Bioactive Materials 44 (2025) 131–151

Contents lists available at ScienceDirect

Bioactive Materials

journal homepage: www.keaipublishing.com/en/journals/bioactive-materials

Review article

Glucose oxidase: An emerging multidimensional treatment option for diabetic wound healing

Yuheng Liao [1], Zhenhe Zhang [1], Yanzhi Zhao [1], Shengming Zhang [1], Kangkang Zha, Lizhi Ouyang, Weixian Hu, Wu Zhou [**], Yun Sun [***], Guohui Liu [*]

Wuhan Union Hospital of Tongji Medical College of Huazhong University of Science and Technology, No. 1277 Jiefang Avenue, Jianghan District, Wuhan, Hubei, 430022, China

ARTICLE INFO

Keywords:
Glucose oxidase
Wound healing
Diabetes
Nanozyme

ABSTRACT

The healing of diabetic skin wounds is a complex process significantly affected by the hyperglycemic environment. In this context, glucose oxidase (GOx), by catalyzing glucose to produce gluconic acid and hydrogen peroxide, not only modulates the hyperglycemic microenvironment but also possesses antibacterial and oxygen-supplying functions, thereby demonstrating immense potential in the treatment of diabetic wounds. Despite the growing interest in GOx-based therapeutic strategies in recent years, a systematic summary and review of these efforts have been lacking. To address this gap, this review article outlines the advancements in the application of GOx and GOx-like nanozymes in the treatment of diabetic wounds, including reaction mechanisms, the selection of carrier materials, and synergistic therapeutic strategies such as multi-enzyme combinations, microneedle structures, and gas therapy. Finally, the article looks forward to the application prospects of GOx in aiding the healing of diabetic wounds and the challenges faced in translating these innovations to clinical practice. We sincerely hope that this review can provide readers with a comprehensive understanding of GOx-based diabetic treatment strategies, facilitate the rigorous construction of more robust multifunctional therapeutic systems, and ultimately benefit patients with diabetic wounds.

1. Introduction

As the largest organ of the human body, the skin has a strong barrier function that can effectively resist the attack of external harmful factors. When the skin is damaged, the body rapidly initiates a complex repair mechanism to restore skin integrity through the hemostatic, inflammatory, proliferative, and remodeling phases by the synergistic action of immune cells, fibroblasts, and other cells (Fig. 1A) [1]. However, in diabetic patients, the hyperglycemic microenvironment significantly impairs the wound repair process. The hyperglycemic milieu imparts distinctive pathological characteristics to wounds, encompassing compromised immune function, peripheral neuropathy, secondary bacterial colonization, and an exaggerated inflammatory response (Fig. 1B) [2,3]. These factors collectively impede the processes of wound neovascularization, granulation tissue formation, and re-epithelialization, thereby significantly disrupting the normal wound healing trajectory [4]. The accumulation of advanced glycation end products (AGEs) represents a pivotal biochemical alteration within the diabetic skin milieu [5]. AGEs have been shown to suppress the proliferation of human dermal fibroblasts and mesenchymal stem cells, while simultaneously promoting apoptosis through the activation of the receptor for advanced glycation end products (RAGE) [6]. Additionally, AGEs are known to trigger an escalation in reactive oxygen species (ROS) production, resulting in cellular membrane and endoplasmic reticulum damage, and perpetuating a state of chronic inflammation [7]. In both diabetic patients and relevant animal models, sensory neuropathy of the skin surface has been observed, characterized by diminished dendritic cell density and attenuated neuropeptide secretion [8]. This leads to a reduction in the release of chemokines and growth factors, which in turn impairs the physiological functions of mast cells,

Peer review under responsibility of KeAi Communications Co., Ltd.
* Corresponding author.
** Corresponding author.
*** Corresponding author.
E-mail addresses: 2016XH0120@hust.edu.cn (W. Zhou), 627224540@qq.com (Y. Sun), liuguohui@hust.edu.cn (G. Liu).
[1] These authors contributed equally to this article.

https://doi.org/10.1016/j.bioactmat.2024.10.006
Received 18 July 2024; Received in revised form 6 October 2024; Accepted 6 October 2024

endothelial cells, fibroblasts, and keratinocytes [3]. The chronic inflammation associated with diabetic wounds is further exacerbated by an increase in matrix metalloproteinases (MMPs) and a concurrent decrease in the secretion of tissue inhibitors of matrix metalloproteinases (TIMPs) [9]. The delicate balance between MMPs and TIMPs is crucial for the deposition and remodeling of the extracellular matrix (ECM) [9]. This balance also serves as a critical regulatory mechanism for apoptosis across various cell types, including neutrophils, fibroblasts, and vascular smooth muscle cells [10]. Consequently, the dysregulation of the MMP-TIMP equilibrium adversely impacts the inflammatory, proliferative, and remodeling phases of the wound healing process [10].

Epidemiologic studies have shown that 8.7 %–25 % of diabetic patients may experience diabetic foot ulcers during their lifetime, and these patients often face a high risk of amputation and recurrence [11,12]. Given that there are currently more than 463 million people with diabetes worldwide and this number is expected to climb to 700 million by 2045, it is foreseeable that the number of patients with diabetic trauma will further increase, creating a heavy economic burden and medical pressure on society [13]. Therefore, it is particularly urgent to develop effective strategies for the treatment of diabetic wounds.

The treatment of diabetic wounds has long been a serious challenge in clinical practice. Current clinical approaches to diabetic wound management encompass surgical debridement, application of dressings, negative pressure wound therapy, and hyperbaric oxygen therapy [14]. Despite these measures, the success rate of traditional interventions is suboptimal, with less than 50 % achieving complete healing, and they are often characterized by protracted treatment durations and substantial economic costs [15]. Healthcare professionals face formidable challenges in the management of diabetic wounds, particularly in addressing persistent bacterial infections and the vascular and neuropathic sequelae of chronic hyperglycemia [14]. Topical antibiotic therapy is frequently employed to counteract these infections. However, the swift proliferation of multidrug-resistant bacteria, coupled with the sluggish pace of new antibiotic development, has engendered a therapeutic dilemma. There is an imperative need for innovative strategies to

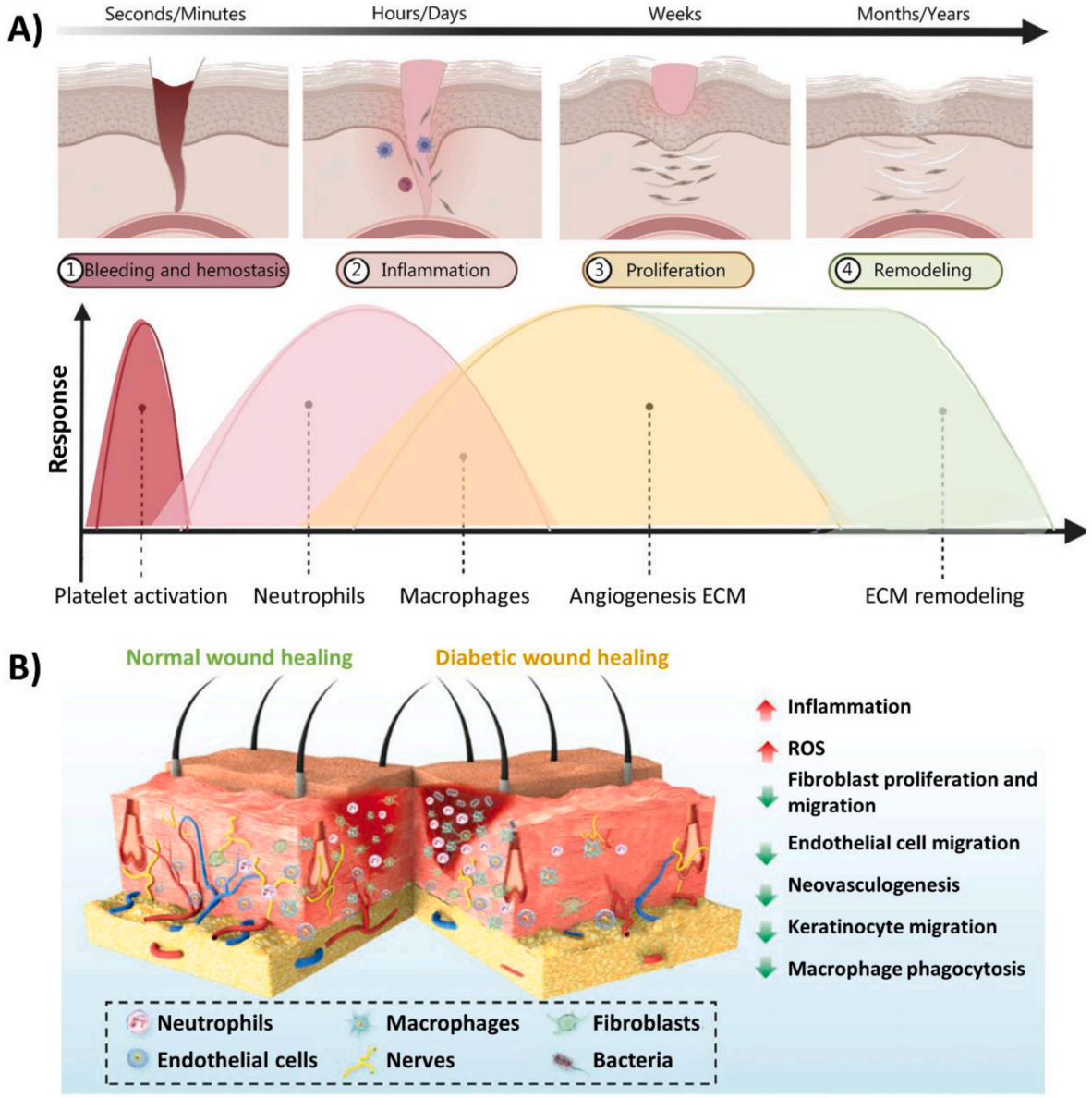

Fig. 1. Schematic illustration of the healing process of normal and diabetic wounds. A) Schematic diagram of the skin repair process. The four phases of trauma repair, hemostasis, inflammation, proliferation, and remodeling phases, occur in order and can overlap. Reproduced with permission [1]. Copyright 2023, BioMed Central. B) Healing differences between normal and diabetic wounds. Reproduced with permission [2]. Copyright 2023, John Wiley and Sons Ltd.

effectively treat infected wounds [14]. For the management of chronic hyperglycemia, insulin therapy is recognized as an efficacious intervention. Nonetheless, the long-term administration of insulin is not without consequence, as it can precipitate a range of complications, including edema, hypoglycemia, and obesity, which can significantly impact patient health [14]. Although treatments such as autografts, allografts, and xenografts have been viewed as potential solutions towards diabetic wound healing in theory, they are limited in practical application by factors such as immune rejection, limited sources, and high costs [16]. In recent years, with the deepening understanding of the diabetic wound microenvironment, scientists have begun to shift their research focus to the development of bioengineered scaffolds. Consequently, a series of biomaterials have been carefully designed and prepared with the aim of modulating pathological processes in diabetic wounds, such as inhibiting excessive inflammation, promoting angiogenesis, and enhancing anti-infection functions. Based on these biomaterials, researchers have proposed a range of innovative therapeutic strategies [17]. However, the most critical problem of diabetic wounds, high localized levels of glucose, remains a pressing scientific issue.

