Coordination Chemistry Reviews 549 (2026) 217376

Contents lists available at ScienceDirect

Coordination Chemistry Reviews

journal homepage: www.elsevier.com/locate/ccr

Nanoenzyme-engineered hydrogels reprogram wound microenvironment to accelerate diabetic wound healing

Lianjun Yu [a,1], Xinxin Sun [a,1], Xiaoyang Zhang [a], Jin Sun [a,b], Zhonggui He [a,b], Jing Li [c,*], Cong Luo [a,b,*], Shenwu Zhang [a,*]

[a] Department of Pharmaceutics, Wuya College of Innovation, Shenyang Pharmaceutical University, Shenyang 110016, PR China
[b] Joint International Research Laboratory of Intelligent Drug Delivery Systems, Ministry of Education, Shenyang Pharmaceutical University, Shenyang 110016, PR China
[c] School of Pharmacy, Shenyang Medical College, Shenyang, Liaoning Province, China

ARTICLE INFO

Keywords:
Nanoenzyme-engineered hydrogels
Diabetic wounds
Dynamic catalysis
Microenvironment reprogramming

ABSTRACT

Diabetic wounds are notoriously refractory to healing due to a self-perpetuating pathological microenvironment, perpetuated by a synergistic interplay of oxidative stress, chronic inflammation, infection, and metabolic dysregulation. Conventional therapeutic strategies often fail to dynamically respond to these challenges or achieve synergistic, multi-targeted interventions. Recently, nanoenzyme-engineered hydrogels have emerged as a promising platform for reprogramming the diabetic wound microenvironment by combining the catalytic activity of nanoenzymes with the dynamic responsiveness of hydrogels. This review comprehensively summarizes recent advancements in nanoenzyme-engineered hydrogels for diabetic wound healing. We begin by delving into the core pathological mechanisms that sustain the hostile microenvironment of diabetic wounds. Subsequently, we catalog the development of rationally designed synergistic nanoenzyme-engineered hydrogels, highlighting precision engineering strategies that tailor catalytic functionalities to specific clinical demands. Furthermore, we elucidate the fundamental mechanisms and multifaceted interactions through which these catalytic systems drive microenvironmental reprogramming. Ultimately, this review aims to establish a solid theoretical framework and offer valuable technical insights to guide the development of next-generation nanoenzyme-engineered hydrogels for effective diabetic wound repair.

1. Introduction

Diabetic wounds pose a formidable clinical challenge due to their persistent non-healing nature, driven by the hyperglycemia-induced dysregulation of the wound microenvironment [1–3]. These wounds are characterized by a vicious cycle of "oxidation-inflammation-infection", where reactive oxygen species (ROS) amplify pro-inflammatory cytokine expression *via* NF-κB activation, perpetuating chronic inflammation [4–6]. Concurrently, hyperglycemia-induced accumulation of advanced glycation end products (AGEs) exacerbates inflammatory responses and extracellular matrix (ECM) degradation through RAGE-mediated signaling, further impeding tissue repair [7]. Paradoxically, although hypoxia typically triggers angiogenesis, diabetic wounds fail to initiate effective neovascularization due to dysregulated vascular endothelial growth factor (VEGF) signaling, resulting in aberrant and dysfunctional vasculature [8,9]. The situation is compounded by the formation of pathogenic biofilms that create antibiotic-resistant niches while secreting immunosuppressive factors to evade host defenses [10–12]. With nearly 25% of diabetic patients at risk of developing foot ulcers and 20-30% progressing to lower-limb amputation, there is an urgent demand for innovative and effective therapeutic strategies [13]. Current approaches are limited by insufficient responsiveness and a lack of capacity to simultaneously address the intertwined pathological axes of metabolic dysfunction, chronic inflammation, and impaired tissue regeneration [14–16].

Nanoenzymes, a class of biomimetic catalytic nanomaterials, have emerged as transformative agents for reprogramming pathological microenvironments due to their robust catalytic stability, multi-enzyme mimetic activities, and programmable physicochemical properties [17,18]. Unlike natural enzymes, nanoenzymes operate without

* Corresponding authors at: Department of Pharmaceutics, Wuya College of Innovation, Shenyang Pharmaceutical University, No. 103 Wenhua Road, Shenyang 110016, China.
E-mail addresses: dddefghijklmn@163.com (J. Li), luocong@syphu.edu.cn (C. Luo), zhangshenwu@syphu.edu.cn (S. Zhang).
[1] These authors contributed equally to this work

https://doi.org/10.1016/j.ccr.2025.217376
Received 28 August 2025; Accepted 11 November 2025

cofactor dependency and maintain high catalytic efficiency across diverse pH and temperature conditions, enabling consistent performance under the harsh oxidative and inflammatory environments characteristic of chronic wounds [19,20]. Their tunable size, surface chemistry, and catalytic functionalities allow precise modulation of local biochemical pathways, including the regulation of oxidative stress, inflammatory cascades, and microbial burdens that impede effective tissue repair [21–23]. Furthermore, the inherent spatiotemporal adaptability of nanoenzymes allows them to respond dynamically to localized microenvironmental cues, providing opportunities for targeted and stage-specific therapeutic interventions [24–26]. These unique attributes position nanoenzymes as promising candidates for addressing the multifaceted barriers to diabetic wound healing, offering a foundation for the development of next-generation therapeutic strategies that demand precise, multi-targeted microenvironmental modulation [27–29].

However, the clinical translation of nanoenzymes is hindered by challenges such as off-target effects, insufficient catalytic selectivity, long-term biocompatibility concerns, and limited wound site retention [30,31]. The complex diabetic wound environment further demands sustained nanoenzymes activity against clearance or inactivation. To address these issues, hydrogels have emerged as promising platforms that enhance nanoenzymes retention and protect their catalytic activity, while offering a moist healing environment and tunable release profiles responsive to wound cues [32,33]. Moreover, the structural versatility of hydrogels enables the design of systems that can respond to dynamic wound microenvironments, allowing for the regulated release of therapeutic agents in response to specific biochemical or biophysical cues [34,35]. By providing spatial and temporal control over nanoenzymes delivery and activity, hydrogels offer a pathway to integrate catalytic therapy with microenvironmental modulation, laying the groundwork for precise and effective interventions in diabetic wound healing [36–39]. Nevertheless, the integration of nanoenzymes into hydrogels introduces its own set of challenges, such as achieving uniform nanoenzymes dispersion, maintaining catalytic efficiency within the polymer network, and ensuring scalable and reproducible fabrication processes, issues that warrant further investigation to fully realize the potential of these hybrid systems.

As materials science, nanotechnology, and biomedicine converge, nanoenzyme-engineered hydrogels are transitioning from bench to bedside. This review systematically dissects the pathogenic mechanisms of diabetic wounds and delineates design principles for synergistic nanoenzyme-engineered hydrogels (Fig. 1). We first unravel the molecular interplay within the "oxidation-inflammation-infection" axis and metabolic dysregulation. We then systematically categorize and analyze various integrated material systems of nanoenzyme-engineered hydrogels, including those based on metal-organic frameworks (MOFs), metal-based, carbon-based, biomimetic, single-atom, and heterojunction nanoenzymes, highlighting their design principles, unique advantages, and therapeutic potential. Subsequently, we explore how these materials achieve environment-driven on-demand regulation and synergistic therapy, focusing on both endogenous signal responsiveness (e.g., pH, ROS, glucose, enzymes) and exogenous energy mediation (e.g., photothermal therapy, ultrasound). We further analyze catalytic precision through temporal control, spatial localization, and substrate selectivity. Finally, we envision intelligent theranostic platforms and interdisciplinary integration to accelerate clinical translation. By framing these advances, this review aims to establish a roadmap for next-generation diabetic wound therapies, bridging regenerative medicine and clinical practice through a "dynamic catalysis-microenvironment adaptation-clinical demand" paradigm.

2. Core pathogenesis in diabetic wound microenvironments

Diabetic wounds persist due to a pathological microenvironment where hyperglycemia-driven metabolic dysfunction, oxidative stress, chronic inflammation, infection, and microcirculatory impairment intertwine, disrupting orderly healing [40–42]. Persistent hyperglycemia leads to AGE accumulation, locking macrophages in a pro-inflammatory state while blocking reparative transitions. Concurrent oxidative stress from mitochondrial dysfunction and reduced antioxidant defenses generates excessive ROS, degrading ECM and inducing cell apoptosis. Meanwhile, chronic infection, fueled by impaired immunity and poor perfusion, exacerbates protease imbalance, destabilizing growth factor signaling and collagen remodeling [43,44]. Together, these factors form a self-perpetuating cycle of non-healing,

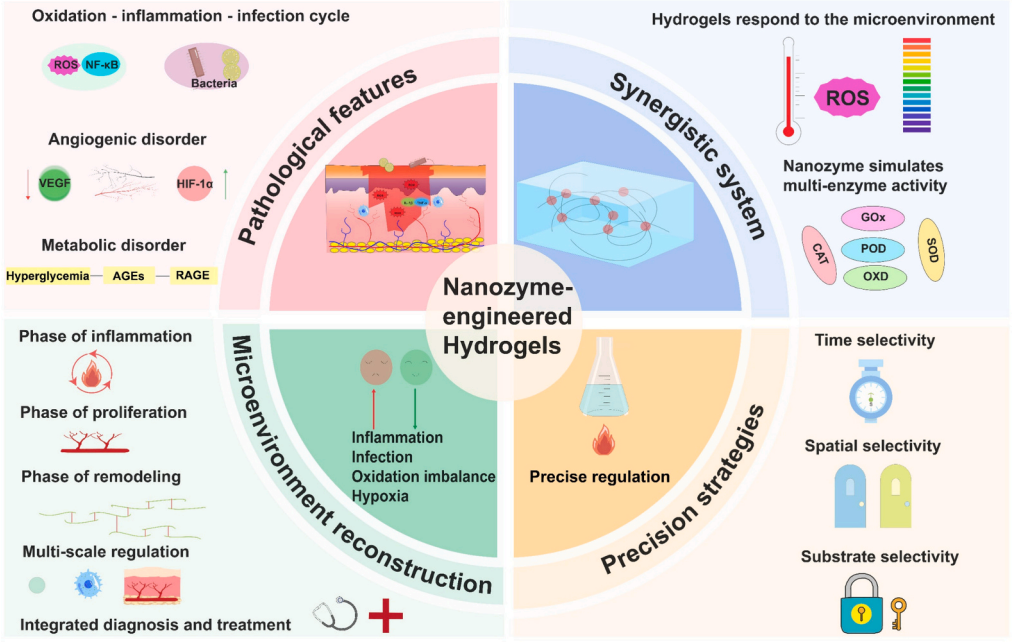

Fig. 1. Schematic illustrates a comprehensive treatment strategy for diabetic wounds. This strategy employs a precisely designed nanozyme-engineered hydrogels collaborative system to catalytically remodel the pathological microenvironment, ultimately addressing the core mechanisms of the condition.

characterized by persistent inflammation, ECM destruction, and failed tissue regeneration.

2.1. Diabetic wound pathophysiology: a target for catalytic reprogramming

A self-reinforcing triad of oxidative stress, chronic inflammation, and infection under hyperglycemia perpetuates tissue damage and impedes the transition to proliferation [45,46]. Excessive ROS from mitochondrial and NADPH oxidase dysfunction sustain NF-κB activation, skewing cytokine balance toward pro-inflammatory signals while suppressing anti-inflammatory mediators [47]. AGEs impair macrophage phagocytosis, promoting bacterial biofilm formation, which activates PAMPs to further amplify ROS and inflammation [48–50]. This vicious cycle maintains ECM degradation, cell apoptosis, and impaired angiogenesis, establishing a central barrier to wound healing.

2.1.1. ROS/NF-κB feedforward amplification

Under normal conditions, transient ROS/NF-κB activation coordinates immune responses and resolves inflammation. In diabetic wounds, persistent hyperglycemia and AGEs drive excessive ROS, sustaining NF-κB hyperactivation and continuous pro-inflammatory cytokine release [51]. This blocks macrophage reparative polarization, degrades ECM, and impairs fibroblast function, locking wounds in chronic inflammation [52].

To break this vicious cycle, researchers have turned to nanoenzyme-based hydrogels as a means to intervene in the inflammatory microenvironment. For example, Meng et al. developed an immunomodulatory nanoenzyme-engineered hydrogel (UAPsBP@Gel), which integrated gold-palladium (AuPd) nanoshell with multiple enzymatic activities to construct a multifunctional catalytic platform [53]. This system achieved regenerative reprogramming of the macrophage phenotype by adopting a dual strategy of consuming local glucose and eliminating excessive ROS, while simultaneously inhibiting the NF-κB inflammatory pathway and activating the Nrf2 antioxidant pathway. When combined with photothermal therapy, this nanoenzyme-engineered hydrogel effectively interrupted the vicious cycle of ROS/NF-κB, alleviated the inflammatory microenvironment, and restored the dynamic process of diabetic wound healing. This integrated strategy not only demonstrated the therapeutic potential of nanoenzyme-engineered hydrogels but also established a novel treatment paradigm for chronic wound healing through simultaneous immuno-metabolic modulation and inflammatory pathway intervention.

2.1.2. Biofilm-mediated immune suppression

Biofilms protect pathogens and suppress immune clearance by masking antigens and creating hypoxic, acidic niches that inhibit immune activation [54]. Hyperglycemia worsens biofilm persistence by promoting nutrient-rich microenvironments and impairing immune cell functions, while vascular insufficiency limits immune infiltration, leading to unresolved infection and inflammation [55].

To overcome biofilm-associated immune evasion, smart nanoenzyme systems with microenvironment-responsive properties have emerged as a promising strategy. Shen et al. constructed an oriented fiber cryogel loaded with ZF-67/GOx (glucose oxidase) nanoenzymes (ZG@AFC), whose core advantage lay in its intelligent response to the acidic microenvironment in the infected area of diabetic wounds [56]. Under acidic conditions, this material activated its GOx and peroxidase (POD)-like cascade activity, consumed local glucose while efficiently generating hydroxyl radicals, directly destroyed the bacterial biofilm structure and killed the pathogens within. After removal of biofilms, as the microenvironment transitioned to a weakly alkaline state, its enzyme activity intelligently switched to functions similar to superoxide dismutase (SOD) and catalase (CAT), thereby eliminating excessive ROS and alleviating inflammation, creating conditions for subsequent tissue repair. *In vivo* experiments confirmed that ZG@AFC effectively broke down bacterial biofilms in wounds, controlled infection, and promoted collagen deposition and epithelial regeneration in a synergistic manner, thereby significantly accelerating the healing process of infectious diabetic wounds. This pH-dependent, self-adapting nanoenzymes not only provide an effective approach for combating biofilm-mediated immunosuppression but also open new avenues for developing intelligent therapeutic systems capable of dynamically responding to pathological microenvironmental changes.

2.2. Metabolic dysregulation and impaired repair

Diabetic wound chronicity is driven by hyperglycemia-induced metabolic disruption, which impairs immune regulation, angiogenesis, and ECM remodeling while sustaining inflammation and infection [57]. Persistent hyperglycemia fuels AGEs accumulation and RAGE activation, triggering oxidative stress and inflammatory cascades that lock wounds in a non-healing state [58].

2.2.1. Hyperglycemia-AGEs-RAGE axis dysfunction

Chronic hyperglycemia accelerates AGEs formation, which binds RAGE to activate NOX and mitochondrial ROS overproduction [59]. This ROS-NF-κB loop drives sustained pro-inflammatory cytokine release while inhibiting macrophage M2 polarization and fibroblast-mediated repair [60]. AGEs-RAGE signaling also disrupts endothelial NO (nitric oxide) production, impairing vasodilation and increasing vascular leakage, while vascular dysfunction and hypoxia further upregulate RAGE, reinforcing this pathological cycle.

To achieve multi-target intervention in this self-perpetuating pathological network, researchers have focused on disrupting the metabolic-inflammatory axis through nanotherapeutic approaches. Zhang et al. designed a zinc-dihydromyricetin (Zn-DHM) nanoplatform that aimed to achieve dual regulation of glucose metabolism and AGEs–RAGE signaling (Fig. 2) [61]. This system effectively inhibited excessive glucose uptake by endothelial cells and down-regulated the expression of hexokinase 2 (HK2), thereby reducing glycolytic flux and AGEs production. RNA-seq further confirmed that the system significantly suppressed genes related to the AGEs–RAGE pathway (such as IL-6 and TNF-α), blocking the inflammatory cascade. In a diabetic mouse model, Zn-DHM treatment achieved a wound closure rate of 99.7%, doubled collagen deposition, and reduced inflammatory cell infiltration by 80%, demonstrating strong potential for promoting diabetic wound healing through metabolic–immune reprogramming. This approach not only validated the therapeutic value of simultaneously targeting the metabolic and inflammatory arms of the AGEs-RAGE axis but also established a paradigm for treating diabetic complications through metabolic-immune reprogramming.

2.2.2. Hypoxia-angiogenesis paradox

Oxygen is essential for wound healing, but diabetic wounds remain chronically hypoxic, which paradoxically suppresses effective angiogenesis while transient hypoxia fails to drive sustained vascular repair [62]. Stabilized HIF-1α under chronic hypoxia fails to adequately induce VEGF and PDGF, while persistent low oxygen exacerbates mitochondrial ROS, further impairing endothelial migration and lumen formation [63]. Hypoxia also disrupts keratinocyte proliferation and immune regulation, sustaining NF-κB-driven inflammation and blocking reparative macrophage transitions [64]. This hypoxia–angiogenesis paradox becomes a critical barrier to wound closure.

To resolve this self-sustaining pathological cycle, advanced oxygen-regulating systems have been developed to actively reprogram the hypoxic wound microenvironment. Guan et al. designed a dual-functional oxygen release system that integrated oxygen-release microspheres (ORMs) with ROS-scavenging hydrogels (ROSS gel) to achieve active reprogramming of the pathological microenvironment [65]. This system underwent precise responsive design at the material level: the ORMs took PVP/ hydrogen peroxide (H_2O_2) as the core and were

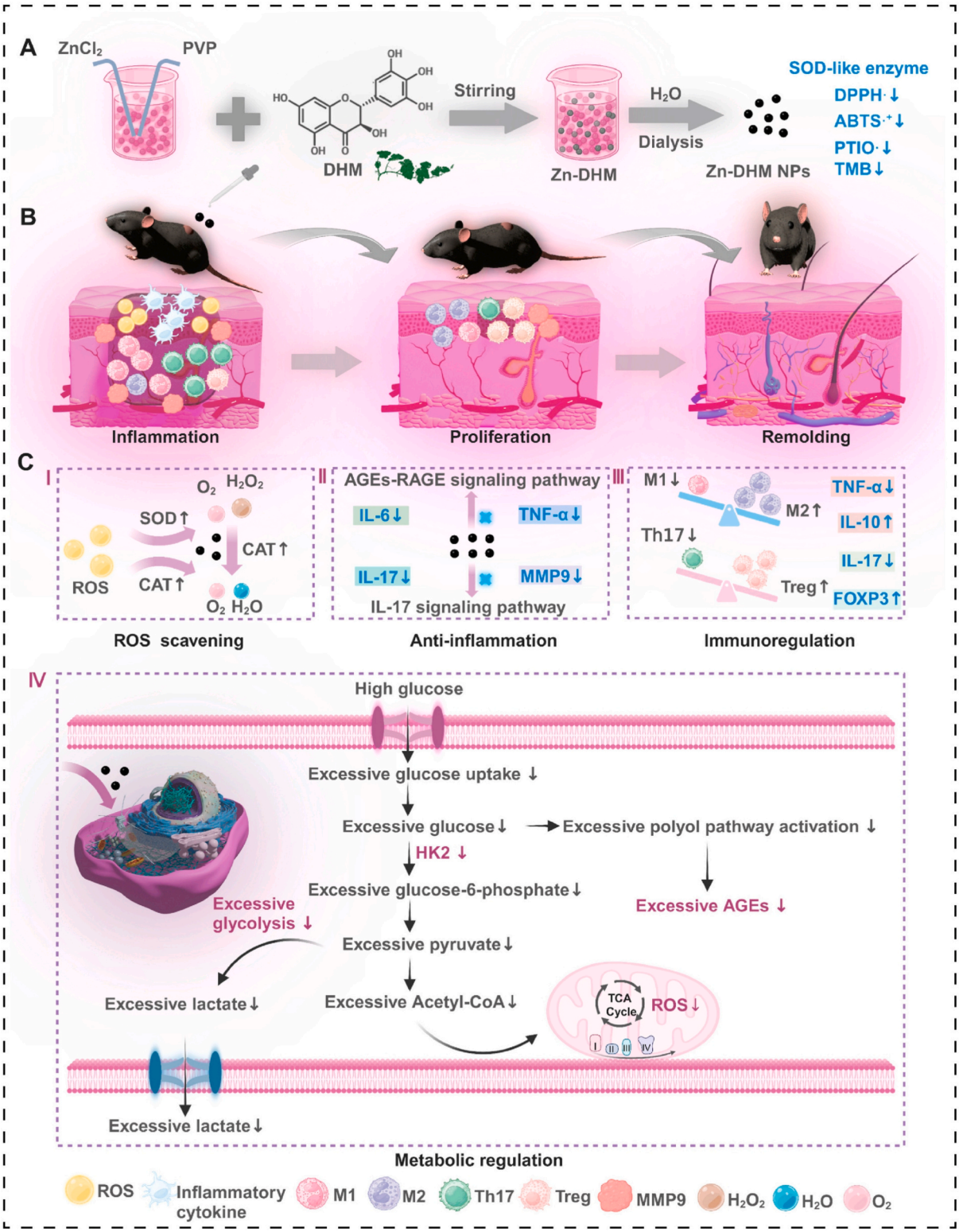

Fig. 2. A The synthesis process and antioxidant properties of Zn-DHM NPs. B Diabetic wounds from the inflammation phase to the proliferation and remolding phases. C The mechanism of promoting early diabetic wound healing: ROS scavenging (I), anti-inflammation (II), immunoregulation (III) and metabolic regulation (IV), from [61]. Copyright (2025), Elsevier Ltd.

coated with a CAT shell on the outside, enabling them to release oxygen controllably and continuously in a hypoxic microenvironment, directly alleviating tissue hypoxia while avoiding cytotoxicity caused by H_2O_2 accumulation. ROSS gel, on the other hand, introduced phenylboronic acid ester groups to dynamically capture and neutralize excessive ROS and maintained a moist microenvironment conducive to repair on the wound surface. The synergy of the two not only physically regulated the distribution of oxygen and ROS, but also activated the Erk1/2/HO-1 signaling pathway at the molecular level, thereby enhancing the metabolic activity and angiogenesis ability of endothelial cells. By

eliminating ROS, this system effectively alleviated oxidative damage, decoupled chronic pathological hypoxia signals from the transient signals promoting angiogenesis, and re-established the balance between angiogenesis and oxidative homeostasis. This integrated oxygen-redox management strategy represents a breakthrough in microenvironment reprogramming, offering a novel approach to resolve the hypoxia-angiogenesis paradox and reignite stalled healing processes in chronic diabetic wounds.

3. Nanoenzyme-engineered hydrogels: integrated material systems and synergistic design

By integrating diverse catalytic nanoenzymes with responsive hydrogels networks, these systems move beyond passive wound management to active microenvironment reprogramming [66]. This integration of multi-scale material design and synergistic functionality closes the gap between complex pathology and effective treatment, laying a robust material foundation for a new generation of diabetic wound therapies [67] (Fig. 3).

3.1. Construction of smart material systems targeting pathological signals

To achieve effective reprogramming of the diabetic wound microenvironment, researchers have designed diverse nanoenzyme-engineered hydrogels. The core design concept involves utilizing nanoenzymes to mimic natural enzyme catalytic functions, integrated with the superior properties of hydrogels, such as excellent moisture retention, drug loading and controlled release capabilities, and adsorption of wound exudates [68,69]. These systems can be broadly categorized based on the composition and structure of the nanoenzymes as follows: MOFs, metal-based, carbon-based, biomimetic, single-atom, and heterojunction systems (Table 1).

3.1.1. Nanoenzyme-engineered hydrogels based on MOFs

MOFs are inorganic-organic porous crystal nanomaterials formed by the self-assembly of metal ions and organic ligands [70]. They have inherent advantages such as large specific surface area, reachable active sites, variable and adjustable pore size, and multi-functional structure

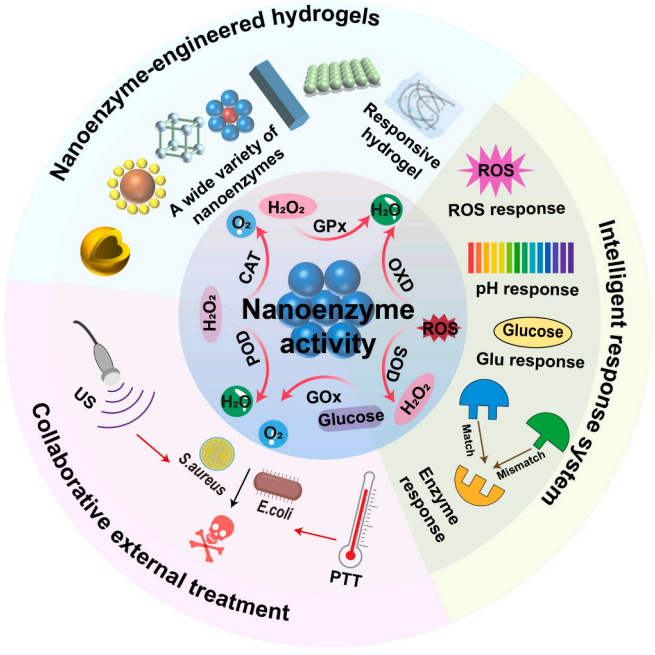

Fig. 3. Nanoenzyme functionalized hydrogels and their intelligent response systems.

[71]. MOF nanoenzyme-engineered hydrogels, as an intelligent responsive biomaterial, have shown great potential in the management of diabetic wounds [72].

In the design of wound dressings that combined catalytic therapy with drug delivery, materials could dynamically respond to and regulate the complex wound microenvironment. For instance, Zhong et al. had developed a cascade nanoenzyme-engineered hydrogel (Ni-MOF@GOx-QT) based on the nickel-based metal-organic framework (Ni-MOF) and GOx [73]. This material utilized high-concentration glucose at the wound site to generate H_2O_2 and an acidic microenvironment catalyzed by GOx, thereby activating the POD activity of Ni-MOF to produce •OH for efficient antibacterial purposes and significantly promoting wound healing in a diabetic rat model. However, once the system was activated, it continued to react and could not automatically terminate based on blood sugar levels, posing a risk of excessive blood sugar consumption. To address this limitation and achieve more precise glucose regulation, subsequent research has focused on developing self-terminating catalytic systems with feedback control mechanisms. In contrast, Tai et al. developed a glucose-responsive bimetallic Zn-Fe MOF nanoenzyme-engineered hydrogel with self-feedback regulation function (GI-M@Gel) (Fig. 4) [74]. This material catalyzed acid production through GOx in a high-sugar environment and activated MOF to release •OH for antibacterial effects. Meanwhile, acidic conditions promoted the degradation of MOF and controlled-release of insulin to achieve blood sugar reduction. When blood sugar returned to normal, the reaction automatically stopped, avoiding the risk of hypoglycemia. Animal experiments had confirmed that this design could effectively regulate the immune microenvironment and accelerate the healing of diabetic infected wounds.

Together, these studies demonstrated the progressive refinement of MOF-based nanoenzyme- engineered hydrogels, evolving from simple catalytic systems to intelligent therapeutic platforms capable of autonomous feedback regulation. This evolution marks a significant advancement toward clinically viable wound management systems that can safely and effectively navigate the complex metabolic challenges of diabetic wounds. A remaining challenge for clinical translation is the long-term stability and predictable biodegradation of MOFs in the dynamic wound environment.

3.1.2. Metal-based nanoenzyme-engineered hydrogels

Metal-based nanoenzymes have attracted extensive attention in diabetic wound management due to their diverse catalytic activities, tunable properties, and relatively straightforward synthesis methods [75]. By integrating these nanoenzymes into hydrogels matrices, researchers can effectively overcome limitations such as short wound retention time, particle aggregation, and enzymatic inactivation, while simultaneously enabling synergistic multi-modal therapies [76]. This category encompasses metal-based nanoenzyme-engineered hydrogels organized according to the type of active metal center, including iron-based, gold-based, silver-based, bimetallic, metal oxide-based, and other metal-based nanoenzyme-engineered hydrogels. Each type leverages distinct catalytic characteristics, such as POD-like, CAT-like, and oxidase (OXD)-like activities, along with inherent antibacterial effects, to address the multifaceted pathological challenges presented by diabetic wounds [77].

3.1.2.1. Iron-based nanoenzyme-engineered hydrogels. Iron-based nanoenzymes have been widely applied in biological clinical applications such as drug targeted delivery and magnetic resonance imaging due to their unique paramagnetism and superparamagnetism [78]. In 2007, Zhang et al. first reported magnetite nanoparticles with POD-like activity [79]. Their inherent enzymatic activity has driven extensive research on iron-based nanoenzymes in various biomedical fields. Iron-based nanoenzyme-engineered hydrogels, by integrating nanomaterials with multi-enzyme activity and natural biopolymers, can precisely

Table. 1
Nanoenzyme-engineered hydrogels and their simulated enzyme activities and functions.

Names	Nanoenzymes	Simulate enzyme activities	Hydrogel matrixs	Function citations	References
OHCN hydrogel	Au-Pt alloy nanoparticles	GOD and CAT	OHA and CMCS	lowering blood glucose, alleviating oxidative damage, and providing O_2	[91]
PDMoT hydrogel	(MoS_2@TA/Fe NSs	POD and CAT	PVA, Dex and borax	anti-bacterial, anti-inflammatory, anti-oxidant and oxygenating	[117]
ODex/gC/MoS_2@Au@BSA hydrogel	MoS_2@Au@BSA nanoenzymes	POD, SOD, CAT and GOX	Odex and GC	anti-microbial, anti-inflammatory, anti-oxidant, hypoglycemic and oxygenator	[118]
MnCoO@PLE/HA hydrogel	MnCoO@PLE nanoparticles	CAT	HA-HYD and HA-ALD	anti-inflammatory, anti-oxidant and oxygenating	[119]
GelMA@Mg-POM	Mg-POM	SOD and CAT	GelMA	anti-inflammatory, anti-oxidant and pro-angiogenic	[98]
GCNC hydrogel	GCNE	GOx and CAT	CS	anti-bacterial, anti-inflammatory, anti-oxidant, hypoglycemic and oxygenator	[120]
SF/CMC@MnO_2 hydrogel	MnO_2 nanosheets	CAT	SF-GMA and CMC-GMA-CHO	anti-inflammatory, anti-oxidant and oxygenating	[121]
Mo, Fe/Cu, I-Ag@GOx gel	Mo,Fe/Cu,I-Ag nanoenzymes	GOx, POD, OXD, SOD and CAT	SA and CS	anti-microbial, anti-inflammatory, anti-oxidant, hypoglycemic and oxygenator	[122]
OBG@CG	Cu_2-xSe-BSA nanoenzymes	GOx and POD	OHA and gelatin	anti-bacterial, anti-inflammatory, anti-oxidant, hypoglycemic and pro-angiogenic	[123]
OCE	CeO_2 nanoenzymes	CAT	OD, DTPH and EPL	anti-bacterial, anti-inflammatory, anti-oxidant, oxygenating and eliminating AGEs	[124]
EGAP@HG	EGAP	CAT	Pol-407 and Pol-188	anti-microbial, anti-oxidant, oxygenating and pro-angiogenic	[125]
PFOB@PLGA@Pt/GelMA/ODex	PFOB@PLGA@Pt	POD, NOX, SOD, CAT and OXD	Gelatin and Polylysine	anti-bacterial, anti-inflammatory, anti-oxidant and oxygenating	[126]
$Cu_{5.4}O$@Hep-PEG hydrogel	$Cu_{5.4}O$@Hep-PEG	SOD, CAT and GPX	starPEG and heparin	anti-inflammatory, anti-oxidant and pro-angiogenic	[127]
TA-Ag-PAA hydrogel	TA-Ag nanoenzymes	POD	PAA	anti-bacterial and anti-oxidant	[128]
CS/FD/IrNPs hydrogel	IrNPs	POD and CAT	CS and FD	hemostasis, anti-bacterial, anti-inflammatory, anti-oxidant, oxygen supply and pro-angiogenesis	[129]
ACPCAH	Au/$Cu_{1.6}O$/P−C_3N_5	SOD, CAT, SOD, GOx and NOX	Arg and HA	anti-bacterial, anti-inflammatory, anti-oxidative, hypoglycemic, oxygen-supplying and pro-angiogenic	[130]

respond to the key pathological features in the microenvironment of diabetic wounds, providing a platform for sequential and multi-target treatment [80].

