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REVIEW

Nanohydrogels for Diabetic Wound Healing: Mechanisms, Applications, and Future Perspectives

Jinyuan Wu[1], Jiaqi Gu[1], Xueping Wu[2,3]

[1]College of Medical Technology, Shanghai University of Medicine & Health Sciences, Shanghai, 201318, People's Republic of China; [2]Institute of Wound Prevention and Treatment, Shanghai University of Medicine & Health Sciences, Shanghai, 201318, People's Republic of China; [3]Laboratory of Tumor Molecular Imaging, Pudong Gongli Hospital, Shanghai University of Medicine & Health Sciences, Shanghai, 201318, People's Republic of China

Correspondence: Xueping Wu, Laboratory of Tumor Molecular Imaging, Pudong Gongli Hospital, Shanghai University of Medicine & Health Sciences, Shanghai, 201318, People's Republic of China, Email wuxp@sumhs.edu.cn

Abstract: Diabetic wound healing remains a significant clinical challenge, characterized by persistent hyperglycemia, chronic inflammation, impaired angiogenesis, and recurrent infections. Traditional wound dressings often fail to address the complex pathological microenvironment of diabetic wounds. Nanohydrogels, particularly nanohybrid systems such as polyhedral oligomeric silsesquioxane (POSS)-based hydrogels, metal-organic framework (MOF) nanozyme hydrogels, and zinc-based polyoxometalate (Zn-POM) hydrogels, have emerged as advanced multifunctional platforms for diabetic wound repair. This review systematically summarizes the pathological mechanisms underlying diabetic wound chronicity and the material properties of nanohydrogels that enable targeted therapeutic interventions. We focus on the unique advantages of nanohybrid systems, including their high water retention, tunable mechanical properties, stimuli-responsiveness, and biocompatibility. Furthermore, we provide a detailed analysis of representative nanohybrid hydrogel applications, highlighting their antibacterial, anti-inflammatory, pro-angiogenic, and cell-promoting functions. Despite promising preclinical outcomes, challenges remain in large-scale production, mechanistic understanding, and clinical translation. Future directions include the development of intelligent, personalized nanohybrid systems and the integration of multi-omics approaches to elucidate their in vivo mechanisms. This review aims to provide a comprehensive and critical overview of nanohybrid hydrogels for diabetic wound healing, offering insights for researchers and clinicians in the field.

Keywords: nanohydrogel, diabetic wounds, wound healing, mechanism of action

Introduction

Driven by accelerating global population aging and shifts in lifestyle, diabetes has emerged as one of the most widespread chronic metabolic disorders of the 21st century. According to International Diabetes Federation (IDF) data for 2025, approximately 589 million adults aged 20–79 worldwide are living with diabetes, corresponding to a prevalence of 11.1%—or roughly one in every nine adults.[1] Projections suggest that by 2050, the total number of affected individuals will rise to 853 million. Type 2 diabetes constitutes 90%–95% of all diabetes cases.[2] Among the most formidable complications are diabetic wounds, which develop in 15%–25% of patients and carry an annual amputation risk of 22%; one diabetes-related amputation is performed every 30 seconds.[3] The healing of these wounds is disrupted by multiple pathological cascades initiated by hyperglycemia, in which sustained high blood glucose promotes the accumulation of advanced glycation end products (AGEs) and bursts of reactive oxygen species (ROS), leading to uncontrolled inflammation, vascular endothelial dysfunction, and impaired fibroblast proliferation. Ultimately, this perpetuates a vicious cycle of chronic inflammation, tissue damage, and compromised repair.[4]

Currently, conventional dressings widely employed in clinical practice, such as gauze and alginate dressings, serve primarily as passive physical barriers. They are limited by their inability to adapt to dynamic changes in the wound microenvironment—such as shifts in pH, elevated reactive oxygen species (ROS), and glucose fluctuations—which hinders

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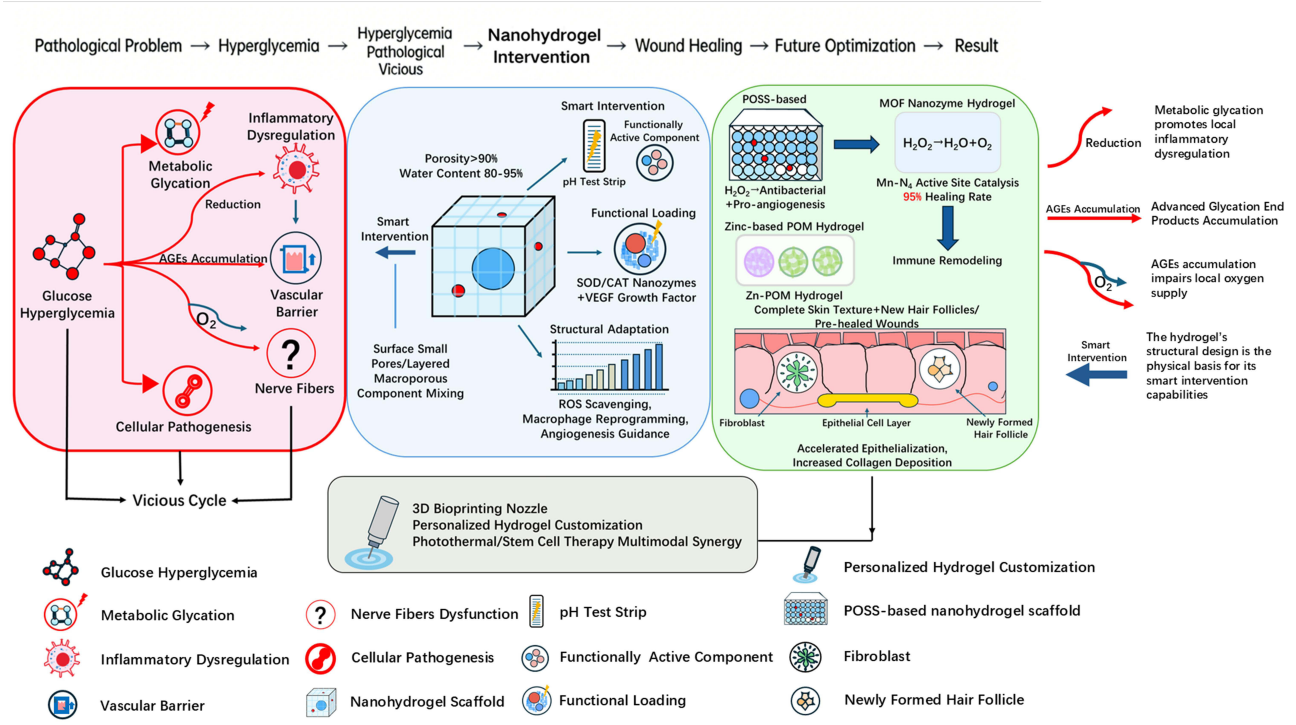
Graphical Abstract



targeted therapeutic intervention. Moreover, these dressings lack inherent antimicrobial and anti-inflammatory properties, leading to high rates of infection recurrence (up to 60%) and a tendency to promote bacterial resistance.[5] Additionally, their poor mechanical compatibility often causes adherence to newly formed tissue upon removal, resulting in secondary trauma and extended healing timelines. Crucially, traditional dressings do not effectively address underlying pathological mechanisms, including local ischemia, hypoxia, and impaired cellular activity, which ultimately restricts their clinical effectiveness.[6]

