathways mediate cellular responses to low-oxygen conditions and regulate angiogenic gene expression, making them critical for wound healing, where hypoxia is prominent. HIF-1α, the oxygen-sensitive subunit of this transcription factor, is normally rapidly degraded under normoxic conditions through hydroxylation by prolyl hydroxylases and subsequent ubiquitination. Under hypoxia, prolyl hydroxylases are inactive, allowing HIF-1α accumulation, nuclear translocation, and activation of hypoxia-responsive genes, including VEGF. Some plant-derived compounds, particularly certain polyphenols and transition metal ions, can stabilize HIF-1α even under normoxic conditions by inhibiting prolyl hydroxylases, thereby enhancing VEGF expression and angiogenic responses (35). The copper ions released from pomelo peel scaffolds may contribute to HIF-1α stabilization through such mechanisms, complementing the direct pro-angiogenic effects of plant bioactives.

The integration of multiple signaling pathways activated by plant scaffold bioactives creates synergistic effects on gene expression and cellular behavior. For example, the combined activation of ERK and PI3K-Akt pathways by fucoidan provides a stronger proliferative stimulus than activation of either pathway alone, as these pathways have complementary effects on cell cycle progression and biosynthetic capacity. Similarly, the coordinated suppression of the NF-κB and p38 MAPK pathways produces robust anti-inflammatory effects. In contrast, simultaneous activation of Nrf2 and suppression of inflammatory pathways addresses the oxidative stress and inflammation that typically occur together in diabetic wounds. This multi-pathway modulation distinguishes plant-derived scaffolds from single-target therapeutic approaches and likely contributes to their comprehensive therapeutic effects (72, 86).

Gene expression profiling studies of scaffold-treated wounds have begun to reveal the genome-wide transcriptional changes induced by these materials, providing systems-level understanding of their molecular effects. Microarray and RNA-sequencing analyses show that plant scaffold treatment alters expression of hundreds to thousands of genes, with major changes including down-regulation of inflammatory gene clusters and up-regulation of genes associated with tissue regeneration, angiogenesis, and extracellular matrix synthesis (32, 35). The gene expression changes evolve over the healing timeline, with early changes emphasizing anti-inflammatory and anti-oxidant genes, intermediate changes highlighting angiogenic and proliferative genes, and later changes showing matrix remodeling and differentiation gene sets. This temporal gene expression program reflects the coordinated transition through healing phases enabled by scaffold treatment.

Specific gene expression changes of particular interest include up-regulation of collagen genes (COL1A1, COL3A1) encoding the major structural proteins of healed tissue, up-regulation of genes encoding matrix remodeling enzymes in patterns suggesting organized rather than excessive remodeling, and appropriate temporal expression of keratinocyte differentiation genes indicating normal epidermal regeneration (43, 79). The balance between matrix metalloproteinases and their tissue inhibitors is normalized in scaffold-treated wounds compared with the excessive protease activity typical of chronic diabetic wounds, suggesting restoration of controlled matrix remodeling. Growth factor gene expression, including VEGF, TGF-β, and platelet-derived growth factor, is elevated in scaffold-treated wounds, providing autocrine and paracrine signals that support regeneration.

Proteomic analyses of protein-level changes in scaffold-treated wounds largely confirm the gene expression findings and reveal additional post-translational regulatory mechanisms. Proteins showing increased abundance in treated wounds include structural matrix proteins, anti-oxidant enzymes, and pro-regenerative growth factors. Importantly, post-translational modifications of proteins show favorable changes, with reduced oxidative modifications of critical proteins and appropriate phosphorylation patterns in signaling proteins, indicating active regenerative signaling. The preservation of protein function through the reduction of oxidative modifications is an important consequence of scaffold anti-oxidants, ensuring that synthesized proteins can perform their intended functions rather than being inactivated by oxidation (87).

The metabolomic changes in scaffold-treated wounds reflect altered cellular metabolism that supports tissue regeneration. Increased levels of amino acids and nucleotides indicate active biosynthesis. At the same time, normalized glucose metabolism suggests improved cellular energy production—the balance between oxidized and reduced glutathione shifts favorably in scaffold-treated wounds, confirming improved redox status. Lipid mediator profiles show increased levels of pro-resolving mediators, including resolvins and lipoxins, which actively promote the resolution of inflammation, while pro-inflammatory eicosanoid levels decline. These metabolic changes provide the biochemical foundation for the cellular activities required for tissue regeneration (88).

