Journal of Drug Delivery and Therapeutics

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Review Article

Smart Nanocarrier Systems for Diabetic Wound Healing: Preclinical Innovations and Clinical Progress in Drug and Gene Delivery

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Article Info:

Article History:

Received 20 Dec 2025
Reviewed 08 Feb 2026
Accepted 26 Feb 2026
Published 15 March 2026

Cite this article as:

Bhat P, Satapathy A, Yadav N, Satapathy A, Chandrakar K, Satapathy A, Bhardwaj SK, Patel N, Smart Nanocarrier Systems for Diabetic Wound Healing: Preclinical Innovations and Clinical Progress in Drug and Gene Delivery, Journal of Drug Delivery and Therapeutics. 2026; 16(3):268-288 *DOI: http://dx.doi.org/10.22270/jddt.v16i3.7630*

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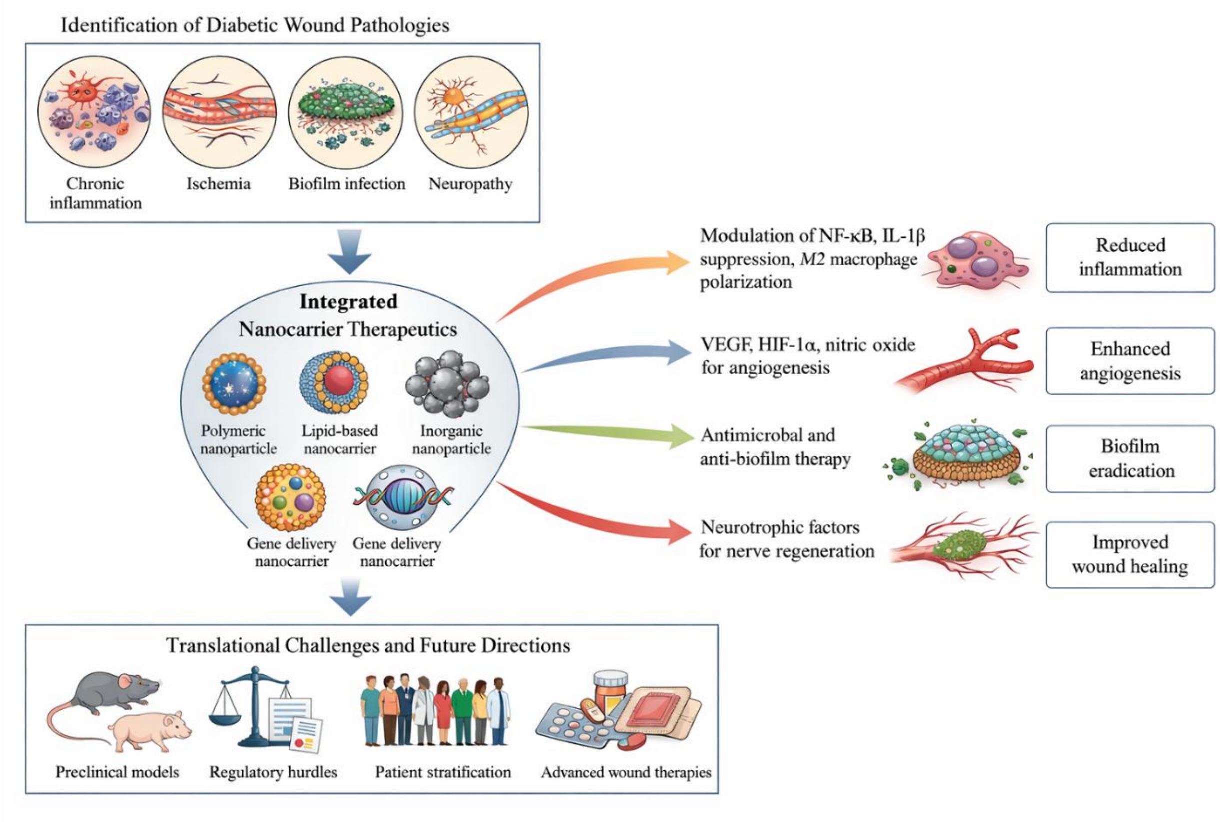
Abstract

Diabetic wounds represent a complex clinical challenge arising from the convergence of chronic inflammation, impaired angiogenesis, oxidative stress, neuropathy, infection, and dysregulated extracellular matrix remodeling. Conventional therapies targeting single pathological components have shown limited efficacy, underscoring the need for integrated and mechanistically informed treatment strategies. This review comprehensively examines nanocarrier-mediated drug delivery systems as a transformative platform for diabetic wound management, integrating herbal, synthetic, semi-synthetic and gene-based therapeutics across preclinical and clinical landscapes. Emphasis is placed on the molecular pathophysiology of diabetic wounds and how advanced nanocarrier platforms enable spatiotemporal control, enhanced bioavailability, and pathway-specific modulation of inflammatory, angiogenic, antimicrobial, and regenerative processes. Material-driven functionalities, including stimuli-responsive release and multifunctional hybrid systems are critically discussed in relation to disorder-specific wound phenotypes. Furthermore, the review evaluates current preclinical models, translational barriers and emerging clinical trends, highlighting the importance of patient stratification and precision wound nanomedicine. Collectively, this work positions nanocarrier-based therapeutics as a promising and adaptable approach capable of addressing the biological heterogeneity of diabetic wounds and advancing toward clinically meaningful outcomes.

Keywords: angiogenesis; diabetic wounds; gene therapy; herbal therapeutics; nanocarriers; wound healing

Graphical abstract



Highlights:

- Nanocarrier systems enable precise spatiotemporal control of therapeutics in diabetic wounds
- Integrated herbal, synthetic and gene therapies address multifactorial wound pathology
- Molecular reprogramming of inflammation and angiogenesis accelerates chronic wound repair
- Smart stimuli-responsive nanomaterials adapt drug release to wound microenvironments
- Advanced preclinical models bridge material science with translational wound biology
- Precision wound nanomedicine supports patient-specific and disorder-targeted therapies

1. Introduction

1.1 Global Burden and Clinical Unmet Needs in Diabetic Wound Healing

Diabetes mellitus represents one of the most pervasive metabolic disorders worldwide, with its chronic complications exerting a disproportionate burden on healthcare systems. Among these complications, diabetic wounds, particularly diabetic foot ulcers (DFUs), remain some of the most debilitating and costly outcomes, affecting a significant proportion of individuals with diabetes during their lifetime and often leading to infection, hospitalization, or lower-limb amputation.[1,2] Despite advances in glycemic control and wound care technologies, the incidence of DFUs continues to rise in parallel with global diabetes prevalence and their complex pathophysiology involving chronic inflammation, immune dysregulation, neuropathy, and impaired tissue regeneration contributes to prolonged healing times, frequent recurrence, and high susceptibility to microbial colonization.[2,3] Standard treatment modalities, including debridement, pressure offloading, topical antimicrobials and growth factor application are largely palliative and fail to address the underlying molecular dysfunctions that distinguish diabetic wounds from acute injuries. The limited efficacy of existing therapies highlights a persistent clinical gap between wound closure and true tissue regeneration, underscoring the urgent need for advanced therapeutic strategies capable of restoring the disrupted healing cascade.

1.2 Diabetic Wounds as a Multifactorial Molecular Disorder

Unlike acute wounds, which progress through well-orchestrated phases of hemostasis, inflammation, proliferation and remodeling, diabetic wounds remain trapped in a pathological state dominated by chronic inflammation and impaired cellular responsiveness. Hyperglycemia-induced metabolic stress alters intracellular signaling pathways, leading to excessive production of reactive oxygen species (ROS), accumulation of advanced glycation end products (AGEs) and sustained activation of pro-inflammatory transcription factors such as nuclear factor kappa B (NF-κB), which drives prolonged pro-inflammatory macrophage polarization and impaired tissue repair.[4,5] At the cellular level, keratinocytes, fibroblasts, endothelial cells, macrophages, and stem/progenitor cells exhibit compromised migration, proliferation and paracrine signaling, with macrophage polarization skewed toward a persistent pro-inflammatory (M1) phenotype while the reparative (M2) phenotype necessary for angiogenesis and extracellular matrix (ECM) remodeling is inadequately induced.[4,6] Concurrently, angiogenic signaling pathways most notably those involving vascular endothelial growth factor (VEGF) and hypoxia-inducible factor-1α (HIF-1α) are functionally suppressed despite local hypoxia, creating a paradoxically anti-angiogenic wound environment that further impedes tissue regeneration.[4,6] Compounding these defects, diabetic wounds are frequently associated with peripheral neuropathy, ischemia and microbial biofilm formation, all of which exacerbate immune dysfunction and chronicity.[7] These overlapping pathophysiological axes transform diabetic wounds into a multifactorial molecular disorder rather than a simple tissue defect, and effective therapeutic intervention requires a systems-level approach capable of simultaneously modulating inflammation, oxidative stress, angiogenesis, infection and tissue regeneration.