Nanohydrogels offer significant advantages over traditional wound dressings, achieved through tailored molecular design and nanotechnology. Their three-dimensional porous network (with porosity exceeding 90%) and high water content (80%–95%) closely mimic the natural extracellular matrix (ECM), offering an optimal scaffold for cellular migration and proliferation.[7] Functionally programmable, nanohydrogels can be loaded with active agents such as antibiotics, growth factors, and nanozymes, enabling synergistic anti-infective, anti-inflammatory, and regenerative therapies.[8] Moreover, their intelligent responsiveness—to pH, reactive oxygen species (ROS), and glucose fluctuations—allows dynamic regulation of drug release. For example, they can accelerate silver ion release in acidic wound environments (pH < 6.5) or trigger controlled insulin delivery under hyperglycemic conditions.[9] As of 2023, several nanohydrogel-based dressings are under clinical investigation, reflecting their considerable translational potential. Recent 2025 studies further expand nanohybrid strategies, including dynamic multistage nanozyme hydrogels for oxidative stress and mitochondrial regulation[10] and injectable nanocomposite hydrogels targeting inflammatory microenvironment remodeling.[11] This article specifically focuses on nanohybrid hydrogels—systems that integrate nanomaterials (eg, POSS, MOF, nanozymes) into hydrogel matrices to achieve enhanced synergistic therapeutic effects. We further aim to provide a systematic and comparative analysis of the design principles, mechanisms of action, and therapeutic outcomes of these advanced systems, addressing a gap in the current literature.

Literature Search Methodology

This review was conducted using PubMed, Web of Science, and Google Scholar databases. Keywords included "nanohydrogel", "diabetic wound", "POSS hydrogel", "MOF nanozyme", "polyoxometalate", and "wound healing". Articles published between 2015 and 2025 were prioritized, with a focus on preclinical and clinical studies reporting mechanistic insights or quantitative efficacy data.

Pathological Mechanisms and Key Features of Impaired Healing in Diabetic Wounds

The healing impairment observed in diabetic wounds stems from a cascade of multidimensional dysregulations induced by hyperglycemia. These dysregulations converge across five core pathological axes—metabolic, inflammatory, vascular, cellular, and neural—forming a self-reinforcing vicious cycle.

Metabolic Dysregulation Driven by Hyperglycemia

Persistent hyperglycemia drives metabolic dysfunction through three principal pathways. First, it leads to abnormal activation of the polyol pathway, resulting in sorbitol accumulation and depletion of nicotinamide adenine dinucleotide phosphate (NADPH), which compromises cellular antioxidant defenses. Second, it accelerates the formation and deposition of advanced glycation end products (AGEs). Binding of AGEs to the receptor for advanced glycation end products (RAGE) triggers downstream signaling that intensifies oxidative stress and inflammatory responses.[12] Third, it upregulates protein kinase C (PKC) activity, modulating the expression of cytokines (CKs) such as vascular endothelial growth factor (VEGF) and transforming growth factor-β (TGF-β), thereby disturbing the balance of tissue repair processes.[13] As a central mediator of metabolic dysregulation, excessive reactive oxygen species (ROS) directly damage cellular DNA, proteins, and lipids, promote apoptosis of fibroblasts and endothelial cells, and enhance glycation-related modifications of extracellular matrix (ECM) proteins such as collagen. These alterations impair the structural integrity and biological function of the ECM, ultimately disrupting cell–ECM adhesion and associated signaling.[14]

Inflammatory Dysregulation and the Chronic Inflammatory Microenvironment

The central pathological characteristic of diabetic wounds is an uncontrolled inflammatory response, manifested by persistent activation of pro-inflammatory signals coupled with inadequate anti-inflammatory signaling. Reactive oxygen species (ROS) induced by hyperglycemia trigger the nuclear factor kappa-B (NF-κB) signaling pathway in macrophages, promoting their polarization toward the pro-inflammatory M1 phenotype. This results in excessive secretion of inflammatory mediators such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α).[15] These cytokines not only cause direct tissue damage but also suppress fibroblast-mediated collagen synthesis and endothelial cell-driven angiogenesis, thereby impairing granulation tissue formation.[16] Concurrently, elevated levels of matrix metalloproteinases (MMPs) secreted by M1 macrophages accelerate extracellular matrix (ECM) degradation, disrupting the balance between tissue repair and degradation in the wound. Meanwhile, the proportion of anti-inflammatory M2 macrophages is markedly reduced. Inadequate secretion of anti-inflammatory factors like interleukin-10 (IL-10) and TGF-β hinders timely resolution of inflammation and delays the activation of tissue-repair programs.[17] This chronic inflammatory state can persist for months or even years, constituting a core barrier to wound healing.

Impaired Angiogenesis and the Ischemic-Hypoxic Microenvironment

Impaired angiogenesis is a central pathological factor contributing to delayed wound healing in diabetes, primarily arising from vascular endothelial dysfunction and structural microvascular abnormalities. Hyperglycemia reduces the activity of vascular endothelial cells (ECs) through mechanisms such as advanced glycation end-product (AGE) deposition and oxidative stress, which significantly diminish the expression and bioactivity of key angiogenic factors such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF).[3,18] Concurrently, diabetic microvascular complications—including basement membrane thickening, luminal narrowing, and hemodynamic disturbances—compromise local blood perfusion in the wound bed, leading to inadequate oxygen tension and nutrient supply. This establishes a persistent ischemic-hypoxic microenvironment.[19] Hypoxia, in turn, further suppresses EC proliferation and migration, weakens angiogenesis capacity, and intensifies oxidative stress and inflammatory signaling, thereby reinforcing a vicious cycle of hypoxia, impaired repair, and aggravated inflammation.[20] Clinical observations indicate

that the local oxygen partial pressure in diabetic wounds is approximately one-third to one-half that of normal wounds, a condition that significantly limits the healing progression.[21]

Cellular Dysfunction in Repair Cells

Hyperglycemia broadly suppresses the functions of key cellular participants in wound repair, including fibroblasts,[22] keratinocytes (KCs),[23] and endothelial cells.[24] Specifically, it reduces fibroblast proliferation and collagen synthesis, impedes keratinocyte migration and differentiation, and impairs the angiogenic capacity of endothelial cells.[25] Collectively, these dysfunctions lead to delayed re-epithelialization, inadequate granulation tissue formation, and disordered vascularization, ultimately compromising the efficiency of wound healing. Neuropathy: Dual Deficiencies in Wound Sensing and Repair Regulation.