In the material design for the microenvironment of diabetic wounds, researchers had developed a variety of hydrogel that could dynamically regulate redox and immune states. For instance, Zhang et al. constructed an iron-modified cerium dioxide nanoenzymes composite astragalus polysaccharide hydrogel (Fe/Ce@APS Gel), in which Fe/CeNP exhibited multi-enzyme activities simulating SOD, CAT, GSH and POD (Fig. 5) [81]. It could not only efficiently eliminate excessive ROS in wounds, but also catalyze the decomposition of H_2O_2 to produce oxygen, alleviating tissue hypoxia. Astragalus polysaccharides synergistically promoted angiogenesis and immune regulation. This hydrogel inhibited the NLRP3/NF-κB pathway by eliminating ROS, promoting the polarization of macrophages from M1 to M2 phenotypes, thereby accelerating the healing of diabetic wounds in animal experiments. However, its antioxidant capacity gradually was consumed during continuous use, and it lacked systematic regulation of the neuro-immune axis.

To further enhance the long-lasting antioxidant capacity and the system-local synergistic regulation ability, Ran et al. had developed a polyphenol conductive nanoenzyme-enhanced redox hydrogel (SFGDP) [82]. This material integrated the conductive nanoenzymes PDA-Fe-PEDOT with POD-like activity. Its quinone-phenol structure reversibly transformed under electrical stimulation, achieving continuous regeneration of antioxidant capacity. In combination with vagus nerve electrical stimulation (VNS), this system not only reduced the levels of systemic inflammatory factors through the brain-spleen axis pathway, but also promoted the M2 polarization of macrophages locally at the wound site, synergistically enhancing collagen deposition, angiogenesis and nerve regeneration, demonstrating healing effects in diabetic infection wound models. The primary challenge for iron-based systems lies in precisely controlling the Fenton reaction rate to avoid pro-oxidant damage while ensuring sufficient catalytic efficacy.

3.1.2.2. Au-based nanoenzyme-engineered hydrogels. Distinct from the multi-enzyme regulatory approach of iron-based nanoenzymes, gold-based nanoenzymes offer a unique strategy for target-and-activate therapy by leveraging their exceptional GOx-like activity to exploit the inherent high glucose levels in diabetic wound [83]. This ingenious use of pathological glucose as a "fuel" provides reactive substrates for subsequent antibacterial treatment and regulates the local microenvironment [84].

To translate this catalytic concept into practical therapeutic applications, researchers have developed sophisticated material systems that leverage the unique properties of gold nanoenzymes. Based on this principle, Sun et al. developed a glucose-activated nanoenzyme-engineered hydrogel [85]. This design constructed a hybrid nanoenzymes with cascade catalytic function by *in situ* reducing and loading gold nanoparticles modified with bovine serum albumin on a two-dimensional metal-organic framework, and integrated it into a polysulfobetaine hydrogel. The core advantage lay in that BSA modification not only enhanced the stability and dispersibility of gold-based nanoenzymes, but also significantly boosted their GOx activity, which could efficiently catalyze the conversion of glucose at the wound site into glucomic acid and H_2O_2. The former created a local acidic environment, while the latter further activated the POD-like activity of MOF, catalyzing the generation of highly toxic •OH to eliminate bacteria. This glucose-triggered cascade reaction ingeniously resolved the issue of limited activity of traditional nanoenzymes in physiologically weakly alkaline environments and under conditions of insufficient endogenous H_2O_2. Animal experiments confirmed that this hydrogel effectively lowered local blood sugar levels at the wound site, eliminated bacterial infections, promoted epithelial formation and collagen deposition, and achieved the best healing effect in diabetic infection wound models. However, the relatively high cost of gold and the potential long-term biological fate of these nanoparticles in the body remain considerations for large-scale clinical application.

3.1.2.3. Ag-based nanoenzyme-engineered hydrogels. Silver nanoparticles are renowned for their broad-spectrum and potent

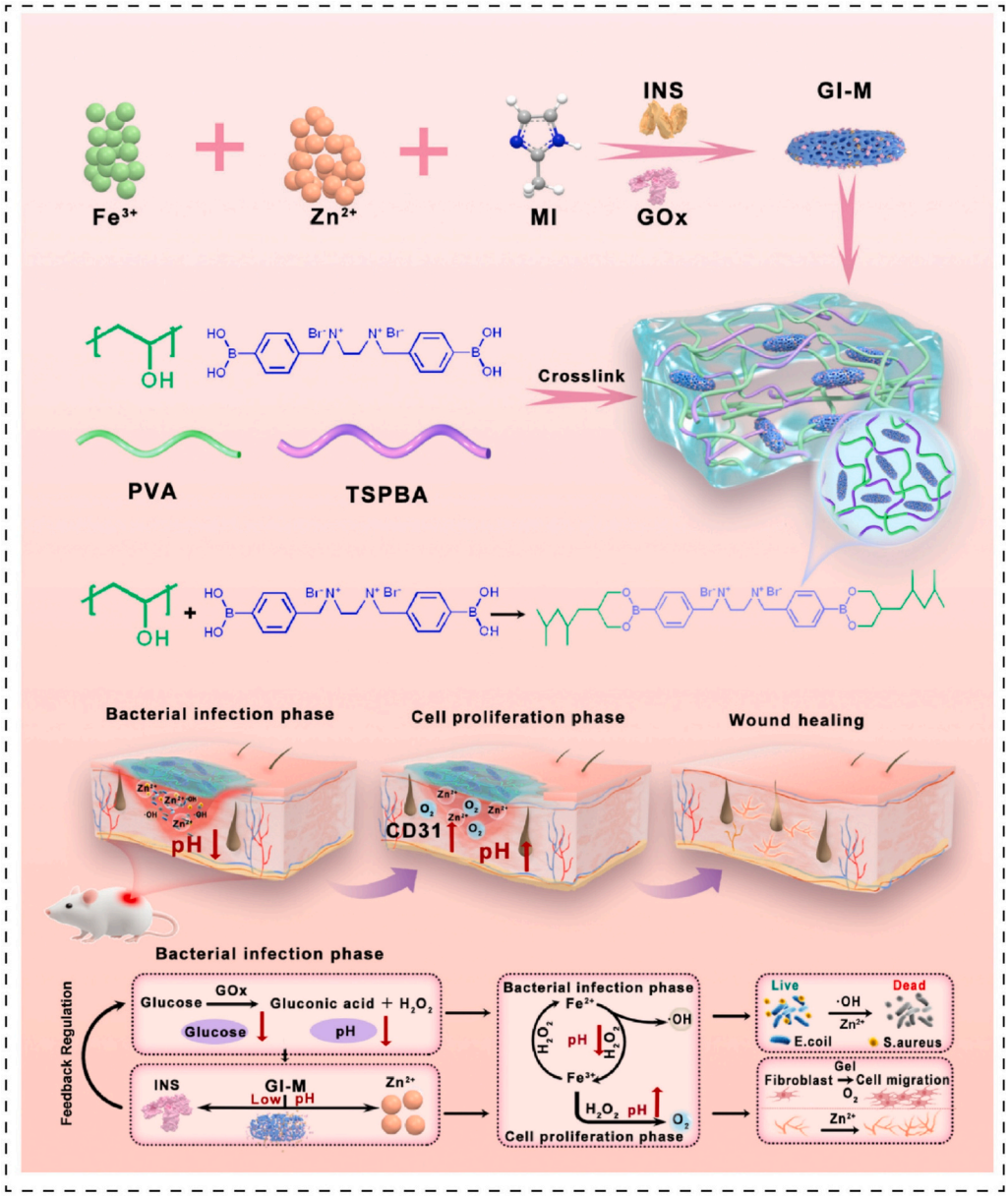

Fig. 4. Schematic illustration of the multifunctional hydrogel with cascade enzyme-mimetic activity for the treatment of diabetic infected wounds, from [74]. Copyright (2025), Elsevier Ltd.

antibacterial capabilities, effectively destroying bacterial cell membranes and inhibiting their biosynthesis, making them an ideal choice for dealing with infectious wounds [86]. For instance, Wang et al. had developed a nano-enzyme dressing of nitrogen-doped carbon co-modified silver single atoms and nanoparticles, which was encapsulated in cationic guar gum gel [87]. This material possessed multi-enzyme activities such as OXD, POD and glutathione peroxidase (GPX), and could efficiently generate active oxygen. The silver ions released in a coordinated manner damaged the bacterial membrane structure, inhibited energy metabolism and triggered oxidative stress. The bactericidal rates against MRSA and *E. coli* reached 95.32% and 90.38% respectively, demonstrating a strong anti-biofilm ability.

However, traditional silver nanoparticles were prone to aggregation, had biological toxicity during the synthesis process, and had a single function, making it difficult to deal with the complex problems of the microenvironment of diabetic wounds. For this purpose, Liu et al. had developed a dynamic hyaluronic acid hydrogel with nano-cross-linking of tea polyphenols [88]. This system synthesized and stabilized silver nanoparticles through the green reduction of tea polyphenols and integrated them into a dynamic network formed by the cross-linking of hyaluronic acid modified by phenylboronic acid through borate ester bonds. Its design advantages lay in the fact that tea polyphenols not only served as reducing agents and stabilizers to achieve the green synthesis and uniform dispersion of silver particles, but also their phenolic hydroxyl structure endowed the hydrogel with antioxidant and anti-inflammatory capabilities. Dynamic borate ester bonds endowed the material with glucose responsiveness, enabling intelligent degradation in high-sugar environments and accelerating the targeted release of TP@Ag NPs. Experiments showed that this hydrogel effectively eliminated ROS, inhibited the release of pro-inflammatory factors, and its bactericidal rate against *E. coli* and *S. aureus* exceeded 90%. In a diabetic mouse model, it significantly accelerated wound closure, promoted collagen deposition, angiogenesis and tissue remodeling, demonstrating comprehensive healing promotion functions. A key ongoing challenge is to balance the potent antibacterial efficacy of silver with its potential cytotoxicity towards host cells to ensure optimal tissue regeneration.

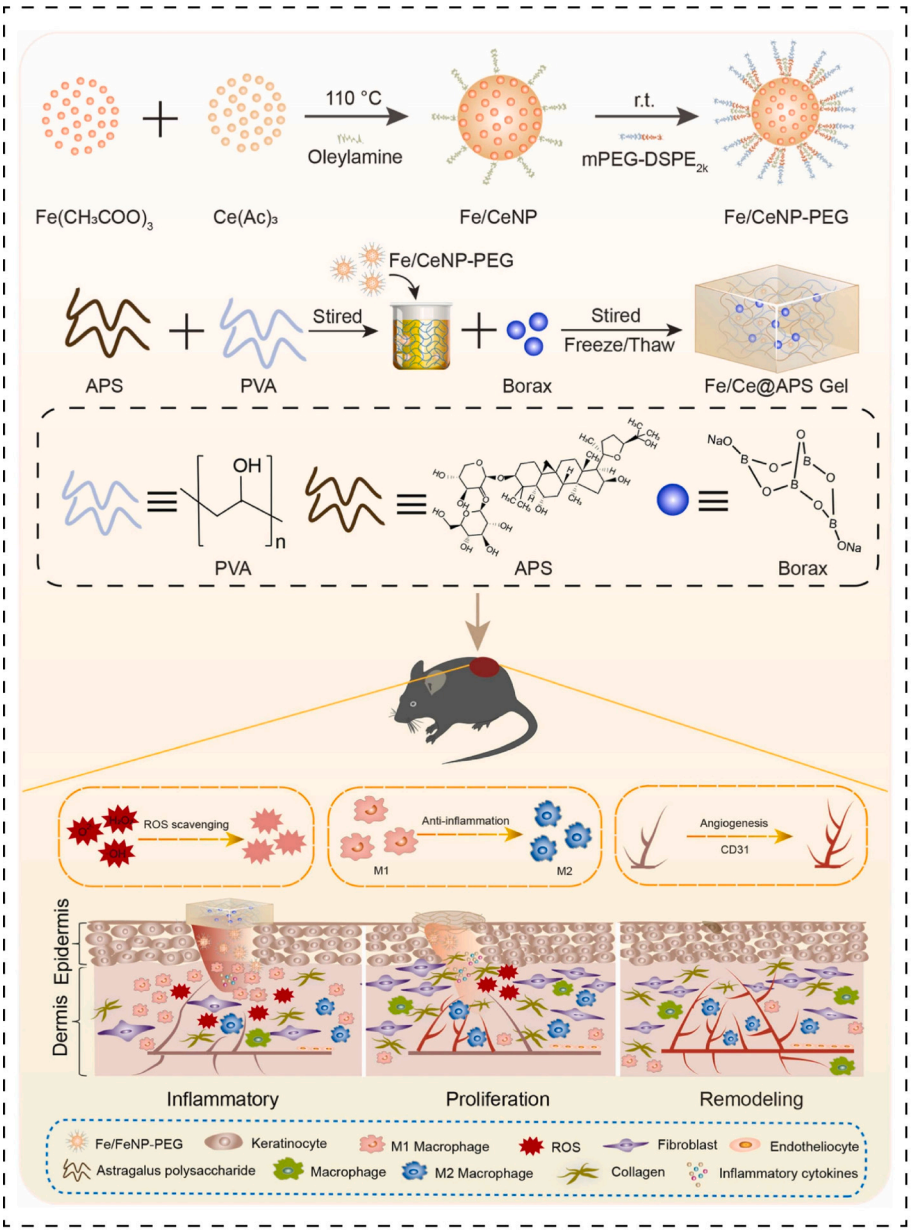

Fig. 5. Schematic illustration of the phased treatment of diabetic wounds using multi-fucntional nanoenzyme-infused astragalus polysaccharide hydrogel. In the inflammatory phase, nanoenzymes and APS effectively reduces excessive ROS accumulation in the wound, modulates macrophage phenotype polarization and mitigates inflammatory responses. During the proliferation phase, APS enhances fibroblast proliferation and migration and promotes angiogenesis. In the remodeling phase, the hydrogel supports collagen deposition and hair follicle regeneration, thus accelerating the wound healing, from [81]. Copyright (2025), Elsevier Ltd.

3.1.2.4. Bimetal-based nanoenzyme-engineering hydrogels. In the field of diabetic wound healing, nanoenzyme-engineered hydrogels have received extensive attention due to their controllable enzyme activity and good biocompatibility [89]. Among them, compared with single-metal-based nanoenzyme-engineered hydrogels, bimetal-based nanoenzyme-engineered hydrogels exhibit superior multi-enzyme simulation activity and stability through synergistic catalytic effects, providing a new strategy for improving the complex pathological microenvironment of diabetic wounds [90]. Based on gold-platinum bimetallic nanoenzymes, Zhang et al. had developed a multifunctional self-healing hydrogel (OHCN) [91]. This material formed a gel base by cross-linking and oxidizing hyaluronic acid with carboxymethyl chitosan through a Schiff-base reaction, and was doped with Au-Pt alloy nanoparticles that exhibited dual mimetic activities of GOx and CAT. The hydrogel could effectively lower blood sugar in the wound microenvironment, eliminate ROS, release oxygen, and synergistically regulate multiple adverse factors such as hyperglycemia, high oxidative stress, and hypoxia. In a diabetic rat model, the OHCN hydrogel significantly promoted angiogenesis, collagen deposition, and epithelial regeneration, and accelerated wound healing.

However, the antibacterial ability of this type of gold-platinum nanoenzyme-engineered hydrogels mainly depended on the gel substrate itself; its killing effect on drug-resistant bacteria and its regulation of the local micro-ecology of the wound remained insufficient. To address this, Zhang's team further developed a multifunctional hydrogel dressing that integrated quantum-sized gold-copper bimetallic nanoclusters and GOx [92]. This system constructed a cascade catalytic platform by embedding Au-Cu nanoclusters possessing dual POD- and GPX-like activities within a Schiff-base cross-linked carboxymethyl chitosan/chondroitin sulfate network: GOx consumed wound glucose to generate H_2O_2, which was then catalyzed by the Au-Cu nanoclusters to produce highly reactive •OH while depleting the antioxidant

glutathione inside bacteria, thereby efficiently eliminating drug-resistant strains such as methicillin-resistant Staphylococcus aureus. In addition, the hydrogel responded to the slightly acidic environment by releasing chondroitin sulfate, effectively reducing pro-inflammatory factor levels. In a diabetic mouse model, this engineered hydrogel achieved rapid healing of infected wounds and supported tissue regeneration. The design complexity and precise control of the metal ratio in bimetallic systems pose challenges for reproducible manufacturing.

3.1.2.5. Metal oxides based nanoenzyme-engineered hydrogels. Compared with metal-based nanoenzyme-engineered hydrogels, metal oxide-based nanoenzymes offer lower preparation costs and simpler fabrication, though with reduced stability [93]. Beyond enzymatic mimicry, they possess unique properties such as magnetism and electrical conductivity, making them suitable for stimuli-responsive smart hydrogels dressings in wound care. For example, Zhu et al. developed a novel antioxidant nano-platform by synthesizing mesoporous Cu-CeO_x nanoenzymes and incorporating JSH-23 into the mesopores [94]. This platform, Cu-CeO@JSXH-23, effectively scavenged hydroxyl radicals (•OH) while catalyzing the elimination of O_2^- and H_2O_2, contributing to the wound healing process.

In response to the fact that most existing studies had focused on a single antioxidant function, making it difficult to synergistically regulate the complex pathological microenvironment in which highly ROS, hypoxia, and bacterial infections coexisted in diabetic wounds, as well as the insufficient long-term stability and sustained antibacterial performance of traditional nanoenzymes, Zhao et al. developed a composite hydrogel system (PACV) loaded with cerium dioxide nanoenzymes and vancomycin [95]. This system constructed a hybrid hydrogel with a porous structure through photocrosslinking technology, in which CeO_2 NPs simulated the activities of CAT and SOD, continuously eliminated ROS, and catalyzed oxygen production to alleviate hypoxia. Vancomycin was simultaneously introduced to achieve efficient inhibition of Staphylococcus aureus and Pseudomonas aeruginosa. Experiments showed that this hydrogel exhibited excellent antioxidant and antibacterial properties, good biocompatibility, controllable mechanical properties, and long-term stability. In diabetic mouse models, PACV hydrogel significantly promoted the healing of infected wounds, effectively regulated inflammatory responses, and facilitated angiogenesis and collagen deposition, demonstrating broad application prospects in the treatment of complex diabetic wounds. The potential for metal ion leaching and the long-term environmental impact of some metal oxides warrant further investigation.

3.1.2.6. Other metal-based nanoenzyme-engineered hydrogels. In the field of diabetic wound healing, manganese-based nanoenzyme-engineered hydrogels have attracted extensive attention due to their excellent antioxidant, antibacterial and angiogenic properties, providing a new strategy for the treatment of chronic and difficult-to-heal wounds [96]. Luo et al. had constructed a multifunctional hydrogel (O-GG/HA@EM) by compounding an ε-polylysine/MnO_2 nanoenzymes with oxidized gellan gum and hyaluronic acid [97]. The hydrogel exhibited excellent injectability and tissue adhesion, efficiently scavenged ROS, and relieved wound-site hypoxia. Concurrently, it exerted broad-spectrum antibacterial activity *via* the cationic character of ε-polylysine. Animal experiments had shown that the hydrogel significantly accelerated wound healing in diabetic mice.

Molybdenum-based nanoenzymes have shown great potential in the repair of chronic diabetic wounds due to the enzyme-like catalytic activity endowed by their polymetallic oxygen cluster structure, excellent ROS clearance ability and good biocompatibility. Pu et al. had constructed a magnesium-doped molybdenum-based polyoxometalate nanoenzymes (Mg-POM) and physically loaded it into a methacrylated gelatin network; ultraviolet cross-linking yielded an injectable, rapidly gelling GelMA@Mg-POM hydrogel [98]. The material continuously released Mg-POM nanoenzyme that efficiently scavenged diverse ROS and mimicked CAT/SOD oxygen-producing activity. Within the diabetic wound milieu, the hydrogel eliminated ROS and released Mg^{2+}, thereby polarizing macrophages from pro-inflammatory M1 to reparative M2, up-regulating anti-inflammatory factors, promoting endothelial tube formation and fibroblast collagen secretion, and simultaneously achieving antioxidant protection, immune modulation, angiogenesis, and matrix reconstruction, which markedly accelerated wound healing in a rat model. Li et al. developed hybrid nanoenzymes (BPQD@MOF) based on black-phosphorus quantum dots and copper-based MOFs and integrated them into a dynamically cross-linked hydrogel coating a 3D-printed titanium-alloy scaffold [99]. Within the microenvironment of diabetic bone defects, the material exerted cascade catalysis: BPQD lowered local glucose *via* GOx-like activity, Cu-MOF eliminated ROS and generated oxygen to relieve hypoxia through SOD- and CAT-like activities, and near-infrared irradiation triggered BPQD photothermal antibacterial effects. The system promoted M2 macrophage polarization by scavenging ROS and metabolic reprogramming, effectively regulating the immune microenvironment in a diabetic rat model of infected bone defect while concurrently promoting angiogenesis and bone regeneration. For these emerging metal systems, a comprehensive understanding of their metabolic pathways and long-term biosafety is crucial for clinical advancement.

3.1.3. Carbon-based nanoenzyme-engineered hydrogels

In carbon-based nanomaterial systems, covalent organic frameworks (COF), due to their highly ordered crystal structure and programmable pore characteristics, exhibit more precise functional integration capabilities and outstanding physiological and environmental stability compared to traditional carbon dots or amorphous carbon-based nanoenzymes [100,101]. COFs are constructed through strong covalent bonds, which not only have adjustable pore sizes and excellent pH tolerance, but also can precisely integrate enzyme mimicking active centers, photoresponse units and metabolic regulatory groups, providing an ideal platform for the complex regulation of the microenvironment of diabetic wounds [102]. For instance, Zhu et al. had developed a pegylated porphyrin-based Cu-COF nanoenzymes [103]. Copper centers endowed the material with both POD- and GPX-like activities, catalyzing •OH generation while depleting antioxidant glutathione to achieve ROS cascade amplification. The porphyrin core additionally produced oxygen and photothermal effects under illumination, constructing a multimodal synergistic antibacterial regimen. By self-supplying H_2O_2 and cascade catalysis, the design overcame natural-enzyme substrate dependence and exhibited potent killing of Staphylococcus aureus under diabetes-mimicking conditions.

Beyond antibacterial utility, COFs also excelled in regulating wound metabolism and matrix remodeling after incorporation into hydrogels. The Wu team had constructed a Zn (II)-porphyrin COF hydrogel exhibiting GOx-like activity that locally consumed glucose and reduced accumulation of harmful advanced glycation end-products [104]. ROS-responsive diselenide bonds within the hydrogel triggered intelligent Zn^{2+} release, imparting combined antibacterial and reparative actions. Near-infrared photothermal effects further enhanced pathogen clearance. The system simultaneously suppressed matrix metalloproteinase-9 activity, up-regulated endogenous antioxidant enzymes such as SOD and GPX, and promoted secretion of anti-inflammatory cytokines IL-10 and TGF-β1, ultimately accelerating collagen deposition and angiogenesis in diabetic wounds. The primary challenges for carbon-based systems, particularly COFs, involve scaling up their synthesis with high crystallinity and ensuring their complete biodegradation without residual toxicity.

3.1.4. Biomimetic nanoenzyme-engineered hydrogels

In recent years, biomimetic nanoenzyme-engineered hydrogels have demonstrated unique advantages in the treatment of chronic diabetic wounds due to their ability to simulate natural enzyme activity,

intelligent responsiveness, and multiple biological functions [105]. Compared with traditional nanoenzyme-engineered hydrogels, this type of material can not only respond more accurately to changes in the wound microenvironment, but also break the vicious cycle of diabetic wound healing through the synergistic effect of multiple mechanisms [106]. Based on this, Feng et al. had designed an intelligent engineered hydrogel (GOZCR) co-loaded with cerium-curcuminate nanoenzymes and zinc-oxide microspheres [107]. The material had constructed a dual dynamic network by oxidizing sodium alginate, gelatin and borate, and possessed excellent biocompatibility, pH-responsive release characteristics and enhanced mechanical properties. The cerium-curcuminate nanoenzymes effectively mimicked superoxide-dismutase and CAT activities, scavenged various ROS and released oxygen, alleviating oxidative stress and hypoxia. Zinc-oxide microspheres endowed the hydrogel with potent antibacterial capacity. In a diabetic-infected rat model, the hydrogel intelligently released the nanoenzymes, markedly eliminated bacteria, reduced inflammation, promoted angiogenesis and collagen deposition, and achieved nearly complete wound closure within 14 days.

Although cerium-curcuminate-nanoenzyme-engineered hydrogels exhibited good performance in modulating oxidative stress and inflammation, their ability to improve persistent hypoxia and to regulate immune-cell phenotypes remained to be deepened. To this end, Zhao's team had developed a biomimetic nanoenzyme-engineered hydrogel with H_2O_2-activated oxygen-generating capability (MnCoO@PDA/CPH) (Fig. 6) [108]. The system combined polydopamine-modified MnCoO nanoenzymes with polyvinyl alcohol, hyaluronic acid and polyaniline derivatives to construct a dual-network structure that was both conductive and contained dynamic borate-ester bonds. It continuously decomposed wound-site H_2O_2 to release oxygen, effectively relieving tissue hypoxia and oxidative stress, while exhibiting controllable mechanical properties and electrical activity. In a diabetic rat model, the hydrogel markedly accelerated wound closure and improved healing quality by modulating the immune microenvironment, enhancing epithelial regeneration, promoting orderly collagen deposition and functional angiogenesis, demonstrating synergistic advantages in repairing complex diabetic wounds. The main challenge lies in accurately mimicking the sophisticated feedback mechanisms of natural biological systems and ensuring the stability of these complex biomimetic constructs under clinical conditions.

3.1.5. *Single-atom nanoenzyme-engineered hydrogels*

Single-atom nanoenzymes, with their atomically dispersed active centers, can maximize catalytic efficiency and have become a cutting-edge direction in the design of nanoenzyme-engineered hydrogels [109]. Compared with traditional nanoenzymes, single-atom nanoenzymes have significant advantages in terms of active site utilization and catalytic specificity, and are particularly suitable for complex microenvironments such as diabetic wounds that need to efficiently eliminate various ROS and have both antibacterial and angiogenic functions [110]. Dai et al. developed zinc single-atom carbon-dot nanoenzymes (Zn/C-dots) that exhibited multi-enzyme activity, scavenged diverse free radicals, and specifically alleviated oxidative stress [111]. After incorporation into ROS-responsive hydrogels, the sustained-release nanoenzymes effectively reduced inflammation, promoted angiogenesis, and accelerated wound healing in diabetic wound models. To further confront the coexistence of hyperglycemia and drug-resistant bacterial infection, the Lan team constructed a spatially confined single-atom cascade nanoenzymes system (Au-Pt@ZIF-8/Apt@gel) (Fig. 7) [112]. In the wound's acidic milieu, the material released Zn^{2+} and Au-Pt nanoenzymes that consumed glucose and generated ROS through a chain reaction, achieving efficient bacterial clearance. Its confined structure markedly enhanced catalytic activity and robustly promoted collagen deposition and epithelial regeneration in animal models, offering a new strategy for treating diabetic wounds. The synthesis of single-atom nanoenzymes with high loading density and stability, preventing atomic aggregation during storage and application, is a significant hurdle for their widespread use.

3.1.6. *Heterojunction nanoenzyme-engineered hydrogels*

In the treatment of diabetic wounds, heterojunction nanoenzyme-engineered hydrogels have received extensive attention due to their excellent ROS scavenging ability and multiple biological functions [113]. Compared with traditional nanoenzymes, this type of material significantly enhances catalytic activity and biocompatibility by constructing heterogeneous interfaces and regulating electronic structures [114]. Li et al. constructed an electronically regulated bio-heterojunction nanoenzymes containing Cu-O-Zn bonds and loaded it

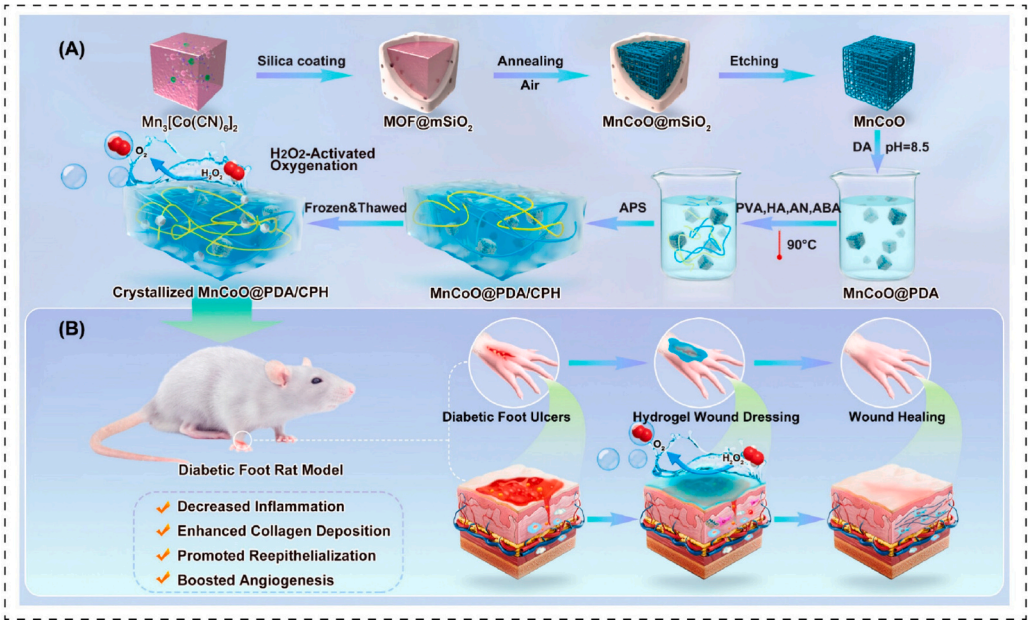

Fig. 6. Scheme illustrating the fabrication process and further application of the hydrogel. (A) Scheme depicting the fabrication procedures of MnCoO@PDA/CPH hydrogel. (B) Scheme depicting MnCoO@PDA/CPH hydrogel with H_2O_2-activated oxygenation property for promoting diabetic wound healing, from [108]. Copyright (2023), American Chemical Society.