1.3 Barriers to Effective Drug Delivery in the Diabetic Wound Microenvironment

One of the central challenges in diabetic wound management lies in the hostile wound microenvironment, which severely limits the therapeutic efficacy of conventional drug delivery approaches. Elevated protease activity, excessive exudate, acidic pH, oxidative stress and impaired local blood perfusion collectively compromise drug stability, penetration and bioavailability, making it difficult for bioactive molecules to remain effective within the wound bed.[8,9] Growth factors and peptides are rapidly degraded by proteases present in chronic wounds, while small-molecule drugs often fail to reach or maintain therapeutic concentrations at the wound site for sustained periods due to poor tissue penetration and rapid washout.[9,10] Furthermore, systemic drug administration is frequently contraindicated due to off-target effects and reduced local accumulation, particularly in ischemic tissues and topical formulations though attractive suffer from poor retention, uncontrolled diffusion and insufficient cellular uptake in the complex diabetic wound milieu.[8,11] These delivery-related limitations, rather than the lack of potent bioactive agents, have emerged as a critical bottleneck in diabetic wound therapeutics.

1.4 Rationale for Nanocarrier-Mediated Drug Delivery in Diabetic Wounds

Nanocarrier-based drug delivery systems offer a compelling solution to the multifaceted challenges posed by diabetic wounds. By virtue of their tunable physicochemical properties, nanocarriers can protect encapsulated therapeutics from premature degradation, enhance penetration into wound tissues and enable controlled or stimuli-responsive drug release. Importantly, nanocarriers can be engineered to interact with specific cellular targets, such as macrophages, endothelial cells, or fibroblasts, thereby improving therapeutic precision and reprogramming the chronic inflammatory microenvironment characteristic of diabetic wounds.[12,13] In the context of diabetic wounds, nanocarriers have demonstrated the ability to modulate the inflammatory microenvironment, scavenge excess ROS, promote angiogenesis, inhibit microbial biofilms and restore extracellular matrix homeostasis through multifunctional designs that combine anti-inflammatory, antioxidant and regenerative cues.[12,14] Their versatility allows for the delivery of a wide spectrum of therapeutic payloads, including herbal bioactives with poor solubility, synthetic and semi-synthetic drugs with narrow therapeutic windows and nucleic acid-based therapeutics aimed at gene regulation and cellular reprogramming, underscoring their potential to overcome conventional delivery barriers in chronic wound care.[13,14]

1.5 Scope and Objectives of This Review

This review provides a comprehensive and integrative analysis of nanocarrier-mediated drug delivery strategies for diabetic wound healing, encompassing herbal, synthetic, semi-synthetic and gene-based therapeutic modalities. Emphasis is placed on elucidating the molecular mechanisms underlying diabetic wound pathology and how nanocarrier systems are being rationally designed to overcome biological and delivery barriers. By critically examining both preclinical and clinical evidence, this review aims to bridge the gap between experimental innovation and clinical translation. Additionally, it highlights emerging trends, unresolved challenges and future directions in the development of multifunctional nanocarrier platforms for chronic diabetic wound management. Through this lens, the review seeks to position nanomedicine not merely as a delivery tool, but as a transformative therapeutic paradigm for diabetic wound care.

2. Molecular Pathophysiology of Diabetic Wounds: Targetable Disorders

Diabetic wounds represent a convergence of metabolic, vascular, immunological and neurological abnormalities that collectively disrupt the tightly regulated wound-healing cascade with hyperglycemia, immune dysregulation and impaired cellular signaling intersecting to perpetuate chronicity rather than resolution.[15] Rather than a failure of a single pathway, diabetic wound chronicity emerges from sustained molecular dysregulation across multiple cellular compartments, including persistent pro-inflammatory macrophage activation, oxidative stress, impaired angiogenic and growth factor responses and disrupted cellular migration and differentiation.[15,16] Understanding these interconnected molecular derangements spanning metabolic disturbances, inflammatory signaling cascades, extracellular matrix remodeling deficits and neurovascular dysfunction is essential for the rational design of nanocarrier-based therapeutic interventions capable of restoring functional healing by simultaneously targeting these multifactorial pathological axes.[16]

2.1 Hyperglycemia-Driven Cellular and Metabolic Dysregulation

Chronic hyperglycemia acts as the primary upstream driver of molecular dysfunction in diabetic wounds, initiating a cascade of metabolic stress pathways that impair cellular homeostasis.

2.1.1 Advanced Glycation End Products (AGEs) and RAGE Signaling

Persistent hyperglycemia promotes the non-enzymatic glycation of proteins and lipids, leading to the accumulation of advanced glycation end products (AGEs) within the wound microenvironment. AGEs interact with their cognate receptor, RAGE, expressed on keratinocytes, endothelial cells, macrophages and fibroblasts and this engagement activates downstream signaling cascades, including MAPKs and NF-κB, resulting in sustained transcription of pro-inflammatory cytokines such as TNF-α, IL-1β and IL-6 that perpetuate chronic inflammation in diabetic wounds.[17,18] At the tissue level, AGE-RAGE signaling reduces keratinocyte migration, suppresses fibroblast collagen synthesis, accelerates extracellular matrix degradation, and stiffens the wound matrix through cross-linking of collagen fibers, impairing Mechan transduction and further inhibiting cell motility and reparative responses.[17,18] These molecular and biomechanical disruptions contribute to prolonged inflammatory states and delayed healing, highlighting the critical role of AGE-RAGE signaling as a therapeutic target in diabetic wound repair.

2.1.2 Polyol and Hexosamine Pathway Activation

Excess intracellular glucose is diverted into the polyol pathway, where aldose reductase converts glucose into sorbitol, consuming NADPH and depleting cellular antioxidant reserves; reduced NADPH availability compromises glutathione regeneration, amplifying oxidative stress within wound cells and contributing to the persistent redox imbalance observed in diabetic wounds.[19] Simultaneously, increased flux through the hexosamine biosynthetic pathway leads to elevated production of UDP-N-acetylglucosamine (UDP-GlcNAc) and consequent aberrant O-GlcNAcylation of transcription factors and signaling proteins, which alters gene expression patterns essential for cell proliferation, differentiation, and repair.[19,20] These hyperglycemia-induced metabolic shifts collectively impair keratinocyte differentiation, fibroblast function, and endothelial responsiveness further exacerbating chronic wound pathology and delaying healing in diabetes.[20]

2.2 Chronic Inflammation and Immune Dysregulation

Inflammation is a necessary early phase of wound healing; however, diabetic wounds are characterized by a failure to resolve inflammation, resulting in prolonged tissue damage and delayed repair.

2.2.1 Macrophage Polarization Imbalance

Macrophages orchestrate wound healing through dynamic phenotype switching, but in diabetic wounds these cells remain locked in a pro-inflammatory M1 phenotype, marked by high expression of inducible nitric oxide synthase (iNOS), TNF-α and IL-1β, with an impaired transition to the reparative M2 phenotype associated with arginase-1, IL-10 and TGF-β.[21,22] This polarization imbalance not only disrupts angiogenesis, inhibits fibroblast activation, and limits extracellular matrix deposition, but M1 macrophages also perpetuate oxidative stress and reinforce a self-sustaining inflammatory loop that impairs the progression to later healing phases.[21,23] Therapeutic strategies that successfully modulate M1/M2 balance either by promoting M2 polarization pathways or suppressing persistent M1 activation have shown promise in accelerating resolution of chronic inflammation and improving diabetic wound repair in recent preclinical models.[22,23]

2.2.2 Dysregulated Cytokine and Chemokine Networks

Elevated levels of pro-inflammatory cytokines in diabetic wounds suppress growth factor signaling and impair stem/progenitor cell recruitment, while reduced expression of chemokines such as stromal cell-derived factor-1 (SDF-1) limits endothelial progenitor cell homing and neovascularization, contributing to poor vascular repair in chronic wounds.[24]

2.3 Oxidative Stress and Mitochondrial Dysfunction

Oxidative stress represents a central pathological hallmark of diabetic wounds, where hyperglycemia-induced activation of NADPH oxidases and mitochondrial electron transport chain dysfunction leads to excessive ROS generation that damages cellular lipids, proteins and DNA, impairing keratinocyte proliferation and fibroblast viability.[25] Moreover, ROS accumulation destabilizes hypoxia-inducible factor-1α (HIF-1α), paradoxically suppressing angiogenic responses in hypoxic wound tissue and further perpetuating a cycle of mitochondrial dysfunction and impaired healing.[25]

