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# Synergistic integration of exosomes and natural compounds in 3D-printed bioscaffolds: Revolutionizing diabetic wound healing through multifunctional therapeutic platforms

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**ABSTRACT**

Chronic wounds associated with diabetes, particularly diabetic foot ulcers, are a common complication and a significant public health challenge because they heal slowly and carry a high risk of amputation. Non-healing diabetic wounds are linked to local infection, compromised immune function, vascular damage, nerve impairment, and fragile peripheral skin. Exosomes derived from stem cells share many biological effects with their source cells but have lower immunogenicity and no tumorigenic potential, while demonstrating enhanced effectiveness in promoting wound healing. Exosomes enhance wound healing by stimulating angiogenesis and cell proliferation and by regulating inflammation. When genetically modified or combined with materials, exosomes exhibit improved therapeutic capabilities, including enriched active components, targeted delivery, and enhanced penetration across physiological barriers, thereby surpassing the limitations of conventional single treatments. Natural compounds with medicinal properties have demonstrated the capacity to facilitate tissue repair. Extensive research has examined the regenerative potential of plant-based and naturally occurring substances with inflammation-reducing, oxidative stress-mitigating, pathogen-inhibiting, and collagen-enhancing properties. 3D bioprinting, an additive manufacturing technique guided by computer-generated designs, produces biocompatible 3D structures. These tissue-engineered dermal replacements outperform conventional wound-healing techniques by offering greater procedural consistency, regulatory-compliant manufacturing standards, and precise delivery of living cellular elements, signaling proteins, and bioactive compounds. This review aims to explore the synergistic integration of exosomes and natural compounds within 3D-printed bioscaffolds for diabetic wound healing. It highlights the multifunctional therapeutic potential of these advanced platforms in enhancing tissue regeneration and repair. The article also discusses current challenges and future perspectives in translating these innovative strategies into clinical applications.

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## Introduction

Current estimates suggest that diabetes mellitus (DM) affects roughly 500 million individuals globally, and this figure is expected to increase substantially in the coming years. In the United States, annual expenditures exceeding $300 billion are attributed to healthcare costs and diminished workforce productivity associated with DM (1). DM is a prevalent and serious metabolic condition marked by microvascular complications, frequently linked to diabetic ulcers. These ulcers are characterized by slow healing, frequent recurrence, risk of amputation, and increased mortality (2). Standard treatments for diabetic wounds include controlling blood sugar levels, removing necrotic tissue, managing infections, applying dressings, reconstructing blood vessels, and offloading pressure from the wound. However, these approaches often yield suboptimal results, highlighting the need for a deeper understanding and more effective strategies. Tissue repair is a multifaceted, evolving biological process that depends on meticulously orchestrated cellular and molecular interactions spanning four distinct phases: hemostasis, inflammation, proliferation, and tissue remodeling. These sequential yet overlapping stages collectively facilitate optimal wound closure. Nevertheless, sustained hyperglycemia interferes with normal inflammatory cascades and impairs critical reparative mechanisms, including granulation tissue formation, neovascularization, and re-epithelialization at the wound site (3).

Over 100 distinct physiological mechanisms have been documented to compromise tissue repair in diabetic

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individuals. Among these mechanisms are impairments in growth factor synthesis and functionality (4, 5), deficient neovascularization (4, 6), compromised macrophage function (7), diminished collagen accumulation, disrupted epidermal barrier integrity, reduced granulation tissue formation (8), attenuated keratinocyte and fibroblast motility and replication, decreased epidermal nerve density (9), impaired osseous regeneration, and dysregulation of the balance between extracellular matrix deposition and its proteolytic degradation by matrix metalloproteinases (10).

Investigations have demonstrated that endothelial cells within ulcerated tissue from diabetic patients exhibit structural disarray and are unable to assemble into functional tubular configurations (11). Consequently, augmentation of neovascularization may be a critical therapeutic target to facilitate wound closure in diabetes. Nevertheless, persistent elevations in blood glucose and lipid concentrations, coupled with heightened oxidative stress in diabetic individuals, disrupt numerous metabolic cascades essential for tissue repair, resulting in cellular impairment and reduced function of reparative cell populations. These pathophysiological alterations underlie the deficient capillary formation characteristic of diabetic ulcers (12).

Under these circumstances, the localized inflammatory cascade becomes exaggerated, culminating in excessive synthesis of chemotactic mediators, proteolytic enzymes, and additional bioactive molecules that compromise the efficient mobilization of essential growth factors and endothelial cell populations, thereby inflicting collateral impairment upon the reparative mechanisms (13, 14). Furthermore, aberrant or uncontrolled neovascularization yields structurally deficient capillaries that exhibit heightened susceptibility to permeability and mechanical failure, thereby amplifying the inflammatory burden and exacerbating the deterioration of wound integrity (15). One of the initial stages of the wound-healing process involves the infiltration of inflammatory cells at the wound site. This inflammatory response involves the accumulation of macrophages, which play a critical role in healing. Depletion of monocytes/macrophages leads to delayed re-epithelialization, reduced collagen deposition, impaired angiogenesis, and decreased cell proliferation (16). Findings from both laboratory research and clinical studies reveal that wound healing in diabetic patients deviates significantly from the prototypical repair sequence observed under normal physiological conditions, with disruption of the orderly progression through the standard healing stages. Such wounds are distinguished by pathological alterations, including substantially elevated serum levels of IL-1β, TNF-α, and MCP-1 (17). Given that macrophages are the principal producers of inflammatory cytokines, their dysregulation is a pivotal contributor to defective wound closure in the diabetic population. They play an essential role in the inflammatory phase by initiating the healing process and promoting the formation of new tissue (18). In addition to macrophages, elevated neutrophil expression negatively impacts wound-healing mechanisms, as neutrophil infiltration is a key contributor to prolonged inflammation (19). The physiological conditions in diabetic wound healing exhibit dynamic spatial inflammation patterns, distinguishing early injuries from chronic non-healing wounds. Early wounds lack an inflammatory storm, whereas long-term non-healing wounds exhibit excessive, prolonged inflammation due to an overabundance of M1 macrophages (20). In the early-wound pattern, both impaired peripheral neuropathy and mast cell instability hinder the development of an acute pro-inflammatory response (21). The inhibition of an acute pro-inflammatory response reduces the levels of soluble mediators that serve as endogenous danger signals, thereby impairing the recruitment of neutrophils and macrophages to diabetic wound sites (22).

Reactive oxygen species (ROS) are key regulators across multiple stages of wound healing, with low levels necessary to combat external damage (23). However, excessive oxidative stress on tissues, coupled with diminished anti-oxidant capacity, leads to a redox imbalance, a primary contributor to nonhealing diabetic wounds (24). Clinical evidence indicates that chronic diabetic ulcers exhibit a pronounced oxidative stress milieu, primarily attributable to sustained hyperglycemia and localized tissue ischemia, both of which impede normal wound healing. Patients with prolonged type 2 diabetes mellitus demonstrate markedly diminished enzymatic anti-oxidant capacity (25). Oxidative stress can impair diabetic wound healing through skin damage, neuropathy, ischemic lesions, and localized infections. Studies examining the interplay between tissue hypoxia and oxidative burden have shown that these conditions may down-regulate the expression of microRNA biosynthetic machinery in fibroblast cultures (26). Contemporary evidence documents increased circulating concentrations of advanced glycation end products (AGEs) alongside up-regulated expression of their cognate epidermal receptors in diabetic patients (27). The interaction between AGEs and endothelial surface receptors initiates a cascade that results in aberrant ROS generation. Within the pathological milieu of diabetic wounds, AGEs appear to impair contractile processes, prolong the inflammatory phase, and adversely affect extracellular matrix (ECM) deposition and remodeling (28).

In diabetic patients, wound infection represents a significant complication (29). At the cellular level, there is an increase in acute inflammatory cells, a lack of cellular proliferation, and limited epidermal migration (30). Diabetic individuals exhibit impaired leukocyte function, with metabolic changes that reduce neutrophil and macrophage recruitment to the wound site and impair chemotaxis (31). These cellular alterations increase the likelihood of wound infections. Staphylococcus aureus (S. aureus) is the most prevalent single pathogen (76%) in diabetic wounds and foot ulcers, contributing to delayed wound healing (32). Wound infections may progress to bacteremia or sepsis, resulting in significant morbidity and mortality (33).