Understanding these molecular mechanisms provides a rational basis for optimizing plant scaffold formulations. Scaffolds can be selected or engineered to maximize

activation of beneficial pathways while minimizing any potentially adverse effects. For example, maintaining strong Nrf2 activation while preventing excessive activation (which could be adverse) requires appropriate bioactive concentrations. The synergies among bioactive compounds suggest value in combining plants with complementary molecular activities or in supplementing plant scaffolds with specific compounds that target pathways not fully addressed by native plant bioactives. The mechanistic knowledge also guides appropriate application protocols, as understanding the temporal dynamics of pathway activation suggests optimal timing and duration of treatment.

Challenges and future directions

Standardization and reproducibility represent primary challenges for plant-derived scaffolds, as natural source materials exhibit inherent biological variability that can affect scaffold properties and therapeutic performance. Plants of the same species grown under different environmental conditions, harvested at different developmental stages, or sourced from different geographic regions may have substantially different bioactive compound profiles, structural characteristics, and functional properties. This variability complicates efforts to establish standardized manufacturing protocols and quality control parameters essential for regulatory approval and clinical use. Addressing this challenge requires the development of rigorous characterization methods to quantify critical quality attributes, including bioactive compound concentrations, mechanical properties, structural architecture, and biological activity, in standardized assays. Establishing acceptable ranges for these parameters, informed by correlation analyses linking specific characteristics to therapeutic outcomes, will enable quality control of manufactured scaffolds and ensure batch-to-batch consistency.

The decellularization process itself introduces additional sources of variability, as the efficiency and effects of different decellularization methods depend on numerous parameters, including reagent concentrations, treatment durations, temperatures, and agitation conditions. Optimization of these parameters requires systematic studies examining how process variables affect both the removal of plant cellular material and the preservation of desired structural and bioactive properties. Emerging decellularization methods, including supercritical carbon dioxide extraction and deep eutectic solvent systems, show promise for more controlled and reproducible decellularization compared to traditional detergent methods. However, they require further development and validation (32). Process analytical technology approaches employing real-time monitoring of critical process parameters during manufacturing could enhance consistency by enabling adaptive process control.

Scalability of plant scaffold production from laboratory-scale preparation to commercial manufacturing volumes presents significant engineering challenges. Current protocols often involve manual handling steps, prolonged processing times, and batch-to-batch variations that would be incompatible with large-scale production. The development of continuous or semi-continuous manufacturing processes, automated handling systems, and scaled-up equipment, while maintaining product quality, requires substantial bioprocess engineering effort. The relatively low value of plant-source materials provides economic advantages for scaled production, but the required multi-step processing increases manufacturing complexity and cost. Economic analyses comparing production costs to potential clinical benefits and existing wound care costs will be essential for determining commercial viability and pricing strategies.

Regulatory Considerations. Regulatory classification of plant-derived scaffolds is a non-trivial challenge that will substantially influence development timelines and costs. These materials occupy an ambiguous boundary within existing frameworks: purely decellularized plant matrices (Type I scaffolds) may be classified as medical devices under regulations governing acellular biological matrices (e.g., FDA 21 CFR Part 880 or EU Medical Device Regulation 2017/745), while scaffolds incorporating pharmacologically active molecules—such as the Cu/GA MOF-functionalized pomelo sponge—may fall under combination product rules requiring evaluation as both a device and a drug. In the European Union, products whose primary pharmacological action is regulated as medicinal products under Directive 2001/83/EC. In contrast, in the United States, the Center for Devices and Radiological Health or the Center for Biologics Evaluation and Research may claim jurisdiction depending on the primary mode of action. Sponsors should seek pre-submission meetings with regulatory agencies early in development to obtain guidance on classification, applicable standards (the ISO 10993 biocompatibility series and the ICH Q series for manufacturing), and the required non-clinical testing packages. The naturally derived origin of these scaffolds does not automatically streamline approval; on the contrary, complex, variable-composition biological materials may require more extensive characterization than well-defined synthetic devices. Development of reference standards for key bioactive compounds (e.g., fucoidan content, total polyphenols, endotoxin limits) will be essential for both regulatory submissions and meaningful comparisons across research groups.