2.4 Impaired Angiogenesis and Microvascular Dysfunction

Effective wound healing requires rapid neovascularization to restore oxygen and nutrient supply, yet in diabetic wounds angiogenesis is profoundly impaired despite persistent hypoxia, largely due to dysfunctional endothelial responses, oxidative stress and downregulation of key angiogenic pathways.[26,27]

2.4.1 VEGF Resistance and HIF-1α Destabilization

Although VEGF expression may be elevated in response to hypoxia, endothelial cells often exhibit reduced responsiveness because of receptor downregulation and impaired downstream signaling through PI3K/Akt pathways and oxidative stress together with proteasomal degradation destabilizes HIF-1α, limiting transcription of angiogenic genes essential for neovascularization.[26,28]

2.4.2 Endothelial Nitric Oxide Synthase (eNOS) Dysfunction

Reduced eNOS activity and nitric oxide bioavailability compromise vasodilation, endothelial cell migration and capillary formation, while peroxynitrite formation from interactions between NO and superoxide further exacerbates endothelial injury, reinforcing microvascular dysfunction and limiting nutrient delivery to healing tissues.[26,29]

2.5 Peripheral Neuropathy and Neurogenic Inflammation Deficits

Diabetic neuropathy contributes to impaired wound healing by disrupting neuro-immune crosstalk; loss of sensory nerve fibers reduces local release of neuropeptides such as substance P and calcitonin gene-related peptide (CGRP), which normally promote vasodilation, immune cell recruitment and keratinocyte proliferation, resulting in diminished early inflammatory signaling and delayed tissue repair, particularly in pressure-prone regions of the foot.[27,30]

2.6 Extracellular Matrix Remodeling and Fibrotic Imbalance

Diabetic wounds exhibit excessive matrix degradation due to sustained overexpression of matrix metalloproteinases (MMP-2, MMP-9) and reduced levels of tissue inhibitors of metalloproteinases (TIMPs), preventing stable collagen deposition and granulation tissue formation; fibroblasts in diabetic wounds also display impaired responsiveness to TGF-β signaling, limiting myofibroblast differentiation and wound contraction.[26,31]

2.7 Infection Susceptibility and Biofilm Formation

The immunocompromised wound environment, combined with poor vascularization and neuropathy, predisposes diabetic wounds to persistent infection, where polymicrobial biofilms protect pathogens from host immune responses and antibiotic penetration, secrete proteases and toxins that degrade growth factors and ECM components and further delay healing while reinforcing chronicity.[26,32]

3.Nanocarrier Platforms for Diabetic Wound Drug Delivery

The complexity of diabetic wound pathophysiology necessitates drug delivery systems that are not only biocompatible but also adaptive to a dynamically hostile microenvironment characterized by oxidative stress, protease excess, hypoxia and microbial burden. Nanocarrier platforms have emerged as versatile materials-engineered systems capable of overcoming these barriers through controlled drug protection, targeted delivery and stimuli-responsive release.[33,34] This section critically examines the material science foundations of nanocarrier systems designed for diabetic wound applications.

3.1 Design Considerations for Nanocarriers in the Diabetic Wound Microenvironment

The rational design of nanocarriers for diabetic wounds requires a departure from conventional systemic nanomedicine paradigms toward materials optimized for topical, localized and microenvironment-responsive delivery.[33,35]

3.1.1 Size, Shape, and Surface Charge

Nanocarrier size directly influences wound penetration, cellular uptake and retention within the extracellular matrix. Particles ranging from 50-300 nm have demonstrated optimal penetration into wound tissue while minimizing rapid clearance through exudate.[33] Spherical nanoparticles are most commonly employed due to synthetic ease; however, emerging evidence suggests that anisotropic nanostructures (e.g., nanofibers, nanorods) may enhance cellular interactions and matrix integration. Surface charge plays a critical role in biological interactions, with mildly cationic nanocarriers enhancing adhesion to negatively charged cell membranes and biofilms.[33,36]

3.1.2 Surface Functionalization and Targeting Strategies

Surface modification with polymers such as polyethylene glycol or chitosan, peptides, or antibodies enables improved wound retention and cell-specific targeting, including macrophage and endothelial cell markers that enhance therapeutic precision.[34]

3.1.3 Stimuli-Responsive and Microenvironment-Adaptive Release

Diabetic wounds exhibit distinctive biochemical cues-acidic pH, elevated ROS levels, protease overexpression and bacterial enzymes-that can be exploited for on-demand drug release. Smart nanocarriers engineered with pH-sensitive linkers, ROS-cleavable bonds, or enzyme-degradable matrices allow spatially and temporally controlled payload release, improving efficacy and safety.[33,37]

3.2 Organic Nanocarrier Systems

Organic nanocarriers dominate diabetic wound research due to their tunable chemistry and biodegradability. Polymeric nanoparticles from PLGA and chitosan provide sustained drug release and bio-adhesion, whereas lipid-based carriers like liposomes and ethosomes facilitate intracellular delivery.[33,38]

3.2.3 Solid Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLCs)

SLNs and NLCs combine lipid matrix advantages with improved drug stability, making them suitable for delivering poorly soluble therapeutic agents and enhancing diabetic wound repair.[34]

3.3 Inorganic Nanocarriers and Hybrid Systems

Metallic nanoparticles such as silver, zinc oxide, and cerium oxide show intrinsic antimicrobial and antioxidant activities; when integrated into hybrid platforms, they offer multifunctional therapeutic properties.[33,39] Mesoporous silica nanoparticles (MSNs) enable high drug loading and controlled release, although concerns about biodegradability remain for clinical translation.[34]

3.4 Smart and Bioactive Nanocarriers

Smart nanocarriers, including ROS-responsive materials and enzyme-triggered systems, release drugs in response to pathological wound cues. For example, MMP9-responsive nanozyme hydrogels can adaptively clear excessive ROS and modulate macrophage phenotype in vivo.[33,40] Dual-responsive pH/ROS composite systems have also been shown to co-regulate inflammation and vascularization.[37]

3.5 Integration with Wound Dressings and Scaffolds

Embedding nanocarriers within hydrogels and nanofibrous mats enhances clinical applicability by providing structural support, moisture balance and sustained therapeutic delivery, mimicking native extracellular matrix architecture and promoting wound closure.[36,41]

3.6 Translational Considerations and Manufacturing Challenges

Despite promising outcomes, clinical translation remains challenged by manufacturing scalability, sterilization and regulatory compliance. Material selection, degradation profiles and long-term biocompatibility must align with regulatory expectations to enable clinical adoption.[34,42,43,44]

Table 1: Nanocarrier Platforms for Diabetic Wound Drug Delivery

Nanocarrier Class	**Core Materials**	**Key Physicochemical Features**	**Primary Advantages in Diabetic Wounds**	**Limitations / Challenges**	**Ref.**
Polymeric nanoparticles	PLGA, PCL, chitosan, PEGylated polymers	Tunable size, degradability, surface charge	Sustained release, protection from proteases, good wound retention	Polymer toxicity (cationic), burst release	45,46
Lipid-based nanocarriers	Liposomes, transfersomes, ethosomes	Bilayer structure, deformability	Enhanced cellular uptake, membrane fusion, versatile drug loading	Stability issues, oxidation	47,48
Solid lipid nanoparticles (SLNs)	Solid lipids (glyceryl monostearate)	High physical stability	Improved drug loading vs liposomes, occlusive effects	Limited loading of hydrophilic drugs	47,49
Nanostructured lipid carriers (NLCs)	Solid + liquid lipids	Reduced drug expulsion, flexible core	Long-term topical delivery, controlled release	Complex formulation, scalability	50
Inorganic nanoparticles	Ag, Au, ZnO, CeO_2	Intrinsic antimicrobial/redox activity	Biofilm disruption, ROS scavenging, microbial control	Long-term safety concerns, potential heavy metal toxicity	51
Mesoporous silica nanoparticles	Silica with tunable pores	High surface area, pore control	High drug/gene loading, multifunctionality	Biodegradability issues, potential accumulation	50,51
Hybrid nanocarriers	Polymer–metal, lipid–silica, organic–inorganic	Multifunctionality	Combined bioactivity + delivery, synergistic effects	Regulatory complexity, manufacturing control	45, 51
Smart nanocarriers	ROS/pH/enzyme-responsive polymers, dual-responsive hydrogels	Stimuli-triggered release	Site-specific drug action, controlled therapeutic availability	Manufacturing complexity, stability, cost	52