Glucose oxidase (GOx) is a natural enzyme that binds glucose and catalyzes its conversion to gluconic acid and hydrogen peroxide (H_2O_2), and is therefore considered a candidate for regulating the high-glucose microenvironment in diabetic wounds. By delivering GOx to the wound, glucose levels can be reduced in situ. In addition, the gluconic acid produced by the reaction activates the pH response system by lowering the local pH. Moreover, the produced H_2O_2 can also be used as a substrate for the Fenton reaction system, which further generates hydroxyl radicals for antimicrobial use. Thus, a series of multifunctional glucose oxidase-based drug delivery systems have been developed in recent years and have been found to be more effective in promoting diabetic wound healing in animal models.

With the advancement of nanotechnology, a number of metals have been found to have natural enzyme-like properties, hence the name nanozyme. Among them, ultra-small nanogold and platinum nanoparticles have been found to have GOx-like activity. Compared to natural enzymes, these nanozymes have the advantage of low cost and good stability. Given the high porosity, high specific surface area and compositional tunability of nanomaterials, the well-designed nanozyme systems exhibit unique multi-enzyme-like activities. These nanozyme systems not only possess GOx-like enzyme activity, catalase (CAT)-like activity and peroxidase (POD)-like enzyme activity, but also achieve multiple functions such as hypoglycemia, antimicrobial and oxygenation in diabetic wound treatment through their intrinsic cascade catalytic effect. Therefore, these nanozyme systems show great potential and application prospects in synergistic treatment of wounds.

In recent years, therapeutic strategies based on GOx and GOx-like nanozymes have been widely developed and applied in diabetic wound treatment. However, there has not yet been a comprehensive and systematic summary of this field. Aiming to fill this gap, this article first provides an in-depth elucidation of the reaction mechanism of GOx, followed by a detailed exploration of the current research status and potential applications of GOx and GOx-like nanozymes in wound healing. Subsequently, based on different carrier types, we detail the GOx-activated systems applied to diabetic wound therapy, covering a variety of innovative platforms such as hydrogels, metal-organic frameworks (MOF), supramolecular structures, and heterojunctions. On this basis, we also review GOx-based synergistic strategies for wound therapy, revealing the potential of these strategies in enhancing therapeutic efficacy and promoting diabetic wound healing. Finally, the article points out the challenges facing current research and looks forward to future directions, aiming to provide valuable guidance and insights for future research.

2. GOx's reaction mechanism and potential application in diabetic wound healing

2.1. GOx's catalytic reaction mechanism

GOx is a dimeric glycoprotein consisting of two identical 80 kDa polypeptide chain subunits and two non-covalently bound flavin adenine dinucleotides (FAD) [18]. The FAD cofactor acts as an electron carrier in the catalytic process. GOx efficiently catalyzes the oxidation of β-D-glucose to gluconic acid and hydrogen peroxide (H_2O_2) [19]. The catalytic reaction contains a reduction step and an oxidation step. Initially, in the reduction half-reaction, GOx catalyzes the oxidation of β-D-glucose to D-glucono-δ-lactone, which then hydrolyzes the product to gluconic acid, while the FAD of GOx is reduced to $FADH_2$. In the oxidation half-reaction, $FADH_2$ is re-oxidized by oxygen to form FAD and H_2O_2 (Fig. 2A) [20].

2.2. GOx's potential application in diabetic wound healing

The entire process of glucose catabolism by GOx (including consumption of glucose, oxygen and production of gluconic acid, H_2O_2) has clear or potential therapeutic implications in diabetic wounds, although the physiological effects of individual processes are controversial (Fig. 2B).

2.2.1. Glucose consumption

Notably, we believe that glucose consumption is the most important part of the GOx-catalyzed reaction. For instance, in cancer therapy, GOx is used to consume glucose and mediate starvation therapy due to the strong dependence of cancer cells on glucose [21,22]. Similarly, in diabetic trauma, the effect of GOx is more direct. A prolonged high-glucose environment is detrimental to skin wound healing in many ways, such as accumulation of advanced glycation end products, peripheral neuropathy, impaired ECM deposition, impaired angiogenesis and imbalance of immune regulation dominated by neutrophils, macrophages, and Tregs [5,6,23]. By catabolizing glucose in local tissues, GOx lowers catabolizes glucose in local tissues and lowers local glucose levels, which helps to rectify these unfavorable factors for wound healing. In addition, some researchers have suggested that bacteria urgently need glucose uptake to promote their rapid growth during skin infections, and thus GOx also mediates starvation therapy to inhibit bacterial growth [24].

2.2.2. Oxygen consumption

Vascular damage resulting from skin trauma typically induces localized hypoxia. Under physiological conditions, this localized hypoxia triggers an upregulation of hypoxia-inducible factor-1 alpha (HIF-1α) expression, which promotes cell proliferation and migration, thereby aiding in angiogenesis [25]. However, the heightened susceptibility to infection in diabetic wounds generates excessive oxidative stress, characterized by elevated levels of reactive oxygen species (ROS). Consequently, this overproduction of ROS can downregulate HIF-1α, angiopoietin-1, and angiopoietin-2, thereby impairing endothelial cell proliferation and migration, which are critical processes for effective wound healing [26]. In the field of oncology, the hypoxic characteristics of the local environment in malignant tumors can affect the activity of GOx, prompting researchers to focus on the oxygen-consuming behavior of GOx [27]. To address this issue, direct oxygen delivery or the use of nanozymes to catalyze the production of oxygen is often employed [19]. The catalytic reaction of GOx consumes oxygen, potentially exacerbating the hypoxia in diabetic wounds, which is a potential concern in wound healing but has not received adequate attention [28]. The difference in emphasis may stem from the fact that tumors, located within the body, derive almost all their oxygen from blood, whereas GOx used on the body surface in wounds can utilize oxygen from the external environment.

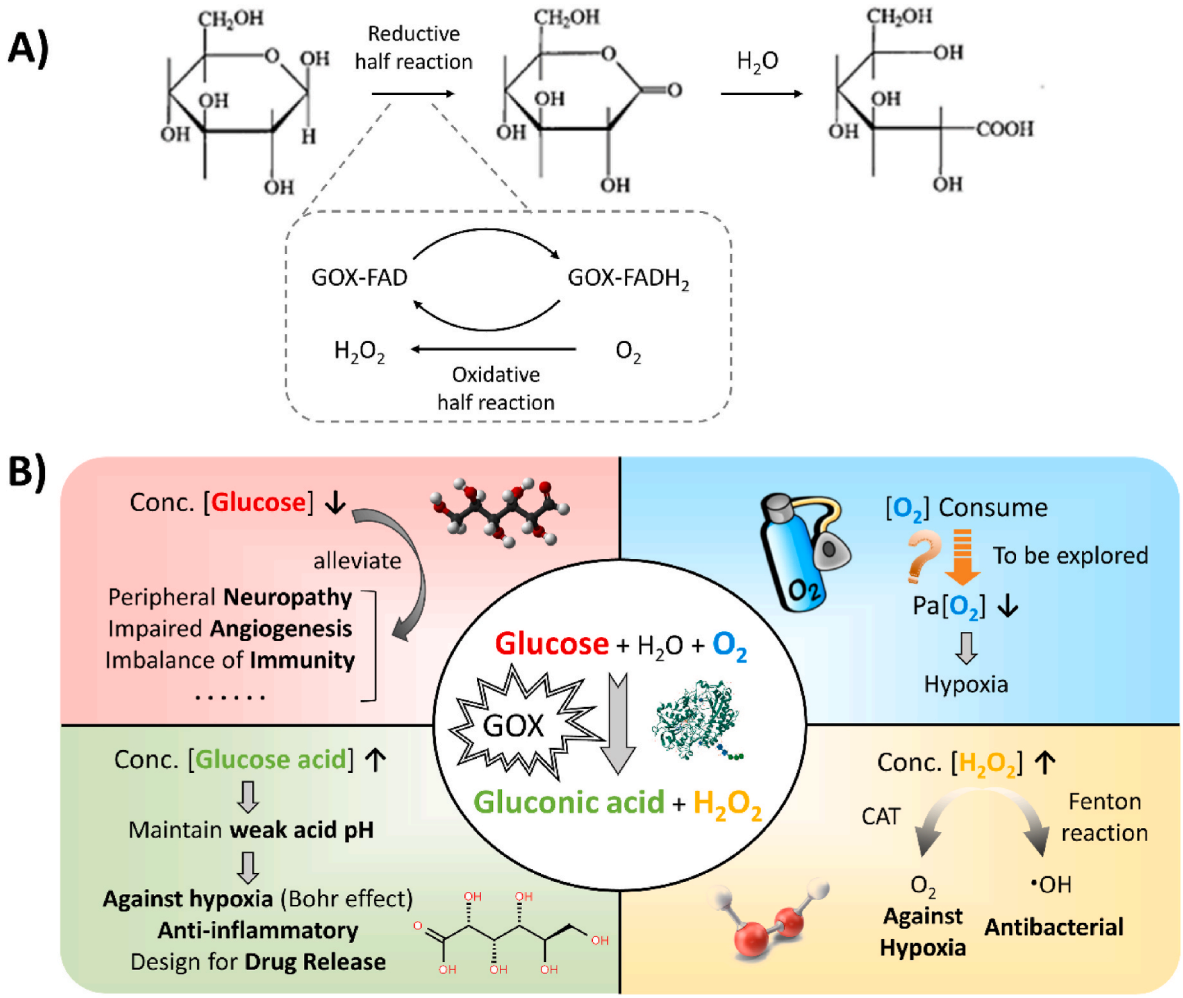

Fig. 2. Schematic representation of the catalytic reaction mechanism of GOx and its potential application in diabetic wound healing. A) Representation of the GOx reaction. Reproduced with permission [20]. Copyright 2009, Elsevier Inc. B) GOx-catalyzed reaction is closely linked to diabetes wound healing.

We believe that the oxygen-consuming behavior of GOx should also be given attention in the context of diabetic wound treatment. Meanwhile, it is crucial to consider the specific site of GOx reaction when evaluating whether its oxygen depletion response exacerbates tissue hypoxia. In the majority of studies, GOx or GOx-like nanozymes were integrated into hydrogels or metal-organic frameworks (MOFs) and applied directly to the wound surface. These systems are often designed to be porous and permeable, facilitating access to glucose from the wound surface and oxygen from the external environment for the enzymatic reaction [29]. Based on this, it is postulated that GOx does not exacerbate tissue hypoxia under these conditions. Conversely, other research has developed wound dressings with a microneedle structure designed to penetrate the surface biofilm and localize the therapeutic action of GOx in deeper tissues [30]. In such scenarios, external oxygen may not readily permeate the wound surface, and GOx could potentially consume a greater proportion of the oxygen within the tissue, thereby exacerbating hypoxia within the wound microenvironment. Therefore, further investigation is necessary to fully understand the impact of GOx on tissue oxygenation and to optimize its application in diabetic wound management.