***Exosomes as multifunctional mediators***

Exosomes enhance angiogenesis by increasing endothelial cell arrangement and vascular stability, as well as reducing inflammation in macrophage contraction, through a diverse range of miRNAs and proteins (11, 15). Exosomes are small extracellular vesicles (EVs), typically 30–150 nm in diameter. Intraluminal vesicles form through inward budding of multivesicular bodies in the endosome-lysosomal pathway. With the help of vesicle transport proteins, these multivesicular bodies merge with the cell membrane, releasing intraluminal vesicles called exosomes (34). Exosomes carry key functional components, including proteins, mRNAs, miRNAs, noncoding RNAs, and metabolites, that can influence cellular RNA and protein levels, thereby affecting cell shape and function. Notably,

stem cell-derived exosomes share biological roles with their parent cells but offer advantages such as small size, ease of penetration across barriers, low immunogenicity, simple storage, and no risk of tumor formation (35). Numerous studies indicate that exosomes greatly improve tissue repair by enhancing regenerative capabilities (36). A study showed that MSC-derived exosomes enhance diabetic wound healing by modulating macrophage polarization (37). Recent studies have emphasized the significant potential of exosomes for wound repair (38).

Angiogenesis, the process of forming new blood vessels from existing ones, is a complex, multistep process that includes endothelial cell activation, proliferation, migration, invasion, sprouting, and the maturation and stabilization of newly formed vessels. Every step involves intricate interactions between endothelial cells and their surrounding extracellular environment (39). Various biological factors, including vascular endothelial growth factor (VEGF), microRNAs (miRNAs), and angiopoietin-2 (Ang-2), possess the ability to promote angiogenesis (40-42).

Vascular Endothelial Growth Factor (VEGF) is a critical regulator of angiogenesis. In healthy wound healing, VEGF stimulates the proliferation and migration of endothelial cells, promoting new blood vessel formation. However, in diabetes, VEGF expression and signaling are often diminished, resulting in poor angiogenic response and delayed wound closure (39, 43). VEGF binds to its receptor (VEGFR2) on endothelial cells, activating downstream pathways (such as PI3K/Akt/mTOR) that drive cell proliferation, migration, and new vessel formation (44). Exosomes from mesenchymal stem cells (MSCs) and other sources can up-regulate VEGF and other pro-angiogenic factors, stimulating new blood vessel formation in diabetic wounds (45).

miRNAs are highly conserved noncoding RNAs (18–24 nucleotides) that control target gene expression by promoting mRNA degradation or inhibiting translation. Growing evidence suggests that miRNAs are key regulators of angiogenesis (46).

Ang-1 and Ang-2 are the best-studied growth factors in the angiopoietin/TIE signaling pathway, a key regulator of angiogenesis. The angiogenic function of hucMSC-Exs in skin wound healing was confirmed in a rat burn model, a role linked to their enrichment with Ang-2(39).

Excessive inflammation plays a key role in the persistence of diabetic wounds. Irregular macrophage polarization and the overproduction of cytokines lead to a prolonged, un-regulated inflammatory response that can cause further tissue damage (47). Mesenchymal stem cell-derived exosomes (MSCs-Exos) can suppress T cell differentiation, activation, and proliferation, and reduce IFN-γ release (48). They also lower the levels of pro-inflammatory cytokines such as TNF-α, iNOS, IL-1β, and IL-6, while enhancing the expression of the anti-inflammatory cytokine IL-10 (39, 49, 50). Additionally, MSCs-Exos promote wound healing by inducing M2 macrophage polarization via delivery of exosome-derived miR-223, which regulates pknox1 expression (51). These effects are also evident in diabetic wounds. When native AMSC-Exos are applied topically to full-thickness skin wounds on the dorsal side of diabetic mice, they reduce the expression of inflammatory cytokines, including IL-6, TNF-α, CD14, CD19, and CD68, thereby enhancing wound healing (52). The combination of intraperitoneal administration of an Nrf2 activator and subcutaneous injection of BMSC-Exos also produces similar anti-inflammatory benefits by modulating inflammatory mediators. This approach leads to lower levels of pro-inflammatory cytokines (TNF-α and IL-1β) and higher levels of anti-inflammatory cytokines (IL-4 and IL-10) (53). Intradermal injection of MSC-Exos from human menstrual blood can promote macrophage polarization from the M1 to M2 phenotype, with greater effectiveness compared to menstrual blood-derived MSCs. Exosomes derived from mesenchymal stem cells in menstrual blood show promising potential to enhance wound healing in a diabetic mouse model (54).

Extracellular vesicles derived from mesenchymal stem cells (MSCs) have demonstrated the capacity to augment cellular proliferation and neovascularization in diabetic wound models. Exosomes isolated from adipose-derived MSCs (AMSC-Exos) accelerated dermal wound closure in diabetic murine models with full-thickness cutaneous defects through mechanisms including enhanced mitotic activity, attenuated programmed cell death, and enhanced angiogenic responses. Additionally, these exosomes facilitated restoration of epidermal barrier integrity and induced formation of abundant, architecturally organized, and densely arranged nascent collagen fibers (52). Bone marrow-derived MSC exosomes (BMSC-Exos) have been documented to reconstitute physiological skin architecture in rat models with full-thickness dermal injuries via modulation of transforming growth factor-β isoforms—specifically reducing TGF-β1 expression while enhancing TGF-β3 levels through suppression of the TGF-β/Smad signaling cascade (55). Umbilical cord MSC-derived exosomes (UCMSC-Exos) exhibited enriched concentrations of miR-21, miR-23a, miR-125b, and miR-145, which collectively inhibited myofibroblast transdifferentiation and prevented excessive fibrotic deposition, thereby mediating anti-scarring effects via the TGF-β2/Smad2 signaling axis *in vivo* (56).

Mesenchymal stem cells isolated from human umbilical cord tissue (hucMSCs) represent a multipotential, self-perpetuating cell population that has gained widespread adoption in clinical investigational settings. Extracellular vesicles secreted by hucMSCs (hucMSC-exos) have demonstrated therapeutic efficacy comparable to that of their parent cells across diverse pathological conditions, exhibiting cytoprotective effects against programmed cell death, immunomodulatory capacity to attenuate inflammatory cascades, and regenerative potential to facilitate tissue repair and remodeling (52, 57).

Adipose tissue-derived stem cells (ADSCs) are a multipotent cell population characterized by their capacity for multilineage differentiation, robust proliferative potential, and self-renewal (58, 59). Extracellular vesicles secreted by ADSCs (ADSC-exos) function as critical paracrine effectors, demonstrating a broad spectrum of biological activities. These exosomal fractions have emerged as prominent mediators of paracrine signaling that facilitate tissue regenerative processes. ADSC-exos accelerate dermal wound closure by modulating human dermal fibroblasts (HDFs), HaCaT keratinocyte lines, and other cellular targets through multiple intracellular signaling cascades (60, 61). Furthermore, ADSC-exos may augment collagen biosynthesis throughout the wound repair process by activating the PI3K/Akt signaling axis (62). Previous studies demonstrated that exosomes harvested from

ADSCs engineered to overexpress nuclear factor erythroid 2-related factor 2 (Nrf2) substantially diminished ulcer dimensions in diabetic rat hindlimb models by stimulating neovascularization and endothelial cell expansion, consequently expediting wound resolution (49). Bone marrow mesenchymal stem cells (BMMSCs) are among the most commonly utilized stem cells in clinical research. Compared to human umbilical cord mesenchymal stem cells (hucMSCs) and adipose-derived stem cells (ADSCs), BMMSCs are more difficult to isolate and pose greater risks during acquisition (63, 64). Research on BMMSC-derived exosomes (BMMSC-exos) has explored their potential as a future therapeutic approach in various disease models. These studies have demonstrated that BMMSC-exos can enhance tissue regeneration and reduce tissue fibrosis through anti-apoptotic, anti-oxidant, and anti-inflammatory effects (65, 66). Contemporary investigations have further demonstrated that exosomes derived from bone marrow mesenchymal stem cells (BMMSC-exos) facilitate cutaneous wound repair by augmenting proliferative capacity and migratory behavior in human spontaneously immortalized keratinocyte (HaCaT) cell populations. This therapeutic effect is mediated via the microRNA-93-3p/apoptotic peptidase activating factor 1 (APAF1) regulatory axis (67).