4. Nanocarrier Enabled Delivery of Herbal Therapeutics for Diabetic Wound Healing

Herbal therapeutics have long been employed in wound management due to their broad biological activity, intrinsic biocompatibility and multi-target pharmacology. In the context of diabetic wounds, phytochemicals offer unique advantages by simultaneously modulating oxidative stress, inflammation, angiogenesis and extracellular matrix remodeling. However, their clinical translation has been hindered by poor aqueous solubility, chemical instability, rapid degradation, and limited tissue penetration. Nanocarrier mediated delivery systems have emerged as transformative tools to overcome these limitations, enabling precise and sustained modulation of wound healing molecular pathways while enhancing solubility, stability and bioavailability of herbal actives. Nanocarrier systems such as nano-emulsions, phytosomes and nanoparticles enhance herbal bioactive delivery for diabetic ulcers by improving stability and targeted release.[53,54]

4.1 Molecular Targets of Phytochemicals in Diabetic Wound Healing

Phytochemicals exert pleiotropic effects by interacting with multiple intracellular signaling pathways disrupted in diabetic wounds; instead of acting through single high-affinity targets, these compounds modulate signaling networks that collectively restore cellular homeostasis and support reparative processes. Herbal actives modulate NF-κB, COX-2, iNOS and ROS pathways and influence cytokines and growth factors relevant to healing.[54]

4.1.1 Antioxidant Signaling Pathways

Oxidative stress is a central driver of diabetic wound chronicity and many herbal compounds activate endogenous antioxidant defense systems by enhancing nuclear translocation of Nrf2, leading to upregulation of antioxidant response element (ARE)-regulated genes such as HO-1, SOD, catalase and glutathione peroxidase, which help restore redox balance and indirectly stabilize HIF-1α to promote angiogenic signaling. Curcumin and quercetin are well-studied phytochemicals with potent antioxidant activity incorporated into nanostructured carriers for enhanced effect.[55,56]

4.1.2 Anti-Inflammatory and Immunomodulatory Signaling

Many phytochemicals inhibit chronic inflammatory signaling by suppressing NF-κB activation and reducing expression of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) while also promoting macrophage polarization toward the reparative M2 phenotype-effects particularly relevant in diabetic wounds where prolonged M1 macrophage dominance impairs healing. Nanocarrier formulations significantly increase tissue retention and reduce inflammatory burden.[53,57]

4.1.3 Pro-Angiogenic and Pro-Regenerative Pathways

Herbal bioactives enhance angiogenesis by upregulating VEGF, Ang-1, and eNOS, and activating PI3K/Akt and ERK/MAPK pathways to promote endothelial cell survival, migration, and tube formation; several phytochemicals also stimulate fibroblast proliferation and collagen synthesis via TGF-β/Smad signaling, facilitating granulation tissue formation and wound contraction. Nano formulations of flavonoids and polyphenols potentiate these pro-repair mechanisms.[56,58]

4.2 Curcumin: A Prototypical Multi-Target Phytochemical

Curcumin, derived from Curcuma longa, is one of the most extensively studied phytochemicals in diabetic wound healing due to its potent antioxidant, anti-inflammatory and antimicrobial properties. At the molecular level, curcumin suppresses NF-κB and AP-1 signaling, reduces expression of COX-2 and iNOS, enhances Nrf2-mediated antioxidant defenses, promotes macrophage M2 polarization and increases VEGF expression, supporting angiogenesis. Nanocarrier encapsulation using polymeric nanoparticles, lipid carriers, or nanogels dramatically improves curcumin's stability, bioavailability, sustained local release and cellular uptake, leading to enhanced healing in diabetic wound models. Electrospun nanofibers loaded with curcumin and inorganic bioactives accelerated diabetic wound closure and reduced inflammation in vivo.[59,60]

4.3 Flavonoids and Polyphenols: Quercetin and Related Phytochemicals

Flavonoids such as quercetin exert strong antioxidant effects by scavenging free radicals and inhibiting lipid peroxidation, modulate MAPK and PI3K/Akt signaling, reduce inflammatory cytokine production and enhance fibroblast migration. Nanocrystal and nanoparticle systems markedly improve quercetin solubility and bioactivity, increasing wound repair outcomes compared to free quercetin.[61,62]

4.4 Aloe Vera, Centella Asiatica, and Other Traditional Botanicals

Aloe vera contains bioactive polysaccharides and glycoproteins that stimulate fibroblast proliferation, collagen deposition and keratinocyte migration by activating TGF-β and FGF pathways while suppressing inflammatory mediators. Nanovesicles and nanomembrane systems incorporating botanicals like aloe and neem expedite healing in diabetic models by addressing inflammation and enhancing tissue regeneration.[63]

4.5 Antimicrobial and Anti-Biofilm Effects of Herbal Compounds

Several phytochemicals possess intrinsic antimicrobial and anti-biofilm activity by disrupting bacterial membranes, inhibiting quorum sensing and reducing virulence factor expression. When delivered via nanocarriers, these effects are amplified through improved penetration into biofilms and sustained local concentrations and herbal-loaded nanocarriers have demonstrated synergistic antimicrobial effects when combined with metal nanoparticles or conventional antibiotics, offering promising strategies against drug-resistant infections in diabetic wounds. Quercetin-silver nanocomposite hydrogels significantly reduced microbial burden and enhanced re-epithelialization.[61,64]

4.6 Preclinical Evidence and Emerging Clinical Translation

Preclinical studies consistently demonstrate enhanced wound closure, increased angiogenesis, reduced inflammatory markers and improved collagen organization following treatment with nanocarrier delivered herbal therapeutics compared to free phytochemical formulations; while clinical translation remains limited, early phase studies and advanced wound dressing products incorporating herbal nanocarriers suggest favorable safety profiles and therapeutic potential, warranting further controlled clinical evaluation. Phytosome systems and polyherbal nanocarriers have been shown to improve skin absorption and accelerate healing in diabetic ulcers.[53,54]

4.7 Challenges and Future Directions in Herbal Nanotherapeutics

Despite promising outcomes, challenges remain regarding batch-to-batch variability of herbal extracts, standardization of bioactive content and regulatory acceptance. Advanced phytochemical characterization, reproducible nanocarrier fabrication, and robust clinical validation will be critical for widespread adoption. While herbal therapeutics offer broad, multi-target modulation of diabetic wound pathology, synthetic and semi-synthetic drugs provide high potency and defined molecular specificity, which nanocarrier platforms are increasingly being designed to reconcile.

Table 2: Herbal Therapeutics Delivered via Nanocarriers

Herbal Compound	Primary Molecular Targets	Biological Effects in Diabetic Wounds	Nanocarrier Benefits	Evidence Level	Ref.
Curcumin	NF-κB ↓, Nrf2 ↑, VEGF ↑	Anti-inflammatory, antioxidant, angiogenic	Improved solubility, sustained release	Extensive preclinical	65, 66
Quercetin	MAPK ↓, PI3K/Akt ↑	ROS reduction, fibroblast migration	Protection from oxidation	Preclinical	67, 68
Resveratrol	SIRT1 ↑, AMPK ↑	Mitochondrial repair, angiogenesis	Enhanced bioavailability	Preclinical	69, 70
Aloe vera actives	TGF-β ↑, FGF ↑	Fibroblast proliferation, re-epithelialization	Controlled retention	Preclinical	71
Centella asiatica	TGF-β/Smad ↑, MMP ↓	Collagen synthesis, ECM stability	Dose control	Preclinical	66, 72
Berberine	AMPK ↑, NF-κB ↓	Anti-inflammatory, antimicrobial	Enhanced penetration	Emerging	66

5. Nanocarrier Mediated Delivery of Synthetic and Semi-Synthetic Therapeutics for Diabetic Wound Healing

Synthetic and semi-synthetic drugs constitute a cornerstone of modern wound management due to their well-defined pharmacodynamics, reproducible manufacturing, and established regulatory pathways. In diabetic wounds, however, the therapeutic potential of these agents is frequently undermined by poor local bioavailability, rapid degradation, off-target toxicity and impaired tissue perfusion. Nanocarrier-based delivery systems provide a rational strategy to overcome these constraints by enabling localized, controlled and cell-specific drug action while minimizing systemic exposure.[57,58,73,74]