Neuropathy: Dual Deficiencies in Wound Sensing and Repair Regulation

Diabetic peripheral neuropathy (DPN) is a major contributor to impaired wound healing. By reducing pain and tactile sensation, DPN compromises the timely detection and management of minor foot injuries.[26] Furthermore, disrupted neurogenic regulation further compromises local blood supply and immune responses, thereby increasing susceptibility to infection.[27] Clinical evidence confirms a significant association between the presence of DPN and delayed wound healing (Figure 1), suggesting that neuroprotection may constitute a promising therapeutic avenue for improving diabetic wound outcomes. Specific intervention strategies using nanohydrogels, designed to target these five pathological barriers, are summarized in Table 1.

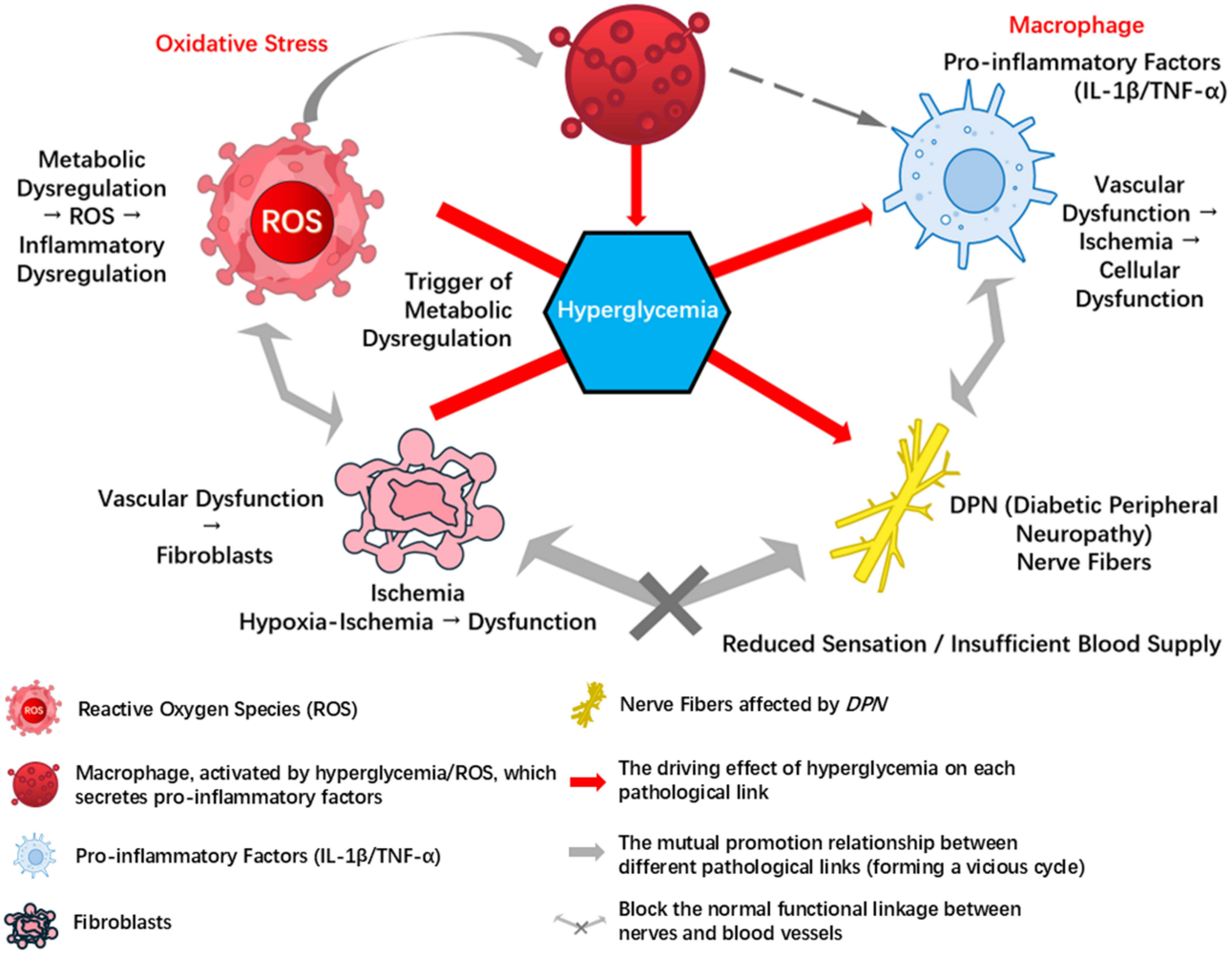


Figure 1 Core pathological mechanisms in diabetic wound healing.

Table 1 Nanohydrogel Intervention Strategies Targeting the Five Pathological Barriers in Diabetic Wounds

Pathological Barriers	Key Mechanisms	Nano-Hydrogel Intervention Strategy	Representative Functional Components	Ref.
Metabolic Dysregulation	AGEs accumulation, ROS burst	ROS scavenging, AGEs inhibitor loading	Nanoenzymes (SOD/CAT mimics), Metformin	[12, 21]
Inflammatory Dysregulation	M1/M2 imbalance, pro-inflammatory factors ↑	Macrophage reprogramming, anti-inflammatory factor delivery	IL-4/IL-10, Zn^{2+}, Curcumin	[16, 25]
Vascular Dysfunction	VEGF↓, hypoxia	Slow-release growth factors, oxygen supply	VEGF/bFGF loading, catalase	[19, 21]
Cellular Inhibition	Fibroblast/keratinocyte function↓	ECM mimicry, topologically guided	RGD peptides, gradient pore size design	[22, 24]
Neuropathy	Dysregulation of neuroregulation	NGF delivery	NGF, BDNF loading	[23, 26]

Notes: ↑ indicates an increase/upregulation; ↓ indicates a decrease/downregulation.
Abbreviations: AGEs, advanced glycation end products; ROS, reactive oxygen species; SOD, superoxide dismutase; CAT, catalase; IL, interleukin; VEGF, vascular endothelial growth factor; bFGF, basic fibroblast growth factor; ECM, extracellular matrix; RGD, arginine-glycine-aspartic acid; NGF, nerve growth factor; BDNF, brain-derived neurotrophic factor.