2.2.3. *Gluconic acid generation*

The gluconic acid generated by the GOx reaction is instrumental in maintaining an acidic microenvironment, which is potentially advantageous for the healing process of wounds, including diabetic chronic wounds. Specifically, the pH level of a wound significantly influences a multitude of factors such as oxygen release, protease activity, angiogenesis, and bacterial pathogenicity. In summary, a weakly acidic milieu is more conducive to the wound healing process [31]. Fibroblasts, which are integral to the wound healing cascade, demonstrate enhanced proliferation, migration, and responsiveness to stimuli at a lower pH (pH = 5.5) as opposed to more alkaline conditions (pH = 6.3, 7.3, 8.1) [32]. The enzymatic activity pivotal to wound healing is also pH-dependent, with alkaline environments impeding the cooperative function of multiple enzymes necessary for effective healing [33]. Specifically, at a pH range of 8.0–8.3, matrix metalloproteinase-2 (MMP-2) and neutrophil elastase display peak activity levels. This can lead to excessive inflammation and counteract the extracellular matrix (ECM) deposition and remodeling processes [34]. Moreover, the Borel effect, which is accentuated in an acidic environment, promotes the release of oxygen from hemoglobin, thus alleviating local hypoxia at the wound site—a factor known to hinder the healing process [35]. Additionally, pH significantly influences bacterial colonization dynamics [36]. Many common pathogenic bacteria exhibit a preference for a neutral pH environment. For instance, Staphylococcus aureus thrives at a pH of 7.0–7.5, Pseudomonas aeruginosa at 6.6–7.0, and Enterococcus faecalis within a broader range of 7.0–9.0 [37]. These pathogens can metabolize urea to produce ammonia, leading to a persistent alkalinization of the wound site, which may further complicate the healing process [38].

Intact skin surface maintains a pH range of 4–6, which is subject to dynamic alterations following trauma as the wound undergoes the sequential phases of hemostasis, inflammation, proliferation, and

remodeling [39]. It is widely recognized that the immediate aftermath of skin injury is characterized by a decrease in local pH due to the disruption of blood supply, heightened glycolysis and consequent lactic acid accumulation, and localized carbon dioxide retention [40]. As the wound transitions from the inflammatory to the proliferative phase, the resolution of the inflammatory response, clearance of necrotic tissue, and re-establishment of blood supply facilitate a shift towards aerobic metabolism, thereby leading to an increase in wound pH [40]. During the advanced stages of healing, characterized by wound epithelialization, extracellular matrix (ECM) deposition, and remodeling, the wound area contracts and the oxygen demand by the wound tissue escalates [40]. This results in a resurgence of glycolysis, lactic acid production, and heightened epithelial secretion at the wound margins, culminating in a subsequent decrease in wound pH [40]. In stark contrast, chronic wounds in diabetic patients often exhibit pH fluctuations within the alkaline range of 7–9 [41]. These wounds are embedded in a more intricate pathological microenvironment, where inadequate revascularization, immune dysregulation, and peripheral neuropathy disrupt the typical wound healing trajectory [41]. Persistent inflammation coupled with pathogenic bacterial colonization induces wound alkalinization, perpetuating a detrimental cycle of "non-healing - wound alkalinization - non-healing," which significantly impedes the healing process [36].

Additionally, a stable acidic environment is conducive to the development of pH-responsive therapeutics and the engineering of specific cascade reactions. For instance, Caixia Sun and colleagues have engineered a soluble nanozyme-based microneedle system loaded with Fe_2C nanoparticles and GOx [42]. In this system, Fe_2C nanoparticles are tasked with catalyzing the conversion of hydrogen peroxide (H_2O_2) into hydroxyl radicals, an antimicrobial process that is contingent upon an acidic environment [42].

It is noteworthy that while an acidic environment is widely recognized for its beneficial effects on wound healing, skin wounds are subject to a myriad of endogenous and exogenous influences. Thus, the strategy of maintaining an acidic wound environment may not be universally optimal. While monitoring the changes in wound pH, it is also essential to consider the causes of these alterations. For instance, clinical studies related to debridement consistently point to similar outcomes, suggesting that wound debridement leads to an increase in pH and that a higher pH (>7.3) may be beneficial for the survival of grafted skin [43]. Furthermore, the majority of pH-responsive hydrogel wound dressings reported to date are designed to degrade at lower pH levels, likely due to the consideration that bacteria in diabetic wound sites can convert glucose into lactic acid, thereby creating a more acidic environment [44,45]. Additionally, this discrepancy may arise from differences between animal models and patients with diabetes. The duration of diabetic wounds in experimentally constructed animal models is relatively short and may still be in the acute phase with an environmental pH value that is acidic. This situation is distinct from the environment during the chronic phase in clinical diabetic patients, where the pH is greater than 7.3.

Consequently, the impact and underlying mechanisms of pH regulation in wound healing, particularly in the context of diabetic chronic wounds, warrant further investigation to fully elucidate the nuances and optimize treatment strategies.

2.2.4. H_2O_2 generation

The generation of H_2O_2 can be utilized for both antimicrobial purposes and oxygenation. By cascading with catalase (CAT), H_2O_2 can be decomposed into water and oxygen, thereby alleviating localized hypoxia at the wound site [46]. As previously discussed, the significance of oxygen consumption and production by nanomaterials equipped with GOx is, to some extent, contingent upon the spatial location where the reaction takes place. Consequently, we posit that in certain wound dressing studies that are confined to the trauma surface, the supplementation of O_2 may not be necessary. Additionally, it is important to note that the oxygen produced through the decomposition of H_2O_2 does not entirely compensate for the O_2 depletion resulting from the GOx reaction [47]. In scenarios where GOx is solely present in diabetic wounds, the enzymatic breakdown of one molecule of glucose consumes one molecule of O_2 and yields one molecule of H_2O_2. Conversely, when CAT is concurrently present, it catalyzes the decomposition of one molecule of H_2O_2, releasing half a molecule of oxygen. The H_2O_2 subjected to CAT's catalytic action is predominantly derived from the GOx reaction [48]. Theoretically, the CAT cascade can reduce the oxygen consumption associated with the GOx reaction by up to 50 %, yet it is insufficient to reverse the hypoxia induced by GOx. Furthermore, through the Fenton reaction, H_2O_2 can be transformed into highly reactive hydroxyl radicals, which possess potent antimicrobial capabilities [49]. Elevated levels of hydroxyl radicals can induce oxidative stress and cause damage to biomolecules such as proteins and nucleic acids, thereby inhibiting bacterial growth and exerting bactericidal effects [50]. It is evident that these hydroxyl radicals, while effective against bacteria, also possess potential toxicity to normal tissue cells [51,52]. However, a majority of the pertinent studies have reported an excellent biocompatibility profile for the materials under investigation, with little definitive rationale provided [46,53].

To address the ostensibly paradoxical phenomenon of hydroxyl radicals exhibiting preferential toxicity towards bacteria over tissue cells, we propose the following four potential explanations.

1) In certain studies, hydroxyl radicals are generated at the wound surface, predominantly impacting the most superficial tissue cells [49,54];
2) The highly reactive hydroxyl radicals have an exceedingly short lifespan (measured in nanoseconds) and a limited diffusion range (measured in nanometers), which enables them to be lethal to proximal bacteria while sparing more distant normal tissues [55];
3) Bacteria have been observed to be more sensitive to hydroxyl radicals compared to tissue cells under identical conditions [56];
4) In some investigations, the materials under study were enriched with immunomodulatory and antioxidant substances that mitigated the effects of reactive oxygen species on normal tissues, without conferring a similar protective advantage to bacteria [57].

We acknowledge that these conjectures may not comprehensively account for the "selective toxicity" of hydroxyl radicals. The delicate balance between the antimicrobial efficacy and potential cytotoxicity of hydroxyl radicals merits further scientific inquiry. Concurrently, we anticipate that future research addressing similar "paradoxical" observations will provide additional insights, ideally supported by robust experimental data.

3. Achieving GOx activity: natural enzyme or GOx-like nanozymes

Theoretically, the catalytic reaction mediated by GOx can exert multiple effects in diabetic wound healing, and the practical realization of these effects is a focal point of interest. The structure and function of GOx, which is chemically a protein, can be influenced by the secretions of the local tissue at the wound site and adverse external environments, such as bacterial infections [58]. Some researchers opt to employ GOx-like nanozymes as substitutes for biological GOx to enhance the stability of GOx-like functions [59]. In Table 1, we compare the differences between natural GOx and GOx-like nanozymes. In summary, GOx-like nanozymes exhibit enhanced chemical stability and superior tunability. The acquisition of nanozymes are more challenging, whereas the preparation conditions for the associated biological materials are comparatively lenient. From the perspective of the Michaelis–Menten kinetic model, there is no significant difference in enzymatic activity between natural GOx and GOx-like nanozymes.

The chemical nature of biological GOx is proteinaceous, which is

Table 1
Comparison between GOx and GOx-like nanozyme.

	Natural GOx	GOx-like nanozyme
Chemical Nature	Protein	Au-based: Au-Cu_2MoS_4 [60] MoS_2@Au@BSA [53] FeOOH@Fe-Serine@Au [61] Au/$Cu_{1.6}O$/P-C_3N_5/Arg/HA [59] Pt-based; PFOB@PLGA@Pt [62]
Accessibility	Easy Directly purchasable, cost-effective	More challenging Nanogold is directly purchasable but expensive; Multicomponent biomaterials are challenging to acquire directly.
Michaelis–Menten kinetic model (glucose as the substrate)	$V_{max} = 3.389 \times 10^{-7}$ M/s $K_m = 30.91$ mM [63] $V_{max} = 1.025 \times 10^{-8}$ M/s $K_m = 1.58$ mM [64]	$V_{max} = 5.6 \times 10^{-8}$ M/s $K_m = 8.81$ mM [61] $V_{max} = 6.77 \times 10^{-8}$ M/s $K_m = 40.5$ mM [59]
Adjustablility (post-usage)	Cannot be actively regulated.	Some nanomaterials can adjust enzyme activity post-usage through ultrasonication.
Stability (in vivo)	Susceptible to protease degradation	More stable and resistant to proteolytic degradation
Considerations in Biomaterials Construction	Below or around room temperature and a narrow pH range (5.0–7.0). Ultrasonication should be avoided. Must be added in the **final stage** of biomaterial assembly.	Broader range of temperatures and pH levels. Ultrasonication is permissible. Can be added at **any stage** of biomaterial construction.

susceptible to disruption in structure and function by tissue secretions or external environmental factors within the unstable skin wound bed. In theory, employing more stable molecules or nanoparticles to mimic the function of GOx could effectively address this issue. We conducted a search on PUBMED using the query "(glucose oxidase) AND (wound healing)" and on the Web of Science using "glucose oxidase (Topic) AND wound healing (Topic)", which yielded a total of 37 articles after manual selection. Among them, 32 utilized biological GOx, while only 5 employed GOx-mimics, all of which were metal nanozymes, including platinum (Pt) and gold (Au) (Fig. 3) [53,59–62].

Interestingly, out of the 5 studies employing nanozyme, 4 were published in 2023 and 1 in 2022. The GOx-related biomaterials and their preparation methods involved in these five studies are presented in Table 2. The utilization of metal-based nanozyme appears to be emerging as a novel research direction in the field of wound repair. Concurrently, it is imperative to recognize that the feasibility of nanozyme as substitutes for biological GOx still requires further validation. We aim to contribute to the discourse by proposing three areas of focus for researchers in the field of GOx-like nanozymes.