5.1 Anti-Inflammatory Synthetic Agents

5.1.1 Corticosteroids and NF-κB Modulation

Corticosteroids such as dexamethasone exhibit potent anti-inflammatory activity through glucocorticoid receptor-mediated inhibition of NF-κB and AP-1 transcriptional activity. While effective in suppressing excessive inflammation, prolonged exposure can impair fibroblast proliferation and angiogenesis. Nanocarrier encapsulation enables spatiotemporally controlled corticosteroid delivery, mitigating inflammation without hindering repair.[57,73,75]

5.1.2 Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs modulate inflammation by inhibiting COX enzymes but are limited by systemic toxicity and reduced efficacy in ischemic wound tissue. Topical nanocarrier delivery enhances NSAID retention within the wound bed and improves local anti-inflammatory action while minimizing systemic uptake.[57,58,74,75]

5.2 Pro-Angiogenic and Vasomodulatory Synthetic Agents

5.2.1 Nitric Oxide (NO) Donors

Nitric oxide plays a critical role in angiogenesis, vasodilation, and antimicrobial defense, yet endogenous NO is deficient in diabetic wounds. Nanocarrier-based NO delivery systems-in the form of NO-releasing polymers or nanodressings-enable sustained localized NO release, promoting endothelial migration, neovascularization and bacterial clearance.[59,73,76]

5.2.2 Statins as Pleiotropic Angiogenic Agents

Statins exhibit pleiotropic actions including upregulation of eNOS and reduction of oxidative stress, but systemic statin therapy often fails to achieve therapeutic concentrations locally. Nanocarrier-mediated topical statin delivery enhances local angiogenic signaling and improves wound closure and capillary density in diabetic models[57,73,74,77]

5.3 Synthetic Growth Factors and Semi-Synthetic Biologics

5.3.1 Platelet Derived Growth Factor (PDGF)

Recombinant PDGF stimulates fibroblast proliferation and angiogenesis through PI3K/Akt and MAPK pathways, but rapid proteolytic degradation limits its efficacy. Nanocarrier encapsulation protects PDGF from enzymatic breakdown and enables sustained release, significantly enhancing therapeutic outcomes.[61,78,79]

5.3.2 Epidermal Growth Factor (EGF) and Fibroblast Growth Factors (FGFs)

EGF and FGFs promote keratinocyte proliferation and re-epithelialization, but instability in protease-rich environments necessitates protective delivery. Nanocarrier systems, including hydrogel-embedded nanoparticles, have shown prolonged growth factor bioactivity and enhanced wound closure rates in diabetic models.[61,62,78,80]

5.4 Antimicrobial and Anti-Biofilm Synthetic Agents

Infection remains a major contributor to delayed healing in diabetic wounds. Nanocarrier-mediated delivery of antibiotics such as vancomycin, gentamicin and ciprofloxacin enhances penetration into bacterial biofilms and sustains local drug concentrations above inhibitory thresholds. Combination nanocarriers co-delivering antibiotics with anti-biofilm agents exhibit synergistic antimicrobial effects.[57,58,73,76,81]

5.5 Semi-Synthetic ECM Modulating Agents

Semi-synthetic agents targeting extracellular matrix remodeling-such as MMP inhibitors or collagen cross-linkers-help restore ECM stability. Nanocarrier delivery allows localized modulation of ECM dynamics, supporting granulation tissue formation and wound contraction [57,58,74,82]

5.6 Preclinical and Clinical Evidence

Preclinical studies demonstrate superior wound healing outcomes with nanocarrier-delivered synthetic and semi-synthetic drugs compared to free formulations, including enhanced re-epithelialization, angiogenesis, reduced inflammation and improved collagen organization.[57,58,73,74,76] Clinically, nanocarrier-based formulations are advancing as advanced wound dressings and localized delivery systems with improved safety profiles and patient compliance.[57,73,75,77]

5.7 Challenges and Future Perspectives

Key challenges include ensuring controlled release without impairing regeneration, minimizing nanoparticle-induced toxicity and achieving scalable manufacturing. Regulatory frameworks must adapt to combination products integrating drugs with advanced nanomaterials. While synthetic and semi-synthetic drugs offer defined molecular specificity, gene-based therapies enable direct modulation of aberrant gene expression underlying diabetic wound pathology.[73,74,83,84]

Table 3: Synthetic & Semi-Synthetic Drugs in Nanocarrier Systems

Drug Class	Representative Agents	Molecular Targets	Therapeutic Role	Nanocarrier Advantage	Ref.
Corticosteroids	Dexamethasone	NF-κB inhibition	Inflammation control	Controlled, localized exposure	85,86
NSAIDs	Diclofenac, Indomethacin	COX-1/2 inhibition	Cytokine suppression	Reduced systemic toxicity	87,88
NO donors	Diazeniumdiolates	NO-cGMP signaling	Angiogenesis, perfusion	Sustained NO release	89,88
Statins	Simvastatin	eNOS ↑, Akt ↑	Endothelial repair	Local angiogenic effect	88,91
Growth factors	PDGF, EGF, FGF	PI3K/Akt, MAPK	Fibroblast/keratinocyte activation	Protease protection	90,88
Antibiotics	Vancomycin, Gentamicin	Bacterial cell wall	Infection control	Biofilm penetration	88,91
ECM modulators	MMP inhibitors	ECM stabilization	Granulation tissue formation	Localized action	91,88

6. Nanocarrier Mediated Gene-Based Therapeutics for Diabetic Wound Healing

Gene-based therapeutics represent a paradigm shift in diabetic wound management by enabling direct modulation of dysregulated molecular pathways rather than downstream symptom control. Unlike small molecule or protein therapeutics, gene and nucleic acid-based interventions can reprogram cellular behavior at the transcriptional and post-transcriptional levels, offering sustained therapeutic effects in chronic non-healing wounds. However, clinical translation of gene therapy in diabetic wounds is fundamentally dependent on safe, efficient and localized delivery, an area where nanocarrier platforms have emerged as indispensable enablers. Nanoparticle-mediated nucleic acid delivery has shown preclinical promise in overcoming enzymatic degradation and poor tissue uptake inherent to free genetic payloads.[63,64,92,93]

6.1 Molecular Rationale for Gene-Based Intervention in Diabetic Wounds

Diabetic wounds are marked by persistent dysregulation of gene expression that disrupts inflammation control, angiogenesis, extracellular matrix remodeling and cellular migration, driven by hyperglycemia, oxidative stress, and chronic inflammation that suppress pro-healing pathways while sustaining inhibitory and degradative signals. This pathology includes reduced expression of angiogenic factors such as VEGF and HIF-1α, overexpression of pro-inflammatory mediators like TNF-α and IL-1β and disrupted microRNA networks that impair endothelial and fibroblast function. Gene-based therapeutic strategies seek to reverse these abnormalities by delivering exogenous genetic material or silencing maladaptive gene expression, thereby reactivating the endogenous wound healing program. Reviews on systemic and topical genetic modulation underscore the multifaceted gene targets relevant to chronic diabetic wounds.[96,97,98]

6.2 DNA-Based Gene Delivery Strategies

6.2.1 Pro-Angiogenic Gene Therapy

Angiogenesis remains one of the most extensively targeted processes in diabetic wound gene therapy. Plasmid DNA encoding VEGF, FGF, or HIF-1α enhances neovascularization, endothelial cell survival and tissue perfusion. However, naked DNA delivery is limited by poor cellular uptake and rapid degradation. Nanocarrier-mediated delivery-using polymeric nanoparticles, lipid-based vectors, or hybrid systems-protects plasmid DNA from enzymatic breakdown and facilitates endosomal escape and nuclear transport. Non-viral nanoparticle vectors have shown enhanced plasmid uptake and prolonged expression in cutaneous tissues in preclinical models.[66,95,102]

6.2.2 Cytokine and Growth Factor Gene Delivery

Delivery of genes encoding anti-inflammatory cytokines such as IL-10 enables sustained local immunomodulation and extracellular matrix synthesis. Nanocarrier-based systems allow localized expression at the wound site, minimizing systemic immunosuppression and off-target effects. Recent work highlights nano-enabled cytokine gene modulation as a route to rebalance inflammatory wounds.[67,93,94]

6.3 RNA-Based Therapeutics: Precision Gene Regulation

6.3.1 Small Interfering RNA (siRNA)

siRNA enables sequence-specific silencing of pathogenic genes and has been applied in diabetic wound therapy to suppress key molecular drivers such as pro-inflammatory cytokines and matrix metalloproteinases. Because siRNA is highly susceptible to nuclease degradation and exhibits poor membrane permeability, effective delivery relies on nanocarrier encapsulation. Cationic polymers, lipid nanoparticles and polymer-lipid hybrid systems promote siRNA condensation, cellular uptake and cytoplasmic release. Topical nanofiber dressings with siRNA against MMP-9 have shown accelerated diabetic wound closure and reduced protease expression in animal models.[68,69,92,100]