Material Properties and Design Principles of Nanogel

Nanohydrogels are promising wound repair materials in the 21st century, with substantial application potential in the management of chronic wounds—especially diabetic wounds—due to their unique physicochemical properties and biomimetic characteristics.[28] Compared to traditional dressings, nanohydrogels exhibit several key advantages.

Their three-dimensional porous network (porosity > 90%) and high water content (80–95%) closely mimic the natural extracellular matrix (ECM) microenvironment, providing an ideal scaffold for cellular migration and proliferation.[7] Through molecular design, their mechanical properties, such as elastic modulus (0.1–20 kPa), and degradation rates (7–28 days) can be precisely tailored to meet the requirements of different wound healing stages.[29]

In diabetic wound therapy, nanohydrogels exhibit specific functional advantages. They can be loaded with active agents, including antimicrobial nanoparticles like antimicrobial silver nanoparticles (AgNPs), anti-inflammatory drugs such as IL-10, or pro-angiogenic factors like VEGF, enabling synergistic anti-infective, anti-inflammatory, and pro--regenerative therapies.[30,31] Stimuli-responsive designs—such as pH-, ROS-, or glucose-sensitive systems—further enable dynamic adaptation to the wound microenvironment and enable precise, on-demand drug release.[31]

To date, various functionalized nanohydrogels—including POSS-based composite hydrogels and MOF nanozyme-integrated hydrogels—have significantly accelerated diabetic wound healing in animal studies, increasing healing rates by 35–50%.[32,33] Several nanohydrogel-based products are currently under clinical investigation, reflecting their translational potential.

Characteristics of Nanogels

High Water Retention Capacity

The three-dimensional crosslinked network of nanohydrogels provides exceptional moisture-retaining properties, typically achieving water absorption of 80–95% relative to their own mass.[34] This capability arises from hydrogen bonding between hydrophilic groups such as hydroxyl or carboxyl groups on polymer chains and water molecules, combined with capillary effects within the porous network.[35] The resulting high moisture retention creates an ideal moist wound environment, consistent with modern moist wound healing principles. On the one hand, the moist setting sustains cellular viability, stimulates growth factor release, and accelerates epithelial cell migration—with reported increases in migration rates of 30–40%;[36] on the other hand, it significantly reduces adhesion between the dressing and wound bed (adhesion <0.5 N/cm^2), thereby minimizing secondary injury during dressing changes.[37] Research has shown that hyaluronic acid-based nanohydrogels can absorb 2–3 times more exudate in diabetic wounds while reducing dressing change frequency by 50%.[38]

Excellent Biocompatibility

The biocompatibility of nanohydrogels is largely determined by their material composition: natural polymers such as chitosan (CS), collagen, and hyaluronic acid exhibit structural similarity to the extracellular matrix (ECM), while synthetic polymers like polyethylene glycol (PEG) and polyacrylamide can be modified to minimize immunogenicity.[39] In vitro studies have demonstrated that after 7 days of co-culture with L929 fibroblasts, cell viability remains above 95%.[40] Key biosafety mechanisms include (1) a near-neutral surface charge (zeta potential between –5 and +5 mV), which reduces nonspecific protein adsorption,[41] and (2) the degradation of the hydrogel into small-molecule sugars or amino acids that can be cleared via renal metabolism.[42] Preclinical studies further confirmed that insulin-loaded chitosan hydrogels applied continuously for 28 days elicited no detectable local or systemic toxicity.[43]

Tunable Mechanical and Structural Properties

Molecular design allows precise control over the mechanical properties of nanohydrogels. For instance, increasing the crosslink density by 1 mmol/cm^3 raises the elastic modulus by 3–5 kPa, enabling the material to adapt to different tissue stiffness requirements—from soft tissues (0.1–1 kPa) to skin (10–20 kPa).[44] Additionally, the introduction of reactive groups such as double bonds or thiols enables crosslinking via photopolymerization or thiol-ene click chemistry, with curing times adjustable between 10 and 300 seconds.[45]

In terms of structural regulation, nanohydrogels prepared by freeze-drying (lyophilization) achieve porosities of 90–98% and pore sizes ranging from 50 to 200 μm, closely matching the spacing of human dermal collagen fibers (20–150 μm).[46] Moreover, gradient pore architectures—featuring a surface layer with pores of 5–20 μm and a deeper layer with pores of 100–300 μm—can simultaneously meet the needs of barrier protection and cellular infiltration.[47] For example, gelatin (Gel)-based hydrogels with anisotropic channels have been shown to increase fibroblast migration speed by 2.4-fold.[48]

Smart Responsiveness

Smart responsive nanohydrogels are regulated through several key mechanisms. First, pH-responsive systems, such as those based on polyacrylic acid derivatives, swell three- to fivefold in the acidic environment typical of diabetic wounds (pH 5.5–6.5) due to protonation of carboxylate groups, resulting in rapid antibiotic release—over 80% within 4 hours.[49] Second, temperature-responsive polymers like poly(N-isopropylacrylamide) (PNIPAM) undergo a sol-gel transition near body temperature when their lower critical solution temperature (LCST) is set between 32 °C and 34 °C, forming gels with mechanical strength up to 15 kPa.[50] Third, enzyme-responsive designs, such as hydrogels crosslinked with matrix metalloproteinase-sensitive peptides, degrade 8–10 times faster in wound regions overexpressing matrix metalloproteinase-9 (MMP-9), allowing localized drug delivery to pathological sites.[51] More recently developed systems integrate glucose oxidase (GOx) to sense real-time blood glucose levels. When glucose exceeds 8 mmol/L, the catalytic production of acid triggers insulin release, achieving glucose-control efficacy 60% higher than conventional delivery methods.[52]

A comparison of physicochemical properties, including pore volume, water content, and mechanical modulus, across different types of nanohydrogels is provided in Table 2.