1) Fundamental Advantage. The fundamental advantage of nanozymes lies in their more stable chemical properties compared to biological GOx. Nanozymes, particularly those based on Pt and Au, are notably stable, leading to a general perception that they are unlikely to engage in unintended biochemical reactions [62]. However, the inertness of these chemical reactions is a double-edged sword. On one hand, it allows GOx-like nanozymes to exert their effects throughout the entire process of wound healing. On the other hand, wound healing is a continuous and dynamic process, and researchers must carefully consider the specific stages of repair where the GOx reaction is applicable. Additionally, Pt and Au are not naturally excreted by biological systems and can accumulate in the bloodstream or interstitial tissues, potentially leading to bio-toxicity. We encourage researchers to rigorously calculate the possible dosages of these metals that could enter the body and compare them with relevant standards to substantiate the safety of these materials.
2) The Activity of GOx-Like Reactions. The five studies utilizing GOx-like nanozymes have all demonstrated the GOx activity of the metallic particles. However, these GOx-like nanozymes were not compared with biological GOx, which lacks rigor in the scientific method [53,61]. We acknowledge the challenges inherent in this comparison, as the dosages of biological GOx and GOx-like nanozymes are not directly comparable, and their activities vary under different pH levels and glucose concentrations [65]. Nevertheless, we deem this comparative work to be valuable. It is evident that for the application of GOx-like nanozymes to be meaningful, their reaction activity must at least be on the same order of magnitude as that of biological GOx. Moreover, the effects of different GOx-like nanozymes are currently difficult to compare directly. Using biological GOx as a benchmark allows for a more intuitive understanding and comparison of the GOx-like reaction activity of the nanozymes. Therefore, we advocate for researchers to semi-quantitatively measure the GOx-like reaction activity of GOx-like nanozymes per unit volume or mass, using the activity of biological GOx as a reference standard.
3) The Breadth and Precision of Enzymatic Reactions. Biological enzymes often catalyze specific or certain types of reactions with high precision. In contrast, metallic nanozymes typically possess a variety of enzymatic activities, which is also one of the advantages of GOx-like nanozymes [53,59]. Ziying Zhou and colleagues have confirmed the excellent multi-enzyme activities of Pt, including GOx-like, POD-like, oxidase (OXD)-like, NADH oxidase (NOX)-like, CAT-like, and superoxide dismutase (SOD)-like activities [62]. The multi-enzyme activities of Pt can synergistically promote wound healing from multiple aspects. However, the possession of multiple functions by a single component is bound to reduce the precision of the enzymatic reactions. Changes in the wound environment, such as pH levels, ROS levels, and oxygen concentration, can lead to nearly uncontrollable overall changes in these enzymatic activities [66,67]. Whether these changes align with the needs of different stages of wound healing remains to be further substantiated by researchers.

4. Enhancing GOx acitivity: synergistic strategies

In the diabetic wound treatment, GOx can exert multiple therapeutic effects, including the reversal of a high-glucose environment (by consuming glucose), oxygen supply or antibacterial action (through the formation of H_2O_2), and maintenance of wound pH (by producing gluconic acid). However, the oxygen-providing and antibacterial effects of the formed H_2O_2 are not significantly pronounced [68]. The Fenton reaction and CAT can decompose H_2O_2, significantly enhancing its physiological effects. Concurrently, photothermal effect, electrochemistry, microneedle strategy, environmental responses, and gas therapy can amplify the therapeutic effects of GOx and act synergistically [69–71]. In addition to these, some researchers have integrated in situ monitoring functions into the GOx therapeutic strategies to monitor environmental parameters [72,73].

4.1. Multi-enzyme strategy

GOx can exert multiple therapeutic effects in diabetic wounds. When used in combination with other enzymes, a synergistic effect with GOx can be achieved, thereby further enhancing the therapeutic outcome. The reaction product of GOx, H_2O_2, possesses the potential for both oxygen provision and antibacterial activity. However, the efficiency of both functions is suboptimal. The use of GOx alone also falls short of

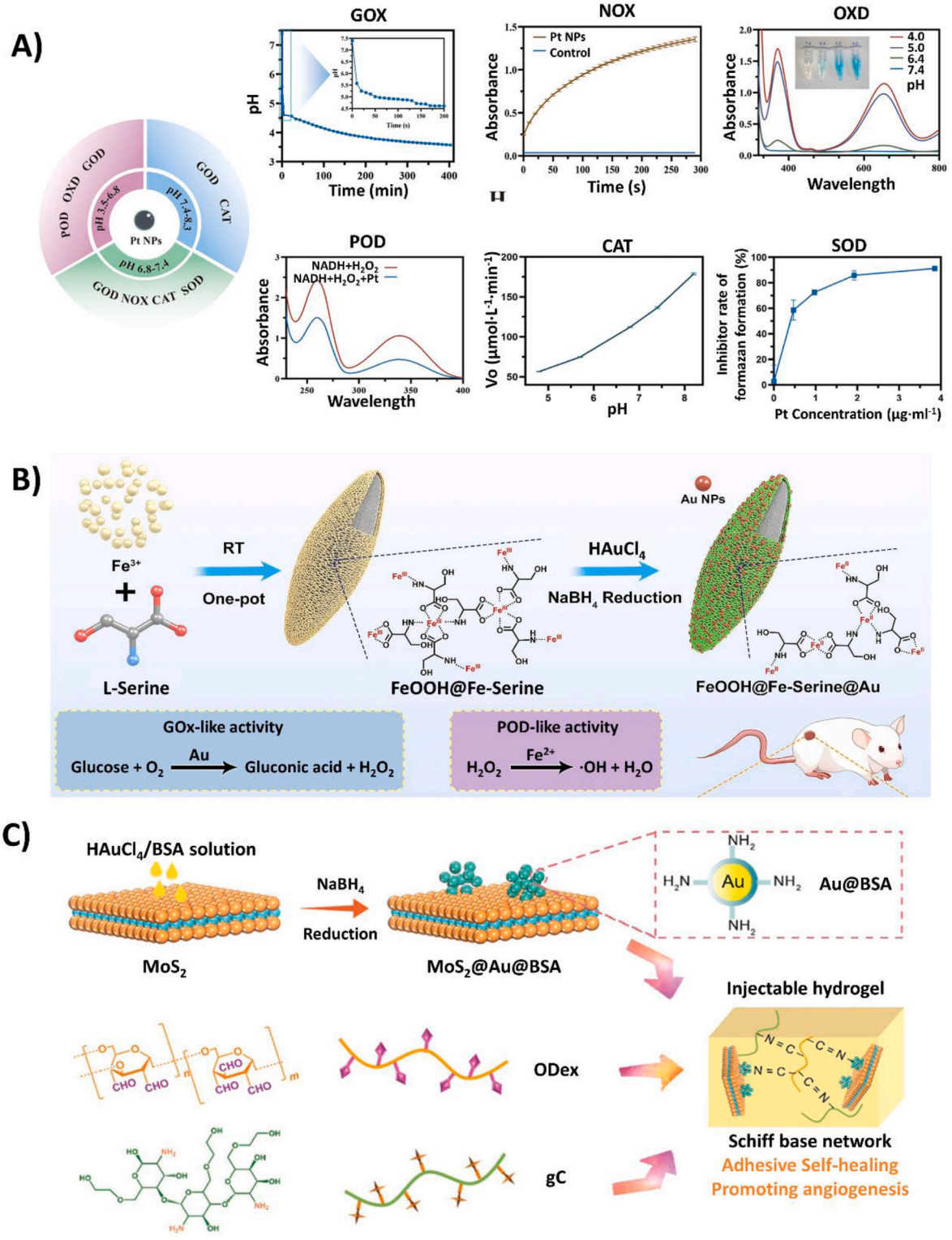

Fig. 3. Schematic diagram of GOx-like nanozyme design. A) Catalytic properties of Pt NPs. Pt NPs exhibit different multienzyme-like activities in different pH intervals. GOX/NOX/OXD/POD/CAT/SOD-like activity of Pt NPs. Reproduced with permission [62]. Copyright 2023, American Chemical Society. B) Schematic illustration of the preparation of FeOOH@Fe-Serine@Au NSs and their GOx-mimicking and POD-mimicking dual-nanozymes catalytic cascade activities against diabetic wound infection. Reproduced with permission [61]. Copyright 2023, Academic Press Inc. C) Synthesis of MoS_2@Au@BSA nanosheets and preparation of injectable hydrogel. Reproduced with permission [53]. Copyright 2022, Wiley-VCH Verlag.

meeting the dynamic demands of diabetic wound healing.

4.1.1. *Multi-enzyme oxygen supply and antibacterial effects*

Researchers have keenly recognized the potential oxygen-providing and antibacterial effects of H_2O_2. By introducing CAT or POD activities, H_2O_2 can be further decomposed to produce O_2, which alleviates hypoxia, or to generate ROS for antibacterial purposes [74].

CAT activity can efficiently convert H_2O_2 into O_2, thereby alleviating

Table 2
Preparation and Characterization of GOx-like nanozymes.

Nanomaterials	Preparation	Characteri-zation	Structure	Ref.
Au-Cu_2MoS_4 (Au-CMS) nanosheets	1. Preparing CMS NSs. 2. Adding $HAuCl_4{\cdot}3H_2O$ and $NaBH_4$, sonicating for 30 min.	TEM EDS XPS XRD	Au: NPs, D = 1.6 nm Entire: NS, D ≈ 100 nm	[60]
MoS_2@Au@BSA nanosheets	1. Prepating MoS_2 NSs. 2. Mixing $HAuCl_4$ solution with BSA, adding into MoS_2 dispersion and sonicating for 30 min. 3. Adding $NaBH_4$, reacting for 12 h to obtain MoS_2@Au@BSA NSs.	TEM STEM EDS XRD XPS	Au: NPs, D ≈ 10–20 nm MoS2: NSs, Interlayer distance = 0.63 nm	[53]
FeOOH@Fe-Serine@Au nanosheets	1. Prepating FeOOH@Fe-Serine NSs. 2. Adding $HAuCl_4$ and $NaBH_4$ under magnetic stirring.	TEM UV–vis spectra XRD FTIR XPS TGA (DTG)	β-FeOOH: NSs, Length = 172.9 ± 55.5 nm Width = 45.2 ± 12.8 nm Au: NPs, D = 4.1 nm Entire: NSs, Length = 237.7 ± 89.5 nm Width = 68.6 ± 22.3 nm	[61]
Au/$Cu_{1.6}O$/P-C_3N_5/Arg/HA (ACPAH)	1. Preprating $Cu_{1.6}O$/P–C_3N_5 NSs 2. Adding $HAuCl_4$, stirring for 1 h, adding pre-cooled $NaBH_4$ solution dropwise. 3. Adding Arg and stirring for 6 h. Adding HA, stirring for 4 h.	Nitrogen Adsorption–desorption isotherms EDS XRD FTIR XPS	Au: NPs, D = 3–5 nm $Cu_{1.6}O$: NPs, D = 3–5 nm ACP: D ≈ 160 nm ACPA: D ≈ 190 nm Entire: Pore size = 7.7 nm	[59]
PFOB@PLGA@Pt	1. Dissolving SH-PEG-NH_2[a] in acetic acid solution, adding aqueous chloroplatinic acid and $NaBH_4$ to obtain Pt NP. 2. Mixing PFOB@PLGA with Pt NP.	STEM EDS Hydrodynamic dimension SEM	Pt: NPs, D = 2–4 nm Entire: NSs, D ≈ 200 nm	[62]

[a] SH-PEG-NH_2: polyethylene glycol (PEG) derivatives containing sulfhydryl (-SH) and amino (-NH_2) functional groups.

the hypoxic environment of the wound. It should be noted that CAT typically exhibits strong activity in neutral or mildly alkaline conditions. However, diabetic wounds tend to be acidic initially, and the GOx reaction produces gluconic acid, which further maintains the weakly acidic environment of the wound, posing challenges for the function of catalase [75]. Jingyang Shan and colleagues constructed Au-Cu_2MoS_4 nanosheets with dual enzyme activities of GOx and CAT [60]. In vitro experiments confirmed the CAT-like activity of Au-Cu_2MoS_4, which decomposes H_2O_2 to produce O_2, but the pH for enzyme activity verification was not clarified. Moreover, the efficiency of Au-Cu_2MoS_4 in decomposing H_2O_2 is calculated as a percentage, while the efficiency of O_2 production is measured in mg/L, making a comparison between the two impossible. Therefore, it is undetermined whether Au-Cu_2MoS_4 exhibits solely CAT-like activity or a combination of CAT and POD-like activities [60].