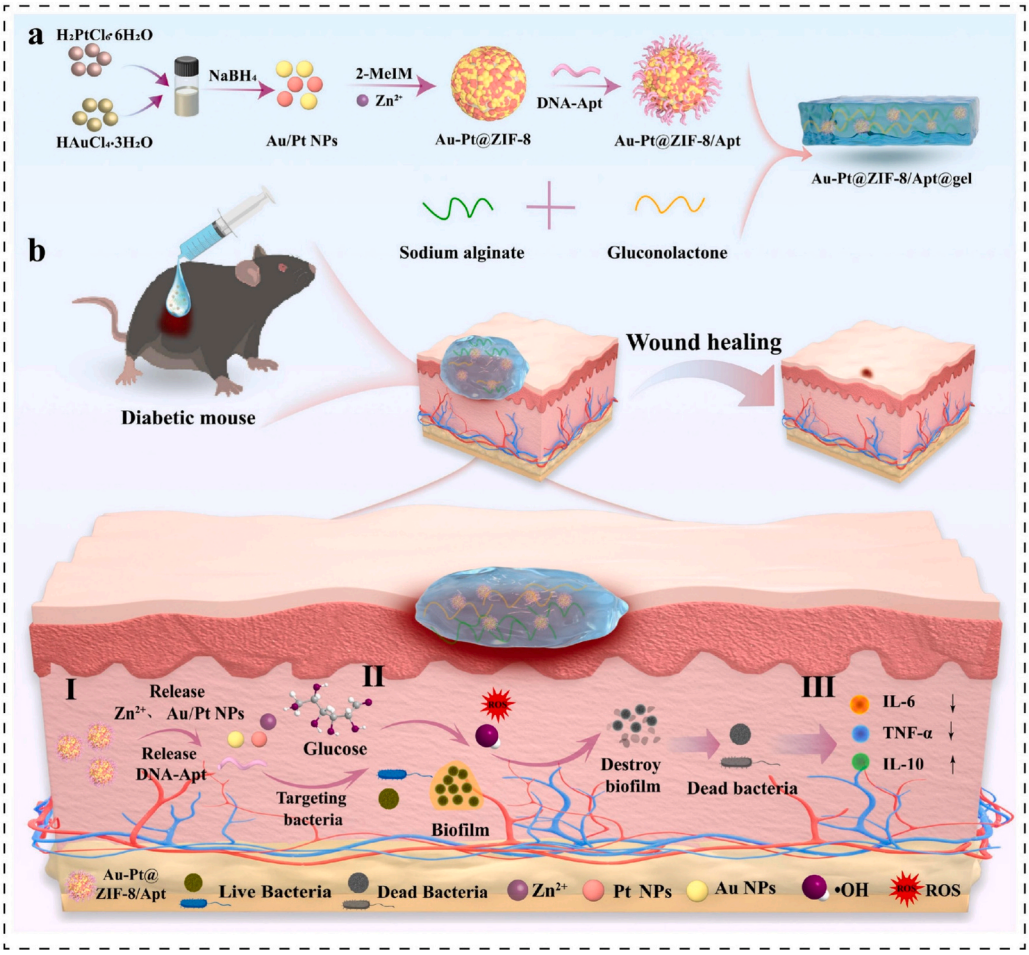

Fig. 7. Schematic diagram of the preparation and application of Au-Pt@ZIF-8/Apt@gel. (a) Synthesis of Au-Pt@ZIF-8/Apt nanoenzymes and preparation of injectable hydrogel. (b) Schematic representation of the wound healing process in mouse skin and the mechanistic process of skin healing. The mechanism process is as follows, I), Au-Pt@ZIF-8/Apt nanoenzymes in an acidic microenvironment, ZIF-8 undergoes cleavage, releasing Zn^{2+}, Au/Pt NPs and DNA-Apt, II), in the presence of a high concentration of glucose, metal ions react with glucose in a cascade nanoenzymes reaction, generating toxic ROS, leading to bacterial inactivation. III), the inactivation of bacteria leads to a decrease in IL-6 and TNF α and an increase in IL-10, thus promoting skin healing, from [112]. Copyright (2025), Elsevier Ltd.

into a gelatin matrix to form an E-bio-HJ/Gel composite system [115]. The material efficiently eliminated H_2O_2 and cooperatively improved the wound microenvironment by promoting M2 polarization of macrophages, suppressing inflammatory mediator release, and enhancing antibacterial performance. In animal experiments, it markedly accelerated full-thickness skin defect closure and tissue regeneration. To overcome the catalytic limitations imposed by the intrinsic band structure of heterojunction nanoenzymes and their poor deep-tissue delivery capacity, Tang's team developed a bilayer GelMA microneedle patch (ACMGM) loaded with APTES-COF-1@MXene heterojunction nanoenzymes (Fig. 8) [116]. By establishing heterointerfaces that facilitated interfacial charge transfer, the material's photocatalytic and enzyme-mimetic activities were significantly enhanced under visible light. Concurrently, the microneedles enabled precise local delivery and retention of the nanoenzymes at the wound site. In a diabetic rat model, the microneedle system combined with illumination effectively alleviated oxidative stress, promoted M2 macrophage polarization and collagen deposition, and substantially accelerated full-thickness skin wound healing. The complexity of rational heterojunction design and the potential long-term stability of the interface in biological environments are key factors determining their future clinical translation.

The diverse classes of nanoenzyme-engineered hydrogels discussed above each offer unique mechanisms for targeting the pathological signals in diabetic wounds. Their evolution from single-function catalysts to intelligent, multi-responsive platforms highlights the field's progression towards sophisticated bio-inspired designs. Future directions will likely focus on the convergence of these technologies. For instance, incorporating single-atom catalysts into MOF or heterojunction structures, or using biomimetic principles to guide the design of more sophisticated metal- and carbon-based systems. The ultimate goal is to create next-generation "smart" hydrogels that can autonomously diagnose the wound status and deliver precise, multi-targeted therapies in real-time, ultimately achieving complete functional restoration of diabetic wounds.

3.2. *Environment-driven on-demand regulation and synergistic therapy*

The successful construction of nanoenzyme-engineered hydrogels is only the first step. How to achieve their "intelligent" diagnostic and therapeutic behaviors in complex *in vivo* environments is another key scientific issue. This section will focus on discussing how to precisely and on-demand regulate the catalytic activity and therapeutic function of nanoenzyme-engineered hydrogels by utilizing the unique endogenous microenvironment of diabetic wounds or applying exogenous energy, and achieve efficient synergy among multiple treatment modes. We will analyze in detail from two dimensions: endogenous microenvironment drive and exogenous energy mediation, how these smart materials respond to specific pathological signals (such as pH, ROS, glucose, enzymes) or external stimuli (such as light, ultrasound), thereby activating their therapeutic functions at the right time and

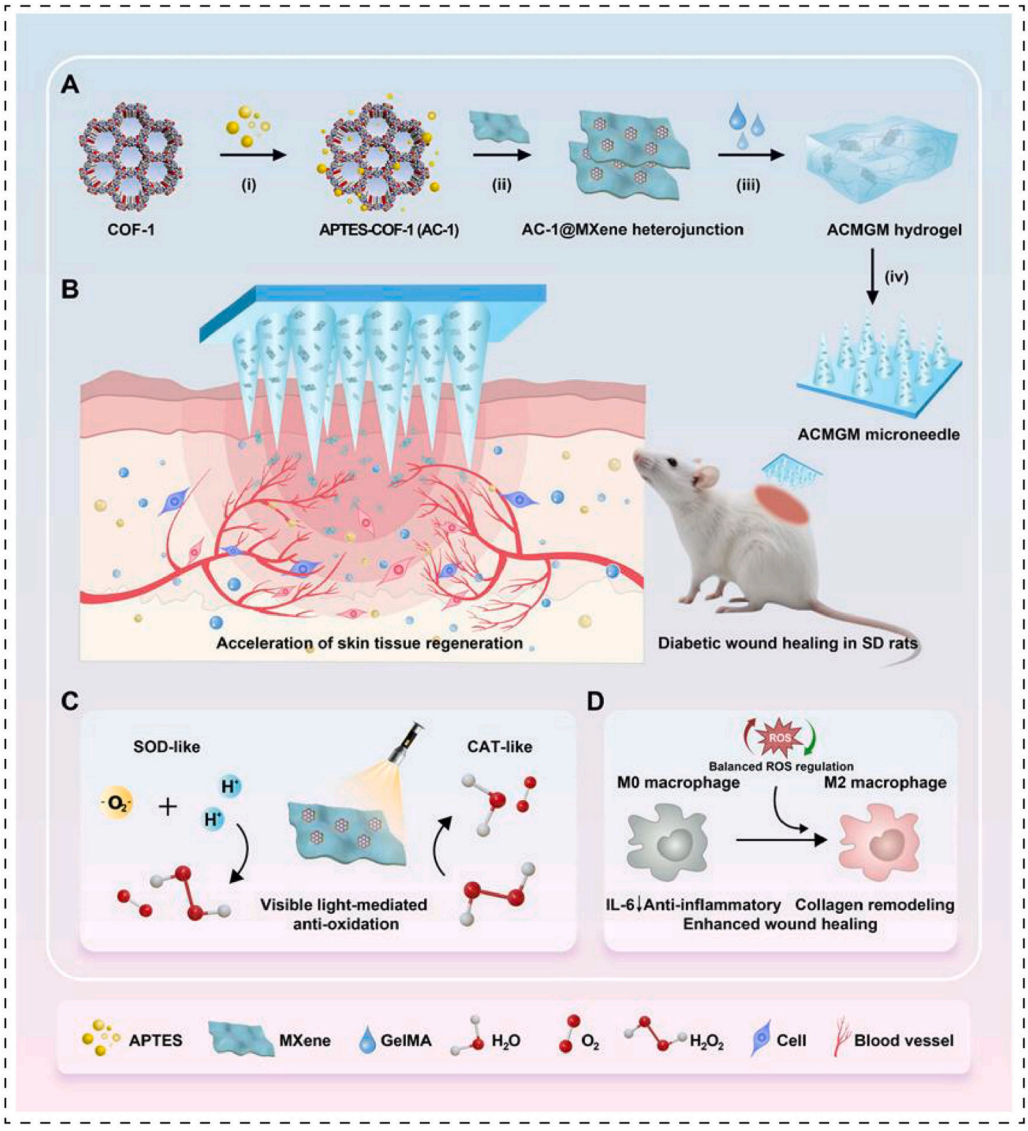

Fig. 8. The preparation and application of the AC-1@MXene heterojunction and the ACMGM microneedle. (A) A diagram showing the preparation processes, including i) surface modification, ii) electrostatic self-assembly, iii) mold casting and iv) microneedle demolding; (B) Diabetic wound healing is accelerated by ACMGM microneedle combined with visible light therapy; (C-D) The potential mechanisms, including electron transfer, ROS elimination, and M2 macrophage polarization, are highlighted, from [116]. Copyright (2025), Ivyspring International Publisher.

place, and maximizing the therapeutic effect of reprogramming diabetic scars through synergistic enhancement effects.

3.2.1. *Endogenous microenvironment-driven activation*

The unique pathological microenvironment of diabetic wounds, which is distinct from that of normal tissues, provides a natural "trigger" for the precise and on-demand treatment of nanoenzyme-engineered hydrogels [131]. This section will delve into how to utilize the endogenous biochemical signals specific to the wound surface to activate and regulate the catalytic activity of nanoenzymes in hydrogels [132]. Specifically, we will focus on the following key microenvironment factors: pH, ROS, glucose, and specific enzymes. Through ingenious material design, nanoenzyme-engineered hydrogels can specifically respond to these signals, achieving "switch" control or rate regulation of catalytic reactions, thereby specifically generating active substances or consuming harmful substances at the lesion site and avoiding off-target damage to normal tissues [133].

3.2.1.1. pH-responsive systems. In the process of diabetic wound healing, in view of the complex problems existing in its microenvironment, it is particularly important to develop intelligent hydrogels materials with multiple responsiveness and functional integration. pH-responsive nanoenzyme-engineered hydrogels have demonstrated significant advantages due to their ability to achieve precise treatment based on the acid-base changes in the wound microenvironment [134]. Li et al. developed a pH-responsive nanoenzyme-engineered hydrogel (PH@MnCoO@ε-PL@PTA) constructed from a schiff-base-cross-linked hyaluronic acid/pectin network that incorporated ε-polylysine-modified MnCoO nanoenzymes and tannic acid nanorods (Fig. 9) [135]. The hydrogel underwent accelerated degradation and released its nanoenzymes under acidic and high-ROS conditions, efficiently scavenging ROS while catalyzing endogenous H_2O_2 decomposition to generate oxygen, thereby alleviating tissue hypoxia and oxidative stress and providing broad-spectrum antibacterial activity. In a full-thickness diabetic rat skin-defect model, the material markedly promoted epithelial regeneration, collagen deposition, and angiogenesis while guiding macrophages toward an anti-inflammatory phenotype.

To further achieve active regulation of the hyperglycemic

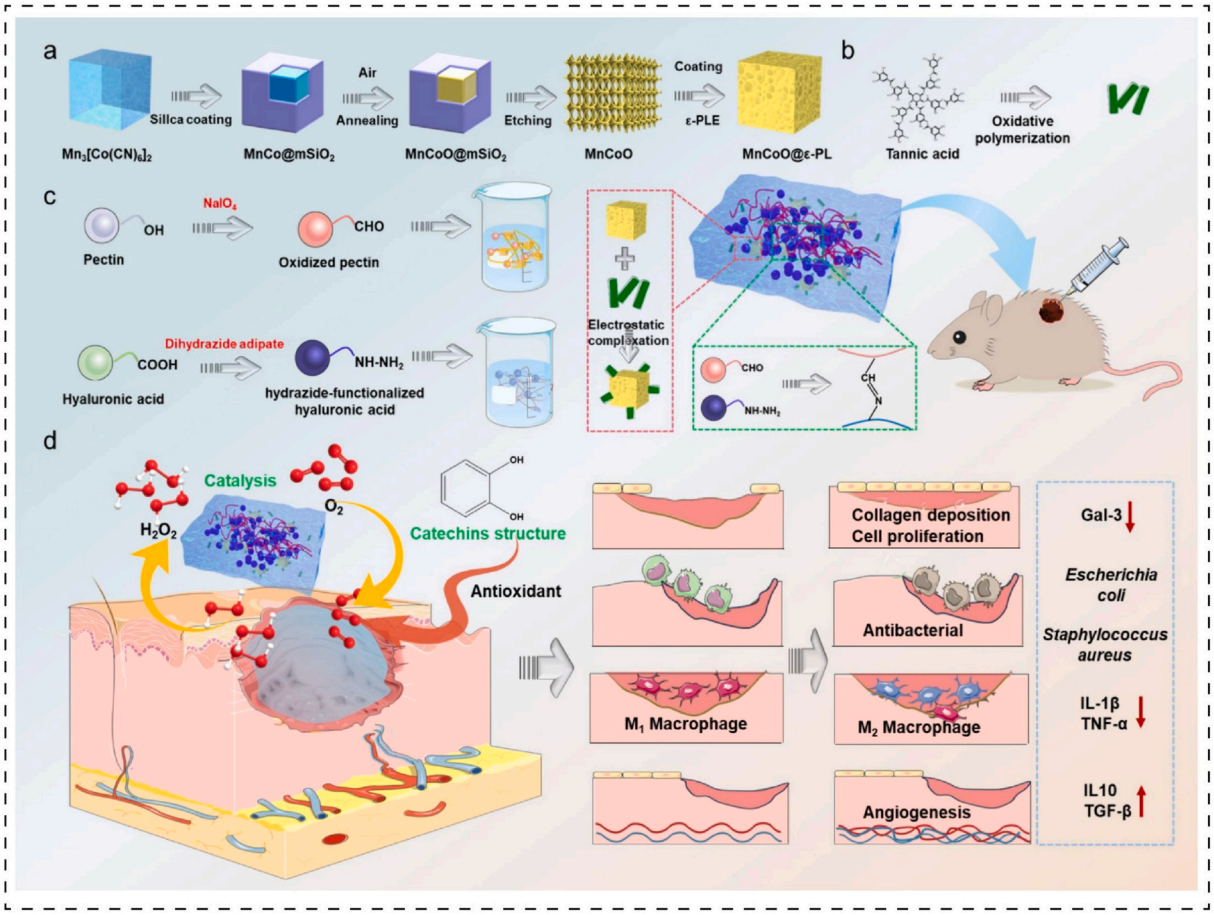

Fig. 9. Schematic illustration of the preparation and application of pH hydrogel. (a) Synthesis of nanoenzymes. (b) Synthesis of PTA. (c) Preparation of injectable PH@MnCoO@-PL@PTA hydrogel. (d) Hydrogel can catalyze H_2O_2 oxidative stress, promoting angiogenesis and collagen deposition,from [136]. Copyright (2024), Elsevier Ltd.

microenvironment and enhance bactericidal efficacy, Zhao et al. had designed a pH-responsive degradable nanoenzyme-engineered hydrogel with cascade catalytic and photothermal antibacterial functions [136]. The system employed poly (vinyl alcohol)- and phenylboronic acid-modified sodium alginate as the matrix, forming a three-dimensional network *via* dynamic borate ester and hydrogen bonds that intelligently degraded in high-glucose, acidic environments to release GOx and metal-tannic acid nanoenzymes. GOx consumed excess wound glucose to produce H_2O_2 and gluconic acid, lowering local pH to activate nanoenzymes POD activity while achieving self-supply of H_2O_2. The nanoenzymes further catalyzed •OH generation and depleted glutathione, and together with near-infrared photothermal effects, produced synergistic antibacterial action. In a diabetic infected rat model, the hydrogel effectively promoted angiogenesis, collagen deposition, and anti-inflammatory macrophage polarization, significantly accelerating wound healing. A key challenge for pH-responsive systems is to maintain precise activation thresholds amidst the dynamic pH fluctuations that occur throughout the different stages of wound healing, avoiding premature or delayed action.

3.2.1.2. ROS-responsive systems. In view of the complex pathological characteristics of the interweaving of high ROS and hypoxic microenvironment in diabetic wound healing, it is of great significance to develop multifunctional dressings that can simultaneously regulate oxidative stress and hypoxia [137]. Chen et al. developed a ROS-responsive hydrogel by combining an iron-based nanoenzyme with CAT-like activity and a dynamic cross-linked network of gelatin and poly (vinyl alcohol) modified with phenylboronic acid, using a synthetic strategy of chemical grafting and UV cross-linking [138]. The material induced cleavage of phenylborate ester bonds in a high-ROS wound microenvironment, enabling gel degradation and controlled release of the nanoenzymes, which then catalyzed the decomposition of endogenous H_2O_2 into oxygen, alleviating oxidative stress and hypoxia. Building on this, Yang et al. further constructed a multifunctional hydrogel integrating drug-loaded hollow mesoporous Prussian blue nanoenzymes and aminoguanidine (PAP@Gel) (Fig. 10) [139]. The system was formed through a dual dynamic cross-linked network of phenylboronic ester bonds and Schiff bases, and featured self-healing, injectable, and bioadhesive properties. In the wound microenvironment, it responded to ROS by degrading and releasing nanoenzymes with SOD and CAT activities, catalyzing oxygen production. Meanwhile, aminoguanidine released hydrogen gas under acidic conditions, collaboratively scavenging ROS, alleviating hypoxia, and regulating inflammation. The photothermal properties of the nanoenzymes endowed them with antibacterial capabilities, while aminoguanidine inhibited the formation of AGEs. In a full-thickness skin defect model of infected diabetes, the hydrogel effectively promoted collagen deposition, angiogenesis, and epithelial regeneration, and regulated macrophage polarization toward the M2 phenotype, accelerating wound healing.

3.2.1.3. Glucose-responsive systems. Glucose-responsive nanoenzyme-engineered hydrogels, as a cutting-edge strategy for diabetic wound management, have attracted much attention due to their ability to actively respond to the high-glucose microenvironment and perform multiple therapeutic functions [140]. Jin et al. had developed a

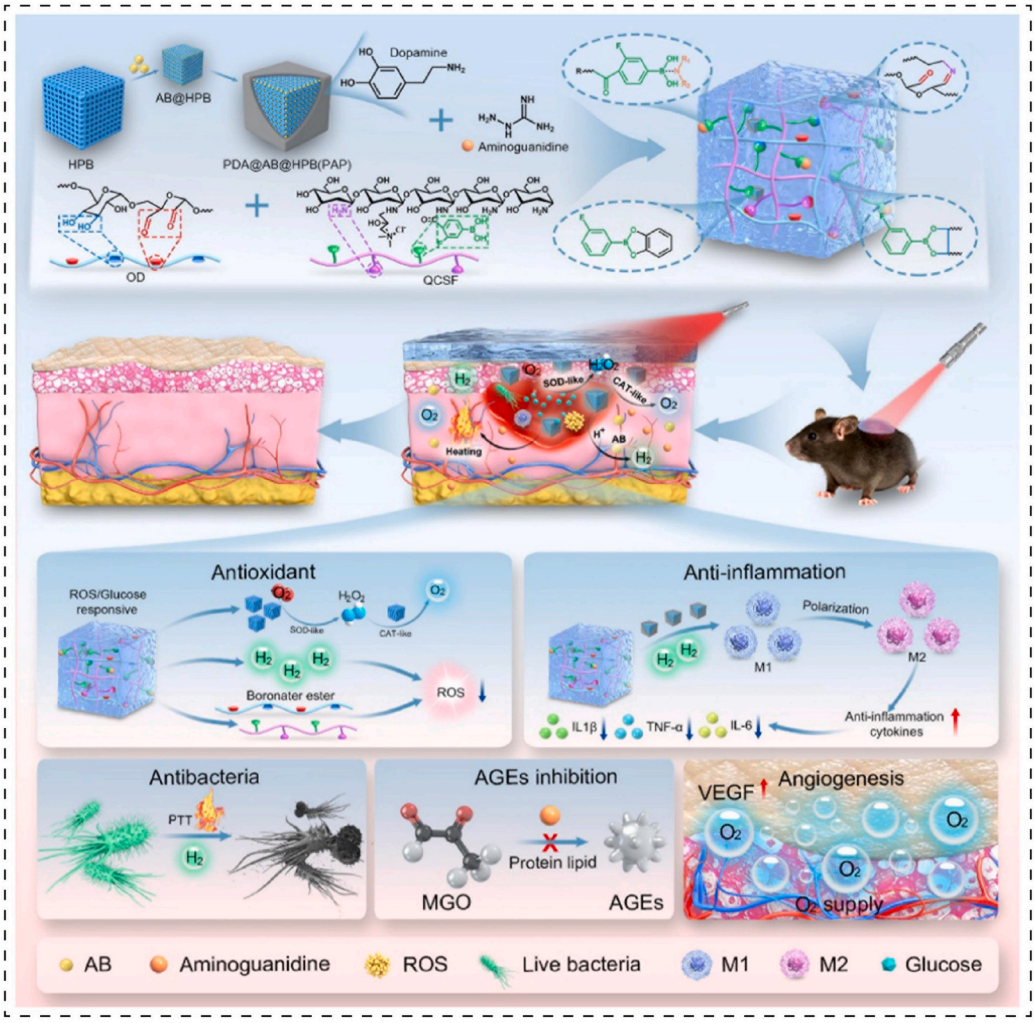

Fig. 10. Schematic diagram of preparing and applying a multifunctional hydrogel for treating diabetic infected wounds,from [139] . Copyright (2025), Elsevier Ltd.

composite nanoenzyme-engineered hydrogel spray (MnO_2@COF-GOx/Gel) that integrated glucose responsiveness, ROS scavenging, antibacterial activity and photothermal therapy (Fig. 11) [141]. The material had been assembled by enveloping MnO_2 nanosheets within a borate-ester COF, covalently linking GOx to create a glucose-responsive nanoenzymes complex, and loading it into a photo-curable methacrylated sodium alginate hydrogel to form a sprayable, rapidly curing wound dressing. In the high-glucose, high-ROS microenvironment of diabetic wounds, the COF coating degraded and released MnO_2 and GOx: GOx catalyzed glucose oxidation to lower local blood sugar, while the resultant H_2O_2 was decomposed into oxygen and water by the CAT-mimicking activity of MnO_2, thereby relieving tissue hypoxia and eliminating ROS. Additionally, MnO_2 produced a pronounced photothermal effect under near-infrared irradiation, conferring potent antibacterial activity. Animal experiments had confirmed that the hydrogel effectively promoted healing of infected wounds in diabetic mouse and rabbit models, demonstrating excellent potential for comprehensive therapy.

3.2.1.4. Enzyme-responsive systems. In the complex management strategies of diabetic wounds, responsive therapy targeting MMP9, which is specifically highly expressed in the excessive inflammatory microenvironment, emerged as a promising intelligent drug delivery strategy. As a key biomarker in the inflammatory stage, abnormally elevated levels of MMP-9 can impede the normal healing process of wounds [142]. Wang et al. constructed an MMP9-responsive nanoenzyme-engineered hydrogel (PGs@PVA) [143]. The material had been prepared by embedding Prussian-blue-nanoenzyme-loaded gelatin nanospheres within a poly (vinyl alcohol) hydrogel. The design relied on gelatin serving as an enzymatic substrate for MMP9, enabling intelligent release of Prussian blue nanoenzymes that exhibited SOD- and CAT-like activities within the highly inflammatory microenvironment. This precisely eliminated excess ROS and shifted macrophage polarization from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype. In a diabetic rat model, the hydrogel effectively accelerated wound healing. Beyond MMP-9, future designs could target other dysregulated enzymes in the diabetic wound, such as myeloperoxidase (MPO), to further broaden the scope of enzyme-responsive precision therapy.

3.2.2. Exogenous energy-mediated regulation and synergistic enhancement

In addition to utilizing endogenous pathological signals, introducing exogenous energy as a remote and controllable regulatory approach can significantly enhance the accuracy and efficacy of nanoenzyme-engineered hydrogels therapy [144]. By remotely controlling the behavior of nanoenzymes in hydrogels through external physical energy fields (such as light, ultrasound, etc.), and achieving a strong combination of catalytic therapy with other treatment modalities, a multimode collaborative treatment platform can be jointly constructed, thereby more effectively reprogramming the microenvironment of diabetic wounds [145].

3.2.2.1. Photothermal therapy (PTT). In response to the complex

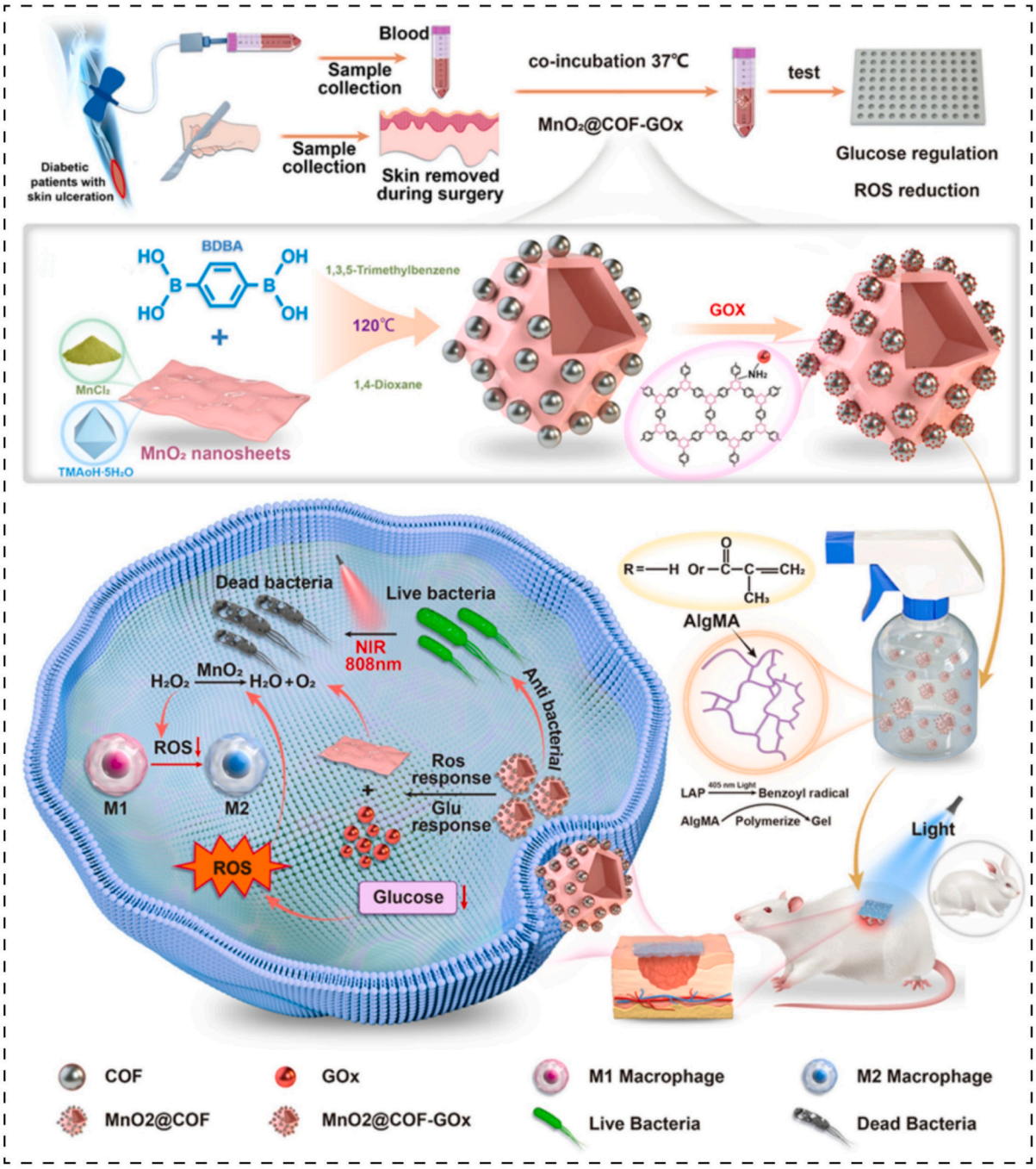

Fig. 11. Schematic diagram of MnO_2@COF-GOx/gel preparation and working principle of promoting diabetic wound healing. The composite is composed of MnO_2 nanosheets coated with COF nanomaterials loaded with GOx, which has been verified *in vitro* and applied to wound models of mice and rabbits by photo sensitive gel *in vivo*. It has been confirmed that it has the effects of regulating blood glucose level, inhibiting inflammatory response and antibacterial, from [141]. Copyright (2025), Elsevier Ltd.

challenges existing in diabetic wound healing, such as impaired angiogenesis, persistent inflammation, elevated ROS levels, and susceptibility to infection, the development of integrated dressings with multiple biological functions has become a current research hotspot [146]. Among them, the nanoenzyme-engineered hydrogels that collaborates with photothermal therapy has demonstrated significant advantages due to its ability to integrate multiple mechanisms such as antioxidation, antibacterial, immune regulation, and angiogenesis promotion. Zhang et al. constructed a composite hydrogel (PCCuT) that integrated multiple enzyme-mimetic and photothermal functions [147]. In their system, sericin-templated copper sulfide nanoparticles (CuS-Se NPs) were surface-modified with a tannic acid-iron metal-phenolic network to yield CuS-Se@TA-Fe nanoenzymes exhibiting SOD- and CAT-like activities. The nanoenzymes were then incorporated into a dynamic cross-linked network of poly (vinyl alcohol), carboxymethyl chitosan and borax, producing a self-healing, tissue-adhesive and shape-adaptable hydrogel. Within the diabetic infected wound milieu, the material had effectively scavenged ROS *via* the nanoenzymes, exerted photothermal antibacterial action, released Cu^{2+} to promote endothelial cell migration and tube formation, and induced macrophage polarization toward the anti-inflammatory M2 phenotype, thereby synergistically accelerating wound healing.