Mechanisms of Nanohydrogel-Mediated Wound Healing

Antibacterial and Anti-Infective Effects

Nanohydrogels combat wound infection through multiple antibacterial strategies. First, direct bactericidal activity is achieved by incorporating chemically modified antimicrobial groups. For example, hydrogels modified with quaternary ammonium salts (QAS) disrupt the membrane integrity of Staphylococcus aureus within five minutes through electrostatic interactions with bacterial phospholipids.[54] Similarly, hydrogels loaded with silver nanoparticles release Ag^+ ions that interfere with bacterial electron transport chains, exhibiting a minimal inhibitory concentration as low as 0.5 μg/mL against methicillin-resistant Staphylococcus aureus.[55] Second, smart responsive systems provide on-demand antimicrobial release. pH-responsive hydrogels accelerate vancomycin release in the acidic environment of infected wounds, achieving up to 92% cumulative release within 24 hours.[56] Temperature-sensitive hydrogels release chlorogenic acid when wound temperature exceeds 38°C, generating an inhibition zone of 15.2 ± 1.3 mm against Pseudomonas

Table 2 Comparison of Physicochemical Properties Among Different Types of Nanohydrogels

Hydrogel Type	Typical Materials	Pore Volume (%)	Water Content (%)	Response Characteristics	Mechanical Modulus (kPa)	Key Application Advantages	Ref.
Natural polymer base	Chitosan, Hyaluronic Acid	85–95	85–92	pH/Enzyme responsiveness	0.5–5	High biocompatibility, easily modifiable	[38, 39]
Synthetic polymer base	PEG, PNIPAM	80–90	80–88	Temperature responsiveness	1–20	Mechanically tunable, intelligently controllable	[44, 50]
Composite Nanomaterials	POSS, MOFs	90–98	88–95	Multiresponsiveness	3–15	Multifunctional integration, synergistic therapy	[47, 53]
Nanozyme functionalization	Zn-POM, Mn-MOFs	85–93	82–90	ROS/Glucose responsiveness	2–10	Catalytic therapy, microenvironment regulation	[32, 33]

Abbreviations: PEG, polyethylene glycol; PNIPAM, Poly(N-isopropylacrylamide); POSS, polyhedral oligomeric silsesquioxane; MOF, metal-organic framework; Zn-POM, zinc-based polyoxometalate; ROS, reactive oxygen species.

aeruginosa.[53] For instance, POSS-quaternary ammonium salt hybrid hydrogels stabilize quaternary ammonium groups via a rigid Si–O–Si backbone, demonstrating significantly higher inhibition rates against Escherichia coli and Staphylococcus aureus compared to conventional dressings.[57]

Modulating the Inflammatory Microenvironment

Nanohydrogels effectively improve the wound inflammatory microenvironment through multiple synergistic pathways. First, manganese-based nanoenzyme hydrogels, leveraging their dual superoxide dismutase (SOD)- and catalase (CAT)-like activities, can significantly reduce wound ROS levels by 78% within 6 hours;[33] Second, Zn^{2+}-loaded hydrogels (Zn^{2+}-functionalized hydrogels) specifically inhibit p38 mitogen-activated protein kinase (p38 MAPK) phosphorylation (62.4% inhibition rate), optimizing the pro-inflammatory M1 macrophage ratio from 7.2:1 to 1.3:1.[58] Concurrently, IL-4-functionalized hydrogels significantly downregulate pro-inflammatory factors TNF-α and IL-6 (by 83% and 76%, respectively) while upregulating anti-inflammatory factor IL-10 expression by 5.2-fold.[59] These effects primarily stem from the nanohydrogel's epigenetic regulation of macrophages, particularly through mechanisms such as inhibiting histone deacetylases to remodel macrophage phenotypes, thereby promoting wound healing.[60]

Nanohybrid-Immune Cell Interactions

Nanohydrogels exert precise regulatory effects on immune cells in the wound microenvironment via their unique physicochemical properties and loaded bioactive components. For example, Zn-POM nanozymes directly inhibit the mitogen-activated protein kinase/interleukin-17 (MAPK/IL-17) signaling pathway in macrophages via zinc ion chelation, as indicated by the inhibitory arrow in Figure 2, reducing the secretion of pro-inflammatory cytokines and inducing M1-to-M2 macrophage polarization. MOF nanozymes modulate hypoxia-inducible factor-1α (HIF-1α) expression in immune cells and endothelial cells by regulating the local oxygen microenvironment, further enhancing the anti-inflammatory and pro-angiogenic immune response. POSS-based hybrid hydrogels enhance immune cell adhesion and activation through their rigid three-dimensional network structure, accelerating the clearance of pathogens and damaged tissue in the wound area. All nanohybrid systems avoid excessive immune activation and maintain the balance of the wound immune microenvironment, which is a key feature distinguishing them from general hydrogels.

Promotion of Angiogenesis

Nanohydrogels promote vascular regeneration through synergistic multidimensional mechanisms. At the molecular level, VEGF@heparinized hydrogels enable sustained growth factor release via electrostatic interactions, achieving a cumulative release of 68.3% over 14 days—extending the half-life by sevenfold compared with free VEGF.[61] Structurally, their gradient pore architecture with 50–100 μm channels effectively guides endothelial cell migration, increasing capillary density by 2.8-fold.[62] Meanwhile, hydrogen peroxide-mimetic hydrogels based on PCN-224(Mn)