MSCs possess unique characteristics that set them apart from other cell types, making them an excellent source for exosomes. Currently, hucMSCs and BMMSCs are the most frequently registered MSCs in clinical studies (68), while autologous ADSCs are commonly used in cosmetic surgery. Due to their technical maturity and safety profile, these MSCs are promising candidates for exosome production in future applications (34). While exosomes from various MSC sources share core therapeutic functions, a critical comparison reveals distinct advantages and limitations that may guide source selection for diabetic wound applications. Human umbilical cord-derived exosomes (hucMSC-exos) are often highlighted for their potent immunomodulatory and pro-angiogenic effects, likely due to their fetal tissue origin and high levels of factors such as Ang-2 (39). They provide a readily available allogeneic source without donor-site morbidity. In contrast, adipose-derived exosomes (ADSC-exos) are readily obtained in large quantities via liposuction and exhibit particular efficacy in promoting fibroblast proliferation and collagen synthesis via the PI3K/Akt pathway (60, 62), making them attractive for targeting deficits in ECM deposition. However, their profile may vary with donor age and metabolic health. Bone marrow-derived exosomes (BMSC-exos), the historical gold standard, exhibit robust paracrine activity, but their harvest is invasive, and yields are low. An emerging point of debate concerns whether the parent cell's immunological age influences exosome function in the chronic inflammatory milieu of diabetic wounds. For instance, do exosomes from younger donors or fetal sources possess superior anti-senescence effects compared to those from aged or diabetic donors? This question remains largely unresolved and represents a significant gap in the field, underscoring the need for standardized comparative studies under diabetic-mimicking conditions.

***Natural compounds as bioactive regulators***

According to epidemiological data published by the World Health Organization (WHO), traditional medical practices constitute the primary healthcare modality for roughly 80% of the world's population. Among this demographic, plant-derived therapeutic agents account for approximately 85% of all remedies utilized. (69-73). Plant-derived natural compounds offer significant potential for enhancing wound healing while minimizing scar tissue formation. These bioactive substances exhibit antimicrobial and anti-oxidant properties that contribute to wound repair by promoting coagulation, preventing infections, and accelerating the healing process (74, 75). The primary mechanisms through which natural products contribute to wound healing include their anti-oxidant, anti-inflammatory, and antimicrobial properties.

ROS are oxygen-derived small molecules that function as oxidizing agents and can cause cellular damage, yet they are essential in initiating the normal wound-healing process (76). At moderate levels, ROS help defend tissues against infections and promote proper wound repair by activating cell survival pathways (1, 77). However, excessive ROS production leads to oxidative stress, resulting in cellular damage and a heightened inflammatory state (78). Anti-oxidants, including polyphenols, counteract this by donating electrons to ROS, preventing them from stripping electrons from critical biomolecules such as proteins and DNA. Furthermore, anti-oxidants trigger a series of reactions that convert ROS into more stable compounds, thereby regulating their levels in wound tissues and supporting the healing process (77, 79).

The inflammatory phase plays a critical role in wound healing, but excessive or prolonged inflammation in the early stages can lead to complications such as scarring, fibrosis, and delayed recovery (80, 81). While inflammation helps prevent infections and clears dead cells and debris, an overactive response can be detrimental. Key mediators of inflammation, including interleukins, TNF-α, inducible nitric oxide synthase (iNOS), and chemokines, are released during this phase (17, 82). Initially, proinflammatory M1 macrophages predominate, combating pathogens and initiating tissue repair. Later, anti-inflammatory M2 macrophages become more prevalent, promoting tissue remodeling and the resolution of inflammation (8).

Plant-derived substances such as berberine and eugenol exhibit strong anti-oxidant effects that can aid diabetic ulcer recovery by modulating pro-inflammatory cytokines and the wound-healing environment. A study conducted in 2023 showed that a hydrogel containing berberine and a polysaccharide from *Bletilla striata* significantly reduced inflammation and achieved a remarkable healing rate of 94.90 ± 1.81% by day 14 in diabetic ulcer mouse models, owing to its potent anti-inflammatory and anti-oxidant properties (83). Moreover, eugenol, a phenolic compound in clove oil, has antibacterial and anti-inflammatory effects that could be used to treat diabetic foot and antibiotic-resistant infections (84). Also, Thymol, derived from thyme, showed anti-inflammatory effects in streptozotocin-induced diabetic rats by reducing pro-inflammatory factors and promoting tissue repair, potentially aiding in the treatment of diabetic ulcers (85).

During the early phase of wound infection, gram-positive bacterial species, notably *Staphylococcus aureus* and *Streptococcus pyogenes*, represent the primary colonizing microorganisms. Subsequently, Gram-negative pathogens such as *Escherichia coli* and *Pseudomonas aeruginosa* come to dominate in the later stages of infection, thereby facilitating

the transition toward chronicity (86). Phytochemical investigations have revealed that phenolic-enriched extracts from *Diospyros mespiliformis, Haplophyllum tuberculatum,* and *Mangifera indica* exhibit substantial anti-oxidant, anti-inflammatory, and antimicrobial efficacy across diverse experimental wound-healing paradigms (87-89). Rocha and colleagues (90) characterized the therapeutic potential of both the residual water from hydrodistillation and essential oil fractions obtained from *Artemisia campestris* L., demonstrating that the aqueous residue exhibited marked anti-oxidant and anti-inflammatory bioactivity without inducing cytotoxic effects in macrophage or fibroblast cultures. Conversely, the essential oil fraction exhibited anti-oxidant properties and pronounced antifungal activity, particularly against *Epidermophyton floccosum*, a causative agent of superficial and cutaneous mycoses, while concurrently promoting wound closure.

***Rationale for Synergy: Conceptual frameworks***

The interaction between natural compounds and exosomes goes well beyond simple additivity; in many cases, their combined effects become truly multiplicative, unfolding through several interconnected mechanisms that are worth examining closely. Hydrophobic compounds like curcumin can embed themselves within the exosomal lipid bilayer, thereby markedly improving their solubility in aqueous environments, shielding them from premature degradation, and enabling more precise targeted delivery, directly addressing one of the longstanding pharmacokinetic challenges these molecules face (91). At the same time, exosomes often exert influence by modulating miRNA-regulated pathways (such as miR-223's role in driving macrophage polarization (51), while certain natural compounds, such as glycyrrhizic acid, can simultaneously engage complementary signaling axes like Nrf2 to counteract oxidative stress (92); when these two systems converge, the intervention reaches across a much broader and more integrated biological network. Another powerful strategy involves pre-treating mesenchymal stem cells with natural agents like salidroside before exosome harvest (12), which results in "engineered" exosomes carrying a richer, more potent cargo, a method many in the field consider more efficient and biologically relevant than attempting to load compounds into exosomes after they've already been isolated. Yet a key question remains unresolved and continues to spark debate: which approach ultimately yields superior synergy: Co-encapsulating the natural compound and exosome together within one delivery system, or preconditioning the parent cells to generate inherently stronger exosomes? Although the current literature offers compelling demonstrations of both strategies, the absence of rigorous head-to-head comparative studies still prevents the field from establishing clear, evidence-based guidelines for protocol optimization. In Daoyong Li *et al.*'s study, the authors explored the impact of curcumin-loaded macrophage-derived exosomes on wounds in patients with diabetes. The synergistic effectiveness of Exos-cur stems from curcumin's ability to reduce inflammation and oxidative damage, as well as exosomes' capability to deliver bioactive molecules effectively. *In vitro* studies showed that Exos-cur improved human umbilical vein endothelial cell (HUVEC) proliferation, migration, and angiogenesis while combating oxidative stress and inflammation. *In vivo* studies showed that Exos-cur markedly enhanced diabetic wound closure and contraction and improved re-epithelialization and collagen deposition. The combination of curcumin and exosomes enhances stability, bioavailability, and therapeutic efficacy compared with curcumin alone. Thus, Exos-cur serves as an effective biomaterial for wound management in patients with diabetes (91).

Curcumin can be applied to exosomes (for example, curcumin-loaded exosomes or Exos-cur), where it is either incorporated into the exosomal membrane or lumen. The incorporation raises resistance to enzymatic degradation and oxidative stress. The hydrophobic part of curcumin allows it to interact with the lipid bilayer of exosomes, thereby increasing membrane rigidity and hindering cargo spillover. The increased half-life of curcumin leads to greater persistence and a longer duration of exosomes in biological environments, thereby enhancing the sustained delivery of therapeutic curcumin to tissues and reinforcing the treated region (91).

Zhang *et al.* investigated the combined benefits of glycyrrhizic acid (GA)- hydrogel microparticles encapsulating MSC-derived exosomes (MSC-Exos) for diabetic wound healing. GA helps glycyrrhizic acid over-mesenchymal stem exosomes with anti-inflammatory and anti-oxidative functions. It stabilizes exosome bioactivity by preventing degradation of MSC-Exos, thus improving their delivery and efficacy. The hydrogel microparticles gradually release exosomes, enhancing their retention at the wound site. In diabetic models, GA-encapsulated MSC-Exos induced angiogenesis, reduced inflammation, and accelerated wound healing compared with exosomes or GA alone. This synergy aids re-epithelialization, collagen deposition, and tissue regeneration, which could prove valuable for the management of diabetic wounds (92).