To exploit the pathological features of diabetic wounds more precisely, Chen et al. had developed a bimetallic nanoenzymes microneedle patch (Au_2Pd_3@PH) with self-cascading catalytic capability (Fig. 12) [148]. Ultra-small Au_2Pd_3 nanoenzymes were synthesized by liquid-phase co-reduction and encapsulated within temperature-sensitive poly (vinyl alcohol)/hyaluronic-acid hydrogel microneedles. Upon near-infrared laser irradiation, the microneedles melted and released the nanoenzymes, whose GOx-like activity converted excess wound glucose into gluconic acid and H_2O_2. This not only lowered local glucose and pH but also created an acidic environment that activated the POD-like activity of the nanoenzymes, transforming H_2O_2 into highly toxic hydroxyl radicals for chemodynamic therapy. The superior photothermal properties of Au_2Pd_3 further augmented bactericidal efficacy and propelled the cascade reaction. In a diabetic infected wound model, the platform had effectively promoted healing by actively modulating the hyperglycemic microenvironment and achieving PTT/chemodynamic synergistic sterilization. The primary challenge for PTT lies in achieving precise spatiotemporal control over temperature *in vivo* to maximize antibacterial and catalytic efficacy while minimizing collateral thermal damage to nascent healing tissues.

3.2.2.2. Ultrasound (US) therapy. In recent years, US has provided new ideas for the treatment of diabetic wound infections due to its advantages such as non-invasiveness, deep tissue penetration ability and no reliance on exogenous photosensitizers [149]. However, its therapeutic effect is often limited by the hypoxic environment at the lesion site. In response to this challenge, researchers have begun to focus on developing intelligent delivery systems that can actively improve the microenvironment and enhance ultrasonic effects. Chen et al. designed an injectable hydrogel (CaO_2/GOx/Ti_3C_2@Alg) that triggered a cascade reaction within the acidic milieu of diabetic abscesses: CaO_2 decomposed to supply Ca^{2+}, which ionically cross-linked with sodium alginate to achieve *in situ* gelation while releasing oxygen to relieve tissue hypoxia; the co-loaded GOx catalyzed local excess glucose to generate H_2O_2 and gluconic acid, the latter further accelerating CaO_2 decomposition and the former driving *in situ* oxidation of Ti_3C_2 MXene into highly catalytic TiO_2 nanoenzymes [150]. Under ultrasound stimulation, the system had efficiently eradicated MRSA and its biofilm in a diabetic mouse abscess model.

To eliminate dependence on external ultrasound and cooperatively modulate the immune microenvironment, Yang et al. had developed injectable hydrogel (POMHH) based on polymolybdate clusters hyaluronic acid (Fig. 13) [151]. By incorporating molybdenum polyoxometalate clusters, the material continuously produced singlet oxygen *via* the Russell mechanism using endogenous H_2O_2 without external oxygen, achieving potent antibacterial efficacy under hypoxia. Furthermore, ultrasound-triggered rapid redox cycling of molybdenum in POM simultaneously scavenged multiple ROS and released oxygen, alleviating oxidative stress and tissue hypoxia while steering macrophage polarization from pro-inflammatory M1 to reparative M2, thereby reshaping the immune milieu. In a diabetic infected wound model, this "dual-mode" dynamically regulated hydrogel had demonstrated the capacity to synergistically address multiple pathological factors. Although ultrasound offers superior tissue penetration, the heterogeneous energy distribution within complex wound beds can lead to uneven treatment effects, necessitating innovative material designs to ensure uniform response and activation.

The interplay between endogenous microenvironment-driven activation and exogenous energy-mediated regulation defines the frontier of intelligent wound management. The former offers autonomous, pathological-factor-targeted therapy, while the latter provides unmatched spatiotemporal control and the potential for powerful synergistic effects. The future lies in the seamless integration of these paradigms, designing closed-loop systems where exogenous energy is applied based on real-time feedback from endogenous biomarkers, creating truly adaptive and personalized therapeutic platforms for diabetic wounds.

4. Precision design of nanoenzyme-engineered hydrogels

Rational nanoenzyme-engineered hydrogels design for diabetic wounds requires spatiotemporal catalytic alignment with clinical needs, enabling infection control, inflammation resolution, and tissue

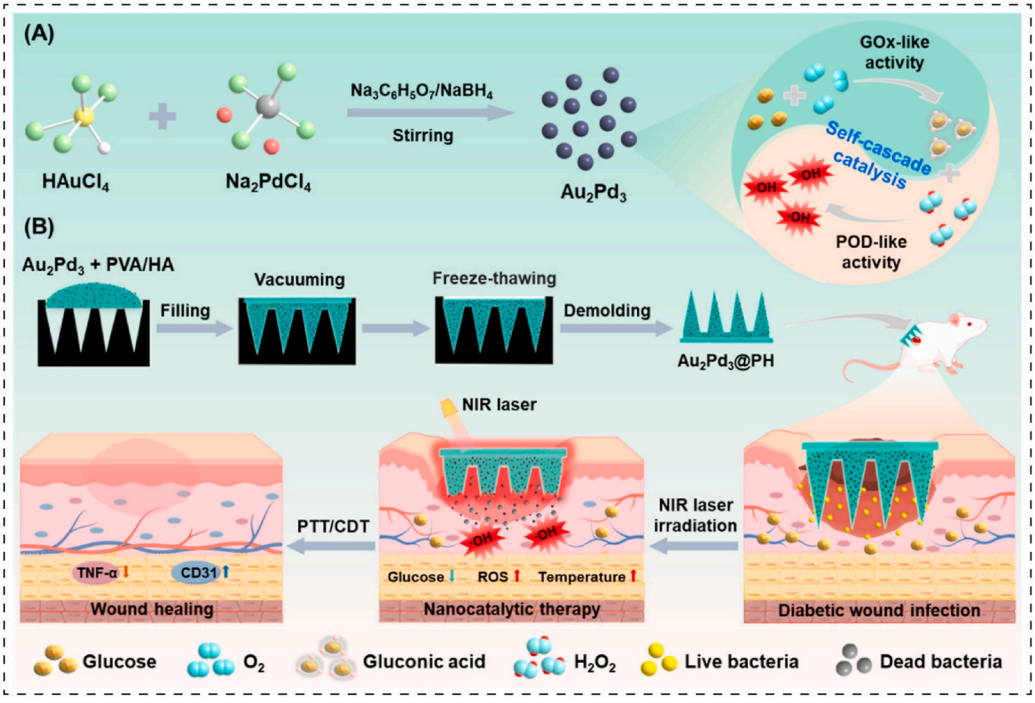

Fig. 12. Illustration of the synthesis of Au_2Pd_3@PH (A) and its application (B) for the treatment of the diabetic wound infections, from [148]. Copyright (2025), American Chemical Society.

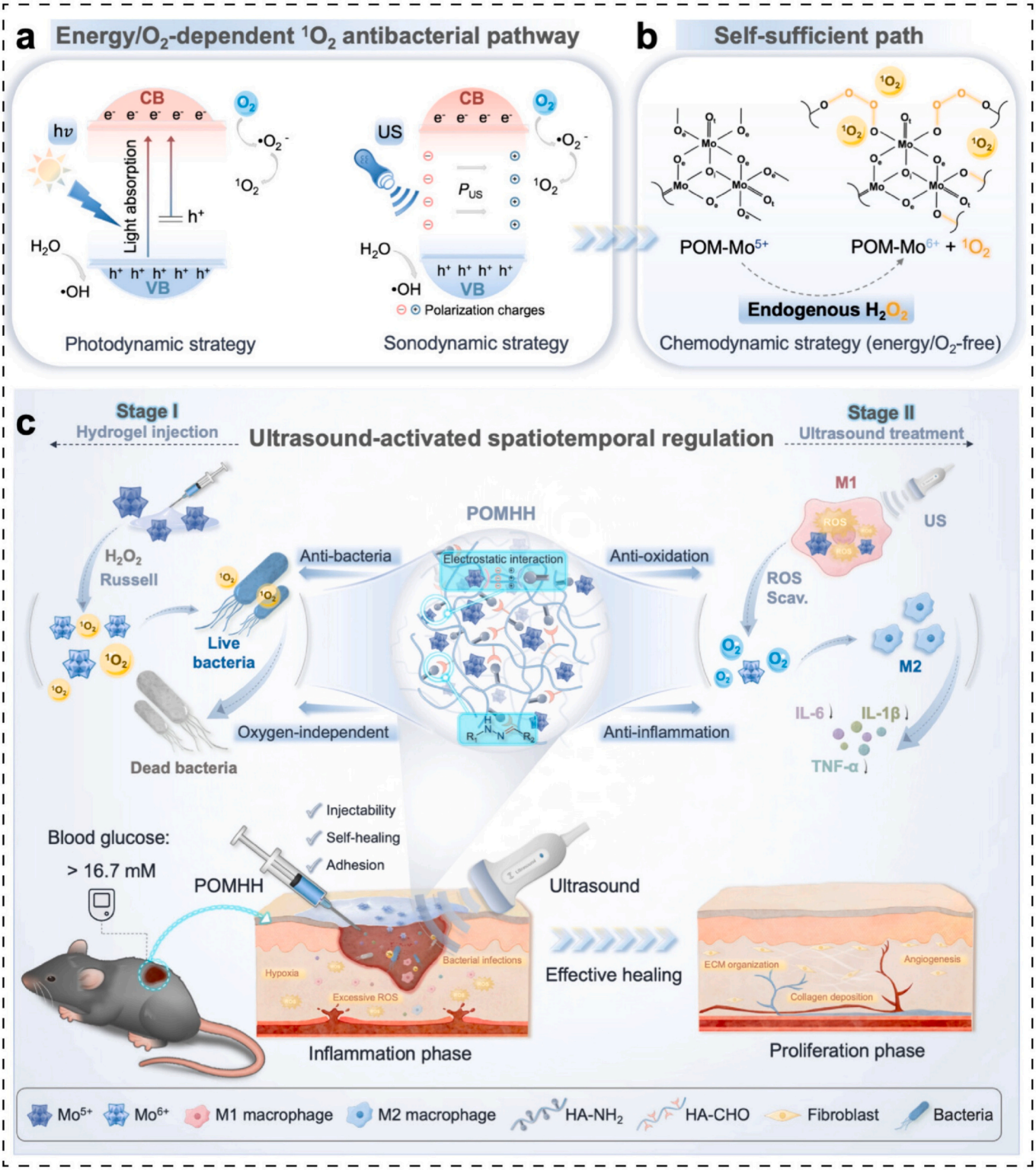

Fig. 13. Illustration of a POMHH with US-mediated spatiotemporal controllability for diabetic wound healing, from [151]. Copyright (2025), American Chemical Society.

regeneration in a coordinated manner [152]. Stimuli-responsive triggers (pH, ROS, glucose, MMPs) allow stage-specific activation, while 3D printing and photopolymerization enable spatially compartmentalized antimicrobial and pro-angiogenic actions [153]. Microenvironment-responsive designs target pathological features like hyperglycemia, hypoxia, and ROS overload, while scalable fabrication with modular photothermal or sensing functionalities enables on-demand therapy and real-time monitoring, bridging catalytic precision with clinical practicality for precision wound care [154].

4.1. *Temporal control of catalytic kinetics*

Achieving spatiotemporally controllable catalytic therapy requires the catalytic kinetics of nanoenzymes to adaptively adjust in response to

the dynamically changing wound microenvironment. A key challenge is ensuring these kinetic adaptations align with the distinct biological needs of different healing stages. To address this, Jiang et al. constructed an injectable nanoenzyme-engineered hydrogel based on double dynamic bonds (OBG@CG), achieving temporal control of catalytic kinetics through a pH-responsive nanoenzymes polymerization-depolymerization process (Fig. 14) [124]. During the acidic phase of wound infection (pH 4.5-6.5), the loaded GOx catalyzed glucose to produce H_2O_2 and gluconic acid, further lowering local pH and triggering the aggregation of Cu_2Se-BSA nano-enzymes. This structural transformation activated their POD-like activity, efficiently generating •OH radicals that disrupted membrane integrity and bacterial defense systems, achieving a 99% clearance rate against *S. aureus* and *E. coli*. When the wound entered the repair stage (pH > 6.5), microenvironmental neutralization promoted nanoenzymes depolymerization, releasing trace Cu^{2+} to activate the HIF-1α/VEGF signaling pathway and thereby stimulate endothelial cell migration and angiogenesis. This pH-timed regulation of catalytic kinetics enabled diabetic rat wounds to achieve 99.05% closure within 14 days.

Building on strategies that respond to microenvironmental cues, achieving more precise, programmed temporal control through rational material design has emerged as a new frontier. Peng et al. constructed a programmed timing release multifunctional nanoenzyme-engineered hydrogel (PTMH), achieving precise time control of catalytic behavior through a bilayer structure design [155]. The upper layer of the system was a thermosensitive PNIPAM hydrogel loaded with $Cu_{5.4}O$ ultrafine nanoenzymes, and the lower layer was ZnO nanoenzymes coated with sodium alginate. In the early stage of wound healing (0-3 days), the lower ZnO layer generated ROS through photocatalysis under visible-light irradiation, effectively eliminating bacteria and activating M1-type macrophages to enhance immune clearance. As the lower alginate matrix degraded within 3 days, the upper thermosensitive hydrogel came into direct contact with the wound tissue and released $Cu_{5.4}O$ nanoenzymes, which then scavenged excessive ROS, dampened overt inflammation and promoted angiogenesis. This physically timed switch, based on material degradation, bypassed the limitations of a single pH response and ensured that antibacterial and anti-inflammatory functions were delivered within the appropriate time window. Animal experiments showed that PTMH-treated diabetic infected wounds achieved 97.48% closure within 14 days, significantly outperforming single-layer hydrogel.

4.2. Spatial localization of catalytic sites

Building upon the achievement of programmed temporal regulation, a new challenge in diabetic wound treatment lies in further enhancing

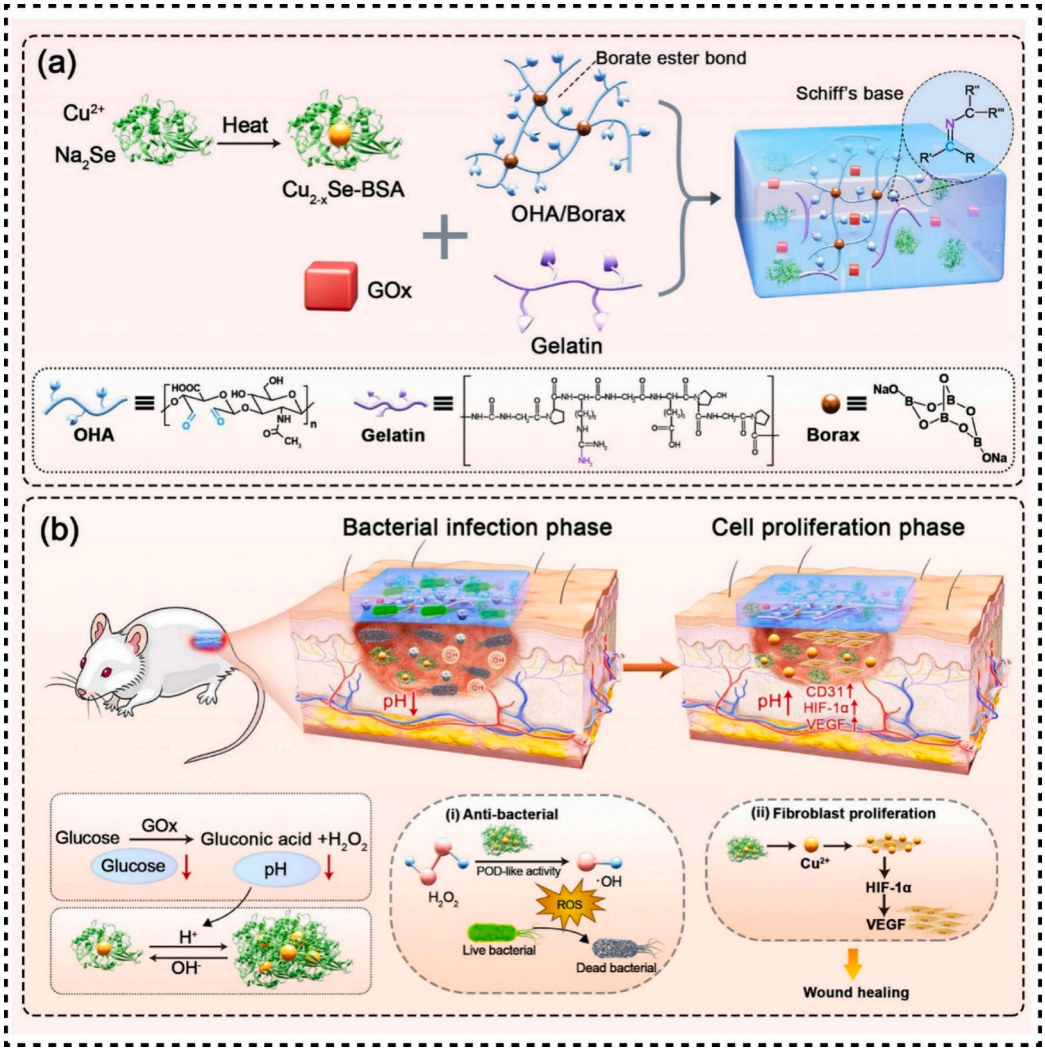

Fig. 14. Schematic of the preparation and application of OBG@CG. (a) Synthetic route of OBG@CG. (b) Mechanisms by which OBG@CG promotes diabetic wound recovery. BSA: Bovine Serum Albumin; OBG: OHA/borax-gelatin hydrogel; OBG@G: OBG@GOx; OBG@C: OBG@Cu_{2-x}Se-BSA; OBG@CG-N: OBG@Cu_{2-x}Se-PEG-GOx; OBG@CG: OBG@Cu_{2-x}Se-BSA-GOx, from [124]. Copyright (2024), Elsevier Ltd.

therapeutic precision through spatial localization of catalytic sites. Yu et al. designed a multifunctional nanoenzyme-engineered hydrogel microneedle patch (MN@Ag@MSN@CeO_2), which achieved precise spatial localization of catalytic function through a unique core-shell structure [156]. This system employed γ-polyglutamic acid as the matrix and incorporated Ag@MSN@CeO_2 nanoparticles with a sandwich architecture: the CeO_2 core exerted SOD/CAT dual-enzyme activity *via* the Ce^{3+}/Ce^{4+} redox cycle, scavenging ROS in deep tissue and driving M2-macrophage polarization; the MSN interlayer released Si^{4+} in response to the microenvironment to promote neovascularization; the outer Ag layer penetrated the biofilm and exerted pinpoint bactericidal action in the acidic infected zone. This spatially addressed catalytic design allowed each therapeutic module to act simultaneously on distinct pathological regions-Ag eradicated surface bacteria, CeO_2 provided anti-oxidant/anti-inflammatory effects in deeper tissue, and Si^{4+} supported vascular reconstruction across the wound bed-achieving spatiotemporal synergy of antibacterial, anti-inflammatory and pro-angiogenic functions. In a diabetic rat model the microneedle system accomplished 98.5% wound closure within 12 days, increased collagen deposition 2.8-fold and markedly enhanced epithelialization, underscoring the unique advantages of spatially localized catalysis in orchestrating complex wound-microenvironment reconstruction.

Compared with previous nanoenzymes strategies focusing on single functions or simple carriers, a significant breakthrough in improving catalytic efficiency and biological safety has been achieved by constructing nanoreactors with spatially confined catalytic functions. For instance, Tang et al. encapsulated copper oxide nanoparticles with multi-enzyme activity in PEG-b-PCL polymer vesicles to form a nanoreactor (CuO@PS) capable of releasing Cu^+ in a lysosomal acidic environment, and uniformly loaded it into a temperature-sensitive Pluronic F127 hydrogel (Fig. 15) [157]. Constructed as a composite nanoenzyme-engineered hydrogel (CuOPS@GEL), this material rapidly gelled at wound temperature to form a localized coating. The matrix simultaneously immobilized the nanoreactor in space and controlled its release, while its semi-permeable membrane allowed ROS and other damage-associated molecules to enter the catalytic chamber. Inside the isolated nanospace, free radicals were efficiently scavenged and oxidative stress was alleviated, avoiding the toxicity that would arise from direct exposure to copper ions. In addition, the gel maintained a moist wound environment and, together with Cu^+ released from the nanoreactor, activated the intracellular ATOX1–ATP7A/B–LOX signaling axis and the MEK/ERK pathway, thereby promoting high-quality, multi-stage repair of chronic diabetic wounds, including inflammatory modulation, cell migration, and angiogenesis. This spatial confinement strategy effectively balances catalytic efficacy with biosafety, representing an important direction for future nanoenzymes design.

4.3. *Substrate-specific catalytic selectivity*

Beyond spatial localization, regulating specific pathological pathways through precise substrate recognition and selective catalysis is crucial for enhancing diabetic wound therapy. Chao et al. designed the MOF-818 nanoenzymes with SOD/CAT dual-enzyme activity, and achieved selective clearance of ROS through the precise coordination of Cu^{2+}/Cu^+ with the Zr node [158]. The nanoenzymes exhibited outstanding substrate recognition within the wound microenvironment. Its SOD-like activity eliminated 84% of superoxide anions, while its CAT-like activity efficiently decomposed H_2O_2, surpassing traditional CeO_2 and MnO_2 nanoenzymes When encapsulated in a temperature-sensitive gelatin hydrogel (MOF/Gel), the mesoporous structure enriched local ROS substrates, further enhancing catalytic specificity. In a diabetic rat model, MOF/Gel achieved 92% wound closure on day 14 by precisely regulating the oxidative microenvironment.

Advancing from tissue-level substrate selectivity, researchers have further explored precise metabolic regulation at the suborganelle level. The Fe_3O_4 nanoenzymes developed by Zhou's team achieved organelle specific catalysis through pH-dependent dual-enzyme activity [159]. In a cytoplasmic neutral environment, it exhibited CAT-like activity to decompose H_2O_2, whereas under lysosomal acidic conditions it switched to POD-like activity to generate •OH. This compartmentalized catalytic behaviour selectively activated the AMPK signalling pathway, improving glucose uptake and insulin sensitivity. In a diabetic mouse model, Fe_3O_4 treatment lowered fasting blood glucose by 36% and elevated AMPK phosphorylation in metabolic tissues to an extent comparable to metformin, highlighting the substantial potential of subcellular-site-selective catalysis in systemic metabolic regulation. The pursuit of substrate-specific catalytic selectivity, from tissue to organelle levels, marks a leap toward precision medicine in diabetic wound care.

5. Catalytically driven microenvironment reprogramming and healing

Nanoenzyme-engineered hydrogels remodel the diabetic wound microenvironment through catalytic and dynamic interactions, enabling stage-adaptive interventions across inflammation, regeneration, and remodeling phases [160]. In the inflammatory phase, they scavenge excessive ROS and exhibit antimicrobial activity to control infection and reduce inflammation [161]. During the regenerative phase, catalytic products such as oxygen and NO activate VEGF-related pathways, promoting angiogenesis and cell migration. In the remodeling phase, nanoenzymes regulate MMP activity, facilitating orderly collagen remodeling. These systems achieve multi-scale regulation: enzymatic catalysis restores redox balance at the molecular level, modulates

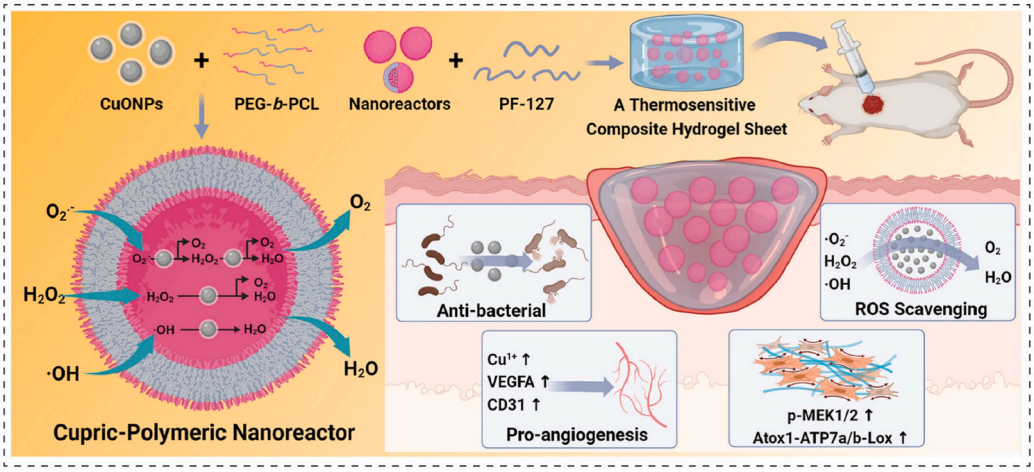

Fig. 15. Cupric-polymeric nanoreactors integrate into copper metabolism to promote chronic diabetic wounds healing, from [157], Copyright (2024), Elsevier Ltd.

macrophage polarization and fibroblast activation at the cellular level, and constructs protective biochemical networks at the tissue level. Integrating pH/ROS-responsive catalysis, biosensing, and controlled release enables real-time microenvironment monitoring and targeted intervention, providing precise, spatiotemporal therapeutic strategies for diabetic wound healing [162].

5.1. Stage-adaptive therapeutic modalities

Nanoenzyme-engineered hydrogels establish a stage-adaptive therapeutic model aligned with the pathological features of diabetic wound healing (Fig. 16 and Table 2). In the inflammatory phase, they clear excessive ROS through CAT and POD activities while releasing antimicrobial metal ions such as Ag^{+} and Zn^{2+} to inhibit infection and suppress inflammation. During the regenerative phase, SOD-like activity alleviates hypoxia by generating oxygen, while NO or VEGF mimics promote angiogenesis and granulation tissue formation. In the remodeling phase, nanoenzymes regulate mechanical signals and metabolic pathways, guiding orderly collagen deposition and preventing excessive scarring. By coordinating catalytic activity and the timed release of biological factors, these systems create a logical progression of "anti-inflammation, regeneration, and homeostasis", promoting efficient diabetic wound healing [163].

5.1.1. Inflammatory phase

The inflammatory phase of diabetic wounds is marked by chronic, unresolved inflammation driven by hyperglycemia-induced vascular damage, hypoxia, and persistent infections [164]. Dysfunctional immune responses result in excessive secretion of pro-inflammatory cytokines and impaired clearance of pathogens, while mitochondrial dysfunction and NADPH oxidase activation lead to ROS accumulation. This creates a vicious cycle of "oxidative stress – inflammation – infection", hindering the transition to the proliferative phase and delaying healing [165]. Therefore, breaking this cycle is critical for promoting wound repair, which can be achieved by addressing two key aspects: restoring redox homeostasis for effective antimicrobial action and modulating cytokine networks to resolve inflammation.

5.1.1.1. Antimicrobial action via redox homeostasis. Persistent hyperglycemia and oxidative stress in diabetic wounds provide a favorable environment for bacterial proliferation while exacerbating inflammation. Restoring redox homeostasis has become a key antimicrobial strategy, as it enables efficient bacterial killing while preventing oxidative damage to healthy tissues. To achieve this, multifunctional nanoenzyme-engineered hydrogels have been developed to precisely regulate ROS generation and elimination through cascade catalysis and dynamic response.

To directly address the complex microenvironment where hyperglycemia and bacterial infection coexisted in diabetic wounds, Zhang et al. constructed a microenvironment-responsive repair syste [91]. This system took a gold-platinum nanoalloy with biomimetic activities of GOx and CAT as the core, and encapsulated it in a self-healing hydrogel constructed by the reaction of hyaluronic acid oxide and carboxymethyl chitosan through Schiff base. This ingenious design enabled the material to actively recognize and utilize excessive glucose at the wound site, the gold-platinum nanoenzymes first catalyzed glucose to produce gluconic acid and H_2O_2, and then further converted H_2O_2 into hydroxyl radicals with bactericidal effects, thereby precisely triggering an antibacterial cascade reaction at the lesion site. This nanoenzyme-engineered hydrogel system ingeniously transformed the recognition of pathological microenvironments into therapeutic impetus. While killing pathogenic bacteria, it also effectively consumed excessive glucose and H_2O_2, reshaping the redox homeostasis of the wound.

However, the above-mentioned cascade strategy based on gold-platinum nanoenzymes still needs to overcome two key challenges in practical applications: the pH sensitivity of the nanoenzymes and the oxygen dependence of GOx. Overcoming these two points is the key to achieving stable and sustained responses in a complex wound microenvironment. Based on a profound understanding of this contradiction, Li et al. further designed a pH-responsive multifunctional nanoenzyme-engineered hydrogel (Mo, Fe/Cu, I-Ag@GOx), aiming to achieve more precise and adaptive reprogramming of the microenvironment of diabetic wounds (Fig. 17) [123]. The core of this system was to load GOx onto a nanocomplex composed of molybdenum/iron-carbon dots and copper/silver iodide, and then form a hydrogel with injectable, adhesive

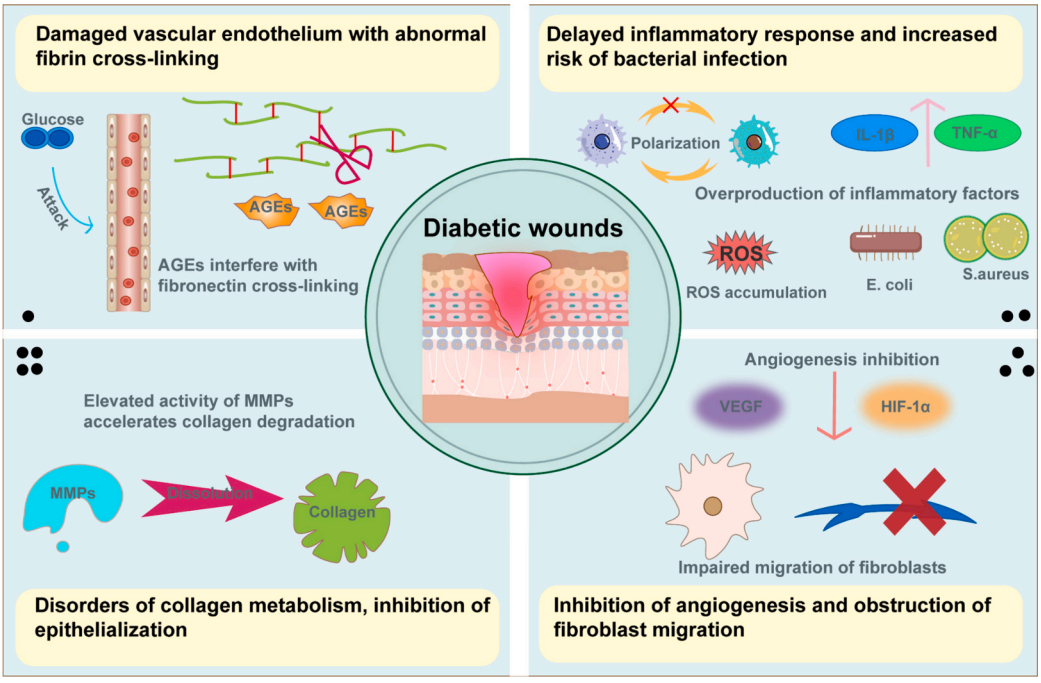

Fig. 16. Schematic representation of the diabetic wound microenvironment: hyperglycemia, excessive inflammation, impaired angiogenesis, and metabolic disorders.