The raw materials required for the Fenton reaction, mediated by POD-like activity, are simple, environmentally adaptable, and potent in effect. Researchers have widely applied the Fenton reaction to amplify the antibacterial effects of H_2O_2, a reaction product of GOx. Approximately two-thirds of the studies on diabetic wound treatment using GOx have employed the strategy of cascading the Fenton reaction with GOx, as shown in Table 3. The Fenton reaction can be mediated by various metals, such as Fe, Cu, Mo, Mn, V, and can also be mediated by iron-containing enzymes like hemoglobin and HRP [53,76]. Most of these catalysts require a weakly acidic environment to exhibit POD-like activity, decomposing H_2O_2 and forming hydroxyl radicals. Particularly for metal ions, these catalysts can form precipitates in neutral and alkaline environments, thereby losing their catalytic performance [61,77]. The weakly acidic environment of diabetic wounds meets the catalytic requirements, and the gluconic acid formed by the GOx reaction maintains a local weak acidity, allowing the Fenton reaction to continue persistently. The ROS formed by the Fenton reaction include hydroxyl radicals, singlet oxygen ($^1O2$), and superoxide anion radicals ($\cdot O^{2-}$) [78]. Among them, ·OH exhibits the primary antibacterial effect [50].

Table 3
Multi-enzyme strategies based on GOx for diabetic wound research.

Enzyme activity	Substances performing enzymatic activity	Ref.
Oxygen Supply (CAT-like Activity)	Au-Cu_2MoS_4	[60]
Antibacterial (POD-like Activity)	Fe^{2+}	[30,64]
	Fe_2C	[42]
	Fe_2O_3	[79]
	Cu-MOF	[80,81]
	Cu_2O	[82]
	$Cu_{2-x}S$	[57]
	Fe-Cu MOF	[83,84]
	MoS_2	[24]
	Mn^{2+}	[85]
	Vanadium (V)	[86]
	Hemoglobin	[54,87]
	HRP	[76,88]
Multi-Enzyme Activities	Fe_3O_4: CAT, POD	[46]
	Ce: SOD, CAT	[89]
	Pt: GOX/POD/OXD/NOX/CAT/SOD	[62]
	Au-Cu: SOD-CAT-GOx-POD/NOS	[59]
	MoS_2-Au: GOx/CAT/SOD	[53]

4.1.2. Dynamic regulation of multi-enzyme systems

To meet the dynamic demands of diabetic wound healing, researchers have begun to explore spatiotemporal regulation strategies centered around GOx. Xuancheng Du and colleagues utilized Fe_3O_4 to simulate both CAT and POD activities for the treatment of infected diabetic wounds [46]. Under acidic conditions (pH~5.5) and neutral conditions (pH~7.5), Fe_3O_4 exhibits good CAT and POD-like activities, respectively. During the inflammatory phase of the wound, the GOx/-POD cascade reaction continuously produces hydroxyl radicals, spatially targeting and eradicating acidic biofilms to shorten the inflammatory phase. Additionally, the GOx/CAT cascade reaction produces O_2 spatially, targeting neutral wound tissues, and accelerating the proliferation and remodeling phases of wound healing by addressing hyperglycemia, hypoxia, and excessive oxidative stress [46]. Furthermore, Ziying Zhou leveraged the multi-enzyme mimetic activities of Pt

(GOX/POD/OXD/NOX/CAT/SOD) to exert antibacterial and diabetic wound healing effects (Fig. 3A) [62]. In this system, the GOx reaction reduces glucose concentration in the wound and adjusts the pH environment from alkaline to acidic. POD/OXD/NOX-like activities are activated to exert a synergistic antibacterial effect through the generation of ROS. In the later stages of wound healing, CAT/SOD-like activities reshape the redox microenvironment, clearing excess ROS and facilitating the transition of the wound from the inflammatory phase to the proliferative phase [62].

Multi-enzyme activity implies a richer therapeutic strategy, but there seems to be a "contradictory effect" among them. For instance, POD forms ROS, while SOD plays an antioxidant role; CAT and POD are sometimes different activities of the same enzyme at different pH levels and typically do not function simultaneously [90]. Precisely regulating the activities of multiple enzymes at different times and spaces is challenging and requires rigorous proof. Hao Zhang's team constructed a FeOOH@Fe-Serine@Au nanosystem that possesses both GOx and POD activities [61]. The Zhang group investigated the pH-dependent enzymatic activities of GOx and POD in this biomaterial. Experimental results indicate that at weakly acidic conditions (pH = 5), the POD activity predominates, whereas at neutral to weakly alkaline environments (pH = 7–9), the GOx activity is predominant [61]. This demonstrates that the dual enzymatic activities of the biomaterial can be modulated by the pH of the wound, synergistically exerting therapeutic effects at different stages of wound healing. However, in some studies on multi-enzyme systems, only the presence of enzymatic activity has been demonstrated, with a lack of validation for spatial and temporal regulation [62]. We encourage researchers to focus on the variations in multi-enzyme activities under different environmental conditions (such as pH, temperature, and oxygen levels) based on the characteristics of diabetic wounds at various stages. This approach is essential for more rigorously proving and discussing the principles and mechanisms by which multi-enzyme activities contribute to the therapeutic effects in wound treatment.

4.2. Electrochemical strategies

Linlin Wang and colleagues designed a glucose oxidase biofuel cell (GBFC) for the treatment of diabetic wounds (Fig. 4A) [88]. The cell patch is supported by two flexible carbon cloths with excellent conductivity and carries MAF-7 (a well-established metal-organic framework) encapsulating HRP and/or GOx. The anode contains GOx/HRP, which continuously catalyzes the aerobic oxidation of glucose and the decomposition of H_2O_2, generating abundant ROS. Concurrently, the GBFC can produce an electric field in the wound environment, causing negatively charged bacteria to firmly adhere to the anode surface and be precisely killed by the ROS generated at the anode [88]. Similarly, Xiangli Zhang and colleagues fabricated a self-powered enzymatic microneedle patch composed of anodic and cathodic microneedle arrays (Fig. 4B) [76]. They immobilized GOx and HRP in ZIF-8 and further loaded it onto a hydrogel with a microneedle structure. In this study, ZIF-8 loaded with GOx on one side of the hydrogel acts as the anode, while the other side loaded with HRP acts as the cathode [76].

HRP itself can utilize H_2O_2 produced by the GOx reaction to form ROS with stronger antibacterial effects [68,91]. The involvement of electrochemical strategies further enhances the stability and efficiency of this cascade reaction. Studies have shown that weak current can stimulate the proliferation and migration of vascular endothelial cells and keratinocytes, thereby promoting wound healing [92]. Xiangli Zhang also claimed that the therapeutic effect of their patch is attributed to the combined effects of blood glucose reduction, antibacterial, anti-inflammatory, and bioelectrical stimulation [76]. Regrettably, Zhang's study did not demonstrate the promotion of cell proliferation or migration by the application of bioelectrical stimulation alone in vitro or in vivo [76]. Moreover, Linlin Wang suggested that negatively charged bacteria would be adsorbed onto the anode surface and then precisely killed by ROS produced at the anode [88]. This concept is very ingenious, but the study did not prove that the biofuel cell could affect bacterial migration or adsorption [88]. It should be noted that in

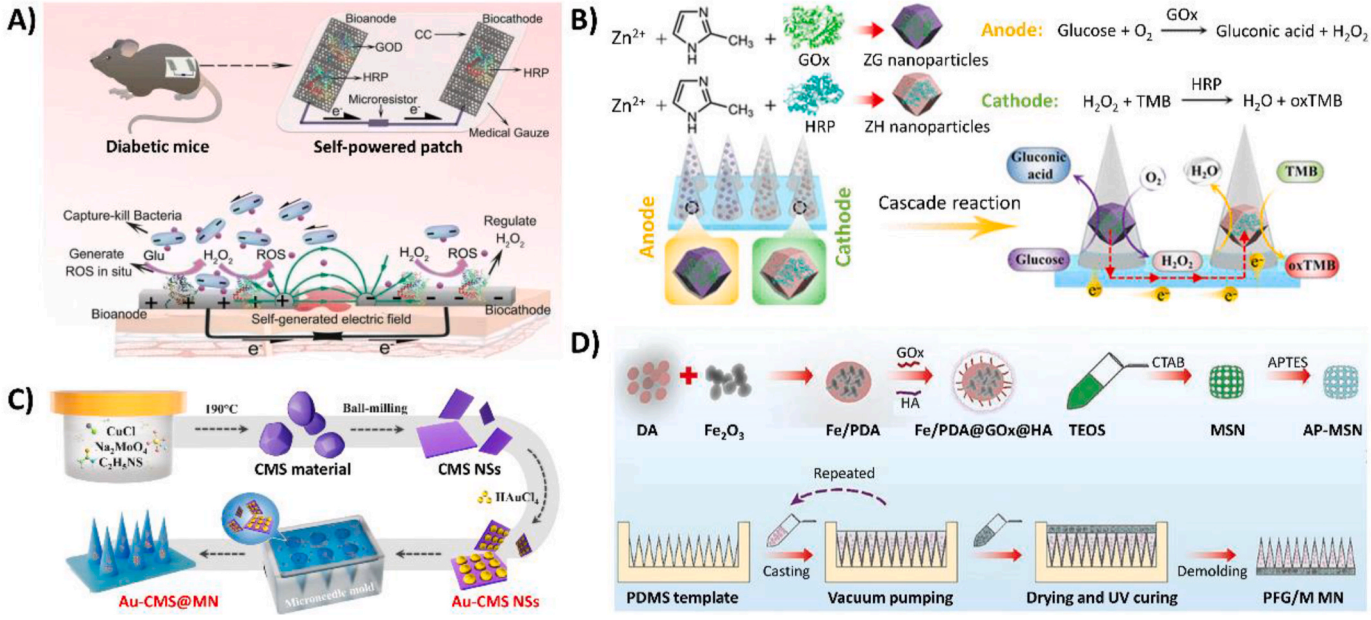

Fig. 4. Schematic illustrations of GOx synergistic electrochemical and physical microneedling strategies for the treatment of diabetic wounds. A) The schematic representation of a GBFC-powered antibacterial patch for treating diabetic wounds; The illustration of the working principle of this patch for regulating local glucose, generating abundant ROS in situ, and precisely sterilizing driven by an electric field. Reproduced with permission [88]. Copyright 2022, Royal Society of Chemistry. B) Schematic of the enzyme cascade reaction generated by the self-powered MN patch. Reproduced with permission [76]. Copyright 2023, American Association for the Advancement of Science. C) Schematic illustration of NIR-II responsive microneedle patches for the efficient administration of diabetic wound infection. Au-Cu_2MoS_4 nanosheets (Au-CMS NSs) were prepared to fabricate Au-CMS@MN and used for treating diabetic wound infection. Reproduced with permission [60]. Copyright 2023, Elsevier BV. D) Schematic illustration of the preparation of Fe/PDA@GOx@HA, AP-MSN and PFG/M MN. Reproduced with permission [30]. Copyright 2023, Wiley-VCH Verlag.

conventional strategies without electrochemical methods, the enzymatic strategy of GOx + HRP can decompose glucose everywhere in the wound, produce H_2O_2, and further produce ROS [93]. However, the electrochemical strategy limits the production site of ROS to the anode, which seems to weaken the antibacterial effect to some extent [94]. Therefore, we believe that in the research of GOx synergistic electrochemical strategies, whether microorganisms at the cathode can be effectively adsorbed to the anode is a very key issue that needs to be further explored.