6.3.2 MicroRNA (miRNA) Therapeutics

MicroRNAs coordinate entire gene networks rather than single targets and dysregulation of miRNAs such as miR-146a and miR-126 contributes to impaired angiogenesis, persistent inflammation and fibroblast dysfunction in diabetic wounds. Nanocarrier-mediated delivery of miRNA mimics or inhibitors allows restoration of physiological miRNA signaling; for example, triple-targeting miRNA-loaded core-shell nanoparticles embedded in hydrogel have improved coordinated wound repair by enhancing angiogenesis, reducing inflammation and promoting re-epithelialization.[70,96,101]

6.4 Emerging Genome Editing Approaches

CRISPR/Cas-based gene editing offers the potential for permanent correction of pathological gene expression. Although still in early experimental stages for wound healing, CRISPR systems targeting inflammatory or angiogenic regulators have shown promise in preclinical models. Non-viral nanocarrier systems-including lipid nanoparticles and polymeric complexes are being explored to deliver CRISPR/Cas components locally, mitigating risks associated with viral vectors and systemic exposure. However, safety, off-target editing and ethical considerations remain major translational hurdles. Gene editing via nanocarriers remains promising but requires further optimization for diabetic wound contexts.[71,92,103]

6.5 Nanocarrier Platforms for Gene and RNA Delivery

6.5.1 Polymeric Gene Carriers

Cationic polymers such as polyethyleneimine (PEI), chitosan, and poly (β-amino esters) efficiently condense nucleic acids into nanoscale complexes. While effective, polymer toxicity and inflammatory activation necessitate molecular weight control and surface modification for safety.[72,97,99]

6.5.2 Lipid-Based Gene Delivery Systems

Lipid nanoparticles and lipoplexes exhibit high transfection efficiency and favorable biocompatibility. Advances in ionizable lipid chemistry have significantly improved endosomal escape and reduced cytotoxicity, positioning lipid-based nanocarriers as leading platforms for clinical translation, especially for siRNA and mRNA therapeutics.[94,102]

6.5.3 Hybrid and Stimuli-Responsive Gene Nanocarriers

Hybrid nanocarriers integrate polymeric stability with lipid-mediated transfection efficiency. Stimuli-responsive systems-triggered by pH, ROS, or enzymatic activity-enable spatially controlled gene release within the diabetic wound microenvironment. Smart release systems are being actively developed to match the molecular complexity of chronic wounds.[72,97,101]

6.6 Preclinical Evidence and Translational Progress

Preclinical studies using diabetic rodent models demonstrate that nanocarrier-mediated gene therapy significantly accelerates wound closure, enhances angiogenesis, reduces inflammation, and improves tissue architecture compared to conventional treatments. Sustained gene expression at the wound site has been shown to overcome the transient effects of protein-based therapies. Advances in nanocarrier design for gene and RNA delivery, driven in part by recent clinical successes in RNA vaccines and therapies are accelerating translational feasibility for wound care.[93,94,95,98,99,100,101,102,103]

6.7 Challenges and Future Outlook

Key challenges include ensuring localized and transient gene expression, minimizing immune activation and achieving scalable manufacturing under regulatory compliance. Integration of gene-based nanotherapeutics into advanced wound dressings and smart biomaterials is expected to play a critical role in overcoming these barriers. While individual gene-based interventions offer powerful molecular control, diabetic wounds are inherently multifactorial. The next section focuses on integrated and combinatorial nanocarrier strategies that simultaneously target inflammation, angiogenesis, infection and tissue regeneration across distinct diabetic wound sub-disorders.[92-103]

Table 4: Gene-Based Therapeutics and Molecular Targets

Genetic Payload	Target Pathway	Biological Outcome	Nanocarrier Role	Translational Status	Ref.
VEGF plasmid DNA	Angiogenesis	Neovascularization	Protection, nuclear delivery	Preclinical	104,105
HIF-1α DNA	Hypoxia response	VEGF stabilization	Sustained expression	Preclinical	105,106
IL-10 DNA	Immunoregulation	M2 macrophage shift	Local immune modulation	Preclinical	107
siRNA (TNF-α)	Inflammation	Cytokine suppression	Cytoplasmic delivery	Preclinical	108
siRNA (MMP-9)	ECM remodeling	Reduced matrix degradation	Enzyme-responsive release	Preclinical	109
miR-126 mimic	Endothelial signaling	Angiogenesis	Network-level regulation	Preclinical	104,110
miR-146a mimic	NF-κB inhibition	Inflammation resolution	Immune reprogramming	Preclinical	110,111
CRISPR/Cas (emerging)	Gene editing	Permanent correction	Non-viral local delivery	Early-stage	106,111

7. Integrated Nanocarrier Strategies Targeting Disorder-Specific Pathologies in Diabetic Wounds

Diabetic wounds do not represent a uniform pathological entity but rather a convergence of overlapping and mutually reinforcing sub-disorders, including chronic inflammation, ischemia-driven angiogenic failure, infection and biofilm persistence, neuropathic dysfunction, and defective extracellular matrix remodeling.[111,112] Monotherapeutic approaches targeting single pathways have therefore demonstrated limited clinical success.[113] Integrated nanocarrier strategies-capable of co-delivering multiple therapeutic agents or sequentially modulating distinct molecular pathways-offer a rational and necessary evolution toward effective diabetic wound management.[114-116]

7.1 Targeting Chronic Inflammation and Immune Dysregulation

7.1.1 Molecular Drivers of Inflammatory Chronicity

Persistent activation of NF-κB signaling, excessive reactive oxygen species (ROS) production and sustained M1 macrophage dominance collectively prevent inflammatory resolution in diabetic wounds.[117,118] Elevated TNF-α and IL-1β suppress growth factor signaling and induce protease overexpression, leading to extracellular matrix (ECM) degradation and impaired re-epithelialization.[119]

7.1.2 Combinatorial Nanocarrier Approaches

Integrated nanocarrier systems have been developed to concurrently suppress pathological inflammation and promote immune resolution in diabetic wounds by combining multiple therapeutic mechanisms within a single platform.[120] Representative strategies include co-delivery of anti-inflammatory agents such as dexamethasone or curcumin alongside IL-10 plasmid DNA or miR-146a, providing rapid cytokine suppression followed by sustained immune reprogramming.[121,122] ROS-responsive nanocarriers further enhance selectivity by releasing immunomodulatory payloads specifically within oxidative wound microenvironments, driving macrophage polarization toward the pro-reparative M2 phenotype and restoring angiogenic signaling.[123]

7.2 Promoting Angiogenesis in Ischemic Diabetic Wounds

7.2.1 Ischemia-Driven Molecular Deficits

Impaired angiogenesis in diabetic wounds arises from HIF-1α destabilization, VEGF resistance, endothelial dysfunction and reduced nitric oxide bioavailability, collectively compromising microvascular perfusion and vessel maturation.[124,125]

7.2.2 Multi-Cargo Pro-Angiogenic Nanocarriers

Advanced nanocarrier systems overcome angiogenic deficits through coordinated molecular interventions targeting both vascular initiation and stabilization.[126] These include co-delivery of VEGF plasmid DNA with antioxidant phytochemicals to stabilize HIF-1α, as well as sequential delivery platforms in which early nitric oxide release improves perfusion followed by sustained VEGF or Ang-1 expression to support functional neovascularization[127,128]

7.3 Combating Infection and Biofilm-Associated Wound Chronicity

7.3.1 Biofilm-Driven Therapeutic Resistance

Biofilms protect pathogens from antibiotics and immune clearance while secreting proteases that degrade growth factors and ECM components, creating a persistent inflammatory and proteolytic wound microenvironment.[129]

7.3.2 Synergistic Antimicrobial Nanocarrier Systems

Integrated antimicrobial nanocarriers combine conventional antibiotics with quorum-sensing inhibitors, anti-biofilm agents and metal nanoparticles such as silver or zinc oxide to enhance biofilm penetration and maintain sustained local antimicrobial activity.[130,131]

7.4 Addressing Neuropathic Deficits in Diabetic Wounds

7.4.1 Neurogenic Contributions to Impaired Healing

Peripheral neuropathy reduces sensory nerve-derived trophic support, impairing neuro-immune signaling, vasodilation and keratinocyte proliferation. Loss of neuropeptides such as CGRP and substance P delays early wound healing cascades.[132]