Table. 2
The preparation and functional stages of nanoenzyme-engineered hydrogels.

Nanoenzyme-engineered hydrogels	Nanomaterials used	Incorporation methods into hydrogels	Stages in diabetic wound healing	References
GelPBA-MA/PVA@Fht	Ferrihydrite (Fht) nanozymes	Physical mixing	Inflammatory, Proliferative	[138]
PSBMA/Cu-TCPP(Fe) @Au@BSA	Cu-TCPP(Fe)@Au@BSA nanozymes	Physical mixing	Inflammatory, Proliferative	[85]
Au-Cu/GOx/CMC-OCS	Au-Cu nanoclusters (NCs)	Physical mixing	Inflammatory, Proliferative, Remodeling	[92]
POMHH	Molybdenum-based polyoxometalate (POM) nanoclusters	Chemical crosslinking and physical mixing	Inflammatory, Proliferative, Remodeling	[151]
ACMGM	APTES-COF-1@MXene heterojunction nanozymes (AC-1@MXene)	Chemical crosslinking	Inflammatory, Proliferation, Remodeling	[116]
Au_2Pd_3@PH	Ultrasmall bimetallic Au_2Pd_3 nanozymes	Physical mixing	Inflammatory, Proliferation	[148]
CTCG hydrogel	CeO_2 @TA/Cu (CTC) NPs	Physical mixing	Inflammatory, Proliferation, Remodeling	[183]
SeNPs@CS-CNFs	Selenium nanoparticles (SeNPs)	Physical mixing	Inflammation, Proliferation, Remodeling	[181]
ZG@AFC	ZIF-67/GOx nanozymes (ZG nanozymes)	Physical mixing	Inflammatory, Proliferative, Remodeling	[56]
PTMH	ZnO nanoparticles and $Cu_{5.4}O$ ultrasmall nanozymes	Physical mixing	Inflammatory, Proliferative, Remodeling	[155]

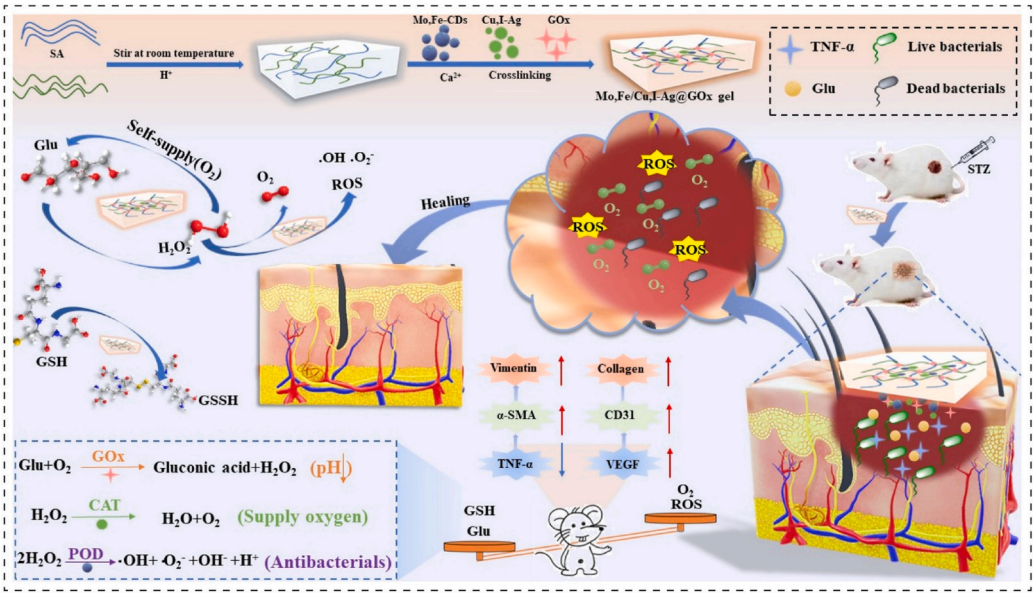

Fig. 17. Schematic diagram of the construction of Mo,Fe/Cu,I-Ag nanoenzymes hydrogel and cascade reaction for the mechanism of infected diabetic wound healing, from [123]. Copyright (2024), Elsevier Ltd.

and soluble properties through the cross-linking of sodium alginate and chitosan under the action of Ca^{2+}. This ingenious multi-level structure design enabled it to actively sense and adapt to the dynamic changes of the microenvironment. Firstly, its pH response characteristics ensured the stable performance of multiple enzyme activities (including GOx, POD, OXD, CAT and SOD) under the complex acid-base conditions of the wound. Subsequently, in a high-sugar microenvironment, it was "activated" and initiated an efficient cascade reaction. On the one hand, it generated ROS to destroy the bacterial membrane structure, achieving direct sterilization. On the other hand, by consuming glucose, eliminating excess ROS and releasing oxygen, it collaboratively reshaped the healing microenvironment that was unfavorable for bacterial survival but beneficial for tissue regeneration. In the diabetic wound infection model, it achieved a bacterial clearance rate of nearly 99.1% within 7 days and significantly accelerated the wound healing process.

Furthermore, the problem of bacterial resistance caused by the abuse of traditional antibiotics further exacerbates the difficulty of healing diabetic wound infections. To address this challenge, combining photothermal therapy with nanoenzyme-engineered hydrogels antibacterial strategies to achieve efficient removal of drug-resistant bacteria through the synergistic effects of physical and chemical means has emerged as an emerging approach. Based on this, Ren et al. developed a novel PNMn hydrogel, in which nitrogen-doped hollow carbon-based nanoenzymes (MnCN) anchored to manganese was integrated into the polyacrylic acid (PAA) hydrogel matrix [166]. The ingenuity of this design lay in endowing the material with a dual antibacterial mechanism. On the one hand, the nanoenzymes generated three different types of ROS through catalytic reactions to carry out multi-target oxidative killing on bacteria. On the other hand, under the irradiation of near-infrared laser, this hydrogel produced a significant photothermal effect. By coordinating with the catalytic action of nanoenzymes, it jointly destroyed the bacterial membrane structure and induced the leakage of contents. *In vitro* antibacterial experiments achieved a sterilization rate close to 100%. In the *in vivo* infection model, it efficiently eliminated bacteria through this synergistic mechanism, significantly accelerating wound healing.

In addition, researchers are also striving to endow the materials themselves with more refined perception and self-adaptation capabilities to the pathological microenvironment. Based on this concept, Feng

et al. reported an intelligent wound dressing composed of a traditional alginate (Alg) hydrogel and a novel copper hydrogen phosphate (CuP) nanoenzymes [167]. The core innovation of this system lay in its "dynamic switching" catalytic characteristic. In the typically alkaline microenvironment of diabetic wounds, the nanoenzymes exhibited CAT-like activity, releasing oxygen by catalyzing the decomposition of H_2O_2, thereby alleviating hypoxia and promoting angiogenesis. Once a bacterial infection occurred, leading to local acidification of the microenvironment, their catalytic behavior intelligently switched to POD-like activity, which, in synergy with the released copper ions, generated highly toxic •OH to precisely eliminate pathogenic bacteria and biofilms. This built-in "pH switch" mechanism enabled it to automatically adjust the treatment strategy without external intervention. *In vitro* experiments showed that the material had an antibacterial rate of 100% against *S. aureus* and *E. coli* under the assistance of near-infrared light, and maintained excellent antibacterial performance in different pH environments, demonstrating strong environmental adaptability and promising prospects for clinical transformation.

5.1.1.2. Inflammatory regulation through cytokine modulation. Persistent inflammation in diabetic wounds is closely linked to the overproduction of pro-inflammatory cytokines and insufficient anti-inflammatory responses [168]. NO plays a critical role in modulating this balance by inhibiting NF-κB signaling, thereby reducing the production of TNF-α, IL-1β, and IL-6, while simultaneously promoting the secretion of anti-inflammatory cytokines such as IL-10 and TGF-β to facilitate inflammation resolution [169].

Based on an in-depth understanding of the potential of NO in regulating inflammation and the microenvironment, Xiang et al. constructed an injectable nanoenzyme-engineered hydrogel (AZG-Gel) based on chitosan (CS) and Pluronic F127. It was loaded with arginine-modified Zn-MOF and GOx, which were specifically used to reshape the inflammatory microenvironment of infectious diabetic wounds [170]. The intelligence of this system lay in its cascade response design. GOx first catalyzed the conversion of excessive glucose at the wound site into gluconic acid and H_2O_2. This process not only consumed harmful high glucose but also actively lowered the pH of the microenvironment. The acidic microenvironment then triggered the disintegration of the Zn-MOF framework. The released arginine was converted into NO *in situ* using the generated H_2O_2. In this way, the system, by perceiving and utilizing the unique "high sugar" feature of diabetic wounds, actively converted it into therapeutic NO signaling molecules, effectively down-regulating the pro-inflammatory factors TNF-α and IL-6, while up-regulating the anti-inflammatory factor IL-4, achieving a closed-loop management from "recognizing pathological signals" to "executing inflammatory regulation".

However, the regulation of a single NO is slightly insufficient for the complex pathological microenvironment of diabetes. If the activities of multiple enzymes can be integrated, it will be more conducive to the synergistic reconstruction of the pathological microenvironment. Following this train of thought, Pu et al. developed a regenerative microenvironment modulator (AHAMA/CS-GOx@Zn-POM) to achieve synergistic repair of diabetic wounds through a multifunctional nanoenzyme-engineered hydrogel system (Fig. 18) [171]. This system, while retaining the hypoglycemic and microenvironmental acidification activation capabilities of GOx, introduced Zn-POM nanoclusters with POD and SOD activities. This design achieved triple microenvironment reconstruction. Firstly, GOx continuously consumed glucose, fundamentally reducing high glucose toxicity. Secondly, Zn-POM efficiently eliminated ROS and prevented the accumulation of by-products such as H_2O_2, maintaining the redox steady state. Finally, Zn-POM actively reprogrammed pro-inflammatory M1-type macrophages into anti-inflammatory M2-type ones by inhibiting the MAPK/IL-17 signaling pathway, fundamentally reversing the chronic inflammatory state. In the diabetic rat model, this material successfully reversed the pathological microenvironment to a regenerative microenvironment, achieving a wound healing rate of 90% within 14 days.

5.1.2. Proliferative phase

The proliferative phase aims to reconstruct the vascular network and ECM to support wound closure, but diabetic wounds are hindered by impaired angiogenesis and ECM imbalance [172]. Hyperglycemia inhibits endothelial cell migration and angiogenesis through AGE-RAGE signaling, while oxidative stress damages endogenous stem cells and growth factors, reducing regenerative potential [173]. Concurrently, fibroblast dysfunction and abnormal MMP activation impair ECM synthesis and accelerate matrix degradation, while AGEs induce disordered collagen crosslinking, leading to a rigid, unorganized matrix. This "vascular deficiency and matrix imbalance" restricts granulation tissue formation and re-epithelialization, delaying wound closure [174].

5.1.2.1. Angiogenic microenvironment engineering. Restoring blocked angiogenesis in diabetic wounds, improving local hypoxia and nutrient supply are the core to reversing the stagnation of diabetic wound healing. The active reconstruction of the pathological microenvironment through advanced material design provides a brand-new idea for activating the internal repair program. For example, Wu et al. proposed an innovative "seed and soil" strategy [175]. This system simultaneously reshaped the microenvironment of diabetic wounds through miRNA-loaded cerium oxide nanoenzyme-engineered hydrogel. The core lay in the precise division of labor of material components: cerium oxide nanoenzymes acted as "microenvironment scavengers", continuously neutralizing excessive ROS on the wound surface, reversing the pro-apoptotic oxidative stress "soil" into a microenvironment that supported regeneration. Meanwhile, the hydrogel network served as a "gene delivery platform", precisely releasing pro-angiogenic miRNAs ("seeds") under protective conditions where ROS were effectively cleared, thereby synergistically inducing angiogenesis and collagen deposition.

In addition to gene regulation, directly regulating cell behavior by using gas signaling molecules is another effective approach. Chen et al. developed a multifunctional thermosensitive nanoenzyme-engineered hydrogel (Cu-MOF/GOx-Gel) that integrates catalytic and gas therapeutic functions (Fig. 19) [176]. As GOx consumes H_2O_2, NO is gradually released from the hydrogel, thereby promoting angiogenesis and collagen accumulation, which accelerates wound healing. The design of this system ingeniously constructed a self-driven cascade reaction. The loaded GOx first catalyzed the high-concentration glucose at the wound site to generate H_2O_2. This process not only consumed harmful metabolic wastes but also provided a substrate for subsequent reactions. Subsequently, Cu-MOF nanoenzymes utilized the generated H_2O_2 to catalyze arginine to continuously produce NO. This material-guided endogenous release of NO directly promoted the proliferation and migration of endothelial cells, effectively accelerating the process of angiogenesis and tissue repair.

In addition to gas molecules, specific therapeutic metal ions also show great potential. Based on this, Zhang et al. constructed Cu/Mg-MOF@CS/PL hydrogel [91]. This material intelligently released Cu^{2+} and Mg^{2+} in a wet environment, and the two reshaped and regenerated the microenvironment through a synergistic effect. On the one hand, they directly promoted cell proliferation and the high expression of VEGF, on the other hand, they collaboratively regulated intracellular ROS homeostasis and oxygen metabolism. In the diabetic rat model, this treatment achieved a wound healing rate of 90.6% on the 14th day, confirming the effectiveness of promoting angiogenesis through ion regulation to recreate the microenvironment.

5.1.2.2. ECM remodeling. ECM remodeling is essential for wound repair as it provides structural support and biochemical cues for tissue regeneration. However, diabetic microenvironments characterized by chronic

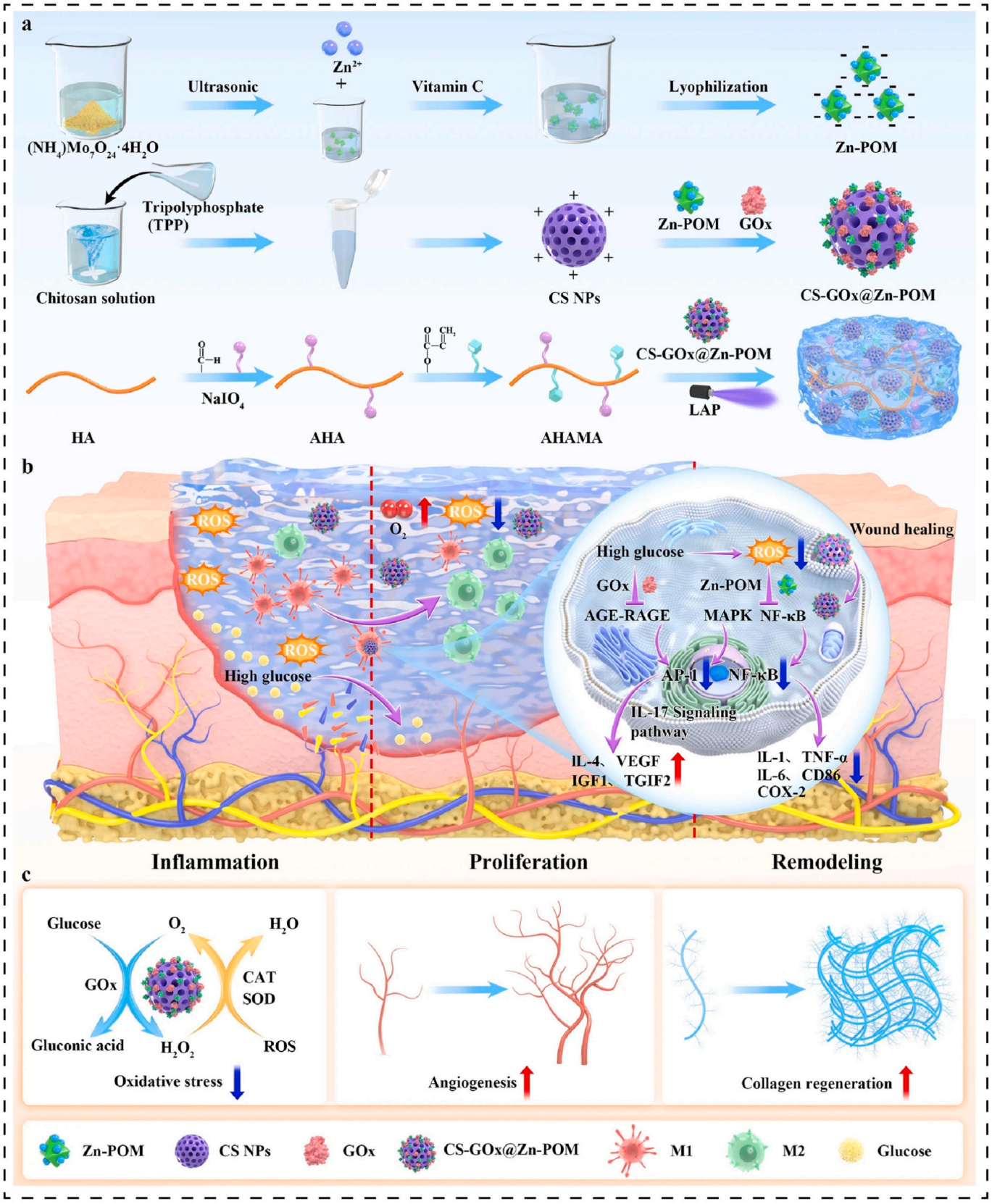

Fig. 18. Illustration of nanoenzyme functionalized hydrogel for the treatment of diabetic wounds. a Preparation process for the nanoenzyme functionalized hydrogel. b Diagram of the mechanism by which nanoenzyme functionalized hydrogel promotes diabetic wound healing and Zn-POM regulates macrophages. c The cascade reactions by which nanoenzyme functionalized hydrogel facilitate glucose consumption, ROS scavenging, angiogenesis, and collagen regeneration, from [171]. Copyright (2024), Springer Nature.

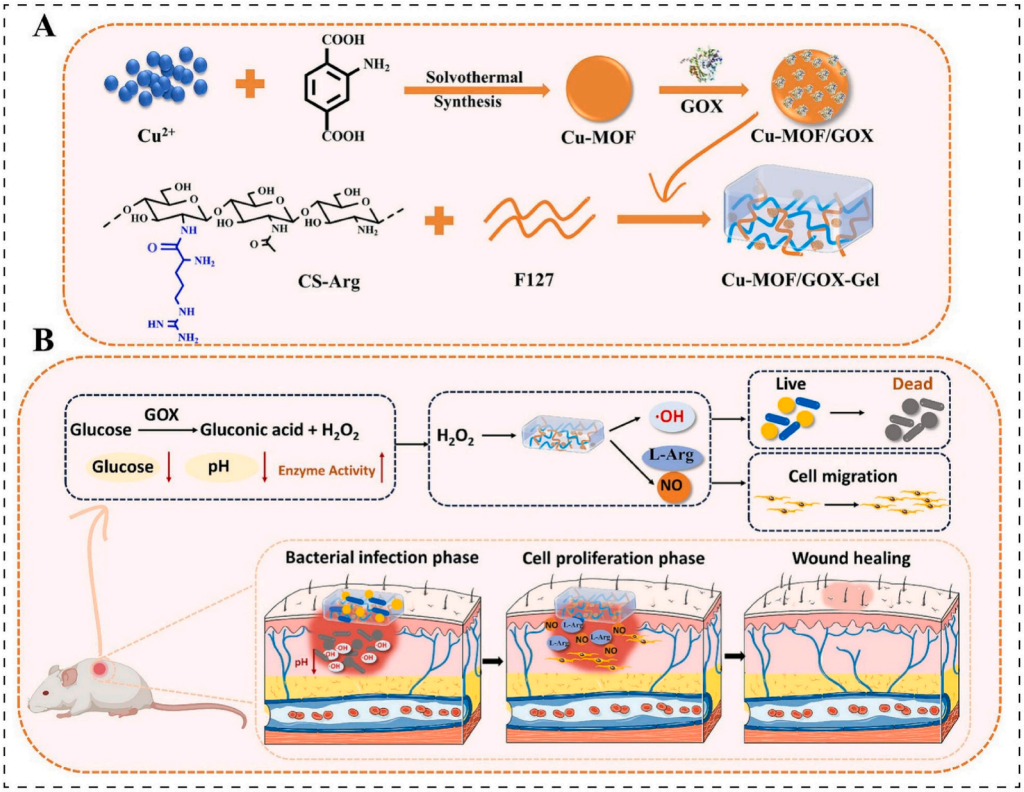

Fig. 19. (A) Cu-MOF, Cu-MOF/GOx and Cu-MOF/GOx-Gel preparation. (B) Mechanisms underlying wound healing mediated by Cu-MOF/GOx-Gel, from [176]. Copyright (2024), Elsevier Ltd.

inflammation and oxidative stress disrupt collagen alignment and impair ECM metabolism, delaying healing. To promote the orderly remodeling of damaged ECM in diabetic wounds, researchers have designed a variety of nanoenzyme-engineered hydrogel with dynamic catalytic regulation and antibacterial functions, aiming to actively intervene and optimize the microenvironment of the wound [177]. For instance, Ma et al. constructed a multifunctional silver enzyme nanogel system (Ag-nGHC), the core of which lies in integrating GOx, horseradish peroxidase (HRP), and CAT into a cascade reaction system and generating a synergistic effect with the antibacterial activity of silver ions [178]. This hydrogel performed a coherent biochemical response in the microenvironment of the wound surface, GOx consumed glucose and generated H_2O_2, after which HRP and CAT worked in synergy to regulate the transformation and decomposition of H_2O_2, producing ROS for sterilization while preventing their accumulation and damage to tissues. Meanwhile, the continuous release of silver ions further enhanced the antibacterial effect. Animal experiments confirmed that the wound closure speed of diabetic rats treated with Ag-nGHC was significantly accelerated. H&E staining showed that the regeneration of tissue hair follicles was enhanced and the collagen arrangement was denser, effectively achieving the structural reconstruction of ECM.

Compared with the above-mentioned strategy of constructing a cascade reaction by introducing exogenous enzyme complexes, another approach is to endow the material itself with stronger microenvironment perception and multi-functional integration capabilities. Based on this, Pu et al. developed an injectable, customizable silk fibroin/carboxymethyl cellulose @ manganese dioxide (SF/CMC@MnO_2) nanocomposite hydrogel [122]. In the microenvironment of high ROS, hypoxia and overexpression of MMP-2/9 in diabetic wounds, this hydrogel played multiple active regulatory roles. The MnO_2 nanosheets converted the excessive H_2O_2 in the wounds into O_2 through their CAT-like activity, directly alleviating local hypoxia. Meanwhile, the SF component in the material efficiently affinity and neutralized the overexpressed MMP-2/9, down-regulating its protein expression by more than 80%, thereby effectively protecting collagen from degradation. In the full-thickness skin defect model of diabetic mice induced by STZ, the hydrogel treatment reduced the wound size to 23.7% within 7 days and achieved basic closure and hair follicle regeneration within 14 days.

5.1.3. *Remodeling phase*

The remodeling phase aims to optimize collagen crosslinking and scar maturation, but diabetic wounds often face persistent ECM disorganization, excessive fibrosis, and fragile scars due to metabolic dysfunction and chronic inflammation [179]. Disrupted collagen turnover, abnormal MMP/TIMP balance, and impaired vascular-neural regeneration further hinder stable healing, leading to recurrent ulceration [180].During the remodeling period of diabetic wound healing, collagen deposition, angiogenesis and tissue remodeling are the key links that determine the quality of healing. However, the continuous oxidative stress and inflammatory response in the high-glucose microenvironment often led to delayed repair and scar formation. Nanoenzyme-engineered hydrogels have become ideal carriers for promoting repair during the remodeling period because they can simulate the activity of natural enzymes and regulate the microenvironment .

Based on this, Bi et al. developed a self-healing hydrogel loaded with selenium nanoparticles/chitosan/cellulose nanofibers (SeNPs@CS-CNFs) and used it as a delivery system for adipose-derived mesenchymal stem cells (ADSCs) for the repair of diabetic wounds [181]. This hydrogel constructed a three-dimensional porous network through DF-PEG-DF cross-linked chitosan and cellulose nanofibers, and introduced selenium nanoparticles with GPX-like enzyme activity, endowing it with excellent antioxidant capacity. It eliminated excessive ROS and protected ADSCs from oxidative damage. Meanwhile, the immune microenvironment was optimized by regulating inflammatory factors (such as reducing TNF-α and increasing IL-10). In the diabetic rat model, this

hydrogel not only demonstrated excellent injectable and self-healing properties, but also significantly accelerated wound closure, promoted the orderly deposition of collagen and angiogenesis, effectively facilitating the transformation of wounds to the remodeling stage, providing a new material strategy for achieving functional wound healing in diabetes. Although the hydrogel strategy centered on stem cell loading and antioxidation has shown potential in regulating the microenvironment of diabetic wounds, it still has limitations in deep tissue delivery, complex infection control, and the coordinated regulation of multiple stresses such as hypoxia and hyperglycemia. In response to the above challenges, Xuan et al. developed a cerium oxide nanoenzyme-enhanced microneedle system based on amyloid fiber template synthesis, achieving multi-dimensional remodeling of the microenvironment of diabetic wounds [182]. Using lysozyme amyloid fibrils as templates, cerium-oxide nanoenzyme with ultra-fine size, high Ce^{3+}/Ce^{4+} ratio and uniform distribution were synthesized *in situ*. These nanoenzymes were then co-assembled with tannic acid and GOx to construct micron-scale patches with cascade catalytic activity. The resulting microneedles exhibited excellent mechanical strength and skin-penetrating ability. Moreover, they achieved ROS scavenging and hypoxia relief through GOx-mediated glucose consumption coupled with the SOD-CAT cascade of the nanoenzymes. Meanwhile, the amyloid-fibril skeleton conferred broad-spectrum antibacterial activity and promoted cell proliferation, and steered macrophage polarization toward the M2 anti-inflammatory phenotype. In an infected diabetic rat wound model, the microneedle system markedly accelerated wound closure, enhanced collagen deposition, angiogenesis and epithelial regeneration, thereby demonstrating strong potential for efficient functional tissue recovery during the remodeling phase (Fig. 20).

5.2. Multiscale regulatory mechanisms

Nanoenzyme-engineered hydrogels achieve precise regulation of the diabetic wound microenvironment through a molecular-cellular-tissue multilayer cascade mechanism. Molecular level, based on enzyme-like catalytic reactions (e.g. ROS scavenging, gas transmitter generation), it dynamically regulates redox balance and expression of key signaling molecules, and reshapes the molecular network homeostasis [184]. Cellular level, through catalytic products or surface functional groups, we can directionally regulate the polarization of macrophages to M2 type and inhibit the storm of inflammatory factors; activate the differentiation of fibroblasts to myofibroblasts to enhance collagen secretion; and at the same time, promote the migration of keratinocytes and the epithelialization process [185]. Tissue level, construct a three-dimensional porous scaffold to provide mechanical support and guide the growth of neovascular network; establish a local biochemical gradient field through slow release of antibacterial or healing factors to synergistically enhance the anti-infective and regenerative capacity of tissues, and ultimately achieve the integration of "molecular signaling - cell behavior programming - tissue function repair" across the scale of regulation [186].

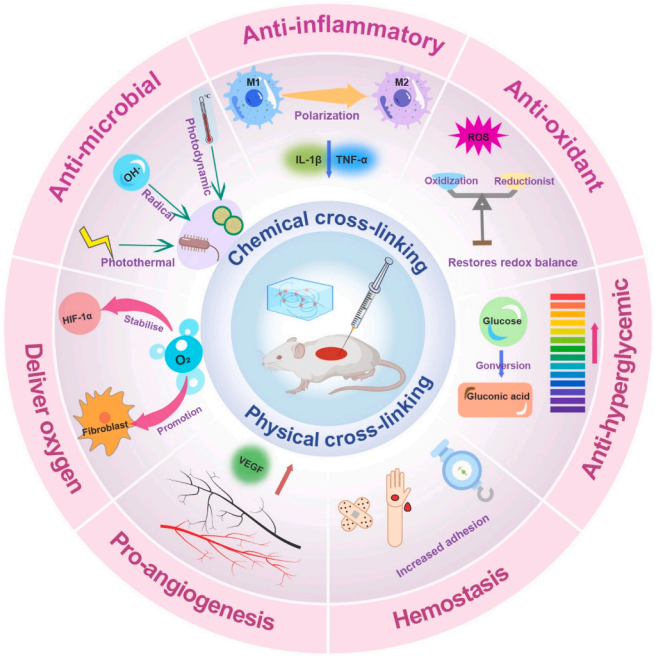

Fig. 20. Schematic representation shows the multiple therapeutic effects of nanoenzyme-engineered hydrogels on the pathological microenvironment of diabetic wounds, accelerating the healing of diabetic wounds.

5.2.1. Molecular-level signaling modulation

Persistent inflammation and oxidative stress triggered by the high-glycemic microenvironment in diabetic wounds often result in delayed healing, and the central mechanism involves aberrant regulation of NLRP3 inflammatory vesicle activation with the cGAS-STING signaling pathway [187]. It has been revealed that mitochondrial oxidative damage in endothelial cells exacerbates the vicious cycle of inflammation by releasing oxidatively damaged mitochondrial DNA (Ox-mtDNA), which activates the macrophage cGAS-STING pathway and promotes pro-inflammatory M1 phenotypic polarization [188].

To achieve precise intervention in this pathological mechanism, He et al. developed a multifunctional nanoenzyme-engineered hydrogel (CeO_2-Y@ZIF-8@Gel), which reshaped the immune microenvironment at the molecular scale through multi-path synergy at the material level [189]. The hydrogel system, with the ZIF-8 nanoframework as the carrier, loaded CeO_2 nanoenzymes with SOD and CAT activities, which actively eliminated excessive ROS and decomposed H_2O_2 into water and oxygen, thereby effectively inhibiting the activation of NLRP3 inflammasomes. Meanwhile, the ROCK inhibitor Y-27632 released in the material repaired mitochondrial DNA damage, reduced the leakage of Ox-mtDNA, blocked the activation of the cGAS-STING pathway, and guided macrophages to polarize toward the anti-inflammatory M2 phenotype. The hydrogel matrix adopted quaternary ammonium-modified GelMA, which not only endowed the system with long-lasting antibacterial performance but also prolonged the retention and action time of the drug at the lesion site through the sustained-release mechanism. In animal models, this material system significantly accelerated wound healing, reduced the levels of inflammatory factors, and promoted angiogenesis. This study achieved active remodeling of the immune microenvironment of diabetic wounds by targeting the dual signaling axes of NLRP3 and cGAS-STING.