Ning Xu *et al.* studied the combined effects of Curcuma zedoaria polysaccharide (CZP) with platelet-rich plasma (PRP) exosomes, which were incorporated into a chitosan/silk hydrogel sponge for the treatment of diabetic wounds. CZP enhances the stability and bioactivity of PRP exosomes, thereby improving therapeutic delivery. The chitosan/silk hydrogel also acts as a protective barrier, ensuring sustained release and retention of exosomes at the wound site. In diabetic rat models, this combination is more effective than either CZP or exosomes alone, significantly improving wound closure, angiogenesis, and collagen deposition. The combined action minimizes inflammation and oxidative damage, thereby promoting re-epithelialization and tissue repair. This method provides a novel class of materials for wound management in diabetic patients (93). Naturally sourced polysaccharides are a key resource for additives and complementary or alternative medicines in the food and pharmaceutical industries, offering cost-effective solutions. Recent studies increasingly indicate that certain polysaccharides are effectively utilized as healing agents or wound dressings for treating skin and epithelial wounds (94). *Curcuma zedoaria* (Berg.) Rosc., a member of the family Zingiberaceae, is widely recognized in Asian countries such as China, Korea, and Japan as a traditional remedy for alleviating inflammation, pain, wounds, and skin disorders (95).

Exosomes derived from medicinal plants, which naturally release bioactive nanotherapeutics with cell membrane-like structures and consistent nanoscale dimensions, have demonstrated remarkable biocompatibility and biodegradability (96). Additionally, their ability to cross

biological barriers makes them highly promising as therapeutic nanoplatforms for treating a wide range of diseases (97). Ginseng is a medicinal plant commonly utilized as a therapeutic agent, functional food, and nutritional supplement for vascular conditions. Numerous studies and clinical applications have demonstrated that ginseng and its extracts promote angiogenesis, which is crucial for treating various diseases, such as diabetic skin ulcers, where impaired angiogenesis is a major obstacle to healing (98). Tan *et al.* evaluate the therapeutic utility of ginseng-derived exosomes (GExos) for diabetic ulcers characterized by impaired angiogenesis resulting from endothelial cell (EC) dysfunction under high-glucose (HG) conditions. The GExos demonstrated the ability to deliver bioactive content to ECs, biomimicking cell membrane structures to support angiogenesis by reprogramming glycolysis. The GExos can up-regulate anaerobic glycolysis and down-regulate oxidative stress, thereby restoring ED proliferation, migration, and tubule formation under HG conditions. The *in vivo* full-thickness diabetic skin ulcer mouse model study showed that GExos caused angiogenesis and reconstruction of the nascent vessel network with biosafety. The GExos worked synergistically with the natural compounds they encapsulated, such as ginsenosides, to enable targeted delivery and increased therapeutic effect, thereby further enhancing therapeutic utility by modulating metabolic pathways for vascular regeneration. This strategy establishes an emerging paradigm for investigating phytogenic extracellular vesicles as innovative nanoscale therapeutic agents targeting vascular dysfunction induced by chronic hyperglycemia. The work enables a new paradigm for the development of plant-based exosomal therapies for the treatment of diabetic ulcers while providing a promising rationale for vascular diseases (99).

### *3D-printed bioscaffolds: The integration platform*

Over the past ten years, 3D printing has emerged as a highly versatile and widely used technology for quickly producing synthetic replacements in regenerative medicine (100). 3D bioprinting facilitates the development of personalized scaffolds that replicate the structure of natural skin tissue, enabling precise placement of various cell types and creating optimal cellular environments to support cell infiltration, vascularization, and tissue ingrowth. These scaffolds, engineered with tailored porosity, pore size, and interconnectivity, offer a promising approach for customized skin regeneration (101, 102).

3D bioprinting encompasses techniques such as laser-assisted, inkjet, and extrusion-based printing, which use bioinks and biomaterials, often integrated with cells or bioactive molecules, to fabricate multilayered tissue structures that emulate natural human tissue. This technology facilitates digital customization and automated production of personalized artificial scaffolds tailored to individual patient needs (103). With technological advancements, 3D bioprinting is increasingly recognized as a promising approach for wound treatment. This sophisticated additive manufacturing technique enables the creation of three-dimensional scaffolds that closely resemble natural human tissues (103). 3D-printed bioscaffolds, with their exacting control over pore size and architecture, are ideal delivery vehicles for exosomes and natural products, such as ginseng-derived exosomes (GExos). The tunability of the scaffolds enables sustained exosome release for delivery to diabetic ulcer areas, facilitating angiogenesis and tissue regeneration (104). Three-dimensional materials, notably hydrogels, have attracted significant interest for wound-healing applications. Three-dimensional polymeric networks exhibiting high aqueous absorption capacity, termed hydrogels, structurally mimic the native extracellular matrix architecture and possess superior biocompatibility alongside tunable physicochemical properties. These biomaterials exhibit considerable therapeutic potential as advanced wound care platforms by maintaining a conducive regenerative milieu and functioning as controlled-release vehicles, thereby conferring protective encapsulation and temporally modulating exosomal cargo delivery. Their high biocompatibility and plasticity support cellular infiltration and vascularization, critical for diabetic wound healing (105). Compared to conventional hydrogel fabrication techniques, 3D bioprinting technology enables the creation of more intricate bio-scaffolds that mimic natural tissue, offering customizable and tunable properties (106).

3D bioprinting has the potential to create bespoke scaffolds for patients. It can accurately deliver exosomes and bioactive molecules, leveraging their synergistic properties to reprogram glycolysis and improve angiogenesis in a high-glucose environment (107). 3D-printed scaffolds can incorporate bioinks loaded with exosomes and natural compounds, enabling sustained, intermittent drug delivery to maintain therapeutic concentrations. This is particularly useful to sustain the pro-angiogenic effects observed in diabetic ulcer models (108). Exosomes and natural compounds were loaded onto 3D-printed scaffolds, and their multifunctional capabilities were complemented through hemostatic, angiogenic, and anti-inflammatory properties to address the woven pathophysiology of diabetic ulcers (109). 3D printing's reproducibility and scalability provide an ideal platform for fabricating bioscaffolds that exhibit an even distribution of exosomes and natural compounds, thereby enhancing the clinical translatability of diabetic wound-healing therapies (104). 3D-printed bioscaffolds holding both exosomes and natural compounds improve therapeutic efficacy through both the 3D-printed scaffolds existing as structural scaffolds and the bioactive molecules in the scaffold modulating biological pathways, such as glycolysis, to resume endothelial cell activity and regenerate new vessels in diabetic ulcers (110).

### *Scaffolds as exosome delivery systems*

In recent years, researchers have focused on combining extracellular vesicles (EVs) with a diverse range of biocompatible materials to retain or enhance specific biological functions. This directional research has wide ramifications because, rather than compromising EVs, combining them with hydrogels, polymers, scaffolds, etc., can help maintain EVs' stability and activity, enabling more reliable and prolonged delivery for tissue engineering and regenerative medicine applications (111).

Exosomes, in combination with 3D-printed scaffolds, are an attractive option for improving diabetic wound healing. Several studies demonstrate that incorporating exosomes, particularly those derived from adipose mesenchymal stem cells, into bioactive and biodegradable 3D scaffolds enhances healing by promoting faster wound closure, increased formation of new epidermis and dermis, and increased angiogenesis and collagen deposition in diabetic wound models. These studies also demonstrated enhanced

healing-related gene expression (e.g., TGF-β, bFGF, and VEGF) and decreased inflammatory markers (e.g., TNF-α and IL-1β), resulting in improved tissue regeneration and reduced inflammation compared to scaffolds or exosomes alone (112).

Different materials and scaffold designs have been evaluated, including collagen-based microporous scaffolds and hydrogel-based scaffolds. These scaffolds provide an environment that supports the sustained, localized release of exosomes at the wound site, promoting wound healing by enhancing cellular activity and tissue repair processes (113, 114). For example, 3D-printed patches made with methacrylated hyaluronic acid (MeHA) were used to control exosome release, thereby enhancing epithelialization, vascularization, and nerve regeneration in diabetic ulcer models (113). In summary, the integration of 3D printing technology and exosome therapy offers a complementary strategy that leverages the structural and functional advantages of engineered scaffolds alongside the regenerative potential of exosomes to address the multifaceted challenges of diabetic wound healing (112). These studies (Table 1) demonstrate that combining exosomes with 3D-printed scaffolds enhances diabetic wound healing by promoting angiogenesis, reducing inflammation, and improving tissue regeneration.