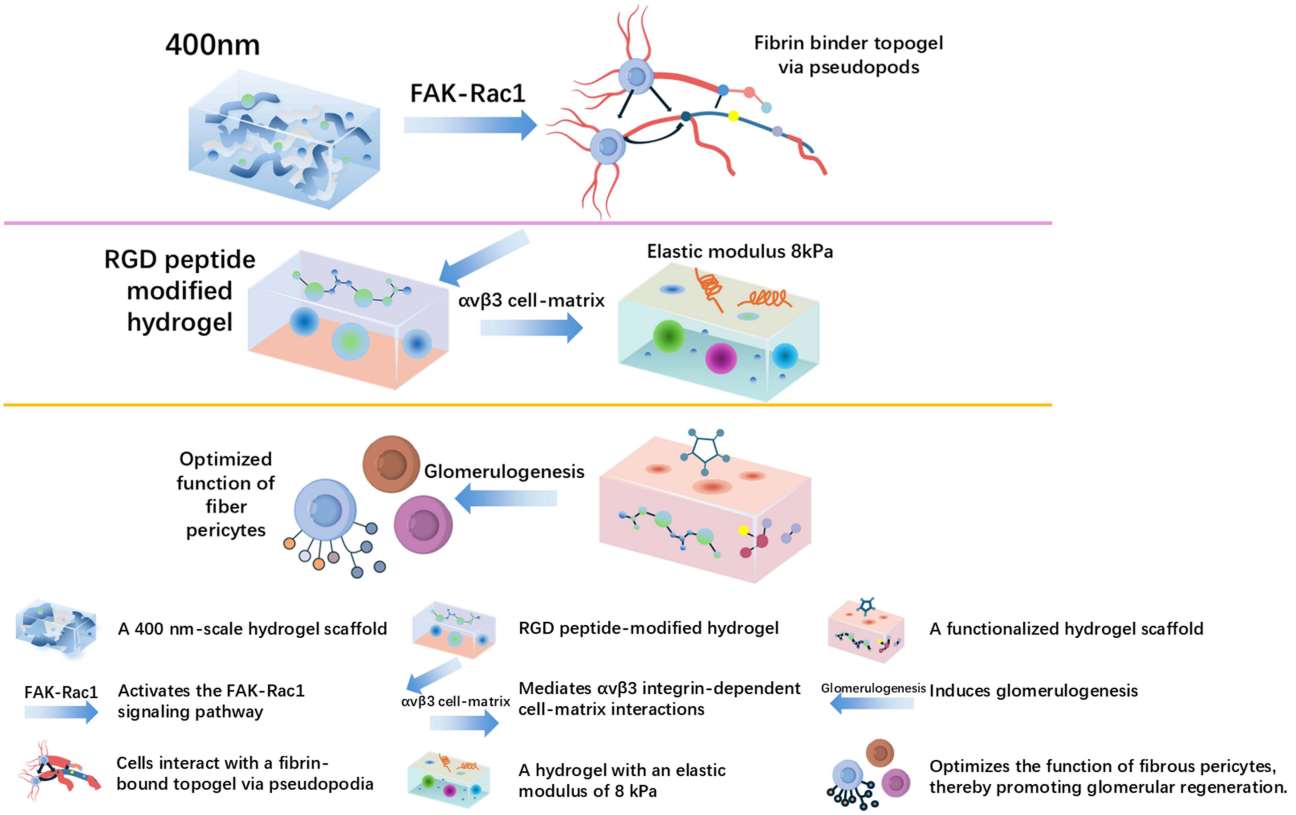


Figure 2 Multifunctional mechanisms of nanohybrid hydrogels.

MOF significantly improve hypoxic wound microenvironments, raising local oxygen partial pressure by 215% and upregulating HIF-1α expression 3.1-fold.[63] Furthermore, POSS hydrogels loaded with adipose-derived stem cell (ADSC)-derived exosomes exhibited pronounced pro-angiogenic activity in diabetic wound models, yielding a cluster of differentiation 31 positive (CD31+) vascular density of 48.2 ± 3.7 vessels per field—significantly higher than the control group (16.5 ± 2.1; $p < 0.001$).[64]

Enhancing Cell Proliferation and Migration

Nanohydrogels enhance cellular activity through integrated biophysical and biochemical mechanisms. At the microstructural level, a grid-like architecture with 400 nm spacing increases fibroblast migration speed by 140% and promotes pseudopodium formation by activating the focal adhesion kinase-Rac1 (FAK-Rac1) signaling pathway.[65] In terms of molecular recognition, arginine-glycine-aspartic acid (RGD)-modified hydrogels improve keratinocyte proliferation 2.3-fold through integrin αvβ3-mediated cell-matrix interactions.[66] Regarding the mechanical microenvironment, hydrogels with an elastic modulus of 8 kPa optimally support fibroblast function, achieving collagen secretion levels of 15.6 ± 1.2 μg/mg protein.[67] Preclinical studies further confirmed that hyaluronic acid-gelatin composite hydrogels significantly improve wound healing in diabetic pig models, reducing epithelialization time from 28 ± 3 days to 19 ± 2 days.[68] These results demonstrate that precise control over the physicochemical properties of nanohydrogels can effectively stimulate and guide the behavior of wound-repair cells, thereby accelerating the healing process (Figure 2).

Application Examples of Nanogel in Diabetic Wound Repair

Functionalized Caged Polyhedral Oligomeric Silsesquioxane (POSS)-Based Multifunctional Hydrogel Systems

The multifunctional hydrogel system based on caged polyhedral oligomeric silsesquioxane (POSS), developed by Teng Wei and Li Weichang's team at the Affiliated Stomatological Hospital of Sun Yat-sen University, utilizes the unique molecular-level dispersion properties of POSS to modulate chain dynamics. Covalently modified POSS nanocages

function as octavalent crosslinkers, forming a three-dimensional hydrogel network through in-situ crosslinking. The rigid cage structure, together with its high crosslinking density, restrains excessive swelling of the hydrogel matrix and improves structural stability, thereby avoiding wound-healing impairment caused by swelling under clinical use.

While the functionalized POSS crosslinker builds the 3D network, it simultaneously introduces abundant quaternary ammonium sites (QAS), conferring broad-spectrum antibacterial activity to the hydrogel.[69] To further enable mechanically active contraction for accelerated wound closure, the authors incorporated temperature-responsive poly (N-isopropylacrylamide) (PNIPAM) into the hydrogel backbone, creating a mechanically responsive 3D network. Concurrently, a long-chain polymer rich in catechol groups was synthesized and processed into an adhesive fiber membrane via electrospinning, which was placed as an interlayer between the hydrogel and the wound tissue. This adhesive interlayer offers several advantages, including easy application, conformability to various wound shapes, efficient exudate absorption, and minimal interference with nutrient and metabolic exchange.[70]

The unique network architecture of the hydrogel, coupled with its intelligent responsiveness-mediated contraction, provides an ideal platform for the delivery of drugs and bioactive components. Using exosomes as a model bioactive cargo, the hydrogel system enabled their controlled and sustained release, effectively promoting angiogenesis in injured tissues. The therapeutic performance of the hydrogel dressing was assessed in a diabetic mouse wound model. Results showed that the self-contracting hydrogel dressing significantly accelerated wound closure compared with control and commercial dressing groups. Its synergistic antibacterial effect and sustained exosome release contributed to markedly improved healing rates in diabetic wounds.

Histological analysis further indicated that the POSS-nanocage-based hydrogel system exhibited potent antibacterial activity, effectively suppressing inflammation in chronic diabetic wounds. Moreover, the released exosomes substantially enhanced angiogenesis, collectively promoting wound healing and tissue regeneration.[69]

Metal-Organic Framework (MOF) Nanozyme Hydrogels

Associate Professor Wang Na et al at Sichuan University reported a MOF nanozyme hydrogel (MCGC hydrogel). By constructing bimetallic MOF nanozymes, they clearly distinguished and separated structural sites and active centers within the MOF coordination network. Inspired by the catalytic active site structure of natural heme, they constructed a porphyrin-based biomimetic Mn-N_4 active site, endowing it with CAT-like catalytic activity.[71]

Through the co-anchoring of MOF nanozymes and the natural antimicrobial compound chlorogenic acid (CGA) within a genipin-crosslinked chitosan hydrogel, they developed a multifunctional, injectable, adhesive, and self-healing hydrogel dressing for diabetic wounds.

Chlorogenic acid, a natural polyphenol abundant in honeysuckle, exhibits antibacterial and antiviral properties and can inhibit bacterial growth without inducing antibiotic resistance. After loading with CGA, the MCGC hydrogel demonstrated strong antibacterial activity against both Gram-negative and Gram-positive bacteria, achieving inhibition rates of 99.91% against Escherichia coli and 99.97% against Staphylococcus aureus.