5.2.2. Cellular communication networks

One of the central mechanisms of impaired wound healing in diabetes lies in the dysfunctional cellular communication network, especially the dysregulated interaction between fibroblasts and macrophages. Chronic high-glucose environments cause macrophages to hyperpolarize to a pro-inflammatory M1 phenotype, releasing inflammatory factors such as IL-1β and IL-6, inhibiting fibroblast proliferation and migration, and exacerbating oxidative stress, disrupting ECM reconstruction [190,191].

Nanoenzyme-engineered hydrogels, as an emerging type of intelligent biomaterial, can precisely regulate intercellular communication networks, such as immune cell polarization, oxidative stress response, and angiogenesis signaling pathways, by simulating the activity of natural enzymes and interacting with biomolecules in the wound microenvironment. This breaks the vicious cycle in chronic wounds and accelerates the healing process. Based on this, Ge et al. developed a multifunctional hydrogel based on succinylchitosan (NSC) and polyvinyl alcohol (PVA), in which GOx and tannic acid-Cu^{2+} chelated CeO_2 nanoenzymes (CTC NPs) were doped (Fig. 21) [183]. The hydrogel

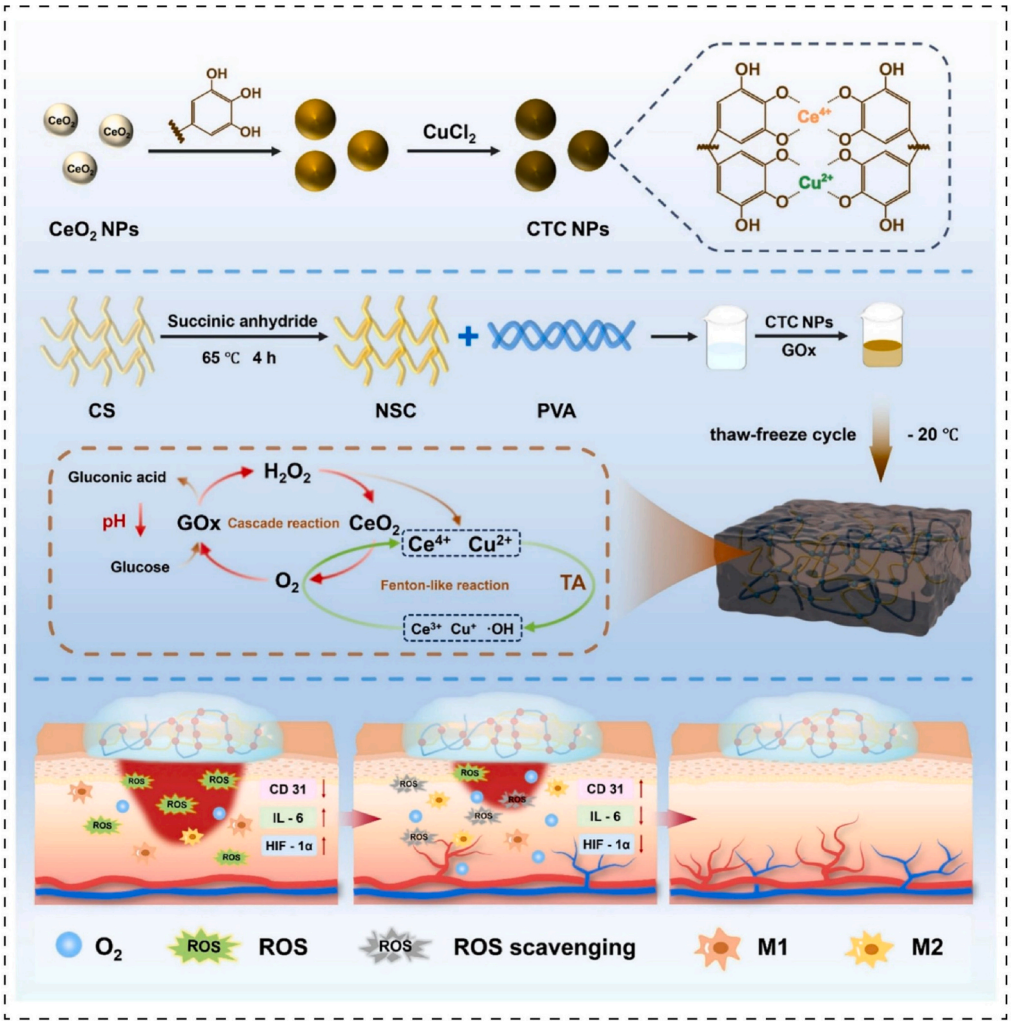

Fig. 21. Schematic diagram of NP hydrogel preparation and mechanism diagram of CeO_2 nanoenzymes synergistic GOx dual-pathway in the treatment of diabetic wounds, from [183]. Copyright (2025), Elsevier Ltd.

system achieved a glucose-driven cascade reaction in the wound microenvironment, GOx catalyzed excess glucose to generate H_2O_2, and the CeO_2 nanoenzymes then decomposed H_2O_2 to produce oxygen, alleviating tissue hypoxia and eliminating excessive ROS, while promoting the polarization of macrophages from the pro-inflammatory M1 to the anti-inflammatory M2 phenotype. In addition, the TA/Cu complex intelligently released Cu^{2+} for targeted antibacterial purposes in an acidic infection environment. In a full-thickness skin-defect model of diabetic mice, this nanoenzyme-engineered hydrogel significantly accelerated epithelial regeneration, angiogenesis and collagen deposition, and achieved nearly complete wound closure within 14 days.

However, the therapeutic effect of the above-mentioned cascade reaction system based on endogenous substrates (glucose and H_2O_2) is largely limited by the concentration and persistence of local metabolites at the wound site. To break through this limitation and achieve active intervention and energy conversion in high-sugar microenvironments, Shen et al. designed an injectable hydrogel system based on photocatalytic heterojunctions, encapsulating Bi_2WO_6/H-TiO_2 composites modified by Bi nanocrystals in a hyaluronic acid matrix [192]. Under visible-light irradiation, this hydrogel utilized glucose at the wound site as a sacrificial agent to simultaneously achieve active degradation of glucose and efficient *in situ* generation of hydrogen. Hydrogen exerted powerful antioxidant and anti-inflammatory effects, while continuous glucose consumption inhibited the accumulation of AGEs at the source, thereby synergistically regulating macrophage polarization and promoting the proliferation and migration of vascular endothelial cells. In the diabetic mouse model, this photocatalytic hydrogel achieved 50% wound closure within 3 days.

5.2.3. *Tissue-level biomechanical integration*

Tissue- level biomechanical integration refers to the process of applying controlled mechanical stimuli to wounds through materials or instruments to coordinate the dynamic balance between cellular behavior and tissue structure, thereby promoting physiological repair [193,194]. In diabetic wounds, the hyperglycemic and hypoxic microenvironment leads to reduced cell survival, impaired fibroblast-to-myofibroblast conversion, disturbed collagen synthesis, and insufficient neovascularization, resulting in a vicious cycle of “mechanical force deficiency” that significantly delays healing [195].

To address the aforementioned challenges, researchers are dedicated to developing nanoenzyme-engineered hydrogels with intelligent responsiveness and enhanced mechanical stability, with the aim of achieving continuous and efficient treatment in the complex dynamic wound environment. Peng et al. constructed fucocan-chitosan-oxidized saponin-coated gold nanoenzymes (Fuc@AuNPs) engineered hydrogel through electrostatic recombination-schift base double network [196]. Hydrogel exhibited unique pH-responsive enzyme activity, functioning as OXD in the acidic microenvironment of infection to generate singlet oxygen for sterilization, while in the nearly neutral normal tissue region, they demonstrated SOD activity to eliminate ROS for anti-inflammatory

effects. The mechanical strength of the hydrogel could be precisely adjusted by regulating the synthetic pH value. Among them, the compressive fracture stress of the FAC-6.0 group reached 82.5 kPa, and the modulus almost completely recovered after three self-healing cycles, which was significantly better than that of the FAC-5.0 group. Animal experiments showed that in the FAC-6.0 group, the wound closure rate reached 99.31% within 14 days, collagen deposition was denser, and the number of regenerated hair follicles increased significantly.

This enhanced mechanical network not only ensures that the dressing adheres firmly to dynamic areas such as joints without easy rupture, but also continuously kills bacteria and antioxidizes through the synergistic effect with nanoenzymes, significantly accelerating the healing of infected wounds. Based on the realization of pH-responsive therapy, in order to further enhance the active regulation ability of the complex wound microenvironment, Sun et al. constructed a PPCN@Pt-AMPs/HGel hydrogel based on gelatin/sodium alginate and loaded with the sonosensitizer pN-224, platinum nanoenzymes and antimicrobial peptide HHC-36 [197]. The platinum nanoenzymes in this system catalyzed oxygen generation in the wound's high-hydrogen-peroxide environment to relieve hypoxia and, in coordination with ultrasound, triggered singlet oxygen for sterilization. Meanwhile, the antimicrobial peptides targeted and disrupted biofilms, creating a triple synergistic mechanism of "oxygen supply-sterilization-anti-inflammation". Most importantly, the nanoenzymes formed physical cross-links with the polymer chains, markedly raising the hydrogel's storage modulus G' relative to the blank gel. Tensile and torsion tests showed that it could be repeatedly bent without fracturing, demonstrating greatly enhanced mechanical stability. In a diabetic rat model of infected wounds, the improved mechanical properties ensured stable dressing coverage at dynamic sites, minimizing secondary injury. After 14 days of combined ultrasound treatment, the residual wound area was only 8.7%, significantly better than the 45.3% observed in the blank group, and promoted type III collagen deposition and angiogenesis, thereby markedly accelerating the healing process.

5.3. Intelligent diagnostic-therapeutic integration systems

Diagnostic and therapeutic integration is crucial in diabetic wound management, and since a chronic hyperglycemic environment impairs angiogenesis, exacerbates inflammation, and slows down the healing process, real-time monitoring of glucose fluctuations and simultaneous implementation of precise interventions are key to breaking the vicious cycle.

In the treatment of diabetic wounds, achieving real-time monitoring and feedback adjustment of the treatment process is the key to improving the therapeutic effect. For this purpose, Han et al. developed an injectable self-healing nanoenzyme-engineered hydrogel (UGV hydrogel) based on hyaluronic acid [198]. They constructed and loaded GOx-manganese dioxide nanoenzymes and VEGF nanovesicles through Schift base reaction, forming an integrated diagnostic and therapeutic platform. In this system, GOx–MnO_2 nanoenzymes catalyzed the conversion of wound glucose into H_2O_2 and Mn^{2+}. The H_2O_2 subsequently reacted with MnO_2 to generate O_2, thereby establishing a self-sustaining glucose-lowering cycle. Meanwhile, the released Mn^{2+} acted as a magnetic-resonance-imaging signal source that tracked local glucose fluctuations in real time. Therapeutically, ultrasound triggered on-demand release of VEGF nanovesicles to promote angiogenesis. In diabetic rats, the wound closure rate reached 98.5% on day 14. MRI signals confirmed a linear correlation between glucose-lowering efficacy and Mn^{2+} intensity. Masson staining revealed a 2.4-fold increase in collagen deposition and a 3.1-fold rise in α-SMA-positive vessel density.

Based on the integration of diagnosis and treatment, in order to further enhance the dynamic monitoring and collaborative treatment capabilities for high-risk infection wounds, Wang et al. designed a conductive hydrogel Gel-6 based on polydopamine nanoenzymes, and constructed a multifunctional diagnosis and treatment platform by integrating GOx, CAT and aluminum ions. [199]. This system exhibited multi-responsive behaviour in the wound microenvironment. PDA nanoparticles triggered a photothermal effect under 808 nm near-infrared irradiation, eradicating 99.99% of Staphylococcus aureus and Escherichia coli and effectively disrupting biofilms. GOx catalysed the conversion of glucose to H_2O_2, which was subsequently decomposed by a CAT cascade to generate oxygen, relieving tissue hypoxia and promoting angiogenesis. Aluminium ions imparted high electrical conductivity to the hydrogel, enabling real-time mapping of wound deformation and healing dynamics through a 3×3 sensor array. In a diabetic mouse model, the Gel-6 group achieved virtually complete wound closure by day 14. CD31-positive vessel density and collagen deposition were markedly superior to those of the other groups, demonstrating the potent synergistic actions of photothermal antibacterial activity, catalytic oxygen regulation and electrical-signal monitoring in accelerating healing.

However, on the basis of the existing research achieving diagnosis and treatment collaboration, how to construct a closed-loop treatment system that does not require external stimulation and can independently respond to the wound microenvironment in a more concise manner has become a key issue to be broken through in this field. In response to this challenge, Yang et al. developed a PF127@Zn/C-G multifunctional nanoenzyme-engineered hydrogel, which demonstrated unique advantages (Fig. 22) [200]. This system constructed an intelligent response platform that relied entirely on changes in the wound's own microenvironment through the self-assembly of Zn^{2+} with carbon quantum dots (CQDs) and co-loading of GOx. When the wound was in a hyperglycaemic state, gluconic acid produced by GOx-catalysed glucose oxidation competitively chelated Zn^{2+}, switching CQD fluorescence from "off" to "on" and thereby enabling real-time, self-powered glucose monitoring. At the therapeutic level, the released Zn^{2+} promoted angiogenesis by activating the PI3K/AKT pathway, while the CQDs simultaneously scavenged excessive ROS, creating an autonomous link between monitoring and treatment. Animal experiments confirmed that the system achieved a 96.28% healing rate on day 10 and completed the entire closed loop from sensing to therapy without any external activation equipment.

6. Conclusions and outlooks

Impaired healing of diabetic wounds remains a major clinical challenge due to complex pathological networks and microenvironmental imbalances. This review examines how nanoenzyme-engineered hydrogels can help overcome chronic wound healing barriers by combining catalytic activity with microenvironmental regulation. We first analyze two core pathogenic circuits: the oxidation-inflammation-infection cycle (ROS/NF-κB feedforward, biofilm-induced immunosuppression) and metabolic disorders (hyperglycemia-AGEs-RAGE axis, hypoxia - angiogenesis paradox). We then propose a synergistic system based on nanoenzyme-engineered hydrogels, in which MOFs, COFs, and metal/metal oxide nanoenzymes enable ROS and MMP-9 regulation, multi-enzyme catalysis, and antibacterial and angiogenic effects. pH/redox dual-gated activation and stiffness-adaptive programming further provide dynamic responsiveness to the hydrogel. We also present design strategies for temporospatial and substrate-specific regulation with clinically translatable fabrication processes. Mechanistically, nanoenzyme-engineered hydrogels regulate redox balance and inflammation in the early phase, promote angiogenesis and ECM remodeling in the proliferative phase, and guide tissue regeneration during remodeling, enabling molecular to tissue-level regulation within an intelligent therapeutic system.

However, several challenges remain. The long-term biocompatibility of nanoenzymes is not fully understood, and some metal-based nanoenzymes may accumulate *in vivo*, posing risks of hepatotoxicity or nephrotoxicity. Degradation products from carbon-based materials may interfere with cellular metabolism. The responsiveness of dynamic

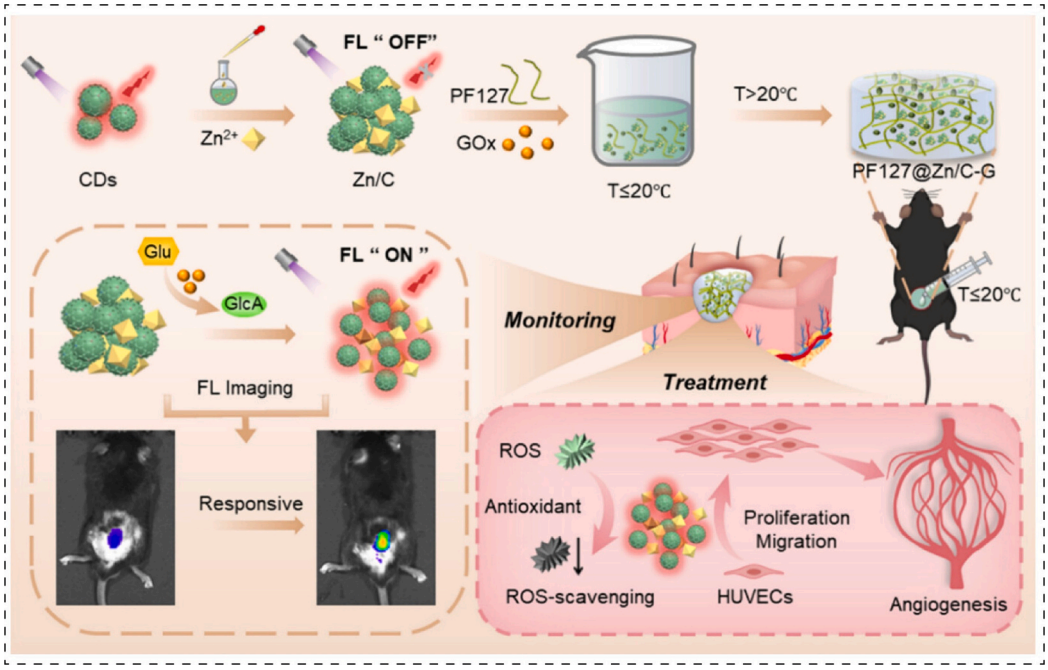

Fig. 22. Schematic diagram of PF127@Zn/C-G hydrogel for the synergistic functions with wound glucose monitoring and healing promotion, from [200]. Copyright (2025), American Chemical Society.

hydrogels is limited under physiological conditions; for example, protein adsorption in wound exudate may passivate pH-sensitive groups, and heterogeneity in redox conditions may lead to uneven catalytic activity. Achieving effective multi-scale regulatory synergy is also challenging; NF-κB inhibition may affect pro-regenerative signals, and the coupling of mechanical programming with angiogenesis needs further clarification. Clinically, most studies rely on small animal models, lacking validation in large animal models. Large-scale production faces challenges such as batch variability of nanoenzymes and difficulties in hydrogel sterilization, which may damage cross-linking networks. Additionally, variations in wound depth and infection strains increase demands on material customization.

Future research should focus on intelligent design, systematic integration, and clinical translation. At the material level, developing biomimetic cascade catalytic systems, such as nanoenzymes mimicking SOD and CAT for sustained ROS scavenging, holds promise. Embedding multi-enzyme systems within DNA origami frameworks may further improve substrate selectivity. The application of artificial intelligence, including molecular dynamics and high-throughput screening, can optimize nanoenzymes active sites, while machine learning may predict relationships between hydrogel mechanics and wound environments. For system integration, combining acoustic therapy with nanoenzymes catalysis could enhance deep-tissue antimicrobial effects, while electrically stimulated hydrogel may promote cell migration and tissue repair. To advance clinical translation, establishing standardized evaluation systems, biodegradation guidelines, and large animal wound models will be essential. Technologies such as microneedle arrays and 3D printing can enable personalized hydrogel application. Interdisciplinary collaboration among synthetic biology, medicine, and data science will support integrated diagnostics and treatment. For instance, nanoenzyme-engineered hydrogels with fluorescent probes could monitor wound pH and infection markers in real time and wirelessly transmit data for closed-loop treatment.

Declaration of competing interest

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

Acknowledgments

This work was financially supported by the Liaoning Revitalization Talent Program (No. XLYC2403107), Shenyang Young and Middle-aged Science and Technology Innovation Talent Support Program (No. RC240393), the Excellent Youth Science Foundation of Liaoning Province (2024JH3/10200046).

Data availability

The authors do not have permission to share data.

References

[1] F. Mohsin, S. Javaid, M. Tariq, M. Mustafa, Molecular immunological mechanisms of impaired wound healing in diabetic foot ulcers (DFU), current therapeutic strategies and future directions, Int. Immunopharmacol. 139 (2024) 112713, https://doi.org/10.1016/j.intimp.2024.112713.
[2] J. Lin, C. Lian, L. Xu, Z. Li, Q. Guan, W. Wei, H. Dai, J. Guan, Hyperglycemia targeting nanomotors for accelerated healing of diabetic wounds by efficient microenvironment remodeling, Adv. Funct. Mater. 35 (2025) 2417146, https://doi.org/10.1002/adfm.202417146.
[3] H. Liu, R. Ai, B.-z. Liu, L. He, Recent advances in hyaluronic acid-based hydrogels for diabetic wound healing, Int. J. Biol. Macromol., 304 (2025) 140797, doi: https://doi.org/10.1016/j.ijbiomac.2025.140797.
[4] Y. Xu, Y. Luo, Z. Weng, H. Xu, W. Zhang, Q. Li, H. Liu, L. Liu, Y. Wang, X. Liu, L. Liao, X. Wang, Microenvironment-Responsive metal-phenolic nanozyme release platform with antibacterial, ROS scavenging, and osteogenesis for periodontitis, ACS Nano 17 (2023) 18732–18746, https://doi.org/10.1021/acsnano.3c01940.
[5] D. Chu, M. Zhao, S. Rong, W. Jhe, X. Cai, Y. Xiao, W. Zhang, X. Geng, Z. Li, X. Zhang, J. Li, Dual-Atom nanozyme eye drops attenuate inflammation and break the vicious cycle in dry eye disease, Nano-Micro Lett. 16 (2024) 120, https://doi.org/10.1007/s40820-024-01322-7.
[6] C. Liu, M. Lv, Q. Xu, J. Xie, Y. You, K. Guo, G. Jiang, L. Hou, H. Yang, Y. Yong, Chronological adaptive polyoxometalate-based hydrogel for diabetic chronic wounds through synchronous bacterial ferroptosis death and immunomodulation, Nano Today 58 (2024) 102415, https://doi.org/10.1016/j.nantod.2024.102415.
[7] Y. Wang, W. Luo, J. Han, Z.A. Khan, Q. Fang, Y. Jin, X. Chen, Y. Zhang, M. Wang, J. Qian, W. Huang, H. Lum, G. Wu, G. Liang, MD2 activation by direct AGE interaction drives inflammatory diabetic cardiomyopathy, Nat. Commun. 11 (2020) 2148, https://doi.org/10.1038/s41467-020-15978-3.

[8] M. Samandari, F. Aghabaglou, K. Nuutila, H. Derakhshandeh, Y. Zhang, Y. Endo, S. Harris, L. Barnum, C. Kreikemeier-Bower, E. Arab-Tehrany, N.A. Peppas, I. Sinha, A. Tamayol, Miniaturized Needle Array-Mediated Drug Delivery Accelerates Wound Healing, Adv. Healthcare Mater. 10 (2021) 2001800, https://doi.org/10.1002/adhm.202001800.
[9] Y. Hu, B. Wu, Y. Xiong, R. Tao, A.C. Panayi, L. Chen, W. Tian, H. Xue, L. Shi, X. Zhang, L. Xiong, B. Mi, G. Liu, Cryogenic 3D printed hydrogel scaffolds loading exosomes accelerate diabetic wound healing, Chem. Eng. J. 426 (2021) 130634, https://doi.org/10.1016/j.cej.2021.130634.
[10] Y. Zhang, T. Yue, W. Gu, A. Liu, M. Cheng, H. Zheng, D. Bao, F. Li, J.-G. Piao, pH-responsive hierarchical H_2S-releasing nano-disinfectant with deep-penetrating and anti-inflammatory properties for synergistically enhanced eradication of bacterial biofilms and wound infection, J. Nanobiotechnol. 20 (2022) 55, https://doi.org/10.1186/s12951-022-01262-7.
[11] A. Vishwakarma, F. Dang, A. Ferrell, H.A. Barton, A. Joy, Peptidomimetic polyurethanes inhibit bacterial biofilm formation and disrupt surface established biofilms, J. Am. Chem. Soc. 143 (2021) 9440–9449, https://doi.org/10.1021/jacs.1c02324.
[12] S. Bose, S.K. Das, Biofilm microenvironment-sensitive anti-virulent and immunomodulatory nano-on-nanodroplets to combat refractory biofilm infection through toxin neutralization and phagocytosis, Adv. Healthcare Mater. 14 (2025) 2403528, https://doi.org/10.1002/adhm.202403528.
[13] A. Alavi, R.G. Sibbald, D. Mayer, L. Goodman, M. Botros, D.G. Armstrong, K. Woo, T. Boeni, E.A. Ayello, R.S. Kirsner, Diabetic foot ulcers: Part I. Pathophysiology and prevention, J. Am. Acad. Dermatol. 70 (1) (2014) e1–1.e18, https://doi.org/10.1016/j.jaad.2013.06.055.
[14] P. Yang, X. Chen, Y. Qin, L. Yu, G. Ge, W. Yin, W. Zhang, W. Li, W. Li, W. Xia, Z. Wu, F. Ding, J. Bai, F. Meng, D. Geng, Regulation of osteoimmune microenvironment via functional dynamic hydrogel for diabetic bone regeneration, Biomaterials 320 (2025) 123273, https://doi.org/10.1016/j.biomaterials.2025.123273.
[15] D. Lou, Y. Luo, Q. Pang, W.-Q. Tan, L. Ma, Gene-activated dermal equivalents to accelerate healing of diabetic chronic wounds by regulating inflammation and promoting angiogenesis, Bioactive Mater. 5 (2020) 667–679, https://doi.org/10.1016/j.bioactmat.2020.04.018.
[16] C. Arden, S.H. Park, X.R. Yasasilka, E.Y. Lee, M.-S. Lee, Autophagy and lysosomal dysfunction in diabetes and its complications, Trends Endocrinol. Metab. 35 (2024) 1078–1090, https://doi.org/10.1016/j.tem.2024.06.010.
[17] R. Xu, Y. Fan, J. Gu, W. Cao, R. Deng, Z. Rana, X. Lu, C. Xu, G. Xiang, H. Li, X. Wang, Enhancing infected wound healing through scavenging reactive oxygen species using synergetic composites of sub-nanoscale TiO_2 with DNA, Adv. Funct. Mater. 34 (2024) 2401307, https://doi.org/10.1002/adfm.202401307.
[18] P. Mishra, J. Lee, D. Kumar, R.O. Louro, N. Costa, D. Pathania, S. Kumar, J. Lee, L. Singh, Engineered nanoenzymes with multifunctional properties for next-generation biological and environmental applications, Adv. Funct. Mater. 32 (2022) 2108650, https://doi.org/10.1002/adfm.202108650.
[19] R. Augustine, A.A. Mamun, A. Hasan, S.A. Salam, R. Chandrasekaran, R. Ahmed, A.S. Thakor, Imaging cancer cells with nanostructures: Prospects of nanotechnology driven non-invasive cancer diagnosis, Adv. Colloid Interf. Sci. 294 (2021) 102457, https://doi.org/10.1016/j.cis.2021.102457.
[20] L. Duan, J. Fan, Z. Li, P. Qiu, Y. Jia, J. Li, Covalent organic frameworks for metal ion separation: Nanoarchitectonics, mechanisms, applications, and future perspectives, Adv. Colloid Interf. Sci. 338 (2025) 103399, https://doi.org/10.1016/j.cis.2025.103399.
[21] J. Hou, Y. Xianyu, Tailoring the surface and composition of nanozymes for enhanced bacterial binding and antibacterial activity, Small 19 (2023) 2302640, https://doi.org/10.1002/smll.202302640.
[22] Z. Wang, R. Zhang, X. Yan, K. Fan, Structure and activity of nanozymes: Inspirations for de novo design of nanozymes, Mater. Today 41 (2020) 81–119, https://doi.org/10.1016/j.mattod.2020.08.020.
[23] X. Liu, H. Zhang, L. Chen, Z. Zheng, W. Li, C. Huang, H. Zhou, Y. Chen, Z. Jiang, J. Liang, Q. Yu, L. Yang, Advanced wound healing with Stimuli-Responsive nanozymes: mechanisms, design and applications, J. Nanobiotechnol. 23 (2025) 479, https://doi.org/10.1186/s12951-025-03558-w.
[24] D. Jian, K. Ye, L. Wang, L. Jin, H. Yang, L. Ma, C. Yi, Z. Mao, J. Wu, Enhance efferocytosis capacity of dendritic cells for diabetic wound healing by nanozyme-loaded nanofiber dressings, Nano Today 64 (2025) 102787, https://doi.org/10.1016/j.nantod.2025.102787.
[25] F. Chao, C. Cao, Y. Xu, Y. Gu, X. Qu, Q. Wang, L.L. Qu, Y. Guo, X. Dong, Sprayable hydrogel for pH-responsive nanozyme-derived bacteria-infected wound healing, ACS Appl. Mater. Interfaces 17 (2025) 5921–5932, https://doi.org/10.1021/acsami.4c18100.
[26] L. Li, K. Xu, K. Wang, C. Huang, Y. Xu, A self-circulated microenvironment-adaptive nanozyme for wound healing acceleration, ACS Appl. Mater. Interfaces 17 (2025) 30505–30515, https://doi.org/10.1021/acsami.5c02743.
[27] J. Yan, Y. Zhao, C. Cui, L. Zhou, Y. Xu, Z. Bai, K. Zhang, J. Tong, Y. Liu, L. Sun, M. Du, Y. Mi, X. Wang, X. Wu, B. Li, Dynamic multistage nanozyme hydrogel reprograms diabetic wound microenvironment: synergistic oxidative stress alleviation and mitochondrial restoration, Mater. Today Bio 32 (2025) 101780, https://doi.org/10.1016/j.mtbio.2025.101780.
[28] Y. Chen, X. Wu, S. Wang, Q. Wu, C. Liang, W. Fan, H. Wang, A. Wu, X. Wang, Microenvironment-Responsive xanthotoxol–copper nanozyme for MRSA-infected wound healing, ACS Appl. Mater. Interfaces 17 (2025) 35168–35180, https://doi.org/10.1021/acsami.5c05402.
[29] K. Lu, H. Ding, M. Long, X. Zhu, X. Lou, Y. Li, N. Gu, Prussian blue nanozyme-functionalized hydrogel with self-enhanced redox regulation for accelerated wound healing, ACS Appl. Mater. Interfaces 17 (2025) 36511–36520, https://doi.org/10.1021/acsami.5c07229.
[30] X. Kuang, M.O. Arıcan, T. Zhou, X. Zhao, Y.S. Zhang, Functional tough hydrogels: design, processing, and biomedical applications, Accounts of, Mater. Res. 4 (2023) 101–114, https://doi.org/10.1021/accountsmr.2c00026.
[31] P. Hu, N. Feng, S. Zhao, J.H. Shi, G.Y. Yang, W.J. Guo, Y.D. Liu, K.L. Fan, Microenvironment-Responsive Injectable Thermosensitive Hydrogel Incorporating Nanozymes for Synergistic Breast Cancer Therapy and Postsurgical Adjuvant Treatment, Adv. Funct. Mater. 35 (2025), https://doi.org/10.1002/adfm.202421176.
[32] M. Hu, Q. Zhang, L. Qin, Innovative applications of multidimensional engineered hydrogels in wound healing, J. Adv. Res. (2025), https://doi.org/10.1016/j.jare.2025.08.006.
[33] X. Xue, Y. Hu, Y. Deng, J. Su, Recent advances in design of functional biocompatible hydrogels for bone tissue engineering, Adv. Funct. Mater. 31 (2021) 2009432, https://doi.org/10.1002/adfm.202009432.
[34] M.A. Mohamed, A. Fallahi, A.M.A. El-Sokkary, S. Salehi, M.A. Akl, A. Jafari, A. Tamayol, H. Fenniri, A. Khademhosseini, S.T. Andreadis, C. Cheng, Stimuli-responsive hydrogels for manipulation of cell microenvironment: From chemistry to biofabrication technology, Prog. Polym. Sci. 98 (2019) 101147, https://doi.org/10.1016/j.progpolymsci.2019.101147.
[35] D. Park, J.W. Kim, K. Shin, J.W. Kim, Bacterial cellulose nanofibrils-reinforced composite hydrogels for mechanical compression-responsive on-demand drug release, Carbohydr. Polym. 272 (2021) 118459, https://doi.org/10.1016/j.carbpol.2021.118459.
[36] H. Li, S. Wei, Q. Ling, R. Wang, T. Liu, H. Yu, P. Zhao, K. Zhang, L. Bian, W. Liao, Nanozyme-reinforced hydrogel spray as a reactive oxygen species-driven oxygenator to accelerate diabetic wound healing, Adv. Mater. n/a (2025) 2504829, https://doi.org/10.1002/adma.20250482.
[37] H. Li, Y. Ren, Y. Zhan, X. Yu, X. Zhang, H. Chen, Q. Li, J. Cheng, Y. Ye, High-entropy nanozyme-driven "Chinese acupuncture" hydrogel microneedles for combined therapy of infected scalds, Mater. Today Bio 33 (2025) 101953, https://doi.org/10.1016/j.mtbio.2025.101953.
[38] S. Xu, J. Zhang, J. Che, Z. Sha, M. Zhang, Z. Zhang, T. Xiang, W. Zhong, L. Wu, G. Lv, B. Cai, L. Xu, C. Xu, Z. Chen, Lysyl oxidase nanozyme-loaded hydrogel for sustained release and promotion of diabetic bone defect regeneration, J. Control. Release 379 (2025) 927–943, https://doi.org/10.1016/j.jconrel.2025.01.070.
[39] S. Zhai, J. You, Z. Yang, Y. Liu, T. He, Y. Wu, X. Wei, M. Li, X. Shi, F. Gao, S. Chu, Near-infrared light-responsive on-demand puerarin-releasing injectable hydrogel for promoting healing of infected wounds, Mater. Today Bio 32 (2025) 101817, https://doi.org/10.1016/j.mtbio.2025.101817.
[40] T. Kolipaka, G. Pandey, N. Abraham, D.A. Srinivasarao, R.S. Raghuvanshi, P. S. Rajinikanth, V. Tickoo, S. Srivastava, Stimuli-responsive polysaccharide-based smart hydrogels for diabetic wound healing: Design aspects, preparation methods and regulatory perspectives, Carbohydr. Polym. 324 (2024) 121537, https://doi.org/10.1016/j.carbpol.2023.121537.
[41] H. Yang, Y. Chen, Y. Rong, Y. Zhou, S. Li, X. Li, H. Wu, D. Lv, X. Cao, P. Wang, J. Zhu, B. Tang, Z. Hu, Multifunctional hydrogel targeting senescence to accelerate diabetic wound healing through promoting angiogenesis, J. Nanobiotechnol. 23 (2025) 177, https://doi.org/10.1186/s12951-025-03274-5.
[42] Q. Gao, F. Hu, Z. Chai, C. Zheng, W. Zhang, K. Pu, Z. Yang, Y. Zhang, S. Ramrkrishna, X. Wu, T. Lu, Multifunctional hydrogel with mild photothermal properties enhances diabetic wound repair by targeting MRSA energy metabolism, J. Nanobiotechnol. 23 (2025) 380, https://doi.org/10.1186/s12951-025-03451-6.
[43] Z. Ming, L. Han, M. Bao, H. Zhu, S. Qiang, S. Xue, W. Liu, Living bacterial hydrogels for accelerated infected wound healing, Adv. Sci. 8 (2021) 2102545, https://doi.org/10.1002/advs.202102545.
[44] A. Uberoi, A. McCready-Vangi, E.A. Grice, The wound microbiota: microbial mechanisms of impaired wound healing and infection, Nat. Rev. Microbiol. 22 (2024) 507–521, https://doi.org/10.1038/s41579-024-01035-z.
[45] Z. Bei, L. Ye, Q. Tong, Y. Ming, T. Yang, Y. Zhu, L. Zhang, X. Li, H. Deng, J. Liu, W. Chen, B. Chu, Z. Qian, Thermostimulated shrinking and adhesive hydrogel dressing for treating chronic diabetic wounds, Cell Reports Phys. Sci. 5 (2024) 102289, https://doi.org/10.1016/j.xcrp.2024.102289.
[46] X. Tan, N. Lin, S. Yang, H. Gong, M. Wang, N. Li, F. Liu, D. Rao, Y. Wu, J. Tang, Q. Yang, AuCu@CuO_2 Aerogels with H_2O_2/O_2 self-supplying and quadruple enzyme-like activity for MRSA-infected diabetic wound management, Adv. Sci. 12 (2025) 2502391, https://doi.org/10.1002/advs.202502391.
[47] Y. Jiang, X. Feng, X. Qiao, Y. Li, X. Li, J. Yang, L. Han, Plant-inspired visible-light-driven bioenergetic hydrogels for chronic wound healing, Bioactive Mater. 41 (2024) 523–536, https://doi.org/10.1016/j.bioactmat.2024.08.003.
[48] Y. Yang, S. Huang, Q. Ma, N. Li, R. Li, Y. Wang, H. Liu, Combined therapeutic strategy based on blocking the deleterious effects of AGEs for accelerating diabetic wound healing, Regenerative Biomater. 11 (2024) rbae062, https://doi.org/10.1093/rb/rbae062.
[49] J. Zheng, Y. Deng, S. Zhao, L. Liu, W. Wang, J. Li, W. Chen, L. Deng, J. Li, Y.-N. Liu, Cascade-driven nanomotors promote diabetic wound healing by eradicating MRSA biofilm infection, Chem. Eng. J. 481 (2024) 148790, https://doi.org/10.1016/j.cej.2024.148790.
[50] X. Hu, R. Ma, P. Zhang, J. Dong, J. Sun, W. Wang, Q. Liu, L. Kong, X. Zhang, Z. Wang, J. Mei, X. Shang, W. Zhu, Z. Su, C. Zhu, Biomimetic metal–organic framework combats biofilm-associated infections via hyperthermia-enhanced bacterial metabolic interference and autophagy-promoted adaptive immunity,