4.3. Physical microneedle strategies

Microneedles, a novel drug delivery system composed of microscale needles, have garnered widespread attention due to their non-invasive nature, simple operation, local controllability, and diverse loading capabilities [95]. Initially used for transdermal drug delivery by penetrating the stratum corneum of the skin, microneedles can puncture the skin to achieve minimally invasive drug administration [96]. In recent years, microneedles have been utilized to load GOx for the treatment of infected wounds. Microneedles can physically disrupt biofilms, breaking them down into planktonic bacteria [97]. At the same time, by adjusting the length of the microneedle tips, the depth of drug delivery can be precisely controlled, ensuring the accurate action of the drug [98]. This is beneficial for the antibacterial efficacy of H_2O_2 and hydroxyl radicals produced by the catalytic action of GOx. Microneedle patches can adhere closely to the wound surface through mechanical interlocking, eliminating the need for suturing and reducing the likelihood of dressing displacement due to body movement [99,100]. In diabetic wound research combining GOx with microneedle strategies, microneedles are constructed using hydrogels, which possess good biocompatibility and drug release capabilities [42,60,76]. After puncturing the wound tissue, the microneedles begin a controlled degradation to mediate drug release, enhancing drug diffusion and therapeutic effect [99].

Shengbo Li and colleagues have suggested that microneedle structures exhibit inherent advantages in antibacterial and anti-inflammatory actions [30]. During the antibacterial process, degraded bacteria and necrotic cells release pathogenic nucleic acid fragments in infected wounds, triggering a strong inflammatory response [101]. The orderly arranged microscale needle tips of microneedles, once designed, may adsorb these pro-inflammatory factors, such as free nucleic acids, while performing antibacterial actions [102,103]. Shengbo Li and colleagues constructed a microneedle patch with antibacterial and immunomodulatory properties (PFG/M MNs) (Fig. 4D) [30]. In the microneedle patch, the researchers integrated polydopamine nanoparticles loaded with ferric oxide, GOx, and hyaluronic acid to the microneedle tips (Fe/PDA@GOx@HA), and amine-modified mesoporous silica nanoparticles (AP-MSNs) to the base. Under the weakly acidic environment of infected wounds, the nanoparticles at the microneedle tips decompose, releasing GOx, iron ions, and PDA, which combine with CDT and PTT strategies for antibacterial action and promote the differentiation of M2 macrophages to enhance wound repair in infections. Additionally, AP-MSNs located at the base can capture pro-inflammatory factors, such as free nucleic acids, to modulate the immune microenvironment [30].

In summary, microneedle technology offers multiple advantages in the healing of infected wounds, including close adherence, biofilm disruption, precise drug delivery, and antibacterial, anti-inflammatory, and tissue regenerative capabilities obtained through loaded drugs.

4.4. Phototherapy strategies

In recent years, light has emerged as an easily applied, non-invasive, and spatially and temporally controllable therapeutic tool, extensively utilized by researchers in the treatment of infected wounds [104,105]. Under illumination of specific wavelengths, the localized thermal effect mediated by photothermal materials can induce protein denaturation and DNA strand breaks, thereby disrupting bacterial integrity [106]. Local thermotherapy can increase blood flow, enhance oxygenation, and promote fibroblast proliferation, thereby facilitating wound healing [107,108]. Furthermore, research by Dong Dong and colleagues has shown that PTT strategy-mediated local thermotherapy can enhance the catalytic activity of GOx and Cu_2O/Pt (POD mimics) [82]. However, PTT alone requires relatively high temperatures to achieve effective antibacterial action, which may cause some degree of damage to normal tissues [109]. The combined application of GOx and PTT can synergistically implement the triple strategy of CDT/PTT/PDT, using PDT that generates ROS and PTT with lower temperatures in diabetic infected wounds, achieving efficient and more specific antibacterial functions [60]. In fact, the increase in local temperature can enhance the permeability of bacterial membranes, facilitating the penetration of ROS generated by the PDT pathway into bacteria and disrupting their integrity [110].

The photothermal cascade reactor (CPNC@GOx-Fe^{2+}) constructed by Lei Chen and colleagues has demonstrated the effectiveness of the aforementioned concept (Fig. 5A) [63]. This nano-reactor selects chitosan-modified palladium nanocubes (CPNC) with near-infrared absorption and high photothermal conversion efficiency as a platform, fixing GOx and Fe^{2+} onto the platform through hydrogen bonding and coordination to enhance the enzyme's thermal stability and resistance to proteolytic enzymes [63]. CPNC@GOx-Fe^{2+} can catalyze the oxidation of glucose to generate hydroxyl radicals. Under irradiation with 808 nm light, the photothermal effect of CPNC endows the cascade reaction system with synergistic antibacterial activity against Streptococcus mutans. This opportunistic pathogen may infect extraction wounds, leading to the development of alveolar osteitis. Concurrently, the continuous generation of hydroxyl radicals from the cascade reaction can trigger the radical polymerization of poly(ethylene glycol) diacrylate (PEGDA) monomers, resulting in the in situ formation of a hydrogel, providing a moist and sterile environment for open wounds. In vitro experiments have confirmed the supramolecular photothermal cascade reaction system's strong synergistic antibacterial activity against various oral opportunistic pathogens. An extraction wound model also validated the effectiveness of synergistic antibacterial effects and in situ wound protection [63].

4.5. Gas therapy

The challenge of wound hypoxia due to vascular damage in diabetic wounds is exacerbated [113]. The oxygen generated by GOx-mediated reactions is consumed in greater amounts, failing to fundamentally correct the hypoxia. Therefore, additional oxygen supply strategies are required to alleviate hypoxia in diabetic wounds and to provide sufficient substrates for the GOx reaction. Yi Deng and colleagues constructed a cascade bioheterojunction (C-bio-HJs) composed of CN/MoS2 and GOx. The CN in C-bio-HJs has the capability to decompose water molecules under sunlight, producing O_2 (Fig. 5B) [24]. Concurrently, the Fenton reaction mediated by MoS_2 can catalyze the H_2O_2 produced by GOx into highly reactive bactericidal hydroxyl radicals, leading to bacterial death [24].

Persistent chronic inflammation and oxidative stress are considered key factors that hinder the healing of diabetic wounds [108]. Anti-inflammatory gases, such as H_2, H_2S, and NO, are used to combat inflammatory states and promote the healing of diabetic wounds. These gases typically possess reducing properties, capable of scavenging ROS, such as superoxide anions and hydroxyl radicals, thereby alleviating oxidative stress [114–117]. This antioxidant effect helps to reduce the production of inflammatory mediators, decrease inflammatory responses, and create a more favorable environment for wound healing. H_2, H_2S, and NO have all been reported to accelerate the healing of diabetic wounds by modulating levels of inflammatory factors, promoting the polarization of macrophages to the M2 type, and promoting angiogenesis, as well as the proliferation and migration of fibroblasts and keratinocytes [118–120]. Additionally, NO possesses natural