During diabetic wound healing, the accumulation of ROS and local hypoxia exacerbate the inflammatory storm and wound edema, hindering wound repair. The PCN-224(Mn) MOF nanozyme mimics CAT-like catalytic activity by constructing a Mn-N_4 bionic chemical structure. It converts accumulated H_2O_2 at the wound site into H_2O and O_2, alleviating oxidative stress while supplying dissolved oxygen to promote wound healing.

After loading the MOF nanozyme, the MCGC hydrogel effectively degraded H_2O_2 and generated substantial dissolved oxygen, achieving an H_2O_2 clearance rate of 87.9% within 12 hours and 97.7% within 24 hours.[33]

In wound healing experiments on type I diabetic mice, the wound healing rate in the MCGC hydrogel-treated group was significantly higher than that in the control group, with a wound healing rate of ≈95% at the treatment endpoint (day 8).

Histopathological analysis revealed that hematoxylin–eosin (HE) staining indicated the MCGC hydrogel effectively alleviated the inflammatory response at the wound site and promoted the regeneration of new hair follicles, sebaceous glands, and other skin appendages. Masson staining demonstrated that the MCGC hydrogel effectively promoted the regeneration and deposition of collagen fibers associated with wound healing at the wound site. Immunohistochemical

analysis indicated that the MCGC hydrogel significantly downregulated the expression of inflammatory factors such as IL-1β, IL-6, and TNF-α at the wound site, successfully accelerating the healing of diabetic infected wounds.[71]

Zinc-Based Polyoxometalate Nanozyme-Functionalized Hydrogel (AHAMA/CS-GOx@Zn-POM)

Researchers from the Affiliated Hospital of North Sichuan Medical College developed a zinc-based polyoxometalate nanozyme-functionalized hydrogel (AHAMA/CS-GOx@Zn-POM). The hydrogel combines aldehyde- and methacrylic anhydride-modified hyaluronic acid hydrogel (AHAMA) with chitosan nanoparticles (CS NPs), and encapsulates zinc-based polyoxometalate nanoenzymes (Zn-POM) and glucose oxidase (GOx).[72]

GOx catalyzes glucose to produce gluconic acid and H_2O_2, thereby mitigating the impact of hyperglycemic microenvironments on wound healing. Zn-POM exhibits peroxidase and superoxide dismutase activities, scavenging reactive oxygen species and H_2O_2—a byproduct of glucose degradation. Furthermore, Zn-POM modulates the immune microenvironment by inhibiting MAPK/IL-17 signaling, reducing pro-inflammatory cytokines, and upregulating anti-inflammatory mediators, thereby inducing M1 macrophage reprogramming to the M2 phenotype. This promotes angiogenesis and collagen regeneration within the wound.[73]

In a rat diabetic wound model, application of AHAMA/CS-GOx@Zn-POM enhanced neovascularization and collagen deposition, accelerating wound healing. This study established an integrated therapeutic system that comprehensively regulates the hyperglycemic microenvironment and remodels the immune microenvironment in diabetic wounds. It was demonstrated to effectively eliminate the toxic effects of the hyperglycemic microenvironment in diabetic wounds and catalyze the harmless degradation of glucose through a cascade reaction, thereby alleviating oxidative stress and improving cellular function.[74]

Compared with POSS and MOF hydrogels, this hydrogel offers the unique advantage of comprehensively regulating the hyperglycemic-immune microenvironment, making it well-suited for diabetic wounds with severe hyperglycemia; however, its cascade reaction efficiency is easily affected by the wound pH, requiring further optimization of the pH response range.

A comprehensive comparison of the three representative nanohydrogel systems in terms of design, mechanisms, and efficacy is provided in Table 3.

Table 3 Comparison of Representative Nanohydrogel Systems: (POSS, MOF, Zn-POM)

Characteristics	POSS-Based Hydrogel	MOF-Nanozyme Hydrogel	Zn-POM-Based Hydrogel
Core Design	Octa-arm POSS crosslinking + temperature response	Bimetallic MOF + CAT-mimetic nanozyme	Zn-POM nanozyme + GOx
Antimicrobial Mechanism	Chemical bactericidal effect of quaternary ammonium salt (QAS)	Natural antibacterial activity of chlorogenic acid (CGA) + H_2O_2 scavenging	Cascade catalysis + immunomodulation
Anti- inflammatory Mechanism	Exosome-mediated angiogenesis	ROS scavenging + downregulation of pro-inflammatory factors (IL-1β, IL-6, TNF-α)	MAPK/IL-17 signaling pathway inhibition + M1→M2 macrophage reprogramming
Angiogenic Mechanism	ADSC exosome loading for sustained release	O_2 generation alleviates hypoxia	Immune microenvironment remodeling + enhanced neovascularization
Smart Response	Thermosensitive contraction enabling drug-controlled release	ROS/pH responsiveness	Glucose/H_2O_2 responsiveness
Efficacy in Animal Models	Significantly enhanced healing rate	8-day healing rate ≈95%	Enhanced angiogenesis and collagen deposition
Clinical Translation Phase	Preclinical studies	Preclinical studies	Preclinical Studies
Ref.	[57, 69]	[71]	[72, 73]

Abbreviations: POSS, polyhedral oligomeric silsesquioxane; MOF, metal-organic framework; Zn-POM, zinc-based polyoxometalate; CAT, catalase; Gox, glucose oxidase; QAS, quaternary ammonium salt; CGA, chlorogenic acid; ROS, reactive oxygen species; IL, interleukin; TNF-α, tumor necrosis factor-α; MAPK, mitogen-activated protein kinase; ADSC, adipose-derived stem cell.

Current Research Challenges

Despite the immense potential demonstrated by nanohydrogels in diabetic wound healing, multiple challenges persist in transitioning from basic research to clinical application:

Bottlenecks in Large-Scale Preparation and Quality Control

Current nanohydrogel preparation largely relies on laboratory-scale precision operations (eg, photopolymerization, freeze-drying), making industrial standardized production difficult.[75] Key issues include: Complex and time-consuming preparation processes (eg, enzyme-catalyzed crosslinking requires precise control of enzyme concentration and reaction time), leading to high production costs; Poor quality stability with structural and performance variations between batches (eg, fluctuations in porosity and mechanical strength); Lack of unified quality evaluation standards, with key metrics such as smart response sensitivity and drug release consistency yet to be standardized within the industry. These issues severely hinder the clinical translation and commercialization of nanohydrogels, necessitating the development of simple, efficient, and scalable preparation techniques (eg, continuous flow synthesis, 3D printing) alongside the establishment of robust quality control systems.