7.4.2 Neuro-Regenerative Nanocarrier Strategies

Emerging nanocarrier systems deliver neurotrophic factors such as NGF and BDNF alongside anti-inflammatory agents, promoting neuronal survival, axonal outgrowth, angiogenesis and restoration of nerve-immune-vascular crosstalk in diabetic wounds.[133]

7.5 Restoring Extracellular Matrix Homeostasis and Tissue Architecture

Excessive MMP activity, reduced TIMP expression and fibroblast dysfunction destabilizes granulation tissue and impair wound contraction in diabetic wounds.[119,123] Multifunctional nanocarriers delivering MMP inhibitors alongside growth factors or pro-regenerative miRNAs stabilize ECM remodeling while promoting organized tissue regeneration.[114,116]

7.6 Temporal and Sequential Therapeutic Programming

A defining advantage of integrated nanocarrier platforms is the ability to temporally program therapeutic delivery, aligning anti-inflammatory and antimicrobial cues with early wound phases followed by angiogenic and regenerative signaling, thereby mimicking physiological repair dynamics.[115,127]

7.7 Translational Implications and Clinical Relevance

Disorder-specific integrated nanocarrier strategies represent a paradigm shift toward precision wound nanomedicine.[111,113] Despite their promise, translational challenges remain, including formulation complexity, regulatory evaluation of combination products and the need for pathology-stratified clinical trial designs. Robust preclinical models that recapitulate diabetic wound heterogeneity remain essential for clinical translation.[112,116]

8. Preclinical Evaluation Models for Nanocarrier-Based Therapies in Diabetic Wound Healing

Robust preclinical evaluation is essential for translating nanocarrier-based therapeutics from bench to bedside. Given the multifactorial nature of diabetic wounds, experimental models must recapitulate not only delayed wound closure but also the underlying metabolic, vascular, inflammatory, neuropathic and infectious components.[134,135] This section critically examines the in vitro, ex vivo and in vivo models used to evaluate nanocarrier-enabled interventions, highlighting their strengths, limitations and translational relevance.

8.1 In Vitro Cellular Models

8.1.1 Hyperglycemic Keratinocyte and Fibroblast Cultures

Primary human keratinocytes and dermal fibroblasts cultured under hyperglycemic conditions (typically 25-35 mM glucose) are widely used to model diabetic wound dysfunction in vitro.[136] These systems reproduce hallmark diabetic impairments, including reduced cell migration, diminished proliferation, compromised extracellular matrix synthesis and heightened oxidative stress.[137] Nanocarrier-based therapeutics are commonly evaluated in these models for cellular uptake efficiency, intracellular trafficking, payload protection and modulation of inflammatory and oxidative signaling pathways such as NF-κB and MAPK cascades.[138] However, monoculture systems lack immune, vascular and microbial components, limiting their predictive value for complex wound environments.[139]

8.1.2 Macrophage Polarization and Immune Models

Murine or human macrophages exposed to diabetic-mimetic conditions are employed to assess immunomodulatory nanocarrier strategies, particularly those targeting M1-M2 phenotypic transitions.[140] These models enable mechanistic evaluation of cytokine regulation and gene-based payload activity but fail to capture the spatial and temporal immune–stromal interactions observed in vivo.[141]

8.2 Advanced In Vitro and Ex Vivo Platforms

8.2.1 Three-Dimensional (3D) Skin Equivalents

Engineered 3D skin equivalents incorporating keratinocytes, fibroblasts and extracellular matrix components provide enhanced physiological relevance compared with 2D cultures.[142] Under diabetic conditions, these models recapitulate delayed re-epithelialization and impaired matrix deposition, allowing assessment of nanocarrier penetration, retention and release kinetics within a structurally relevant tissue context.[143]

8.2.2 Microfluidic and Organ-on-a-Chip Models

Microfluidic wound-on-chip platforms enable precise control of hypoxia, shear stress, immune cell infiltration and spatial drug gradients, offering a powerful tool for evaluating nanocarrier transport, distribution and stimuli-responsive release under dynamic conditions.[144,145] Despite their high informational content, these systems remain technically complex and lack standardization for regulatory testing, limiting widespread adoption.[146]

8.3 In Vivo Diabetic Wound Models

8.3.1 Streptozotocin (STZ)-Induced Diabetic Rodent Models

STZ-induced diabetic mice and rats are among the most commonly used in vivo models, reliably reproducing hyperglycemia-associated impairments in wound repair.[147] These models enable assessment of wound closure kinetics, angiogenesis, inflammation, collagen deposition, and nanocarrier biodistribution. However, predominant wound contraction rather than re-epithelialization limits direct translational relevance to human wound healing.[148]

8.3.2 Genetically Diabetic Models (db/db Mice)

Leptin receptor-deficient (db/db) mice exhibit obesity, insulin resistance, chronic inflammation, and impaired angiogenesis, closely mirroring human diabetic wound pathology.[149] These models are particularly valuable for evaluating integrated nanocarrier strategies targeting inflammation, ischemia and infection, though species-specific immune differences remain a limitation.[150]

8.3.3 Large Animal Models

Porcine diabetic wound models offer skin architecture, vascularization, and healing mechanisms closely resembling humans.[151] Although costly and logistically demanding, they provide critical translational validation for nanocarrier-based wound dressings and scaffolds prior to clinical testing.[152]

8.4 Endpoints and Outcome Measures

Standardized endpoints commonly include wound closure rate, time to complete epithelialization, histological evaluation of angiogenesis and collagen organization and molecular assessment of inflammatory and oxidative stress markers.[153] Biodistribution, local retention, and clearance of nanocarriers are increasingly assessed to understand pharmacokinetics and tissue targeting. Nevertheless, lack of harmonization in outcome measures and reporting standards remains a major barrier to cross-study comparison and clinical translation.[135,146]

8.5 Limitations of Preclinical Models

No single preclinical model fully captures the complexity of human diabetic wounds, particularly factors such as aging, neuropathy, polymicrobial infection, and patient comorbidities. These limitations underscore the necessity for integrated, multi-model validation pipelines to improve predictive accuracy and translational success.[134,152]

9. Clinical Translation and Current Landscape of Nanocarrier-Based Therapies

While preclinical evidence supporting nanocarrier-based diabetic wound therapies is compelling, successful clinical translation requires navigation of regulatory, manufacturing and safety challenges.[154,155] This section examines the current clinical landscape, translational barriers, and emerging opportunities.

9.1 Current Clinical Approaches and Approved Therapies

To date, only a limited number of nanocarrier-based systems have achieved clinical approval specifically for the treatment of diabetic wounds, reflecting the challenges of translating complex nanoscale therapeutics from preclinical models to human patients[156] Most advanced wound care products that incorporate nanomaterials do so indirectly, rather than through active gene or drug delivery and include examples such as nanofiber-based dressings that provide structural support and promote cellular infiltration, silver nanoparticle–embedded antimicrobial dressings that enhance infection control, and growth factor–loaded biomaterial matrices that support tissue regeneration.[157,158]

While these products have demonstrated measurable improvements in wound closure, infection management and overall healing outcomes, they generally lack sophisticated features such as active molecular targeting, controlled or programmable release and precise modulation of the wound microenvironment. This limitation highlights the need for next-generation nanocarrier systems that combine structural support with tailored, responsive therapeutic delivery to address the multifactorial challenges of diabetic wound repair more effectively.[155,159]

9.2 Clinical Trials and Emerging Nanotherapeutics

[160]. These studies report accelerated wound healing rates, reduced local infection and inflammation and generally favorable safety and tolerability profiles, highlighting the potential of nanocarrier systems to enhance the efficacy of conventional wound treatments.[161]

Despite these encouraging results, gene-based nanotherapeutics, such as siRNA or plasmid DNA delivery systems, remain largely restricted to preclinical research or compassionate-use settings due to significant regulatory hurdles, complex manufacturing requirements and the need for extensive long-term safety evaluation.[162] This underscores a persistent gap between experimental innovation and clinical implementation, while emphasizing the transformative potential of nanotechnology once these translational barriers are addressed.

9.3 Regulatory and Manufacturing Challenges

Nanocarrier-based therapies frequently qualify as combination products under regulatory frameworks, requiring coordinated evaluation of their drug, device and material components to demonstrate safety and efficacy.[163] This classification introduces challenges related to scalable and reproducible manufacturing, sterilization strategies that preserve nanocarrier functionality, and rigorous assessment of long-term biocompatibility, biodegradation, and systemic exposure.[164]

Regulatory agencies increasingly emphasize mechanistic understanding of nano–bio interactions, standardized physicochemical characterization and reproducible release kinetics.[165] Consequently, successful clinical translation demands robust material validation, stringent quality control and harmonized regulatory strategies across jurisdictions.