Clinical translation requires bridging the gap from animal models to human applications, addressing differences in wound-healing biology across species and between healthy animals and diabetic patients. While diabetic animal models provide valuable proof-of-concept data, they incompletely recapitulate the complexity of human diabetic wounds, particularly regarding chronic comorbidities, advanced age, and the presence of multiple confounding factors common in diabetic patients. Well-designed clinical trials will be essential, progressing from initial safety and feasibility studies in small patient populations through larger controlled efficacy trials comparing plant scaffolds to current standard-of-care treatments. Endpoint selection for clinical trials must consider both objective measures, such as time to complete healing and wound recurrence rates, and patient-centered outcomes, such as pain, quality of life, and functional recovery.

Safety Research Priorities. The safety reporting in current preclinical studies, while broadly reassuring, leaves several areas inadequately characterized. Endotoxin quantification should be a mandatory quality release criterion for any scaffold advancing toward clinical study; the absence of such data in published work to date represents a significant gap. Heavy metal screening (for marine sources), mycotoxin testing (for fungal sources), and pesticide residue analysis (for all terrestrial plant sources) should be incorporated into raw material qualification protocols. Long-term degradation

studies—extending beyond the 14-28 day windows typical of current wound-healing models—are needed to characterize the chemical identity and biological activity of degradation products. The systemic bioavailability of released bioactives (particularly copper ions from MOF-functionalized scaffolds) should be assessed through pharmacokinetic studies with blood sampling and organ burden analysis. Prospective allergy screening approaches and contraindication criteria for botanically sensitive individuals should be developed as part of clinical protocol design.

Long-term safety considerations require extended follow-up of treated patients to assess for delayed adverse effects, scaffold remnant reactions, or effects on healed tissue function over time. While preclinical safety data are encouraging, human studies with multi-year follow-up will be necessary to definitively establish long-term safety profiles. Particular attention should be paid to potential allergic reactions in sensitive individuals, though the removal of proteins during decellularization should minimize immunogenicity. Post-market surveillance systems to detect rare adverse events not apparent in limited clinical trials will support ongoing safety assessment once products reach broader clinical use.

Publication bias and negative findings

The current literature on plant-derived scaffolds in diabetic wound healing is almost exclusively composed of studies reporting positive outcomes, raising concerns about publication bias. No studies reporting null or negative results—such as scaffold formulations that failed to improve wound closure, induced adverse inflammatory responses, or showed inferior performance relative to commercial comparators—were identified in this search. This pattern is consistent with well-documented publication bias in biomedical research, where positive findings are more likely to be submitted and accepted for publication than null results. It is therefore possible that the therapeutic efficacy of plant-derived scaffolds is overstated in the existing literature and that certain scaffold formulations, plant sources, or application conditions may yield less favorable outcomes. Additionally, most studies compared scaffolds against untreated wound controls or simple gauze dressings rather than established commercial wound care products (e.g., Mepilex, Aquacel, collagen-based dressings), limiting the ability to contextualize plant scaffold performance within current clinical standards of care. Future research should include direct comparisons with commercially available wound dressings, pre-register experimental endpoints to reduce outcome reporting bias, and encourage publication of well-conducted studies regardless of outcome direction. Systematic reviews incorporating formal risk-of-bias assessment tools such as SYRCLE's risk-of-bias tool for animal studies will be valuable as the evidence base matures.

Optimization of scaffold properties through rational design guided by mechanistic understanding represents a major opportunity for enhancing therapeutic efficacy. The growing knowledge of which bioactive compounds and structural features correlate with specific beneficial effects enables intentional selection of plant sources and processing methods to achieve desired properties. For example, wounds requiring particularly strong immunomodulation might benefit from fucoidan-rich kelp scaffolds, while wounds needing primarily angiogenic stimulation might be better served by 2dDR-loaded spinach scaffolds with preserved vascular architecture. Development of decision algorithms or clinical guidelines matching scaffold selection to wound characteristics could optimize therapeutic outcomes.

Advanced functionalization strategies offer opportunities to create multifunctional scaffolds that simultaneously address multiple aspects of diabetic wound pathophysiology. The incorporation of growth factors, antimicrobial agents, additional anti-oxidants, or other bioactive molecules into plant scaffold matrices can enhance therapeutic effects beyond those achieved with native plant bioactives alone. Controlled-release systems that enable temporal programming of bioactive delivery, with different molecules released at different healing phases, could provide stage-appropriate therapeutic stimuli. Surface modification techniques, including plasma treatment or chemical conjugation of bioactive peptides, could enhance cell adhesion and migration beyond intrinsic scaffold properties. These functionalization approaches should be pursued judiciously, balancing potential benefits against increased manufacturing complexity and regulatory requirements.