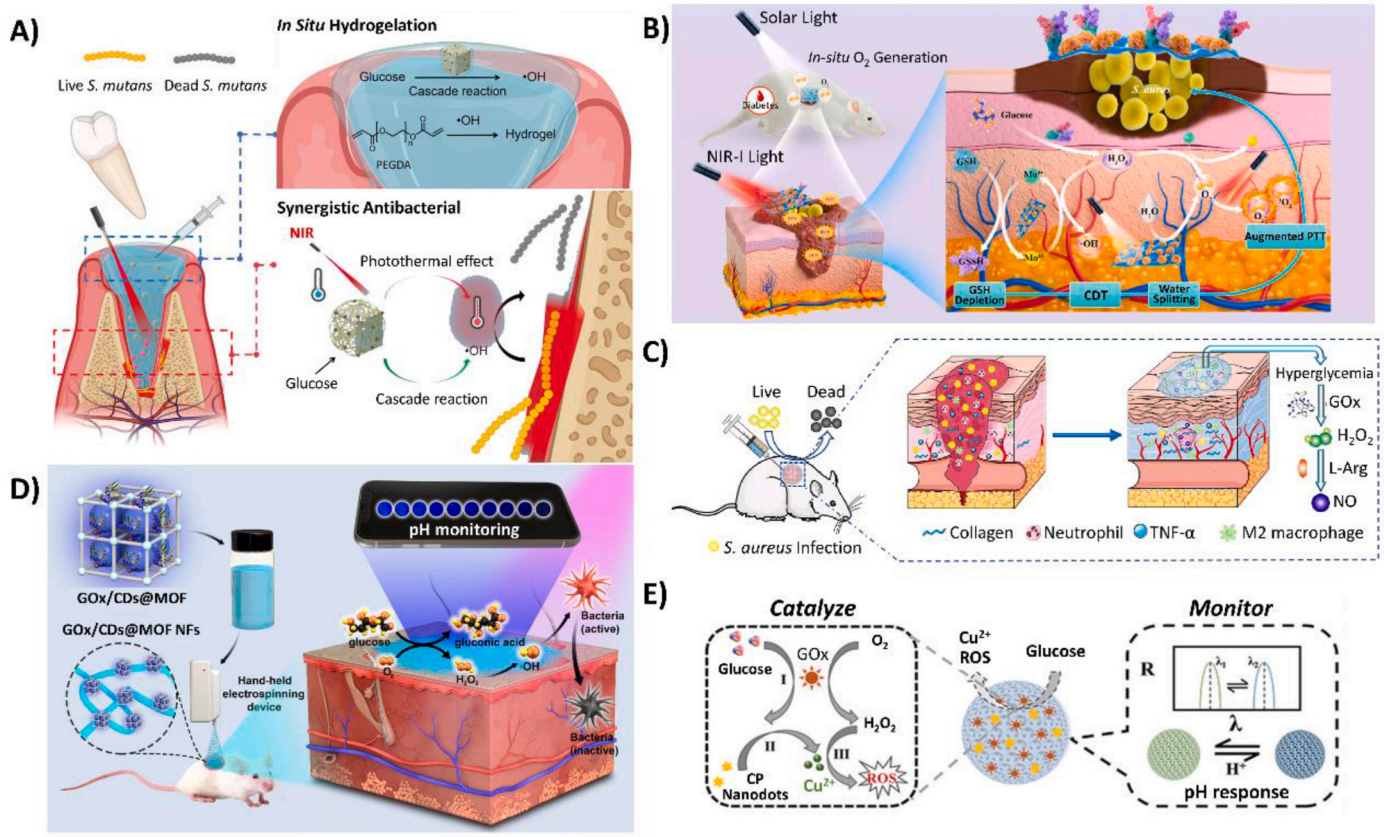

Fig. 5. Schematic illustrations of GOx synergistic phototherapy, gas therapy and environmental monitoring strategies for the treatment of diabetic wounds. A) Schematic illustration of the application of CPNC@GOx-Fe^{2+} in promoting bacteria-induced tooth-extraction wound healing. The nano-reactor CPNC@GOx-Fe^{2+} could produce hydroxyl radicals to induce in situ hydrogelation of PEGDA and performance photothermal and chemodynamic combination therapy to eradicate the bacteria. Reproduced with permission [63]. Copyright 2023, Wiley-Blackwell. B) The GOx-primed cascaded antibacterial actions for the remedy of infected cutaneous regeneration. Reproduced with permission [24]. Copyright 2023, KeAi Communications Co. C) The in vivo wound healing effect of CAHG hydrogel on S. aureus infected wound of diabetic mice: cascaded release H_2O_2-NO, bacterial inhibition, inflammatory reduction, promoting angiogenesis and collagen deposition. Reproduced with permission [111]. Copyright 2023, Elsevier. D) Schematic diagram of GOx/CDs@MOF NF dressing for visual monitoring and antibacterial treatment of diabetic-infected wounds. Reproduced with permission [80]. Copyright 2023, American Chemical Society. E) Cascade reaction and monitoring the ability of cascade structural color microparticles. I represents the catalytic process of GOx; II represents the decomposition of CP nanodots; III represents the generation of ROS. Reproduced with permission [112]. Copyright 2023, Wiley-VCH Verlag.

antibacterial capabilities, able to inhibit and kill a variety of bacteria, including drug-resistant strains [121]. Yuxuan Ge's team used GOx as a carrier and deposited MnS on GOx through biomineralization to construct GOx@MnS nanoparticles [85]. The gluconic acid produced by the GOx reaction can lower and maintain the local pH of the wound, prompting the release of H_2S from MnS to participate in wound healing. Meanwhile, the Fenton reaction catalyzed by Mn^{2+} can continuously convert H_2O_2 into ·OH, exerting antibacterial effects [85]. Experimental results have shown that GOx@MnS has strong bactericidal activity, can suppress inflammatory responses, and accelerate the healing of diabetic wounds by promoting macrophage M2 polarization [85]. Both Yufei Cao and Xiang Zhou have reported wound dressings loaded with GOx that use L-Arg as a source of NO (Fig. 5C) [111,122]. The reaction product H_2O_2 from GOx can oxidize L-Arg to form NO. Both studies reported that the NO released by the wound dressings could exhibit excellent therapeutic efficiency in wound healing by inhibiting bacteria, down-regulating pro-inflammatory factors, promoting macrophage M2 polarization, and promoting collagen deposition and angiogenesis [111, 122].

4.6. Sonodynamic therapy (SDT)

Sonodynamic therapy (SDT) is an emerging treatment modality that leverages the activation of acoustic sensitizers by low-intensity ultrasound waves, thereby inducing the generation of reactive oxygen species (ROS) at the tumor site, leading to the selective destruction of tumor cells [123]. SDT has gained significant traction in the management of infected wounds, attributed to its high ROS yield, non-invasive nature, and precise controllability [124]. Moreover, the integration of judiciously engineered nanomaterials with SDT has been shown to augment nanozymes' activity in response to ultrasound stimuli [125]. The enzymatic activity of GOx is pivotal in GOx-based treatment strategies for diabetic wounds. A common approach among researchers is to modulate the local GOx activity within the wound by selecting scaffold materials that control the release of the enzyme, thereby slowing the release and extending the therapeutic effect [84]. Some researchers opt for nanozymes with enhanced structural stability and diminished susceptibility to environmental influences [62]. However, in these methods, enzyme activity is usually determined at the time of administration, precluding the possibility of precise spatiotemporal modulation. Recently, studies have highlighted the potential of ultrasound-enhanced nanozymes [126]. These nanozymes can absorb energy released by cavitation bubbles, leading to carrier segregation and energy band bending on their surface [127]. This phenomenon results in an enhancement of the enzymatic activity, offering a promising avenue for the precise control of therapeutic nanozyme activity in a dynamic wound environment.

Building upon these principles, Limin Shang and colleagues

developed a novel therapeutic approach by encapsulating phosphorus-nitride graphite nanosheets, enriched with gold (Au), copper oxide ($Cu_{1.6}O$), and arginine, within a hyaluronic acid matrix to form hydrogel sprays [59]. These hydrogels were endowed with SOD-CAT-GOx-POD/NOS penta-enzyme activities. Experimental evidence has demonstrated that the incorporation of ultrasound significantly enhances and precisely modulates the activity of these nanozymes [59]. Concurrently, ultrasound induces the formation of transient pores within the biofilm matrix, facilitating the penetration of nanozymes and augmenting their antimicrobial efficacy [59]. This study reports the synergistic effects of SDT, which integrates antimicrobial properties, accelerated diffusion of biomaterials, and the enhancement and modulation of nanozymatic activity. The combined strategy with the GOx treatment approach has been shown to promote the healing of diabetic wounds in both in vivo and in vitro settings [59].

At present, the application of SDT within the context of GOx treatment strategies for diabetic skin wounds remains limited. This limitation is primarily attributed to the restricted modulation of proteolytic enzymes by ultrasound. Conversely, the amalgamation of ultrasound with nanozymes has demonstrated enhanced therapeutic potential and broader applicability [59]. Considering the nascent stage of GOx-like nanozymes within the research domain, with developments only beginning in 2022, it is plausible to anticipate that ongoing research integrating SDT with GOx-like nanozymes will yield innovative and efficacious methodologies in the management of diabetic wounds.

4.7. Real-time monitoring

In research related to GOx for diabetic wound treatment, scientists meticulously present the properties of materials and therapeutic effects. However, it should be noted that in the scientific process, researchers adopt standardized experimental models and treatment strategies, unifying the location and size of the wound, as well as the method and dosage of drug administration. In contrast to the research process, in clinical practice, healthcare workers face the immense challenge of individualized treatment, including individual differences, wound location and depth, and targeted drug dosages. Therefore, it is necessary to conduct targeted monitoring of key factors in wound healing or important links in drug regulation. Currently, researchers have introduced real-time monitoring strategies for pH and glucose concentration in GOx-based wound treatment strategies (Fig. 5D) [80,112,128].

pH indicator substances with porous structures can be integrated with GOx to achieve integrated treatment and detection. Structural color inverse opal particles are materials with special optical properties that can manipulate light reflection and scattering through their internal periodic nanostructures to produce color [129,130]. This color is not produced by pigments but determined by the physical structure of the material, thus offering advantages such as chemical stability, environmental friendliness, and high resolution [131,132]. Li Wang and colleagues integrated GOx and metal-bioinorganic materials (MB) into structural color inverse opal particles for visual reflection of wound pH (Fig. 5E) [112]. GOx, acting as a glucose scavenger, effectively alleviates the hyperglycemic microenvironment, and the produced H_2O_2 serves as a substrate for MB, generating a cascade of catalytic reactions that produce a large amount of ROS. The abundant microporous structure of inverse opals provides ample space for loading GOx and MB. Moreover, inverse opals will expand or contract at different pH levels, and changes in the pore structure lead to color changes, enabling real-time visual monitoring of pH [112].

GOx can participate in color reactions by catalyzing the decomposition of glucose. D. A. Jankowska's team constructed a biosensor capable of simultaneously detecting wound pH and glucose concentration [128]. The pH sensing is achieved through 5(6)-carboxynaphthofluorescein, a highly pH-responsive fluorophore that is particularly sensitive within the pH range of 6–8. The enzyme-linked reaction involving GOx is used for glucose detection. In the presence of HRP, the fluorophore reacts with H_2O_2 produced by GOx, generating a fluorescent signal quantitatively, thus enabling highly sensitive detection of glucose concentration in wounds [128].

5. Enhancing GOx acitivity: carriers

It has been astutely observed by researchers that the therapeutic effects of GOx, when applied locally to the wound via subcutaneous injection, are rather minimal. Due to the movement of bodily fluids, GOx cannot be continuously enriched at the targeted site, leading to a loss of therapeutic efficacy. Table 4 summarizes the carriers utilized for the immobilization of GOx. By immobilizing GOx onto biocompatible materials, it is possible to protect the enzyme, extend its half-life, and enhance the therapeutic outcome [58]. Additionally, these carriers can be loaded with antibiotics, metal nanoparticles, and heterojunctions to integrate other therapeutic strategies, such as photothermal therapy, cascade reactions and gas therapies, synergistically contributing to the healing of skin wounds [59].

5.1. Hydrogels

The repair of wounded tissue, particularly the healing of chronic wounds such as those associated with diabetes, is a complex and multistage biological process [133]. Concurrently, each stage is challenged by external environmental factors, including infection, inflammation, and ROS [134]. Therefore, wound dressings must possess a variety of functions (hemostasis, antibacterial properties, moisturization, etc.) to facilitate healing once the wound is covered [135]. Gauze remains the most widely used dressing in clinical settings due to its convenience, cost-effectiveness, rapid hemostasis, maintenance of wound dryness, and role as a physical barrier [136]. However, recent studies have indicated that a warm and moist environment can lead to faster and more successful wound healing [137]. Hydrogel dressings have shown great potential in non-invasive treatment and are considered an emerging and effective strategy [138].

As shown in Table 1, hydrogels loaded with GOx have a diverse composition in diabetic wound repair, including dopamine, chitosan, hyaluronic acid, keratin, β-cyclodextrin, and alginate. Hydrogel dressings typically possess a series of common characteristics: good tissue compatibility, adjustable biodegradability, excellent moisturizing ability, appropriate antimicrobial activity, sufficient mechanical strength, and drug loading capacity [108,139]. For example, Jiaxin Yang and colleagues prepared a functionalized DG@gel hydrogel through a two-step process involving co-assembly and phase transfer [29]. They first co-assembled a metal-organic nano-drug using Zn^{2+}, organic ligands, and the small molecule drug deferoxamine mesylate, followed by the incorporation of GOx and phase transfer to complete the hydrogel preparation [29]. Experimental evidence has demonstrated that DG@gel exhibits no cytotoxicity towards human umbilical vein endothelial cells (HUVECs) and mouse embryonic fibroblasts (NIH/3T3), while also possessing superior antibacterial activity against *S. aureus* and *E.coli*. Additionally, DG@gel has an appropriate degradation rate, allowing for sustained action at the wound site for up to 7 days [29].

Furthermore, certain hydrogel scaffolds loaded with GOx also exhibit additional functionalities, such as in situ formation, photothermal properties, and microneedle physical structures, which are briefly introduced below.

In Situ Formation. In contrast to hydrogels formed in vitro and applied topically, hydrogels that form in situ offer a more personalized fit to the physical structure of the wound, thus attracting the attention of researchers [140,141]. Yansong Chen's team developed an in situ hydrogel formation strategy triggered by GOx, using keratin as the raw material (Fig. 7B) [142]. They used a reducing agent to cleave intramolecular disulfide bonds within keratin, releasing free thiol groups, which were then oxidized by H_2O_2 produced from GOx to form intermolecular disulfide bonds, resulting in the in situ formation of the

Table 4
Scaffold materials for direct loading GOx in diabetic wound studies.