Adv. Funct. Mater. 34 (2024) 2310509, https://doi.org/10.1002/adfm.202310509.
[51] Z. Ansari, A. Chaurasia, N. Neha, R.K. Sharma, P.C. Gupta Bachheti, Exploring inflammatory and fibrotic mechanisms driving diabetic nephropathy progression, Cytokine Growth Factor Rev. 84 (2025) 120–134, https://doi.org/10.1016/j.cytogfr.2025.05.007.
[52] Y. Zhu, Z. Ma, L. Kong, Y. He, H.F. Chan, H. Li, Modulation of macrophages by bioactive glass/sodium alginate hydrogel is crucial in skin regeneration enhancement, Biomaterials 256 (2020) 120216, https://doi.org/10.1016/j.biomaterials.2020.120216.
[53] W. Meng, X. Chen, Y. Chen, M. Li, L. Zhang, Q. Luo, C. Wei, G. Huang, P. Zhao, B. Sun, M. Chen, Q. Zhang, J. Chen, Self-Cascade of ROS/glucose-scavenging immunomodulatory hydrogels for programmed therapeutics of infected diabetic ulcers via Nrf2/NF-κB pathway, Small 21 (2025) 2411189, https://doi.org/10.1002/smll.202411189.
[54] Y. Li, W. He, Y. Piao, Y. Wang, M. Peng, H. Li, R. Hu, D. Li, L. Shi, Y. Liu, Bacterial membrane nanovesicles encapsulating prodrug assemblies combine chemical and immunological therapies for chronic bacterial infection, Nat. Commun. 16 (2025) 5246, https://doi.org/10.1038/s41467-025-60570-2.
[55] R. Lu, Z. Luo, Y. Zhang, J. Chen, Y. Zhang, C. Zhang, A multifunctional tissue-engineering hydrogel aimed to regulate bacterial ferroptosis-like death and overcoming infection toward bone remodeling, Adv. Sci. 11 (2024) 2309820, https://doi.org/10.1002/advs.202309820.
[56] Z.H. Shen, L. Du, X.W. Fang, Z. Zhang, X.K. Li, S.C. Xiao, J. Xiao, S.X. Chen, Nanozyme cryogel accelerates diabetic wound healing by targeting biofilms and inflammations of the wound bed, ACS Nano 19 (2025) 35081–35101, https://doi.org/10.1021/acsnano.5c12513.
[57] Y. Zhang, D. Xu, X. Cai, X. Xing, X. Shao, A. Yin, Y. Zhao, M. Wang, Y.-n. Fan, B. Liu, H. Yang, W. Zhou, P. Li, Gut commensal barnesiella intestinihominis ameliorates hyperglycemia and liver metabolic disorders, Adv. Sci., 12 (2025) 2411181, doi:https://doi.org/10.1002/advs.202411181.
[58] X.-Q. Wu, D.-D. Zhang, Y.-N. Wang, Y.-Q. Tan, X.-Y. Yu, Y.-Y. Zhao, AGE/RAGE in diabetic kidney disease and ageing kidney, Free Radic. Biol. Med. 171 (2021) 260–271, https://doi.org/10.1016/j.freeradbiomed.2021.05.025.
[59] S.F. Yan, R. Ramasamy, A.M. Schmidt, Mechanisms of Disease: advanced glycation end-products and their receptor in inflammation and diabetes complications, Nature Clinical Practice, Endocrinol. Metab. 4 (2008) 285–293, https://doi.org/10.1038/ncpendmet0786.
[60] X. Liu, C. Guo, W. Yang, W. Wang, N. Diao, M. Cao, Y. Cao, X. Wang, X. Wang, H. Pei, Y. Jiang, M. Kong, D. Chen, Composite microneedles loaded with Astragalus membranaceus polysaccharide nanoparticles promote wound healing by curbing the ROS/NF-κB pathway to regulate macrophage polarization, Carbohydr. Polym. 345 (2024) 122574, https://doi.org/10.1016/j.carbpol.2024.122574.
[61] S. Zhang, X. Zhao, W. Zhang, X. Wei, X.-L. Chen, X. Wang, Zn-DHM nanozymes regulate metabolic and immune homeostasis for early diabetic wound therapy, Bioactive Mater. 49 (2025) 63–84, https://doi.org/10.1016/j.bioactmat.2025.02.041.
[62] N. Li, X. Lu, Y. Yang, S. Ning, Y. Tian, M. Zhou, Z. Wang, L. Wang, J. Zang, Calcium peroxide-based hydrogel patch with sustainable oxygenation for diabetic wound healing, Adv. Healthcare Mater. 13 (2024) 2303314, https://doi.org/10.1002/adhm.202303314.
[63] G. Li, D. Li, C. Wu, S. Li, F. Chen, P. Li, C.-N. Ko, W. Wang, S.M.-Y. Lee, L. Lin, D.-L. Ma, C.-H. Leung, Homocysteine-targeting compounds as a new treatment strategy for diabetic wounds via inhibition of the histone methyltransferase SET7/9, Exp. Mol. Med. 54 (2022) 988–998, https://doi.org/10.1038/s12276-022-00804-1.
[64] Z.-L. Wang, L.-Y. Li, H.-J. Liu, Y.-L. Fan, Y.-X. Shen, F. Song, L.-L. Zhu, Platelet-Rich Plasma/Chitosan/Chondroitin sulfate immunomodulatory hydrogel Co-Networks for diabetic wound Repair: Functions and molecular mechanisms, Chem. Eng. J. 491 (2024) 152138, https://doi.org/10.1016/j.cej.2024.152138.
[65] Y. Guan, H. Niu, Z. Liu, Y. Dang, J. Shen, M. Zayed, L. Ma, J. Guan, Sustained oxygenation accelerates diabetic wound healing by promoting epithelialization and angiogenesis and decreasing inflammation, Sci. Adv., 2021 7 eabj0153, doi: 10.1126/sciadv.abj0153.
[66] S. Wang, X. Sun, Y. Li, Z. Zhang, J. Sun, Z. He, C. Luo, S. Zhang, Engineering immunomodulatory hydrogels for diabetic wound microenvironment reprogramming, Nano Today 65 (2025) 102870, https://doi.org/10.1016/j.nantod.2025.102870.
[67] Z.W. Fan, C.Z. Liang, J.Y. Zhang, Y.M. Li, L.H. Tan, H. Deng, P.K. Wang, J. L. Wang, J.W. Kang, Y.D. Zhu, H. Fu, J. Tao, Multimodal synergistic strategies for diabetic wound healing using glucose oxidase nanocomposites: therapeutic mechanisms and nanomaterial design, Int. J. Nanomedicine 20 (2025) 5727–5762, https://doi.org/10.2147/Ijn.S515057.
[68] X. Qi, Y. Li, Y. Xiang, Y. Chen, Y. Shi, X. Ge, B. Zeng, J. Shen, Hyperthermia-enhanced immunoregulation hydrogel for oxygenation and ROS neutralization in diabetic foot ulcers, Cell Biomater. 1 (2025) 100020, https://doi.org/10.1016/j.celbio.2025.100020.
[69] X.L. Qi, E. Cai, Y.J. Xiang, C.F. Zhang, X.X. Ge, J.J. Wang, Y.L. Lan, H.B. Xu, R. D. Hu, J.L. Shen, An immunomodulatory hydrogel by hyperthermia-assisted self-cascade glucose depletion and ROS scavenging for diabetic foot ulcer wound therapeutics, Adv. Mater. 35 (2023), https://doi.org/10.1002/adma.202306632.
[70] C. Pettinari, R. Pettinari, C. Di Nicola, A. Tombesi, S. Scuri, F. Marchetti, Antimicrobial MOFs, Coord. Chem. Rev. 446 (2021) 214121, https://doi.org/10.1016/j.ccr.2021.214121.
[71] B.J. Zhang, J.Y. Chen, Z. Zhu, X. Zhang, J. Wang, Advances in immunomodulatory MOFs for biomedical applications, Small 20 (2024), https://doi.org/10.1002/smll.202307299.
[72] F. Liu, J. Song, S. Li, H. Sun, J. Wang, F. Su, S. Li, Chitosan-based GOx@Co-MOF composite hydrogel: A promising strategy for enhanced antibacterial and wound healing effects, Int. J. Biol. Macromol. 270 (2024) 132120, https://doi.org/10.1016/j.ijbiomac.2024.132120.
[73] W. Zhong, D. An, Z. Ma, J. Li, N. Jin, Y. Zhou, M. Ying, X. Li, S. Gao, B. Hu, Y. Zhang, Glucose-activated cascade nanozyme hydrogels for synergistic antibacterial therapy via cascade reaction and microenvironment modulation in diabetic wounds, Talanta 297 (2026) 128690, https://doi.org/10.1016/j.talanta.2025.128690.
[74] Q.-D. Tai, Y. Tang, S.-T. Xie, Y.-Y. Ye, X. Tang, Q. Lyu, Z.-J. Fan, Y.-H. Liao, Glucose-responsive nanozyme hydrogel for glycemic control and catalytic anti-infective therapy in diabetic wound healing, Mater. Today Bio 35 (2025) 102405, https://doi.org/10.1016/j.mtbio.2025.102405.
[75] H. Chen, W. Wang, Y. Li, L. Shu, F. Ni, H. Mei, K. Wu, T. Yan, L. Shi, X. Wang, V_o-$AgFeO_{2-x}$ nanozymes treat infected wounds and promote wound healing, Nano Res 18 (2025) 94907899, https://doi.org/10.26599/NR.2025.94907899.
[76] Z. Li, X. Zhu, J. Xiao, W. Lu, D. Gan, J. Shen, X. Jiang, M. Wang, Bimetallic nanozymes with robust antibacterial effects for infected wound healing through diverse metal-precise regulation strategies, Chem. Eng. J. 513 (2025) 163016, https://doi.org/10.1016/j.cej.2025.163016.
[77] Y. Chen, X. Yang, K. Li, J. Feng, X. Liu, Y. Li, K. Yang, J. Li, S. Ge, Phenolic ligand–metal charge transfer induced copper nanozyme with reactive oxygen species-scavenging ability for chronic wound healing, ACS Nano 18 (2024) 7024–7036, https://doi.org/10.1021/acsnano.3c10376.
[78] J. Feng, X. Deng, P. Hao, Z. Zhu, T. Li, X. Yuan, J. Hu, Y. Wang, Intra-articular injection of platinum nanozyme-loaded silk fibroin/pullulan hydrogels relieves osteoarthritis through ROS scavenging and ferroptosis suppression, Int. J. Biol. Macromol. 280 (2024) 135863, https://doi.org/10.1016/j.ijbiomac.2024.135863.
[79] L.Z. Gao, J. Zhuang, L. Nie, J.B. Zhang, Y. Zhang, N. Gu, T.H. Wang, J. Feng, D. L. Yang, S. Perrett, X. Yan, Intrinsic peroxidase-like activity of ferromagnetic nanoparticles, Nat. Nanotechnol. 2 (2007) 577–583, https://doi.org/10.1038/nnano.2007.260.
[80] Z.-Y. Liao, W.-W. Gao, N.-N. Shao, J.-M. Zuo, T. Wang, M.-Z. Xu, F.-X. Zhang, Y.-M. Xia, Iron phosphate nanozyme–hydrogel with multienzyme-like activity for efficient bacterial sterilization, ACS Appl. Mater. Interfaces 14 (2022) 18170–18181, https://doi.org/10.1021/acsami.2c02102.
[81] X. Zhang, S. Wen, Q. Liu, W. Cai, K. Ning, H. Liu, E. Liu, Y. Huang, F. Zeng, Multi-functional nanozyme-integrated astragalus polysaccharide hydrogel for targeted phased therapy in diabetic wound healing, Nano Today 62 (2025), https://doi.org/10.1016/j.nantod.2025.102739.
[82] J. Ran, H. Xia, C. Liu, Z. Xie, L. Yan, Y. Hou, X. Liu, X. Guo, X. Lu, C. Xie, Polyphenol conductive nanozyme-enhanced redox hydrogel coupled with vagus nerve electrical stimulation for diabetic wound repair, Adv. Healthcare Mater. 14 (2025), https://doi.org/10.1002/adhm.202500027.
[83] J. Yu, T. Chen, X. Wen, H. Shi, L. Wang, Y. Xu, Highly selective nanozyme-based glucose sensing platform via construction of artificial recognition sites on gold nanospheres, Biosens. Bioelectron. 253 (2024) 116169, https://doi.org/10.1016/j.bios.2024.116169.
[84] H. Bai, Z. Ding, J. Qian, M. Jiang, D. Yao, AuPt nanoparticle-based injectable hydrogel as cascade nanozyme for accelerating bacteria-infected wound healing, ACS Appl. Nano Mater. 6 (2023) 17531–17538, https://doi.org/10.1021/acsanm.3c02693.
[85] Y. Sun, Y. Zhu, J. Si, R. Zhang, Y. Ji, J. Fan, Y. Dong, Glucose-activated nanozyme hydrogels for microenvironment modulation via cascade reaction in diabetic wound, Chin. Chem. Lett. 36 (2025) 110012, https://doi.org/10.1016/j.cclet.2024.110012.
[86] W.Q. Wang, X.L. Wei, H.S. Gui, T.X. Yan, B.L. Xu, K.L. Wu, H.Y. Liu, X.W. Wang, Silver-Based nanozyme hydrogel with enhanced multienzyme activity for infected wound treatment, Adv. Healthcare Mater. (2025), https://doi.org/10.1002/adhm.202404535.
[87] X. Wang, J. Huang, J. Zhao, T. Yue, W. Shenyang, Y. Xu, Y. Lu, Y. Zhou, pH-responsive cationic guar gum-based multifunctional hydrogel with silver nanoenzymes: Combined photothermal antibacterial therapy and antioxidant properties for MRSA infected wound healing, Int. J. Biol. Macromol. 292 (2025) 139201, https://doi.org/10.1016/j.ijbiomac.2024.139201.
[88] H. Liu, R. Ai, B.-z. Liu, L. He, Tea polyphenol nano-crosslinked dynamical hyaluronic acid-based hydrogel for diabetic wound healing, Int. J. Biol. Macromol., 282 (2024) 136856, doi:https://doi.org/10.1016/j.ijbiomac.2024.136856.
[89] J.J. Zhu, T. Wen, S.Q. Qu, Q.N. Li, B.W. Liu, W.H. Zhou, G-Quadruplex/Hemin DNAzyme-functionalized silver nanoclusters with synergistic antibacterial and wound healing capabilities for infected wound management, Small 20 (2024), https://doi.org/10.1002/smll.202307220.
[90] L. Huang, Y. Feng, H. Chen, L. Lai, H. Li, A. Li, J. Du, Z. Wang, T. Xin, L. Tian, S. Li, P. Zheng, C. Nie, W. Zhu, Q. Pan, Metal valence transition strategy-engineered bimetallic nanozyme thermosensitive hydrogel for deep-tissue therapy of subcutaneous abscess wounds and bacterial corneal ulcers, J. Colloid Interface Sci. 700 (2025) 138613, https://doi.org/10.1016/j.jcis.2025.138613.
[91] B. Zhang, Y. Lv, C. Yu, W. Zhang, S. Song, Y. Li, Y. Chong, J. Huang, Z. Zhang, Au–Pt nanozyme-based multifunctional hydrogel dressing for diabetic wound healing, Biomater. Adv. 137 (2022) 212869, https://doi.org/10.1016/j.bioadv.2022.212869.

[92] W. Zhang, Y. Chen, K. Xie, R.A. Jun, R. Wang, N. Wang, Y. Li, Y. Song, Multifunctional hydrogel embedded with Au−Cu nanoclusters for catalytic cascade therapy of infected diabetic wounds, Chin. Chem. Lett. (2025) 111481, https://doi.org/10.1016/j.cclet.2025.111481.

[93] Q. Liu, A. Zhang, R. Wang, Q. Zhang, D. Cui, A review on metal- and metal oxide-based nanozymes: Properties, mechanisms, and applications, Nano-Micro Lett. 13 (2021) 154, https://doi.org/10.1007/s40820-021-00674-8.

[94] Z.Y. Zhu, J.X. Ding, M.Y. Qin, L.T. Wang, D.J. Jiang, J.H. Zhao, D.P. Wang, W. T. Jia, Enhanced ·OH-Scavenging activity of Cu-CeO_x nanozyme via resurrecting macrophage Nrf2 transcriptional activity facilitates diabetic wound healing, Adv. Healthcare Mater. 13 (2024), https://doi.org/10.1002/adhm.202303229.

[95] S. Zhao, J. Ling, N. Wang, X.K. Ouyang, Cerium dioxide nanozyme doped hybrid hydrogel with antioxidant and antibacterial abilities for promoting diabetic wound healing, Chem. Eng. J., 497 (2024) 154517, doi:10.1016/j.cej.2024.154517.

[96] X. Jin, W. Zhang, J. Shan, J. He, H. Qian, X. Chen, X. Wang, Thermosensitive hydrogel loaded with nickel–copper bimetallic hollow nanospheres with SOD and CAT enzymatic-like activity promotes acute wound healing, ACS Appl. Mater. Interfaces 14 (2022) 50677–50691, https://doi.org/10.1021/acsami.2c17242.

[97] Q. Luo, C. Yan, R. Ma, L. Dai, W. Shu, A. Asghar, Z. Jia, X. Zhu, S. Yu, E-PL/MnO_2 nanozymes/gellan gum/hyaluronic acid-based multifunctional hydrogel to promote diabetic wound healing, Int. J. Biol. Macromol. 304 (2025) 140777, https://doi.org/10.1016/j.ijbiomac.2025.140777.

[98] C. Pu, Y. Wang, Y. Li, Y. Wang, L. Li, H. Xiang, Q. Sun, Y. Yong, H. Yang, K. Jiang, Nano-enzyme functionalized hydrogels promote diabetic wound healing through immune microenvironment modulation, Biomaterials, Science 12 (2024) 3851–3865, https://doi.org/10.1039/d4bm00348a.

[99] D. Li, Z. Ai, Y. Tian, Y. Wang, C. Zhang, Bioactive prosthetic interface constructed with cascading multi-nanozyme hydrogel to induce M2 macrophage polarization and heal diabetic bone defects, Biomaterials 325 (2026) 123624, https://doi.org/10.1016/j.biomaterials.2025.123624.

[100] X. Tao, Z.-J. Fang, R. Shao, J. Hu, H.-Y. Cheng, S.-Q. Zhu, X. Wang, H. Yu, B. Tan, C. Zhang, Covalent organic framework nanohydrogel-based oxidase-mimicking nanozyme for photocatalytic antibacterial therapy, Angew. Chem. Int. Ed. 64 (2025) e202513754, https://doi.org/10.1002/anie.202513754.

[101] Y. Niu, Y. Wang, H. Cao, M. Guo, J. Qi, Y. Du, F. Hu, S. Qian, Core-shell Co-COF@MOF nanozyme-based dual-catalytic electrochemical immunosensor for ultrasensitive detection of Anti-MCV in early rheumatoid arthritis, Electrochim. Acta 539 (2025) 147100, https://doi.org/10.1016/j.electacta.2025.147100.

[102] J.C. Zhao, L.J. Wang, L.S. Jia, Y.H. Liu, S.P. Cao, J. Wen, W. Li, K. Yang, The engineering screen of photoactive nanozymes based on N-containing covalent organic frameworks for antibacterial application, Small 21 (2025), https://doi.org/10.1002/smll.202408959.

[103] X. Zhu, T. Feng, Y. Chen, Y. Xiao, W. Wen, X. Zhang, D. Wang, S. Wang, J. Liang, H. Xiong, GSH-depleted Cu-covalent organic frameworks for multimodal synergistic therapy against diabetic infections, Chem. Eng. J. 488 (2024) 150770, https://doi.org/10.1016/j.cej.2024.150770.

[104] J. Wu, T. Meng, X.Q. Zhang, S.T. Tang, L. Liu, J. Xue, X.H. Liu, J.J. Wang, J. Y. Wen, D.Y. Hu, G.Y. Zhang, Glucose-Responsive Zn(II)-porphyrin COF adhesive hydrogels with dual-active sites and GOX-like activity for accelerated wound healing, Adv. Healthcare Mater. 14 (2025), https://doi.org/10.1002/adhm.202404076.

[105] J.Y. Zhang, M.D. Lv, X.Y. Wang, F. Wu, C. Yao, J. Shen, N.L. Zhou, B.H. Sun, An immunomodulatory biomimetic single-atomic nanozyme for biofilm wound healing management, Small 19 (2023), https://doi.org/10.1002/smll.202302587.

[106] Y. Jin, J. Zhang, Y. Xu, K. Yi, F. Li, H. Zhou, H. Wang, H.F. Chan, Y.-H. Lao, S. Lv, Y. Tao, M. Li, Stem cell-derived hepatocyte therapy using versatile biomimetic nanozyme incorporated nanofiber-reinforced decellularized extracellular matrix hydrogels for the treatment of acute liver failure, Bioactive Mater. 28 (2023) 112–131, https://doi.org/10.1016/j.bioactmat.2023.05.001.

[107] S. Feng, X. Peng, Y. Deng, Y. Luo, S. Shi, X. Wei, X. Pu, X. Yu, Biomimetic nanozyme-decorated smart hydrogel for promoting chronic refractory wound healing, ACS Appl. Mater. Interfaces 16 (2024) 59862–59879, https://doi.org/10.1021/acsami.4c13220.

[108] Y. Zhao, D. Wang, T. Qian, J. Zhang, Z. Li, Q. Gong, X. Ren, Y. Zhao, Biomimetic nanozyme-decorated hydrogels with H_2O_2-activated oxygenation for modulating immune microenvironment in diabetic wound, ACS Nano 17 (2023) 16854–16869, https://doi.org/10.1021/acsnano.3c03761.

[109] Z. Wan, Q. Liu, Y. Zhe, J. Li, D. Ding, S. Liu, H. Wang, H. Qiao, J. Yang, S. Zhang, X. Mu, Single-atom nanozymes with intelligent response to pathological microenvironments for bacterially infected wound healing, Biomaterials, Science 13 (2025) 1033–1044, https://doi.org/10.1039/d4bm01371a.

[110] J. Song, H. Chen, Y. Lv, W. Yang, F. Zhang, T. Wang, D. Liu, Y. Qu, L. Han, J. Fu, X. Kong, CuO_2-assisting-Zn single atom hybrid nanozymes for biofilm-infected wound healing, Chem. Eng. J. 474 (2023) 145706, https://doi.org/10.1016/j.cej.2023.145706.

[111] S. Dai, L. Yao, L. Liu, J. Cui, Z. Su, A. Zhao, P. Yang, Carbon dots-supported Zn single atom nanozymes for the catalytic therapy of diabetic wounds, Acta Biomater. 186 (2024) 454–469, https://doi.org/10.1016/j.actbio.2024.07.045.

[112] F. Lan, T. Xin, Y. Zhang, A. Li, L. Wan, J. Du, P. Zheng, C. Nie, Q. Pan, W. Zhu, Nanoconfinement-guided in situ co-deposition of single-atom cascade nanozymes combined with injectable sodium alginate hydrogels for enhanced diabetic wound healing, Int. J. Biol. Macromol. 304 (2025) 140814, https://doi.org/10.1016/j.ijbiomac.2025.140814.

[113] W. You, F. Xiao, Z. Cai, J. Zhao, Z. Zhang, W. Hu, Y. Chen, K.L. Choy, Z. Wang, Biofilm-disrupting heterojunction microneedles: dual ROS amplification and glucose deprivation for accelerated diabetic wound healing, Theranostics 15 (2025) 9757–9774, https://doi.org/10.7150/thno.120787.

[114] S. Ma, M. Chen, Y. Wang, J. Wang, Y. Hao, X. Wang, H. Zhang, Y. Wei, Z. Liang, Y. Hu, X. Lian, D. Huang, Gelatin-sodium alginate composite hydrogel doped with black phosphorus@ZnO heterojunction for cutaneous wound healing with antibacterial, immunomodulatory, and angiogenic properties, Int. J. Biol. Macromol. 274 (2024) 133456, https://doi.org/10.1016/j.ijbiomac.2024.133456.

[115] Q. Li, X. Xiao, T. Yan, D. Song, L. Li, Z. Chen, Y. Zhong, W. Deng, X. Liu, Y. Song, L. Wang, Y. Wang, Heterojunction nanozyme hydrogels containing Cu–O–Zn bonds with strong charge transfer for accelerated diabetic wound healing, ACS Appl. Mater. Interfaces 16 (2024) 68950–68966, https://doi.org/10.1021/acsami.4c15715.

[116] J.L. Tang, W.J. Liu, Z.Y. Zhang, Y. Yang, W.W. Cheng, X.Y. Wang, Z.S. Chen, Z. J. Wang, W.K. Hu, ROS-targeting heterojunction-integrated GelMA microneedles for photo-responsive antioxidative action and accelerated diabetic wound healing, Theranostics 15 (2025) 9987–10006, https://doi.org/10.7150/thno.120879.