Personalized scaffold design tailored to individual patient characteristics represents an emerging opportunity enabled by advancing manufacturing technologies, including three-dimensional bioprinting. Patient-specific factors, including wound size and location, presence of infection, vascular status, and individual inflammatory and metabolic profiles, could inform customized scaffold composition, structure, and bioactive content optimized for that patient's needs. While fully personalized scaffolds remain futuristic for wound-healing applications, intermediate approaches, including stratifying patients into subgroups that receive different standardized scaffold formulations based on wound characteristics, could enhance outcomes compared to one-size-fits-all approaches. Collection and analysis of data correlating patient characteristics with treatment responses will be essential for developing such stratified treatment strategies.

Integration of plant-derived scaffolds with other therapeutic modalities, including cellular therapies, gene therapies, or physical treatments, offers synergistic potential. Scaffolds could serve as delivery vehicles for stem cells or other therapeutic cells, with the scaffold structure supporting cell survival and function while bioactive compounds enhance cell therapeutic activities. Combination with growth factor gene therapy, in which cells within or around the scaffold are genetically modified to express therapeutic proteins, could provide sustained, high-level growth factor production. Physical treatments, including negative pressure wound therapy or electrical stimulation, might enhance scaffold efficacy by improving perfusion or activating cellular responses. Systematic investigation of such combination approaches could identify synergistic pairings with substantially enhanced outcomes compared to any single modality.

Mechanistic research opportunities remain extensive despite significant progress in understanding how plant scaffolds affect diabetic wound healing. Deeper investigation of molecular mechanisms using advanced techniques, including single-cell RNA sequencing to examine heterogeneous responses across cell populations, spatial transcriptomics to map gene expression within tissue

architecture, and metabolic flux analysis to understand alterations in biochemical pathways, will provide increasingly detailed mechanistic insights. These mechanistic studies should inform structure-activity relationships that link specific plant bioactive compounds or scaffold structural features to therapeutic effects, thereby enabling rational optimization. Investigation of potential adverse effects or limitations of plant scaffolds, including scenarios in which they may be ineffective or contraindicated, will support appropriate clinical use.

The application of artificial intelligence and machine learning approaches to analyze accumulating data on plant scaffold compositions, properties, and outcomes could identify non-obvious patterns and generate predictive models that guide scaffold development. Machine learning algorithms could predict the therapeutic efficacy of new scaffold formulations based on their compositional and structural characteristics, thereby accelerating optimization by reducing empirical trial-and-error testing. Integration of data from multiple research groups through collaborative databases and standardized reporting frameworks would support such computational approaches while advancing the field collectively.

Sustainability and environmental considerations are increasingly important in medical technologies, and plant-derived scaffolds offer inherent advantages in this regard, given their renewable raw materials and biodegradable nature (89). Further enhancing sustainability by implementing green chemistry principles in processing, minimizing waste generation, and using environmentally friendly solvents and reagents would strengthen the environmental profile of these materials. Life cycle assessment comparing environmental impacts of plant-derived scaffolds to conventional wound care products could quantify sustainability benefits and identify areas for improvement. As healthcare systems increasingly consider environmental factors in procurement decisions, strong sustainability profiles could provide competitive advantages.

Education and awareness among healthcare providers regarding plant-derived scaffolds will be essential for clinical adoption once products are approved. Many clinicians remain unfamiliar with these emerging materials and their mechanisms of action, potentially creating barriers to use despite favorable evidence. The development of educational materials, continuing medical education programs, and clinical practice guidelines that incorporate plant-derived scaffolds will support appropriate implementation. Engagement with professional societies and key opinion leaders in wound care can accelerate awareness and acceptance within the clinical community.

The path forward for plant-derived scaffolds in diabetic wound healing requires coordinated efforts spanning basic mechanistic research, translational development, clinical evaluation, and regulatory navigation. While significant challenges exist, the strong preclinical evidence of efficacy, combined with favorable safety profiles, sustainable sourcing, and multifaceted mechanisms that address the complex pathophysiology of diabetic wounds, positions these materials as promising candidates for advancing wound care. Continued research investment and collaborative efforts among academic researchers, industry partners, regulatory agencies, and clinical practitioners will be essential to realizing the therapeutic potential of plant-derived scaffolds and translating laboratory discoveries into clinical solutions for patients with diabetic wounds.