### *Wound healing: Mechanisms, advantages, and limitations*

A close look at the platforms summarized in Table 1 highlights how different scaffold designs tackle the core challenges of exosome delivery in wound healing, each with its own strengths and clear trade-offs. Hydrogel-heavy approaches, such as those based on MeHA (116) or GelMA (117), stand out for creating a highly moist, biocompatible microenvironment that supports prolonged exosome release while conforming nicely to the irregular contours of chronic wounds, making them especially useful in non-weight-bearing areas. That said, these soft matrices often fall short in mechanical strength, making them less ideal for high-load zones like the plantar surface of the foot, where they risk deformation or premature breakdown under pressure. On the flip side, composite scaffolds that blend synthetic polymers such as PCL (117) or leverage decellularized extracellular matrices such as SIS (114) offer improved structural integrity, tensile strength, and a closer mimicry of native ECM architecture, thereby helping maintain scaffold stability and supporting tissue remodeling over time. The downside here is that these more robust designs can sometimes sacrifice inherent bioactivity or require more elaborate fabrication processes, potentially complicating clinical translation. One striking limitation across the board is the scarcity of direct, head-to-head comparisons: few studies pit the same exosome source against different scaffold types to rigorously evaluate differences in release kinetics, biodistribution, or downstream functional endpoints like wound closure rates and tissue quality. Even where enhanced angiogenesis is frequently reported as a key benefit, the field tends to stop short of deeper characterization of markers of vessel maturity, such as co-localization of CD31 with α-SMA-positive pericytes, which are rarely assessed in detail. Without this kind of evaluation, it's hard to judge whether the new vasculature is truly stable and functional over the long term or prone to regression, which remains a critical blind spot in gauging the real therapeutic durability of these exosome-scaffold strategies.

### *Scaffolds as a natural compound delivery system*

Diabetic wounds, like foot ulcers, are very challenging to heal because of hyperglycemia, impaired blood flow, and microbes. Frequently, traditional wound dressings are inadequate in maintaining an optimal healing environment or delivering bioactive agents effectively (118). Polysaccharides, plant extracts, essential oils, and active ingredients are all plant-based materials that are renewable, biocompatible, and biodegradable. Their therapeutic properties can improve the functionality of scaffolds for diabetic wound healing by controlling infections, reducing inflammation, and regenerating tissues(120). These studies (Table 2) have investigated the effects of integrating 3D-printed scaffolds with natural compounds for diabetic wound healing.

The studies compiled in Table 2 vividly illustrate just how versatile 3D printing has become for engineering advanced wound dressings that harness the bioactive potential of natural compounds, turning preliminary

**Table 1.** Comparative analysis of 3D-printed scaffolds integrated with exosomes for diabetic wound healing: Mechanisms, advantages, and limitations

| Scaffold biomaterial | Origin of exosome | Mechanism of action | Ref. |
|---|---|---|---|
| SIS (decellularized small intestinal submucosa) + Mesoporous bioglass (MBG) + alginate | BMSCs | Stimulate angiogenesis, promote cell migration and proliferation, modulate immune responses | (114) |
| Gelatin/hyaluronic acid/nano-hydroxyapatite (Gel/HA/nHAP) | BMSCs | These bioactive agents facilitate cellular proliferative capacity and migratory behavior, suppress programmed cell death pathways, and enhance the commitment of progenitor cells toward the osteoblastic lineage | (115) |
| Methacrylated hyaluronic acid (MeHA) | hMSC | The proliferative and migratory capacities, as well as the angiogenic potential, were enhanced in human fibroblasts and endothelial cells. Furthermore, the expression levels of particular markers implicated in wound repair were up-regulated | (116) |
| GelMA hydrogel-combined Melt Electrowriting (MEW)-PCL | ADSCs | Cellular proliferation and migration were stimulated, tube formation and re-epithelialization were accelerated, collagen maturation was improved, and angiogenesis was enhanced | (117) |
| Amniotic membrane-scaffold (AMS) | ADSCs | The expression of TGF-β, bFGF, and VEGF genes was up-regulated. In contrast, the expression of TNF-α and IL-1β, along with the cell numerical densities of neutrophils, M1 macrophages, and mast cells, decreased | (117) |
| Chitosan, collagen, hyaluronic acid, chondroitin sulfate | PLMSCs, ADMSCs | Increased re-epithelialization, neovascularization, and decreased inflammatory reaction | (118) |
| PRP, COL-I, Thrombin | ADSCs | Reduces inflammation, promotes cell proliferation, and angiogenesis | (119) |

**Table 2.** Recent studies investigating the effects of integrating 3D-printed scaffolds with natural compounds on diabetic wound healing

| Scaffold composition | Source | Key findings | Ref. |
|---|---|---|---|
| Gelatin (Gel), sodium alginate | *Centella asiatica* extract | Macrophage orchestration and immune responses were promoted, while wound closure, collagen deposition, and re-epithelialization were enhanced | (121) |
| Chitosan and methylcellulose, coated with curcumin | Curcumin | Enhanced antibacterial activity against *E. coli* and *S. aureus*, reduced clotting time, improved re-epithelialization, and reduced inflammation | (122) |
| Sodium alginate (ALG)–xanthan gum (XAN) | Clove essential oil (CLV) | Reduced nitric oxide (NO) concentration, indicating a potential anti-inflammatory effect | (121) |
| BSA hydrogel | Aloe vera (AV) gel | The hydrogel exhibited inherent antioxidant and antibacterial properties, accelerated rapid wound healing, increased collagen deposition, and up-regulated the expression of vascular endothelial growth factor (VEGF) and its receptors | (123) |
| Sodium alginate, methylcellulose | Thyme and cinnamon essential oils | High rates of inactivation were observed against both gram-positive and gram-negative bacteria | (124) |
| Methacrylated decellularized extracellular matrix hydrogel | Copper-epigallocatechin gallate (Cu-EGCG) capsules | The treatment promoted angiogenesis and inhibited inflammation. It suppressed the polarization of macrophages towards the M1 pro-inflammatory phenotype, activated the expression of angiogenesis-related genes within the HIF-1α/vascular endothelial growth factor pathway, and reduced the expression of inflammation-related genes in the TNF-α/NF-κB/MMP9 pathway | (125) |
| Alginate | *Cydonia oblonga* extract | Improved the antibacterial performance, enhancing its ability to absorb wound exudate, and exhibiting good biocompatibility | (126) |
| Sodium alginate, Pectin, glycerol | *Olive leaf* extract (OLE) | Enhance cell motility and accelerate wound healing, and increase collagen I expression | (127) |
| Chitosan | *Osage orange* extract (OGE) | Decreases the swelling capacity, strong antibacterial activity | (128) |

concepts into promising functional platforms. Yet a closer, more comparative look across these works uncovers substantial differences in underlying design logic, the level of therapeutic efficacy demonstrated, and, crucially, how close each system really is to meaningful clinical translation, gaps that the field urgently needs to bridge if it's to move past proof-of-concept stages.

A clear divergence emerges in the strategic priorities driving compound selection. Some approaches lean heavily toward prophylactic protection, loading scaffolds with essential oils from thyme, cinnamon (110), or clove to deliver broad-spectrum antimicrobial activity from the start, which is vital for staving off infection in the high-risk, often contaminated environment of diabetic wounds, where even minor bacterial colonization can derail healing. By contrast, other studies prioritize multifunctional therapeutic intervention, incorporating agents like curcumin (122) or copper-EGCG complexes (125) that simultaneously address deeper pathophysiological drivers: curcumin's well-documented suppression of persistent inflammation through NF-κB pathway inhibition, paired with its ability to boost impaired angiogenesis via HIF-1α and VEGF up-regulation, or copper-EGCG's complementary effects on oxidative balance, inflammation modulation, and vessel formation. This raises a fundamental, still-unresolved question for formulation design: does a single, inherently multi-target compound like curcumin offer clear advantages in terms of simplicity, controlled release, and synergistic bioactivity within one scaffold, or could a deliberate combination, say, an antimicrobial oil co-loaded with a dedicated pro-angiogenic or anti-inflammatory factor, deliver more comprehensive coverage by hitting distinct pathological axes without overlap or antagonism?