[117] Y. Li, R. Fu, Z. Duan, C. Zhu, D. Fan, Construction of multifunctional hydrogel based on the tannic acid-metal coating decorated MoS_2 dual nanozyme for bacteria-infected wound healing, Bioactive Mater. 9 (2022) 461–474, https://doi.org/10.1016/j.bioactmat.2021.07.023.

[118] Y. Li, R. Fu, Z. Duan, C. Zhu, D. Fan, Injectable hydrogel based on defect-rich multi-nanozymes for diabetic wound healing via an oxygen self-supplying cascade reaction, Small 18 (2022) 2200165, https://doi.org/10.1002/smll.202200165.

[119] Z. Li, Y. Zhao, H. Huang, C. Zhang, H. Liu, Z. Wang, M. Yi, N. Xie, Y. Shen, X. Ren, J. Wang, J. Wang, A nanozyme-immobilized hydrogel with endogenous ROS-scavenging and oxygen generation abilities for significantly promoting oxidative diabetic wound healing, Adv. Healthcare Mater. 11 (2022) 2201524, https://doi.org/10.1002/adhm.202201524.

[120] Z.G. Li, X.T. Fan, Z. Luo, X.J. Loh, Y.D. Ma, E.Y. Ye, Y.L. Wu, C.B. He, Z.B. Li, Nanoenzyme-chitosan hydrogel complex with cascade catalytic and self-reinforced antibacterial performance for accelerated healing of diabetic wounds, Nanoscale 14 (2022) 14970–14983, https://doi.org/10.1039/d2nr04171e.

[121] Z. Li, X. Fan, Z. Luo, X.J. Loh, Y. Ma, E. Ye, Y.-L. Wu, C. He, Z. Li, Nanoenzyme–chitosan hydrogel complex with cascade catalytic and self-reinforced antibacterial performance for accelerated healing of diabetic wounds, Nanoscale 14 (2022) 14970–14983, https://doi.org/10.1039/d2nr04171e.

[122] Y. Pu, P. Wang, R. Yang, X. Tan, T. Shi, J. Ma, W. Xue, B. Chi, Bio-fabricated nanocomposite hydrogel with ROS scavenging and local oxygenation accelerates diabetic wound healing, J. Mater. Chem. B 10 (2022) 4083–4095, https://doi.org/10.1039/d2tb00343k.

[123] Q. Li, M. Dong, Q. Han, Y. Zhang, D. Yang, D. Wei, Y. Yang, Enhancing diabetic wound healing with a pH-responsive nanozyme hydrogel featuring multi-enzyme-like activities and oxygen self-supply, J. Control. Release 365 (2024) 905–918, https://doi.org/10.1016/j.jconrel.2023.12.015.

[124] S. Jiang, D. Xie, Z. Hu, H. Song, P. Tang, Y. Jin, J. Xia, Y. Ji, Y. Xiao, S. Chen, Q. Fu, J. Dai, Enhanced diabetic wound healing with injectable hydrogel containing self-assembling nanozymes, J. Control. Release 372 (2024) 265–280, https://doi.org/10.1016/j.jconrel.2024.06.040.

[125] F. Cheng, S. Wang, H. Zheng, H. Shen, L. Zhou, Z. Yang, Q. Li, Q. Zhang, H. Zhang, Ceria nanoenzyme-based hydrogel with antiglycative and antioxidative performance for infected diabetic wound healing, Small Methods 6 (2022) 2200949, https://doi.org/10.1002/smtd.202200949.

[126] S. Wang, Y. Zhang, F. Sun, K. Xi, Z. Sun, X. Zheng, F. Guo, H. Zhong, M. Yang, Y. Shao, B. Huang, M. Dong, S. Ni, L. Sun, Catalase-like nanozymes combined with hydrogel to facilitate wound healing by improving the microenvironment of diabetic ulcers, Mater. Des. 225 (2023) 111557, https://doi.org/10.1016/j.matdes.2022.111557.

[127] Z. Zhou, X. Mei, K. Hu, M. Ma, Y. Zhang, Nanohybrid double network hydrogels based on a platinum nanozyme composite for antimicrobial and diabetic wound healing, ACS Appl. Mater. Interfaces 15 (2023) 17612–17626, https://doi.org/10.1021/acsami.3c00459.

[128] Y. Peng, D. He, X. Ge, Y. Lu, Y. Chai, Y. Zhang, Z. Mao, G. Luo, J. Deng, Y. Zhang, Construction of heparin-based hydrogel incorporated with $Cu_{5.4}O$ ultrasmall nanozymes for wound healing and inflammation inhibition, Bioactive Mater. 6 (2021) 3109–3124, https://doi.org/10.1016/j.bioactmat.2021.02.006.

[129] Z. Jia, X. Lv, Y. Hou, K. Wang, F. Ren, D. Xu, Q. Wang, K. Fan, C. Xie, X. Lu, Mussel-inspired nanozyme catalyzed conductive and self-setting hydrogel for adhesive and antibacterial bioelectronics, Bioactive Mater. 6 (2021) 2676–2687, https://doi.org/10.1016/j.bioactmat.2021.01.033.

[130] R. Wang, S. Xu, M. Zhang, W. Feng, C. Wang, X. Qiu, J. Li, W. Zhao, Multifunctional chitosan-based hydrogels loaded with iridium nanoenzymes for skin wound repair, Carbohydr. Polym. 342 (2024) 122325, https://doi.org/10.1016/j.carbpol.2024.122325.

[131] L. Shang, Y. Yu, Y. Jiang, X. Liu, N. Sui, D. Yang, Z. Zhu, Ultrasound-Augmented multienzyme-like nanozyme hydrogel spray for promoting diabetic wound healing, ACS Nano 17 (2023) 15962–15977, https://doi.org/10.1021/acsnano.3c04134.

[132] Y. Yang, M. Li, G. Pan, J. Chen, B. Guo, Multiple stimuli-responsive nanozyme-based cryogels with controlled NO release as self-adaptive wound dressing for infected wound healing, Adv. Funct. Mater. 33 (2023) 2214089, https://doi.org/10.1002/adfm.202214089.

[133] X. Yu, X. Fu, J. Yang, L. Chen, F. Leng, Z. Yang, C. Yu, Glucose/ROS cascade-responsive ceria nanozymes for diabetic wound healing, Mater. Today Bio 15 (2022) 100308, https://doi.org/10.1016/j.mtbio.2022.100308.
[134] Y. Yuan, H. Zhao, X. Yin, D. Wang, X. Mei, P. Zhang, Alloy nanozyme-reinforced hyaluronic acid-based hydrogel with wound environment-responsive properties for synergistically accelerating infectious wound healing, Int. J. Biol. Macromol. 269 (2024) 131896, https://doi.org/10.1016/j.ijbiomac.2024.131896.
[135] F. Li, Y. Du, Y. Zheng, Y. Liu, X. Zhu, Y. Cui, Y. Yang, Q. Wang, D. Wang, Microenvironment-responsive MOF nanozymes armored cryogels promoted wound healing via rapid hemostasis, infection elimination and angiogenesis, J. Control. Release 384 (2025) 113838, https://doi.org/10.1016/j.jconrel.2025.113838.
[136] H. Li, Y. Wang, X. Che, L. Guo, L. Huang, X. Li, W. Gao, A novel pH/ROS dual responsive engineering hydrogels based on poly(tannic acid)-assisted surface deposition of nano-enzymes with efficient antibacterial and antioxidant activity for diabetic wound healing, Chem. Eng. J. 496 (2024) 153370, https://doi.org/10.1016/j.cej.2024.153370.
[137] S. Zhao, W. Guo, G. Yang, P. Hu, Y. Liu, L. Chen, S. Ning, X. Cao, Y. Pan, J. Shi, W. Jiang, D. Lu, H. Huang, Dual-responsive glucose/pH degradable nanozyme hydrogel with cascade catalytic antibacterial performance for infected diabetic wound treatment, Nano Today 66 (2026) 102906, https://doi.org/10.1016/j.nantod.2025.102906.
[138] Y.H. Chen, B. Yuan, Z.X. Yang, S.F. Yan, K.X. Ren, Q.M. Pi, Y. Liu, J.B. Yin, Catalase-like nanozyme-hybrid hydrogels utilizing endogenous ROS as an oxygen source to synergically regulate oxidative stress and hypoxia for enhanced diabetic wound healing, Biomacromolecules 26 (2025) 1672–1685, https://doi.org/10.1021/acs.biomac.4c01481.
[139] Y. Yang, D. Ding, C. Huang, X. Ding, T. Wang, M. Zhuo, H. Wang, S. Kai, N. Cheng, Development of an aminoguanidine hybrid hydrogel composites with hydrogen and oxygen supplying performance to boost infected diabetic wound healing, J. Colloid Interface Sci. 691 (2025) 137401, https://doi.org/10.1016/j.jcis.2025.137401.
[140] J. He, Z. Li, J. Chen, J. Wang, L. Qiao, B. Guo, J. Hu, NIR/glucose stimuli-responsive multifunctional smart hydrogel wound dressing with NO/O_2 dual gas-releasing property promotes infected diabetic wound healing, Chem. Eng. J. 492 (2024) 152249, https://doi.org/10.1016/j.cej.2024.152249.
[141] N. Jin, Y. Yu, L. Hu, C. Guo, N. Liu, F. Cheng, D. Hu, G. Zhang, S. Ye, Glucose-responsive and NIR-photothermal COF nano-enzymatic hydrogel spray for diabetic wound healing: Integrating ROS scavenging, hypoglycemic, and antimicrobial capabilities to amplify healing efficiency, Chem. Eng. J. 517 (2025) 164486, https://doi.org/10.1016/j.cej.2025.164486.
[142] X. Wei, Z. Zheng, M. Liu, Z. Yang, E. Xie, J. Lin, Y. Gao, R. Tan, Z. She, J. Ma, L. Yang, Enzyme-responsive nanospheres target senescent cells for diabetic wound healing by employing chemodynamic therapy, Acta Biomater. 172 (2023) 407–422, https://doi.org/10.1016/j.actbio.2023.10.015.
[143] J. Wang, H. Zhang, S. Hu, L. Ma, A MMP9-responsive nanozyme hydrogel to promote diabetic wound healing by reconstructing the balance of pro-inflammation and anti-inflammation, J. Mater. Chem. B 13 (2025) 8083–8093, https://doi.org/10.1039/d4tb02857k.
[144] Y. Hu, H. Li, X. Lv, Y. Xu, Y. Xie, L. Yuwen, Y. Song, S. Li, J. Shao, D. Yang, Stimuli-responsive therapeutic systems for the treatment of diabetic infected wounds, Nanoscale 14 (2022) 12967–12983, https://doi.org/10.1039/d2nr03756d.
[145] G. Wang, W. Wang, Z. Chen, T. Hu, L. Tu, X. Wang, W. Hu, S. Li, Z. Wang, Photothermal microneedle patch loaded with antimicrobial peptide/MnO_2 hybrid nanoparticles for chronic wound healing, Chem. Eng. J. 482 (2024) 148938, https://doi.org/10.1016/j.cej.2024.148938.
[146] T. Wang, D. Dong, T. Chen, J. Zhu, S. Wang, W. Wen, X. Zhang, H. Tang, J. Liang, S. Wang, H. Xiong, Acidity-responsive cascade nanoreactor based on metal-nanozyme and glucose oxidase combination for starving and photothermal-enhanced chemodynamic antibacterial therapy, Chem. Eng. J. 446 (2022) 137172, https://doi.org/10.1016/j.cej.2022.137172.
[147] C. Zhang, P. Zhou, S. Li, X. Zhang, Z. Xia, Z. Rao, X. Ma, Y. Hu, Y. Chen, J. Chen, Y. He, G. Tao, R. Cai, From hemostasis to angiogenesis: a self-healing hydrogel loaded with copper sulfide-based nanoenzyme for whole-process management of diabetic wounds, Biomater. Res. 29 (2025), https://doi.org/10.34133/bmr.0208.
[148] W. Chen, F. Yang, X. Chen, C. Jin, N. Yin, M. Sun, Y. Zheng, K. Yang, Z. Wang, D. He, L. Wang, L. Hai, Ultrasmall self-cascade bimetallic Au_2Pd_3 nanozymes encapsulated hydrogel microneedles for photothermal-augmented nanocatalytic therapy of diabetic wound infections, ACS Appl. Mater. Interfaces 17 (2025) 53295–53311, https://doi.org/10.1021/acsami.5c14298.
[149] X. Huang, S. Cheng, F. Gong, X. Yang, Z. Pei, X. Cui, G. Hou, N. Yang, Z. Han, Y. Chen, Y. Cheng, L. Cheng, A closed-loop patch based on bioinspired infection sensor for wound management, Nano Today 57 (2024) 102400, https://doi.org/10.1016/j.nantod.2024.102400.
[150] Y. Chen, L. Zhao, X. Song, J. Zhang, M. Zhang, D. Yang, A. Jiao, Glucose-Responsive injectable hydrogel for enhanced sonodynamic-antibacterial cascade therapy of diabetic abscess, Adv. Funct. Mater., n/a (2025) e14543, doi:10.1002/adfm.202514543.
[151] F.H. Yang, J.Q. Lv, X.R. Gao, K.X. Zhang, Y. Wang, L.T. Huang, Z. Yang, W. Huang, Hydrogel-Powered adversity transformation: on-demand ultrasonic switching strategy for accelerating diabetic wound healing, ACS Nano (2025), https://doi.org/10.1021/acsnano.5c14917.
[152] X. Fan, Z. Li, M. Yue, M. Chen, K. Mao, Y. Liu, W. Jiang, H. Li, Adhesive two-dimensional bimetallic organic framework nanozymes for regulating inflammation and eradicating bacteria in periodontal disease, Chem. Eng. J. 517 (2025) 164263, https://doi.org/10.1016/j.cej.2025.164263.
[153] S. Zhang, F. Ding, Y. Liu, X. Ren, Glucose-responsive biomimetic nanoreactor in bacterial cellulose hydrogel for antibacterial and hemostatic therapies, Carbohydr. Polym. 292 (2022) 119615, https://doi.org/10.1016/j.carbpol.2022.119615.
[154] Y. Wu, X. Xie, G. Luo, J. Xie, X. Ye, W. Gu, A. Mo, Z. Qian, C. Zhou, J. Liao, Photothermal sensitive nanocomposite hydrogel for infectious bone defects, Bone Res. 13 (2025) 22, https://doi.org/10.1038/s41413-024-00377-x.
[155] Y. Peng, Y. Guo, X. Ge, Y. Gong, Y. Wang, Z. Ou, G. Luo, R. Zhan, Y. Zhang, Construction of programmed time-released multifunctional hydrogel with antibacterial and anti-inflammatory properties for impaired wound healing, J. Nanobiotechnol. 22 (2024) 126, https://doi.org/10.1186/s12951-024-02390-y.
[156] D. Yu, L. Chen, T. Yan, Y. Zhang, X. Sun, G. Lv, S. Zhang, Y. Xu, C. Li, Enhancing infected diabetic wound healing through multifunctional nanocomposite-loaded microneedle patch: inducing multiple regenerative sites, Adv. Healthcare Mater. 13 (2024) 2301985, https://doi.org/10.1002/adhm.202301985.
[157] Q. Tang, Y. Tan, S. Leng, Q. Liu, L. Zhu, C. Wang, Cupric-polymeric nanoreactors integrate into copper metabolism to promote chronic diabetic wounds healing, Mater. Today Bio 26 (2024) 101087, https://doi.org/10.1016/j.mtbio.2024.101087.
[158] D. Chao, Q. Dong, Z. Yu, D. Qi, M. Li, L. Xu, L. Liu, Y. Fang, S. Dong, Specific nanodrug for diabetic chronic wounds based on antioxidase-mimicking MOF-818 nanozymes, J. Am. Chem. Soc. 144 (2022) 23438–23447, https://doi.org/10.1021/jacs.2c09663.
[159] Y. Zhou, C. Liu, Y. Yu, M. Yin, J. Sun, J. Huang, N. Chen, H. Wang, C. Fan, H. Song, An organelle-specific nanozyme for diabetes care in genetically or diet-induced models, Adv. Mater. 32 (2020) 2003708, https://doi.org/10.1002/adma.202003708.
[160] Y. Yang, J. Wang, S. Huang, M. Li, J. Chen, D. Pei, Z. Tang, B. Guo, Bacteria-responsive programmed self-activating antibacterial hydrogel to remodel regeneration microenvironment for infected wound healing, Natl. Sci. Rev. 11 (2024) nwae044, https://doi.org/10.1093/nsr/nwae044.
[161] W. Xu, Z. Zhu, Z. Tan, Z. Fan, S. Wei, K. Yang, L. Yuwen, W.J. Yang, E.-T. Kang, L. Wang, Metal-Free nanozyme-hydrogel enabled by conductive polymer nanofibers for multimodal antibacterial therapy, Chem. Mater. 37 (2025) 2106–2124, https://doi.org/10.1021/acs.chemmater.4c02480.
[162] L. Ji, Y. Xiao, K. Xu, X. Wu, O.W. Ojo, L. Diao, K. Mequanint, W. Zhong, P. Zhao, M. Xing, G. Lyu, Smart bandage with multi-sensor system for wound healing and microenvironment monitoring, Chem. Eng. J. 507 (2025) 160509, https://doi.org/10.1016/j.cej.2025.160509.
[163] F. Cui, W. Fu, Q. Chang, J. Wang, Y. Xie, X. Deng, ROS-Modulating bio-heterojunction nanosheets for infected wound healing via nanozyme activity, Small 21 (2025) 2412441, https://doi.org/10.1002/smll.202412441.
[164] L. Wang, G. Chen, L. Fan, H. Chen, Y. Zhao, L. Lu, L. Shang, Biomimetic enzyme cascade structural color hydrogel microparticles for diabetic wound healing management, Adv. Sci. 10 (2023) 2206900, https://doi.org/10.1002/advs.202206900.
[165] Z. Lu, K. Tan, S. Xiang, Y. Zhang, F. Luo, X. Liu, X. Zhao, L. Ouyang, Peptide loaded self-healing hydrogel promotes diabetic skin wound healing through macrophage orchestration and inflammation inhibition, Mater. Today Bio 32 (2025) 101690, https://doi.org/10.1016/j.mtbio.2025.101690.
[166] X. Ren, X. Wang, J. Yang, X. Zhang, B. Du, P. Bai, L. Li, R. Zhang, Multi-Enzyme-Based superabsorbent hydrogel for self-enhanced NIR-II photothermal-catalytic antibacterial therapy, Adv. Healthcare Mater. 13 (2024) 2303537, https://doi.org/10.1002/adhm.202303537.
[167] Y. Feng, L. Su, Z. Zhang, Y. Chen, M.R. Younis, D. Chen, J. Xu, C. Dong, Y. Que, C. Fan, Y. Jiao, H. Zhu, J. Chang, Z. Dong, C. Yang, pH-Responsive wound dressing based on biodegradable CuP nanozymes for treating infected and diabetic wounds, ACS Appl. Mater. Interfaces 16 (2024) 95–110, https://doi.org/10.1021/acsami.3c12997.
[168] Y. Shao, X. Zhou, S. Zhou, J. Long, L. Jin, X. Shi, L. Zhou, Y. Zhang, D. Fan, Injectable DMM/GelMA hydrogel for diabetic wound healing via regulating mitochondrial metabolism and macrophage repolarization, Colloids Surf. B: Biointerfaces 248 (2025) 114488, https://doi.org/10.1016/j.colsurfb.2024.114488.
[169] T. Hao, M. Qian, Y. Zhang, Q. Liu, A.C. Midgley, Y. Liu, Y. Che, J. Hou, Q. Zhao, An injectable dual-function hydrogel protects against myocardial ischemia/reperfusion injury by modulating ROS/NO disequilibrium, Adv. Sci. 9 (2022) 2105408, https://doi.org/10.1002/advs.202105408.
[170] G. Xiang, B. Wang, W. Zhang, Y. Dong, J. Tao, A. Zhang, R. Chen, T. Jiang, X. Zhao, A Zn-MOF-GOx-based cascade nanoreactor promotes diabetic infected wound healing by NO release and microenvironment regulation, Acta Biomater. 182 (2024) 245–259, https://doi.org/10.1016/j.actbio.2024.05.015.
[171] C. Pu, Y. Wang, H. Xiang, J. He, Q. Sun, Y. Yong, L. Chen, K. Jiang, H. Yang, Y. Li, Zinc-based polyoxometalate nanozyme functionalized hydrogels for optimizing the hyperglycemic-immune microenvironment to promote diabetic wound regeneration, J. Nanobiotechnol. 22 (2024) 611, https://doi.org/10.1186/s12951-024-02840-7.
[172] C. Wu, L. Long, Y. Zhang, Y. Xu, Y. Lu, Z. Yang, Y. Guo, J. Zhang, X. Hu, Y. Wang, Injectable conductive and angiogenic hydrogels for chronic diabetic wound treatment, J. Control. Release 344 (2022) 249–260, https://doi.org/10.1016/j.jconrel.2022.03.014.
[173] X. Zhang, S. Leng, X. Liu, X. Hu, Y. Liu, X. Li, Q. Feng, W. Guo, N. Li, Z. Sheng, S. Wang, J. Peng, Ion channel Piezo1 activation aggravates the endothelial

dysfunction under a high glucose environment, Cardiovasc. Diabetol. 23 (2024) 150, https://doi.org/10.1186/s12933-024-02238-7.
[174] X. Zhang, F. Ning, Y. Li, J. Lu, Y. He, C. Feng, C.-M. Dong, Pluripotent polysaccharide coordinated hydrogels remodel inflammation, neovascularization and reepithelization for efficient diabetic wound prohealing, J. Control. Release 377 (2025) 37–53, https://doi.org/10.1016/j.jconrel.2024.11.027.
[175] H. Wu, F. Li, W. Shao, J. Gao, D. Ling, Promoting angiogenesis in oxidative diabetic wound microenvironment using a nanozyme-reinforced self-protecting hydrogel, ACS Central Sci. 5 (2019) 477–485, https://doi.org/10.1021/acscentsci.8b00850.
[176] S. Chen, J. Chen, X. Wang, Z. Yang, J. Lan, L. Wang, B. Ji, Y. Yuan, Glucose-activated self-cascade antibacterial and pro-angiogenesis nanozyme-functionalized chitosan-arginine thermosensitive hydrogel for chronic diabetic wounds healing, Carbohydr. Polym. 348 (2025) 122894, https://doi.org/10.1016/j.carbpol.2024.122894.
[177] D.H. Ramos-Rodriguez, J.K. Leach, Decellularized cell-secreted extracellular matrices as biomaterials for tissue engineering, Small Science 5 (2025) 2400335, https://doi.org/10.1002/smsc.202400335.
[178] Y. Ma, X. Lai, X. Luo, Z. Luo, L. Mao, H. Zhu, X. Fan, J. Kong, Y.-L. Wu, Z. Li, C. He, Multifunctional silver-enzyme nanogels assembly with efficient trienzyme cascades for synergistic diabetic wound healing, Adv. Funct. Mater. 34 (2024) 2405644, https://doi.org/10.1002/adfm.202405644.
[179] J. Gan, C. Liu, H. Li, S. Wang, Z. Wang, Z. Kang, Z. Huang, J. Zhang, C. Wang, D. Lv, L. Dong, Accelerated wound healing in diabetes by reprogramming the macrophages with particle-induced clustering of the mannose receptors, Biomaterials 219 (2019) 119340, https://doi.org/10.1016/j.biomaterials.2019.119340.
[180] D.S. Rudra, U. Pal, N. Chowdhury, N.C. Maiti, A. Bagchi, S. Swarnakar, Omeprazole prevents stress induced gastric ulcer by direct inhibition of MMP-2/TIMP-3 interactions, Free Radic. Biol. Med. 181 (2022) 221–234, https://doi.org/10.1016/j.freeradbiomed.2022.02.007.
[181] J. Bi, H. Wang, H. Luo, C. Qian, J. Zhou, X. Li, X. Qi, S. Shen, J. Cao, Self-healing hydrogels loaded with selenium nanoparticles/chitosan/cellulose nanofibers as carriers of mesenchymal stem cells for diabetic wound healing, Int. J. Biol. Macromol. 322 (2025) 146905, https://doi.org/10.1016/j.ijbiomac.2025.146905.
[182] Q. Xuan, J. Cai, Y. Gao, X. Qiao, T. Jin, M. Peydayesh, J. Zhou, Q. Sun, L. Zhan, B. Liu, P. Wang, H. Li, C. Chen, R. Mezzenga, Amyloid-Templated ceria nanozyme reinforced microneedle for diabetic wound treatments, Adv. Mater. 37 (2025), https://doi.org/10.1002/adma.202417774.
[183] L. Ge, J. Ling, G. Cao, X.K. Ouyang, N. Wang, Nanozyme doped chitosan hydrogel driven by glucose oxidase for dual regulation of ROS homeostasis and macrophage reprogramming in diabetic wound healing, Carbohydr. Polym. (2025) 124534, https://doi.org/10.1016/j.carbpol.2025.124534.
[184] X. Qi, Y. Xiang, Y. Li, J. Wang, Y. Chen, Y. Lan, J. Liu, J. Shen, An ATP-activated spatiotemporally controlled hydrogel prodrug system for treating multidrug-resistant bacteria-infected pressure ulcers, Bioactive Mater. 45 (2025) 301–321, https://doi.org/10.1016/j.bioactmat.2024.11.029.
[185] H. Kim, S.Y. Wang, G. Kwak, Y. Yang, I.C. Kwon, S.H. Kim, Exosome-Guided phenotypic switch of M1 to M2 macrophages for cutaneous wound healing, Adv. Sci. 6 (2019) 1900513, https://doi.org/10.1002/advs.201900513.
[186] G. Li, Y. Huang, L. Zhao, B. Yang, J. Guo, J. Hu, J. Wang, H. Wang, B. Liu, A. Zhang, F. Sun, Q. Luo, Targeting and microenvironment-activated nanoreactor for diabetic chronic wound healing via multienzyme cascade reactions, ACS Appl. Mater. Interfaces 16 (2024) 6315–6326, https://doi.org/10.1021/acsami.3c12427.
[187] Y.-X. Xue, Y.-J. Chen, M.-Z. Qin, F.-F. Shang, Y.-T. Lu, Y.-H. Sun, L.-G. Bian, A. Zhang, Y. Yu, C.-y. Ding, Microglial STING activation promotes neuroinflammation and pathological changes in experimental mice with intracerebral haemorrhage, Acta Pharmacol. Sin., 46 (2025) 2376-2392, doi:https://doi.org/10.1038/s41401-025-01540-8.
[188] X. Liu, M. Shen, T. Bing, X. Zhang, Y. Li, Q. Cai, X. Yang, Y. Yu, A bioactive injectable hydrogel regulates tumor metastasis and wound healing for melanoma via NIR-light triggered hyperthermia, Adv. Sci. 11 (2024) 2402208, https://doi.org/10.1002/advs.202402208.
[189] S. He, Z. Li, L. Wang, N. Yao, H. Wen, H. Yuan, J. Zhang, Z. Li, C. Shen, A nanoenzyme-modified hydrogel targets macrophage reprogramming-angiogenesis crosstalk to boost diabetic wound repair, Bioactive Mater. 35 (2024) 17–30, https://doi.org/10.1016/j.bioactmat.2024.01.005.
[190] Z. Li, C. Zhang, L. Wang, Q. Zhang, Y. Dong, X. Sha, B. Wang, Z. Zhu, W. Wang, Y. Wang, Y. Zhou, Y. Zhang, Chitooligosaccharides promote diabetic wound healing by mediating fibroblast proliferation and migration, Sci. Rep. 15 (2025) 556, https://doi.org/10.1038/s41598-024-84398-w.
[191] X. Zhu, S. Mao, Y. Yang, X. Liu, Q. Liu, N. Zhang, Y. Yang, Y. Li, M. Gao, J. Bao, W. Li, Y. Li, Biomimetic topological micropattern arrays regulate the heterogeneity of cellular fates in lung fibroblasts between fibrosis and invasion, ACS Nano 19 (2025) 580–599, https://doi.org/10.1021/acsnano.4c11113.
[192] Q. Shen, J. Chen, T. Wang, Y. Yang, C. Huang, W. Zhang, G. Tian, N. Cheng, S. Kai, Dual functional photocatalytic hydrogel coupled with hydrogen evolution and glucose depletion for diabetic wound therapy, J. Colloid Interface Sci. 695 (2025) 137753, https://doi.org/10.1016/j.jcis.2025.137753.
[193] D. Mooney, P. Dankers, E. Roche, H. Wang, Engineering active materials for biomedical applications, Adv. Mater. 36 (2024) 2412651, https://doi.org/10.1002/adma.202412651.
[194] R. Paul, M. Rana, A. Gupta, T. Banerjee, S. Kumar Karmakar, A. Roy Chowdhury, Design of biomimetic porous scaffolds for bone tissue engineering, Transp. Porous Media 151 (2024) 1453–1473, https://doi.org/10.1007/s11242-024-02082-z.
[195] D. Wan, J. Yang, X. Cui, N. Ma, Z. Wang, Y. Li, P. Li, Y. Zhang, Z.-H. Lin, S. Sang, H. Zhang, Human body-based self-powered wearable electronics for promoting wound healing driven by biomechanical motions, Nano Energy 89 (2021) 106465, https://doi.org/10.1016/j.nanoen.2021.106465.
[196] J. Peng, C. Liu, M. Mo, Y. Huang, Y. Lu, M. Xiao, X. Zhao, Q. Ruan, H. Ti, Construction of multifunctional hydrogel containing pH-responsive gold nanozyme for bacteria-infected wound healing, Int. J. Biol. Macromol. 283 (2024) 137746, https://doi.org/10.1016/j.ijbiomac.2024.137746.
[197] X. Sun, X. Chen, S. Wang, H. Gu, H. Bao, Z. Ning, X. Feng, Y. Chen, Oxygenous and biofilm-targeted nanosonosensitizer anchored with Pt nanozyme and antimicrobial peptide in the gelatin/sodium alginate hydrogel for infected diabetic wound healing, Int. J. Biol. Macromol. 293 (2025) 139356, https://doi.org/10.1016/j.ijbiomac.2024.139356.
[198] X. Han, S. Chen, Z. Cai, Y. Zhu, W. Yi, M. Guan, B. Liao, Y. Zhang, J. Shen, W. Cui, D. Bai, A diagnostic and therapeutic hydrogel to promote vascularization via blood sugar reduction for wound healing, Adv. Funct. Mater. 33 (2023) 2213008, https://doi.org/10.1002/adfm.202213008.
[199] Q. Wang, W. Qiu, H. Liu, X. Li, X. Qin, X. Wang, J. Yu, B. Li, F. Li, L. Huang, D. Wu, Conductive hydrogel dressings based on cascade reactions with photothermal effect for monitoring and treatment of diabetic wounds, Compos. Part B 242 (2022) 110098, https://doi.org/10.1016/j.compositesb.2022.110394.
[200] X. Yang, X. Duan, L. Zhu, X. Zhao, S. Zhang, S. Ni, S. Wu, Z. Han, W. Deng, D. Sun, Q. Chen, W. Wu, Carbon-Dot-Zn^{2+} assembly hybrid multifunctional hydrogels for synergistically monitoring local glucose and repairing diabetic wound, ACS Appl. Mater. Interfaces 17 (2025) 38874–38889, http://10.1021/acsami.5c06293.