9.4 Patient Stratification and Precision Wound Care

A major barrier to consistent clinical success is the pronounced heterogeneity of diabetic wounds, which vary widely in inflammatory burden, ischemia severity, microbial load and neuropathic involvement.[166] Effective translation of nanocarrier-based therapies will therefore require patient stratification based on wound phenotype, enabling rational selection of anti-inflammatory, angiogenic, antimicrobial, or neurotrophic nanotherapeutic strategies.[167]

Integration of diagnostic tools with therapeutic delivery-such as sensor-enabled or imaging-guided nanocarriers-offers the potential for real-time monitoring and adaptive treatment, ensuring that therapeutics are delivered at the appropriate dose, location and healing stage.[160,168]

9.5 Future Directions and Commercialization Outlook

Advances in smart wound dressings, AI-assisted formulation design and personalized medicine are expected to accelerate clinical translation of nanocarrier-based therapies.[169] Integration of nanocarriers with wearable sensors and stimuli-responsive biomaterials represents a promising frontier for adaptive, real-time wound management. Collectively, the convergence of mechanistic insight, material innovation and translational rigor positions nanocarrier-mediated therapies as a transformative approach for diabetic wound care. The following section synthesizes key insights and future perspectives.

10. Conclusions and Future Perspectives

Diabetic wounds represent one of the most challenging manifestations of metabolic disease, arising from the convergence of chronic inflammation, impaired angiogenesis, oxidative stress, neuropathy, infection and extracellular matrix dysfunction. Traditional therapeutic strategies-largely focused on symptom management or single-target interventions—have proven insufficient to address the multifactorial and dynamic nature of these wounds. As synthesized throughout this review, nanocarrier-mediated drug delivery systems offer a transformative paradigm by enabling spatially, temporally and molecularly precise therapeutic intervention.

10.1 Key Advances Highlighted in This Review

This review highlights several transformative advances that are redefining the management of diabetic wounds. Nanocarrier platforms have shifted the therapeutic paradigm from single-agent interventions to systems-level approaches, integrating herbal, synthetic, semi-synthetic and gene-based therapeutics to simultaneously modulate inflammation, angiogenesis, infection and tissue regeneration. Modern nanomaterials contribute beyond passive delivery by actively shaping wound biology through intrinsic antimicrobial activity, redox modulation, immune regulation and support of extracellular matrix remodeling. At the molecular level, gene-based payloads, miRNAs, and siRNAs delivered via non-viral nanocarriers offer precise control over dysregulated signaling networks, enabling pathway reprogramming rather than simply addressing downstream deficits. Importantly, emerging strategies emphasize the heterogeneity of diabetic wounds, advocating for disorder-specific and phase-aware designs that tailor interventions to wound subtype and healing stage, thereby maximizing therapeutic efficacy and advancing personalized regenerative medicine.

10.2 Persistent Challenges Limiting Clinical Translation

Despite these advances, several substantial barriers continue to limit the widespread clinical adoption of nanocarrier-based therapies for diabetic wounds. Preclinical models often fail to fully recapitulate the heterogeneity, chronicity and comorbidities seen in patients, including aging, neuropathy and vascular complications, which reduces their predictive value. The complexity of multi-payload and “smart” nanocarrier formulations introduces additional challenges in terms of reproducibility, scalable manufacturing and long-term stability. Regulatory ambiguity further complicates translation, as combination product classifications create intricate approval pathways, particularly for gene-based or hybrid systems. Moreover, the lack of standardized clinical endpoints and inadequate patient stratification in trials undermine the reliable assessment of therapeutic efficacy. Overcoming these challenges will require coordinated, interdisciplinary efforts spanning material science, molecular and cellular biology, clinical medicine and regulatory science to enable safe, effective and personalized nanotherapeutic strategies for diabetic wound care.

10.3 Future Perspectives and Emerging Directions

Looking forward, several converging trends are poised to shape the next generation of diabetic wound nanomedicine:

10.3.1 Precision Wound Nanomedicine

Future nanomedicine strategies will focus on tailoring therapeutic interventions to individual wound phenotypes, leveraging molecular and cellular biomarkers of inflammation, ischemia, microbial burden and regenerative potential. By integrating patient-specific diagnostic data, nanocarriers can be customized to deliver the right combination of anti-inflammatory, angiogenic, antimicrobial and regenerative payloads. This precision approach aims to maximize efficacy, minimize adverse effects and support personalized wound care across heterogeneous patient populations.

10.3.2 Smart and Responsive Therapeutic Systems

Stimuli-responsive nanocarriers will allow spatiotemporally controlled, on-demand drug release in response to specific wound cues such as pH changes, elevated reactive oxygen species, proteolytic enzymes, or microbial metabolites. These “smart” systems reduce unnecessary drug exposure, limit systemic toxicity and optimize therapeutic timing. Such platforms could adapt dynamically to evolving wound microenvironments, providing stage-specific interventions that enhance healing efficiency and safety in complex diabetic wounds.

10.3.3 Integration with Digital and Wearable Technologies

Combining nanocarrier-loaded wound dressings with biosensors, wireless communication and AI-driven analytics will enable continuous, real-time monitoring of wound physiology, including temperature, moisture, pH and inflammatory markers. This integration allows adaptive therapeutic modulation, such as triggered drug release or alerts for infection risk. Such digital platforms could improve clinical decision-making, personalize treatment regimens and facilitate remote monitoring, significantly enhancing patient adherence and outcomes.

10.3.4 Non-Viral Gene and RNA Therapeutics

Non-viral nanocarriers are poised to expand the clinical utility of gene editing, RNA interference, and epigenetic modulation in diabetic wound therapy. These systems offer targeted, safe delivery of plasmids, siRNAs, or miRNA mimics without the immunogenicity and insertional risks of viral vectors. By reprogramming dysregulated signaling pathways at the molecular level, they can restore angiogenesis, reduce inflammation and enhance tissue regeneration in a controlled, tunable manner.

10.3.5 Sustainable and Translational Material Design

Future nanotherapeutics will prioritize biodegradable, bio-derived, and environmentally sustainable materials to ensure scalability, safety and global accessibility. Cost-effective production and straightforward storage requirements are critical for resource-limited healthcare settings. Such designs aim to maintain therapeutic efficacy while minimizing environmental impact and manufacturing complexity, bridging the gap between advanced laboratory technologies and clinically translatable, widely deployable wound care solutions worldwide.

10.4 Final Outlook

Nanocarrier-mediated drug delivery has moved beyond proof-of-concept toward a biologically informed, precision-driven approach to diabetic wound care. By integrating molecular pathophysiology with advanced material design and translational strategy, this field is positioned to overcome the long-standing therapeutic stagnation in diabetic wound management. The future success of these technologies will depend not on incremental improvements, but on holistic integration-of biology, materials, patient stratification and clinical pragmatism. Achieving this integration may ultimately transform diabetic wounds from a chronic clinical burden into a manageable and resolvable condition.

List of Abbreviations

Akt: Protein kinase B

AMPK: Adenosine monophosphate-activated protein kinase

BDNF: Brain-derived neurotrophic factor

CRISPR: Clustered regularly interspaced short palindromic repeats

ECM: Extracellular matrix

EGF: Epidermal growth factor

FGF: Fibroblast growth factor

HIF-1α: Hypoxia-inducible factor 1 alpha

IL: Interleukin

MAPK: Mitogen-activated protein kinase

MMP: Matrix metalloproteinase

NF-κB: Nuclear factor kappa B

NGF: Nerve growth factor

NO: Nitric oxide

Nrf2: Nuclear factor erythroid 2-related factor 2

PDGF: Platelet-derived growth factor

PI3K: Phosphoinositide 3-kinase

ROS: Reactive oxygen species

siRNA: Small interfering ribonucleic acid

TGF-β: Transforming growth factor beta

TNF-α: Tumor necrosis factor alpha

VEGF: Vascular endothelial growth factor

Ethics approval and consent to participate: This manuscript is a review. Hence, no experiments in animals or humans are included in this study, so ethical approval and consent are not required.

Clinical Trial No: The manuscript is a review article (not a part of Clinical trial), hence no Clinical trial no is applicable.

Availability of data and material: Data sharing does not apply to this article as no datasets were generated or analyzed during the current study.

Conflict of interest: The authors declare no conflict of interest.

Funding: The authors received no funding for this manuscript.

Acknowledgements: The authors are thankful to the Principal, Columbia Institute of Pharmacy, Raipur, Chhattisgarh, India for providing infrastructural and library facilities to complete this review.

CRediT authorship contribution statement: All authors contributed equally towards preparation of the manuscript

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