Unfortunately, the existing body of work provides plenty of isolated success stories for both philosophies but almost no rigorous, head-to-head comparative experiments that pit single-compound versus multi-compound strategies against each other under identical printing conditions, exosome or compound loading methods, wound models, or outcome metrics (e.g., bacterial clearance kinetics, vessel maturity, collagen remodeling quality, or long-term closure rates in diabetic models). Until such direct comparisons are conducted, optimizing scaffold composition remains largely empirical, hindering progress toward standardized, evidence-based designs that could reliably outperform current clinical options for challenging chronic wounds.

### *Advanced combinatorial platforms (Exosome + Natural Compound + Scaffold)*

This illustration demonstrates how varying

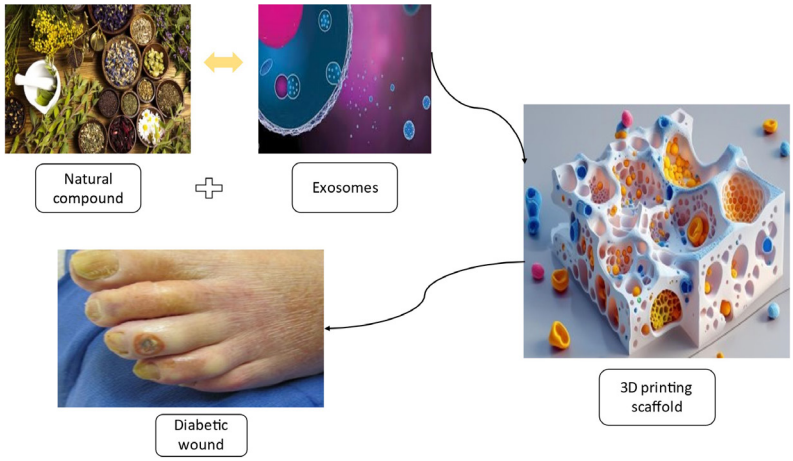


**Figure 1.** Schematic representation of the synergy between natural products and stem cell-derived exosomes

concentrations of natural compounds are combined with exosomes to enhance biological stability, therapeutic efficacy, and targeted delivery of bioactive agents. This synergistic interaction promotes accelerated tissue regeneration, suppresses inflammation, and improves wound healing in diabetic models.

The shift toward triple-component systems integrating exosomes, a natural compound such as curcumin, and a supportive scaffold, as seen in the MEMC-Gel hydrogel platform (129), marks a bold and increasingly common step in simultaneously tackling the complex, multilayered nature of diabetic wound pathology. The thinking behind these designs is straightforward and appealing: map out the key pathophysiological features of diabetic wounds (persistent inflammation, stalled angiogenesis, oxidative stress, impaired barrier integrity) and deliberately pair agents that hit distinct but synergistic targets: exosomes driving vascular repair and tissue regeneration, curcumin dampening chronic inflammation and oxidative damage, and the hydrogel providing a moist, protective, ECM-mimicking environment with sustained delivery.

That said, layering in this extra complexity doesn't come without real trade-offs and open scientific questions. One of the most pressing debates centers on release kinetics and timing: for the best healing trajectory, do we actually want all three components flooding the wound site simultaneously from day one, or would a more physiologically informed, phased release say, kicking off with a strong anti-inflammatory pulse from curcumin to quiet the hyperinflammatory storm first, then transitioning to exosome-driven pro-angiogenic and regenerative signals better recapitulate the natural, sequential phases of wound repair? Most current platforms, including many hydrogel-based ones, default to largely concurrent release profiles, which may oversimplify and miss opportunities to better align with the temporal dynamics of healing (inflammation resolution preceding robust angiogenesis and remodeling). Direct evidence comparing simultaneous versus sequenced delivery in head-to-head setups remains surprisingly sparse, leaving this as a key unresolved issue for rational optimization.

Adding to the challenge is the risk of unforeseen crosstalk or interactions among the natural compound's chemistry, the diverse bioactive cargo within exosomes, and breakdown products from the degrading scaffold matrix, which could alter stability or bioactivity, or even trigger unintended local responses. These potential issues make thorough, long-term biosafety and compatibility profiling essential, yet they're frequently underexplored or only briefly mentioned in preclinical reports. Until we generate more comparative data on release tuning, interaction risks, and true functional durability (beyond short-term closure rates), moving these ambitious triple systems from promising prototypes to reliable, standardized therapies will remain an uphill climb.

Advancements in diabetic wound healing are shifting away from conventional medical therapies toward a combinatorial strategy that utilizes 3D-printed scaffolds, exosome delivery, and herbal medicine. These adjunctive therapeutic strategies leverage the multifunctionality of each therapy to achieve an additive, synergistic effect that optimizes wound closure and, ultimately, wound-healing outcomes. Three-dimensional (3D) printing enables the generation of scaffolds with tightly controlled architecture, porosity, and mechanical properties that closely mimic the native extracellular matrix of the skin. Such scaffolds provide a supportive substrate for cell attachment, proliferation, and differentiation, and can be tailored to irregular wound shapes. Recent investigations have demonstrated that 3D-printed scaffolds (especially those incorporating nanofiber or hydrogel components) can provide a moist wound environment, absorb excess wound exudate, and improve capillary and granulation tissue formation in diabetic wounds (113, 130). Microfluidic bioprinting can also involve encapsulating living cells or microorganisms (in this case, oxygen-producing microalgae) within the scaffold, thereby addressing local hypoxia and stimulating angiogenesis and extracellular matrix formation (130, 131).

Using exosome-loaded hydrogel or nanofiber scaffolds has been shown to expedite diabetic wound healing, enhance fibroblast proliferation, regulate inflammation, and stimulate angiogenesis (113, 114). Herbal medicines, especially those from Traditional Chinese Medicine, are increasingly incorporated into 3D-printed scaffolds to exploit their anti-inflammatory, anti-oxidant, and/or pro-angiogenic properties. For example, scaffolds loaded with Panax notoginseng saponins (PNS) have been shown to stimulate overall cell adherence, proliferation, and migration. In contrast, a gradual release of herbal compounds from the scaffold promotes tissue regeneration and oxidative stress reduction during this process (131). By encapsulating herbal extracts and living autotrophic microorganisms within the scaffold, we achieve sustained drug delivery and photosynthetic oxygenation to mitigate hypoxic cell death and promote more rapid wound closure in diabetic models.

The MEMC-Gelhydrogel is prepared by photopolymerizing methacrylated gelatin (GelMA) in the presence of dopamine, thereby enabling simultaneous encapsulation of MSC-exo and MC-exo. The MEMC-Gel hydrogel is characterized by mechanical strength, tissue adhesion, degradability, absorptivity, and biocompatibility. MEMC-Gel hydrogel's physical properties are suitable for use as a biomedical wound dressing, and are suitable for irregular wounds while maintaining moisture and a moist environment conducive to healing. *In vitro* studies show that MEMC-Gel has potent anti-inflammatory and anti-oxidant effects. The hydrogel inhibits the production of pro-inflammatory cytokines and decreases oxidative stress in the wound milieu, in part through macrophage polarization of the immune response from a pro-inflammatory (M1) phenotypic response to an anti-inflammatory (M2) response. Immunomodulation is important for breaking the cycle of chronic inflammation that impairs diabetic wound healing. MEMC-Gel stimulates angiogenesis and tissue regeneration. The sustained release of MSC-exo and MC-exo from the hydrogel supports fibroblast migration and proliferation, promotes endothelial cell tube formation, and increases the expression of angiogenic factors. These effects collectively hasten the formation of new blood vessels and granulation tissue, which are critical for effective wound closure and tissue repair (129). MEMC-Gel has distinctly enhanced wound healing in diabetic mouse models; it clearly outperformed controls. The hydrogel plays a powerful role across all key aspects of diabetic wound healing. It suppresses both inflammation and oxidative stress and optimizes glycemic control within the wound microenvironment, thereby supporting tissue regeneration. Wound healing leads to enhanced epithelialization and

noticeable collagen deposition, evidence of much more vigorous structural repair than in controls. These findings illustrate the synergistic benefits of exosomes derived from mesenchymal stem cells (MSC-exo) and Momordica charantia (MC-exo) within a gelatin methacrylate (GelMA) and dopamine matrix (129).

All in all, the combinatorial applications of 3D-printed scaffolds, exosome delivery, and herbal medicine open an exciting new avenue for diabetic wound healing. These multiplexed systems provide a platform that can be customized to deliver therapeutic agents for sustained release, enhanced oxygen/nutritional delivery, and improved cellular activity, resulting not only in more efficacious repair but also in much quicker repair. Although preclinical studies have provided encouraging results, future clinical trials will be required to establish clinical efficacy and determine how best to translate these findings into patient care (91, 92, 131).