Incomplete Clarity on Mechanism of Action and in vivo Safety

Although current studies have demonstrated that nanohydrogels can effectively promote diabetic wound healing, their underlying in vivo mechanisms are not yet fully understood. First, the interactions between nanohydrogels and wound cells remain incompletely elucidated, including the cellular uptake pathways of nanoparticles and the specific targets involved in signal-pathway regulation. Second, the precision of in vivo smart-responsive behavior requires further validation, as the heterogeneity of the wound microenvironment may lead to uneven response efficiency. Third, long--term safety data are still limited, particularly regarding the in vivo metabolic fate of nanoparticles and the potential toxic effects of their prolonged accumulation, such as chronic inflammation or organ damage.[76] Moreover, controlling the biodegradation rate of nanohydrogels is critical: excessively rapid degradation may undermine repair efficacy, while excessively slow degradation could trigger foreign-body reactions.

Insufficient Functional Synergy and Clinical Adaptability

Currently, most available nanohydrogels still demonstrate limited functionality or poor synergistic performance. Many hydrogels focus on a single aspect, such as antibacterial or pro-angiogenic activity, and are thus unable to comprehensively address the multidimensional pathological challenges of diabetic wounds. The design of synergistic mechanisms is often inadequate, exemplified by mismatches between the release kinetics of drugs or nanozymes and the distinct phases of wound healing—inflammation, proliferation, and remodeling. Clinical adaptability also remains a challenge; for instance, some hydrogels lack sufficient mechanical strength for use on weight-bearing areas like the foot, while others require improvement in flexibility and breathability to enhance patient comfort.[77]

Furthermore, there is still limited investigation into the combined use of nanohydrogels with other therapeutic modalities—such as negative-pressure wound therapy or stem cell therapy—which prevents the full potential of multimodal treatment strategies from being realized.

Future Development Directions

Based on current research status and challenges, future development of nanohydrogels in diabetic wound healing will focus on five key directions.

Innovation in Novel Materials and Preparation Techniques

Combine the advantages of natural polymers (eg, collagen, alginate) and synthetic polymers (eg, PEG, PLGA) to develop multifunctional composite materials for preparing hybrid hydrogels with high biocompatibility and excellent mechanical properties; Introduce two-dimensional materials (eg, graphene, MXene) to enhance antimicrobial and conductive properties, enabling electrically stimulated repair;[78] Advance 3D bioprinting to enable personalized hydrogel customization to fit diverse wound shapes and sizes; Continuous flow synthesis enhances production efficiency while ensuring batch consistency; Replace conventional chemical crosslinkers with non-toxic alternatives (eg, genipin) to facilitate eco-

friendly preparation processes and minimize residual toxicity; Utilize renewable feedstocks (eg, biomass-derived polymers) for hydrogel synthesis to reduce environmental impact.[79]

In-Depth Analysis and Precision Design of Mechanisms of Action

Apply multi-omics technologies—including transcriptomics, proteomics, and metabolomics—to systematically elucidate the molecular mechanisms through which nanohydrogels regulate the wound microenvironment and to identify key therapeutic targets. Develop personalized hydrogels tailored to patient-specific wound microenvironment characteristics, such as pH, reactive oxygen species levels, and bacterial profiles, thereby designing responsive hydrogel systems that enable precision medicine. Perform comprehensive long-term animal studies and clinical trials to clarify the in vivo metabolism, degradation pathways, and long-term safety of nanohydrogels, generating essential data to support future clinical translation.

Functional Expansion and Development of Synergistic Treatment Strategies

Develop multifunctional integrated hydrogels combining antibacterial, anti-inflammatory, pro-angiogenic, and neurotrophic functions to address the complex demands of diabetic wound healing; Design dual-responsive (eg, pH/ROS, glucose/temperature) or triple-responsive hydrogels for more precise drug delivery and microenvironment regulation; Explore synergies between nanohydrogels and photothermal therapy, photodynamic therapy, or stem cell therapy. For instance, photothermally responsive hydrogels can synergistically achieve antibacterial and pro-angiogenic effects under near-infrared light irradiation, enhancing therapeutic efficacy.[80]

Accelerating Clinical Translation and Commercialization

Develop animal models of diabetic wounds that closely mimic clinical realities (eg, porcine diabetic foot models) to systematically evaluate hydrogel healing efficacy, safety, and usability; Conduct multicenter, large-scale clinical trials to validate the therapeutic efficacy of nanohydrogels across different types of diabetic wounds and advance clinical translation; Optimize production processes to reduce costs; Establish product standards and clinical application guidelines to facilitate the transition of nanohydrogels from laboratory to clinical settings, refine industrialization chains, and provide novel therapeutic options for diabetic patients.

Safety and Regulatory Considerations

Safety and regulatory considerations should be prioritized for the clinical translation of nanohydrogels. First, nanoparticle clearance pathways in the in vivo microenvironment need to be fully elucidated, including the metabolic routes and excretion efficiency of nanocomponents (eg, MOF nanozymes, POSS nanocages) to avoid potential organ accumulation. Second, long-term preclinical studies should be conducted to assess chronic exposure risks, such as systemic inflammation, immunogenicity, or tissue toxicity caused by prolonged retention of nanomaterials. Third, compliance with regulatory guidelines for medical nanomaterials is essential—standards for nanoparticle size distribution, bioavailability, and biodegradation rate need to be strictly followed to meet clinical approval requirements. Additionally, the establishment of unified safety evaluation systems for nanohydrogel-based dressings will help standardize their development and promote their safe translation from preclinical research to clinical practice.

Conclusion

As an interdisciplinary innovation, nanohydrogels achieve precise regulation of the pathological microenvironment in diabetic wounds through material design and functional modification, demonstrating unique advantages in antibacterial, anti-inflammatory, pro-angiogenic, and pro-proliferative effects. The systems reviewed herein—including POSS-based hydrogels, MOF nanozyme hydrogels, and zinc-based polyoxometalate hydrogels—exhibit distinct design features and therapeutic advantages compared with general hydrogels, offering diverse and targeted therapeutic approaches for diabetic wound repair. However, current research faces critical challenges in large-scale preparation, mechanism elucidation, and synergistic functional optimization, necessitating collaborative efforts across materials science, biology, and clinical medicine.

Looking ahead, with the development of novel materials, advances in fabrication techniques, and deeper understanding of action mechanisms, nanohydrogels are expected to develop toward intelligent, personalized, and multimodal synergistic approaches (anchored by emerging 3D bioprinting and multi-omics research). This evolution holds promise for overcoming existing therapeutic bottlenecks, achieving efficient repair of diabetic wounds, and bringing new hope to hundreds of millions of diabetes patients worldwide.

Data Sharing Statement

The original contributions presented in the study are included in the article, and further inquiries can be directed to the corresponding authors.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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