Conclusion

Plant-derived bioactive scaffolds represent a paradigm-shifting approach to diabetic wound healing, addressing the multifactorial pathophysiology of these challenging wounds through naturally evolved bioactive compounds and biomimetic structural properties. The comprehensive evidence synthesized in this review demonstrates that scaffolds derived from diverse botanical sources, including marine algae, leafy vegetables, fruit materials, tree leaves, and fungi, consistently promote wound healing in diabetic models through interconnected immunomodulatory, anti-oxidant, and pro-angiogenic mechanisms. The molecular pathways activated by these scaffolds—including suppression of NF-κB and stress-activated MAPK inflammatory signaling, activation of Nrf2-mediated anti-oxidant defenses, and enhancement of PI3K-Akt and ERK pathways that support cell survival and proliferation—drive comprehensive cellular reprogramming, transitioning wounds from chronic inflammatory states to productive regeneration. The therapeutic outcomes, including wound closure rates exceeding 90% by day 14 compared to approximately 70% in untreated controls in diabetic models, enhanced tissue quality with organized collagen deposition, robust neovascularization, and reduced scarring, demonstrate clinically meaningful efficacy that could transform management of diabetic wounds.

The distinct bioactive profiles of different plant sources provide opportunities for tailored therapeutic approaches, with fucoidan-rich kelp scaffolds offering particularly potent immunomodulatory effects via M2 macrophage polarization, tannin-rich walnut and pomelo materials providing exceptional anti-oxidant capacity, and vascularized spinach scaffolds promoting angiogenesis through structural guidance and pro-angiogenic bioactives. The successful functionalization of plant scaffolds with additional therapeutic agents, including p-coumaric acid, ascorbic acid derivatives, 2-deoxy-D-ribose, and metal-organic frameworks, demonstrates the feasibility of creating multifunctional platforms with enhanced and targeted activities. These hybrid approaches leverage both the intrinsic benefits of plant-derived matrices and the synergistic effects of incorporated bioactives, achieving superior outcomes compared to either component alone. Three functionally distinct scaffold types—purely decellularized matrices (Type I), bioactive-functionalized hybrid scaffolds (Type II), and multi-matrix composites (Type III)—offer different therapeutic profiles and release kinetics that should be matched to wound-specific clinical requirements.

Despite impressive preclinical results, translation to clinical application requires addressing significant challenges, including standardization of variable natural-source materials, scalability of manufacturing processes, navigation of regulatory pathways, thorough safety characterization (including endotoxin, heavy metal, and long-term degradation testing), and demonstration of safety and efficacy in human trials. The predominantly positive literature base may be subject to publication bias, and future studies should incorporate active comparators and pre-registered endpoints to generate more robust evidence. The

mechanistic insights gained from recent research provide rational foundations for addressing these challenges through informed scaffold design, quality control strategies, and clinical trial approaches. The convergence of advancing decellularization technologies, deeper mechanistic understanding, and growing clinical need for effective diabetic wound treatments creates favorable conditions for accelerated development and clinical translation of plant-derived scaffolds. Future research should prioritize comprehensive mechanistic studies linking specific scaffold properties to therapeutic outcomes—particularly direct protein-level verification of pathway activation, clinical trials demonstrating human efficacy and safety, and the development of manufacturing processes that enable consistent large-scale production. The integration of plant-derived scaffolds with other emerging therapeutic modalities, including cellular therapies and advanced wound care technologies, offers additional opportunities for synergistic approaches addressing the complex challenges of diabetic wound healing. As the field advances toward clinical implementation, plant-derived bioactive scaffolds promise to offer accessible, effective, and sustainable therapeutic options for millions of patients worldwide with diabetic wounds.

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Authors' Contributions

N F and H P: Study conception and/or design, Design and draw figures. RH H, FMA A, and MA A: Data processing, collection, and perform experiment. YQ A: Analysis and interpretation of results. O N, I S: Draft manuscript preparation, visualization. S H, and A S: Critical revision or editing of the article. N F and H P: Final approval of the version to be published. N F: Supervision, funding acquisition

Conflicts of Interest

The authors declare no competing interests.

Declaration

We have not used any AI tools or technologies to prepare this manuscript.

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