***Challenges and limitations in exosome applications***

Despite the substantial promise of exosomes as a therapeutic modality for diabetic wound healing owing to their ability to modulate inflammation, promote angiogenesis, facilitate re-epithelialization, and enhance extracellular matrix remodeling, their translation into routine clinical practice remains constrained by several critical limitations. A foremost challenge is the inherently short half-life and rapid clearance of exosomes following administration. Upon local or subcutaneous injection, a significant fraction is rapidly sequestered and cleared by the reticuloendothelial system or lymphatic drainage, often resulting in a biological half-life of only minutes to a few hours (132, 133). In the context of chronic diabetic ulcers, which demand sustained bioactivity over weeks to months, this transient presence severely compromises therapeutic efficacy, necessitating repeated dosing regimens that increase material consumption, elevate treatment costs, and compromise patient adherence. Additional hurdles include suboptimal stability in circulation, imprecise targeting to the wound microenvironment, and biosafety concerns. The bioactive cargo of exosomes, comprising miRNAs, proteins, lipids, and other molecules, is highly dependent on the parent cell type, culture conditions, and preconditioning protocols, introducing heterogeneity and the potential for unintended or off-target effects from unidentified components (134). Moreover, scaling up production to clinically relevant quantities poses formidable obstacles: reliance on expensive fetal bovine serum or growth factor supplements, limited bioreactor throughput, risks of microbial contamination, substantial batch-to-batch variability, and prohibitive costs collectively hinder GMP-compliant manufacturing and regulatory approval (135, 136).

To circumvent these barriers, a range of bioengineering strategies has emerged. Direct modification of exosomes via surface functionalization (e.g., ligand conjugation for enhanced targeting), PEGylation to prolong circulation time, integration with nanoparticles, or cargo loading through electroporation, sonication, extrusion, or transfection has been shown to improve stability, markedly improve retention at the wound site, and enhance cellular uptake while preserving membrane integrity and intrinsic bioactivity (137, 138). For instance, loading specific miRNAs such as miR-21-5p or miR-126 has potentiated pro-angiogenic and anti-inflammatory effects in preclinical diabetic models.

Equally transformative are advanced delivery platforms that afford sustained, localized release and protection against premature degradation. Incorporation of exosomes into biocompatible matrices, including injectable hydrogels, microneedle arrays, 3D-printed scaffolds, and decellularized extracellular matrix (dECM) composites, enables prolonged residency, stimuli-responsive discharge (e.g., in response to pH, ROS, or matrix metalloproteinases), and synergistic interaction with the wound bed (133, 139). Such hybrid systems not only extend exosome half-life but also enhance biocompatibility, minimize immune clearance, and support the dynamic requirements of the healing phases in diabetic tissue.

Collectively, integrating exosome engineering with smart biomaterials, coupled with ongoing improvements in serum-free culture optimization, automated purification (e.g., combining ultrafiltration with affinity chromatography), standardized characterization, and adherence to cGMP principles, holds considerable potential to overcome current impediments and accelerate the clinical deployment of exosome-based therapies for refractory diabetic wounds (139, 140).

***Challenges and limitations in natural compounds application***

Many clinical and *in vivo* studies have shown that medicinal plants promote wound healing by reducing ulcer size, lowering inflammatory markers, and improving measures of epithelialization and vascularization. However, medicinal plants have not yet been accepted as standard therapies in Western medicine, particularly because of variability and potential differences in dosing across plant sources and formulations, as well as limited clinical studies. Bromelain (an herbal protease) is consistently used in clinical practice for enzymatic debridement. While this underscores the impact of plant-derived agents, it also highlights the limited evidence supporting the use of accepted medicinal plant products (141).

A major challenge is the recognized variability inherent in the chemical composition of medicinal plants, which depends on plant species, growth location and conditions, harvesting time, and extraction methods. This variability leads to inconsistent therapeutic efficacy and poses a challenge to the standardization of herbal preparations for clinical application. The number of clinical trials evaluating herbal medicines has varied across formulations (creams, gels, capsules) and dosages, making comparison and evaluation more difficult. Also, the lack of standardized protocols for manufacturing herbal products and quality control in their production limits their clinical use in diabetic wound care, relative to conventional medicine, which dominates treatment decisions (141, 142).

Even though several randomized controlled trials have shown positive effects of herbal products on diabetic wound healing, their small sample sizes, short follow-up periods, and methodological limitations (e.g., no blinding, inadequate control groups) diminish the strength of the evidence for the use of medicinal plants as monotherapy or adjuncts. Furthermore, in many studies, the authors have focused primarily on local wound parameters, without a full assessment of systemic effects or long-term outcomes, which are important in diabetic patients (142, 143).

Infectious diseases caused by multidrug-resistant bacteria and fungi are a serious complication of diabetic

ulcers. Although many plants have been reported to have antimicrobial properties against common pathogens such as Staphylococcus aureus, Pseudomonas aeruginosa, and Escherichia coli, the potency and range of effects vary widely across analgesic combinations and invasive routes. It is unclear whether herbal products can effectively control infection in diabetic patients, given the polymicrobial nature of biofilms and the presence of resistant strains in such wounds. This will limit the standalone use of herbal products and often requires their combination with conventional antibiotics or newer, advanced wound care strategies (144, 145).

The therapeutic efficacy of active compounds in medicinal plants can be restricted by poor bioavailability, stability, and suboptimal penetration into the wound bed. Recent advances, such as nanoformulations and the incorporation of active compounds into hydrogels or dressings, are promising for stability, controlled release, and targeted delivery. At this stage, these technologies are still being evaluated and may face regulatory or manufacturing obstacles to entering the clinic (145, 146).

Diabetic ulcers comprise multicausal pathologies, including chronic inflammation, oxidative stress, defective angiogenesis, and neuropathy. Medicinal plants contain numerous bioactive compounds, and some of these compounds will likely optimize multiple pathways simultaneously. Yet, this complexity complicates the establishment of mechanisms of action and the optimization of a treatment protocol. In addition, the heterogeneity of diabetic wounds between patients will complicate using herbal-based therapies and achieving consistently effective medicine (147).

***Challenges and future prospects of using 3D-printed scaffolds in the treatment of diabetic wounds***

A central technical obstacle in 3D printing for wound care is achieving adequate vascularization of the printed constructs. Effective wound healing requires a sufficient blood supply to provide nutrients and eliminate waste. Nevertheless, establishing functional blood vessels within 3D-printed scaffolds remains a significant difficulty. Strategies such as incorporating vascular channels or applying bioactive factors to promote angiogenesis are under investigation; however, generating fully functional vascular networks in printed tissues remains an active field of study (148). Another notable biological obstacle is the immune response elicited by the introduction of foreign materials into the body, which may lead to inflammation or rejection of 3D-printed constructs. Ensuring the biocompatibility of printing materials is essential to minimize adverse immune reactions. Efforts are underway to develop materials that are both biocompatible and capable of mimicking the natural extracellular matrix (ECM), thereby reducing immune responses and enhancing integration with host tissues (149).

The degradation of materials, especially in biodegradable scaffolds, presents a significant challenge. The rate of degradation critically affects scaffold performance and the wound healing process. Rapid degradation may undermine the scaffold's structural integrity before sufficient tissue regeneration occurs, while overly slow degradation could hinder natural tissue formation and prolong the presence of foreign material at the wound site (150).

The substantial cost of 3D printing and bioprinting technologies limits their accessibility for the large-scale production of 3D-printed pharmaceuticals and bioprinted organs intended for broad public application. The majority of research in these domains remains confined to laboratory settings, and greater focus should be placed on translational studies. Priority ought to be assigned to investigating the effects of 3D-printed and bioprinted products on biological systems through preclinical investigations and case studies, wherever practicable. Additionally, while 3D printing enables the creation of pharmaceuticals with varied sizes and shapes, the development of customized anti-diabetic drug formulations tailored to patients' age and other factors remains unexplored. Currently, research on personalized or individualized treatments is limited, underscoring the need to focus on patient-specific pharmaceutical and biomedical products instead of standardized, "one-size-fits-all" medications. Furthermore, efforts to secure Food and Drug Administration (FDA) approval for 3D-printed and bioprinted products must be intensified. More attention should be directed toward developing, marketing, and promoting the use of these products for the public. Additionally, advancing *in vitro* drug-testing models and addressing ethical concerns related to 3D-printed and bioprinted products are critical areas requiring further focus (151).

***Future directions***

Exosomes, nanoparticles released from cells, have proven to be promising natural delivery vehicles for targeted drug delivery, in part due to their biocompatibility, low immunogenicity, and ability to cross physiological barriers such as the blood-brain barrier. However, therapeutic targeting with exosomes remains below the precision required for delivery to specific tissues or disease sites. To enable efficient, specific targeting, engineering approaches have modified the surface of exosomes to improve delivery specificity and therapeutic efficacy (152).

Approaches to surface modification range from genetically engineering parent cells to express targeting ligands fused to exosomal membrane proteins to direct chemical or physical modification of isolated exosomes. Common strategies include covalently attaching a targeting peptide, antibody, or aptamer via click chemistry or ligand-receptor binding. These modified exosomes could preferentially and more effectively bind to receptors overexpressed on target cells, such as tumor cells or ischemic tissues, thereby improving drug accumulation and therapeutic outcomes. For example, cyclic RGD peptides could bind to integrin receptors on tumor vasculature, and aptamers could bind to cancer-specific markers with very high affinity (152-154).

Engineered exosomes (eExo) derived from 3D cultures using advanced surface-engineering strategies may offer improved targeting capabilities at a feasible scale for therapeutic benefit. However, several issues remain, including ensuring the stability of surface modifications during circulation, preventing rapid clearance by the mononuclear phagocyte system (MPS), and achieving precise control over biodistribution. Future research efforts involve refining modification chemistries, identifying innovative targeting ligands, and improving 3D culture conditions to maximize therapeutic impact (153-155).

***Use of novel natural compounds in 3D printed scaffolds for diabetic wound treatment***

The incorporation of new natural compounds into

3D-printed scaffolds, such as plant-based bioactive molecules and essential oils, is a potentially effective approach to improving healing outcomes by providing both structural support and biological activity.

To improve the performance of biomaterials in tissue engineering and to incorporate adjuvants, techniques such as drug encapsulation (156) and nanoparticle integration (157) have been employed. These strategies improve material characteristics such as mechanical strength, hydrophilicity (158), biological functionality, and the controlled delivery of therapeutic agents from biomaterials (157). The encapsulation of natural compounds, including curcumin, within bioinks that support cell growth and differentiation offers potential anti-inflammatory and antimicrobial benefits, reducing infection risks at the implantation site and promoting accelerated healing and tissue integration. A range of formulations, such as nanoparticles, liposomes, nanogels, and nano-emulsions, has been explored, alongside studies assessing curcumin's efficacy in improving wound healing in streptozotocin-induced diabetic rat models. Photobiomodulation (PBM) therapy employing blue light has been demonstrated to enhance cellular proliferation and reduce oxidative stress. When combined with curcumin-loaded scaffolds, this approach produces a synergistic effect: curcumin can undergo photoactivation, modulating ROS generation (159, 160) and further stimulating pathways that facilitate wound repair. The use of 3D-printed scaffolds with a grid-like architecture enhances the effectiveness of light therapy by allowing deeper light penetration into the scaffold. This configuration also improves oxygen permeability, thereby supporting greater cell viability and tissue regeneration. Moreover, the interconnected pores within the scaffold encourage efficient nutrient diffusion, establishing an optimal microenvironment for stem cell proliferation (161). Additionally, curcumin helps prevent contamination, accelerates wound closure, and supports the use of photobiomodulation (PBM) as an effective tissue repair strategy (162).

3D printing combined with natural bioactive compounds or plant extracts enables the fabrication of multifunctional scaffolds that not only provide mechanical support but also actively participate in wound healing. This integrative approach to wound healing enhances healing by integrating structural, biochemical, and biological cues to address the complex pathophysiology of diabetic wounds and improve tissue repair (130).

### *Incorporation of 4D printing technologies in wound repair*

The emerging domain of 4D printing builds on conventional 3D printing by incorporating the dimension of time into the manufacturing process. This technique uses smart materials that can change their shape or properties in response to external stimuli, such as temperature, pH, or humidity (163, 164). These materials, known as shape-memory polymers or self-healing hydrogels, enable the development of dynamic wound care solutions that adapt to the evolving conditions of the wound microenvironment. For example, 4D-printed wound dressings could alter their permeability or deliver therapeutic agents in a controlled manner in response to changes in moisture levels (165).

The ability to adapt dynamically in real time holds significant potential to improve wound management and accelerate healing. Ongoing research is directed toward the development of 4D-printed dressings capable of releasing anti-inflammatory agents in response to changes in wound pH, as well as the design of smart scaffolds for tissue regeneration that dynamically modify their configuration upon exposure to thermal or biological signals. Additionally, investigations are examining self-adjusting wound patches that alter their stiffness and porosity according to the surrounding tissue environment, thereby enhancing integration with the wound bed (166, 167).

### *Clinical trials*

Exosome research remains in its early stages, with significant potential for advancing from preclinical studies to clinical applications, offering substantial opportunities for further exploration. Several clinical trials and research studies have examined the therapeutic benefit of mesenchymal stem cell-derived exosomes (MSC-Exos) in promoting diabetic wound healing, often in combination with biomaterials such as hydrogels or scaffolds to enhance stability, targeting, and sustained release (168). Although clinical trials combining exosomes, natural compounds, and printed scaffolds are still emerging, preliminary data on each component and their formulations provide a solid rationale for proposing randomized, double-blind clinical trials in the future.

## Conclusion

The integration of exosomes, natural compounds, and 3D-printed scaffolds offers exciting, transformative potential for treating diabetic wounds, shifting away from narrowly focused, single-mechanism therapies toward strategies that can tackle the stubborn, multifactorial chronicity of these injuries. That said, moving beyond the current wave of mostly descriptive, proof-of-concept papers toward approaches that can actually reach patients will require the field to confront several stubborn hurdles head-on and pivot toward more strategic, rigorous research priorities.

First and foremost, we need to move decisively from isolated demonstrations to robust comparative effectiveness studies. The literature is full of promising individual platforms. Still, we lack standardized, head-to-head evaluations that pit different exosome sources (e.g., MSC-derived vs. other origins), classes of natural compounds, or scaffold designs against one another, using consistent wound models, dosing regimens, and outcome measures. Only through such direct comparisons can we begin to build a clear hierarchy of what works best under which conditions and ultimately guide smarter clinical decisions.

Second, delivery systems need to become much smarter about timing and responsiveness. Wound healing unfolds in distinct phases, so why should therapeutics be delivered all at once? The next big leap lies in 4D-printed or stimuli-responsive scaffolds that can adapt dynamically, releasing anti-inflammatory agents early in response to high ROS or low pH, then shifting to pro-angiogenic exosome cargo as the microenvironment stabilizes, or even triggering on-demand release based on biomarkers such as MMP levels. Emerging work on smart hydrogels and shape-changing materials already points in this direction, but integrating these with exosome-natural compound combinations remains largely unexplored territory.

Third, manufacturing and regulatory realities can't be afterthoughts. Producing exosomes at GMP-compliant, clinically relevant scales with consistent quality is notoriously difficult, as upstream cell culture, downstream purification

(often via tangential flow filtration or chromatography), yield, and batch-to-batch variability persist. The same goes for standardizing plant-derived natural extracts. Equally critical is developing agreed-upon potency assays that link specific exosomal miRNAs, surface markers, or compound concentrations directly to meaningful *in vivo* effects (e.g., angiogenesis or inflammation resolution), rather than relying solely on particle counts or basic characterization. Without these tools, regulators will continue to view these products with caution. Finally, embracing patient stratification is essential given how heterogeneous diabetic wounds really are, varying in infection status, vascular compromise, biofilm burden, and comorbidities. Future trials should incorporate predictive biomarkers (such as wound fluid proteomics, miRNA profiles, or genetic markers) to identify which patients are most likely to respond to specific exosome-compound-scaffold combinations, thereby setting the stage for truly personalized regenerative approaches.

Ultimately, the platforms reviewed here are scientifically intriguing and mechanistically sound, but their path to the clinic depends on shifting from enthusiastic cataloging of individual successes to deeper mechanistic insight, rigorous comparative data, and practical solutions for standardization, scalable GMP production, intelligent timed delivery, and patient-specific tailoring. Only by systematically addressing these translational bottlenecks can this promising convergence of technologies genuinely change the outlook for diabetic wound care.

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## Authors' Contributions

Z R was responsible for the conceptualization and writing of this review study, while M S handled the editing and critical revision of the manuscript.

## Conflicts of Interest

No potential conflicts of interest was reported by the authors.

## Declaration

The authors used Grammarly (an AI-assisted writing tool) solely to improve the grammar, spelling, punctuation, and overall language clarity of this manuscript. No artificial intelligence tool was used to generate, interpret, or modify the scientific content, data, and conclusions. The authors ake full responsibility for the accuracy, originality, and integrity of the manuscript.

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