Category	Component	Function (besides loading GOx)	Ref.
Hydrogel	PDA	Loading Fe_2O_3 and hyaluronic acid Photothermal	[30]
	DFO[a] + IDA + Zn^{2+}	Antibacterial	[29]
	Oxidized alginate	pH and Glucose Concentration Monitoring Platforms	[128]
	Polyvinyl alcohol	Loading Fe_2C NPs	[42]
	Fc-QCs[c] + Pβ-CD	Antibacterial	[181]
	Alginate + Hyaluronic acid	Loading Cu_2O/Pt	[82]
	Poly(Lactic-Co-Glycolic Acid)	Loading Pt and Perfluorooctyl bromide	[62]
	Chitosan	Loading vanadium metal-organic polyhedrons	[86]
	Chitosan + Oxidized hyaluronic acid	Loading L-Arg	[111]
	PF-127	Loading Fe^{2+} and TMB	[182]
	Keratin	In Situ Hydrogel Formation	[142]
	Supramolecular G-quadruplex	Loading Hemoglobin	[87]
	Phenylboronic acid-functionalized hyaluronic acid + Guanosine	Loading Hemoglobin	[54]
Metal-Organic Frameworks	$Na_2S_2O_8$@ZIF-67	Antibacterial	[152]
	Ce + Alendronate (AL) + 2-Methylimidazole (HMIM)	SOD and CAT-like activities	[89]
	ZIF-8	Loading Bovine Hemoglobin	[183]
	ZIF-8	Loading HRP	[76]
	ZIF-8	Loading Fe_2O_3	[79]
	Fe-Cu MOF	Antibacterial	[83]
	Cu MOF	Loading Carbon Dots	[80]
	MAF-7	Loading HRP	[88]
	Cu-Zn MOF	Antibacterial	[81]
	2D Cu-TCPP(Fe) nanosheet	Fenton Reaction	[84]
	Au-Cu_2MoS_4 nanosheets	Loading Au (GOx-mimic)	[60]
	MoS_2 nanosheet	Loading Au (GOx-mimic) and bovine serum albumin	[53]
Silicon-Based Particles	Hollow mesoporous silica nanoparticles	Loading Azithromycin	[172]
Supramolecular Structures	CS + SBE-β-CD[b] + Fe^{2+} + GOx	Antibacterial	[64]
	Chitosan-modified palladium nano-cube	Loading Fe^{2+}	[63]
	Supramolecular iron delivery system[e]	Loading Au (GOx-mimic) POD-like activity Antibacterial	[61]
Carbon Nitride	CN/MoS_2	CN: Photocatalytic O_2 Supply MoS_2: Photothermal Effect; Fenton Reaction	[24]
	Carbon nitride/copper sulfide heterojunction	CN: Photocatalytic H_2 Production Glutathione Peroxidase (GPx), POD, and CAT-like activities	[57]
Others	GOx@MnS Nanoparticles	GOx: Carrier to Load MnS MnS: Provide H_2S	[85]
	Phosphorus doped graphitic carbon nitride nanosheets	Loading Au (GOx-mimic), $Cu_{1.6}O$ and Arg	[59]
	Opal hydrogel microparticles[d]	Loading copper peroxide nanodots	[112]
	Ionic-Covalent Organic Framework	Loading Fe	[77]
	Magnetic Fe_3O_4 NPs	CAT and POD-like activities	[46]
	Carbon-based nanozyme[f]	Photothermal Effect POD-like Activity	[49]

[a] DFO: deferoxamine mesylate; IDA: 4,5-imidazoledicarboxylic acid.
[b] SBE-β-CD: Sulfobutyl ether-β-cyclodextrin.
[c] Fc-QCs: ferrocene-modified quaternary ammonium chitosan; Pβ-CD: poly (β-cyclodextrin).
[d] Opal hydrogel microparticles: Composed of 2-hydroxy-2-methylpropiophenone, hyaluronic acid methacryloyl and acrylic acid.
[e] supramolecular iron delivery system: Bilayer structure with β-FeOOH as core and Fe^{3+}/polyamino acid as shell.
[f] carbon-based nanozyme: Composed of chitosan-grafted Fe-doped-CDs and mesoporous polydopamine nanoparticles.

hydrogel [142].

Photothermal Effect. The photothermal effect can elevate the local temperature at the wound site, enhancing the catalytic activity of GOx and disrupting bacterial integrity [143]. Additionally, an increase in tissue temperature can accelerate blood flow in the wound area, stimulate the proliferation of fibroblasts, and reduce inflammation, thereby hastening the wound healing process [108]. Polydopamine (PDA) is not only a common material for generating photothermal effects but also a frequently used component in the preparation of hydrogels [144]. Shengbo Li and colleagues loaded GOx and Fe_2O_3 into PDA and introduced hyaluronic acid to improve hydrogel stability, forming Fe/PDA@GOx@HA nanoparticles that met the requirements for both photothermal effects and drug loading [30].

Microneedle (MN) Patch Structures. As a painless transdermal drug delivery method, microscale needles can easily penetrate the physical barriers of the wound area, such as blood clots, scars, and exudates, to continuously release medications [99]. Meanwhile, microneedles can physically disrupt the integrity of biofilms in infected wounds, reducing bacterial drug resistance [145]. Additionally, microneedle structures can provide mechanical stimulation and allow for the loading of drugs to promote wound healing [146]. Xiangli Zhang and colleagues used polypyrrole-modified dopamine to load nanoparticles containing GOx and HRP [76]. Studies have shown that this microneedle patch possesses antimicrobial properties, high biocompatibility, and effective anti-inflammatory effects, demonstrating rapid and scar-preventing healing [76]. Caixia Sun's team designed a double-layer microneedle structure. Polyvinyl alcohol loaded with GOx and Fe_2C nanoparticles was used for the MN tips, achieving the elimination of biofilms in diabetic wounds [42]. The chitosan backing layer has excellent breathability, moisture absorption, and antibacterial properties, protecting the wound bed from re-infection during the healing process. These MNs, when applied to the wound tissue, break through the barrier effect and rapidly release Fe_2C nanoparticles and GOx in the biofilm activity area, achieving an efficient antibiofilm effect. At the same time, GOx overcomes the limitations of pH and H_2O_2 content, further accelerating the elimination of MRSA biofilms [42].

5.2. Metal-organic frameworks

Metal-Organic Frameworks (MOFs) are a class of emerging porous coordination polymers constructed from metal ions (or clusters) as nodes and organic molecules as ligands. They possess controllable morphology and porosity, high surface area, biocompatibility, degradability, and excellent physicochemical properties (Fig. 6B) [148]. MOFs have demonstrated significant advantages in the field of skin wound healing: 1) Their high porosity and surface area allow for efficient

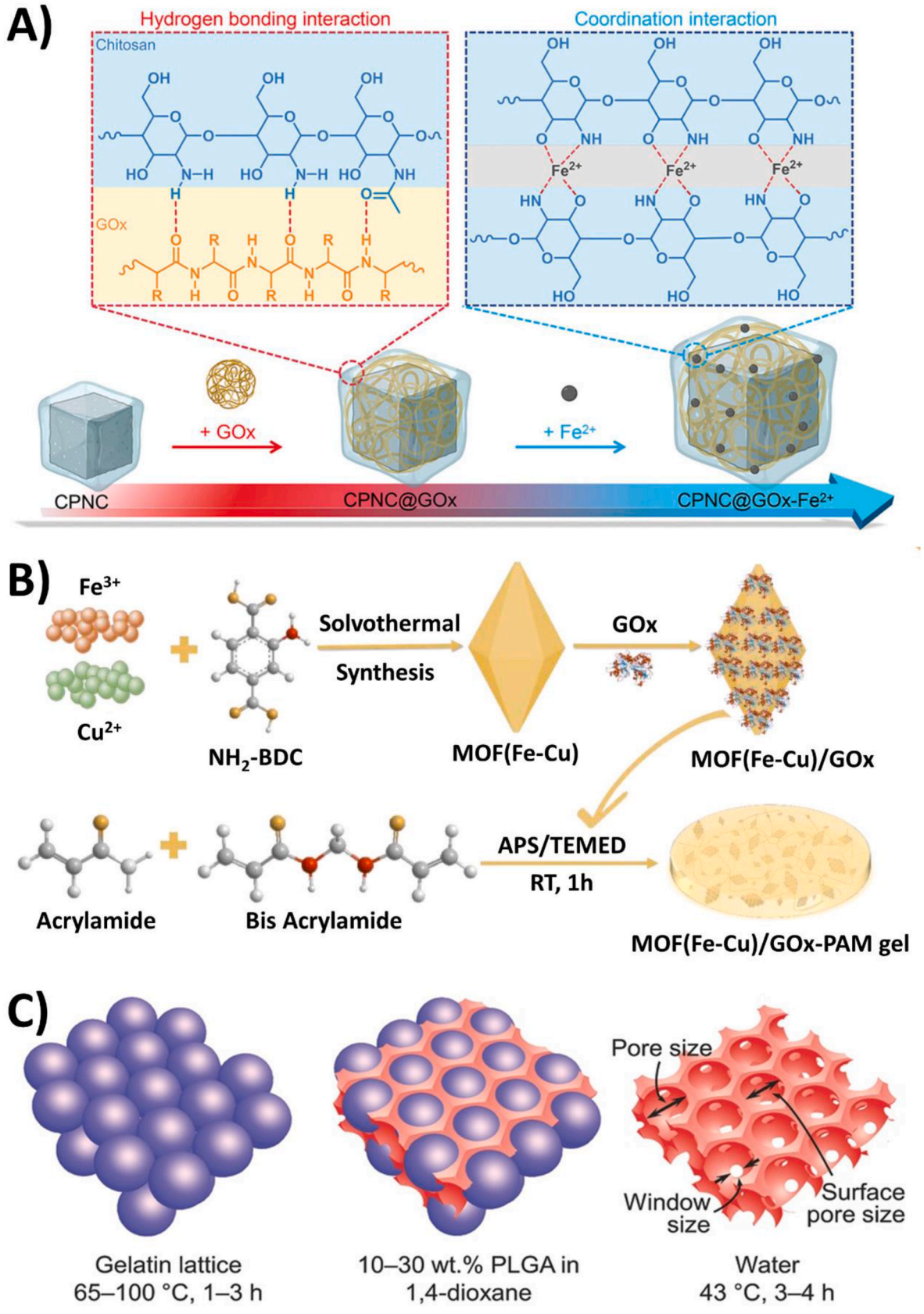

Fig. 6. Schematic representation of the scaffold material encapsulating GOx. A) Step-by-step assembly of the supramolecular photothermal cascade nano-reactor CPNC@GOx-Fe^{2+}. Reproduced with permission [63]. Copyright 2023, Wiley-Blackwell. B) Schematic diagrams of the synthetic routes of MOF(Fe-Cu)/GOx-PAM gel. Reproduced with permission [83]. Copyright 2023, Elsevier BV. C) Schematic illustration showing the major steps involved in the fabrication of an inverse opal scaffold. Reproduced with permission [147]. Copyright 2017, Wiley-Blackwell.

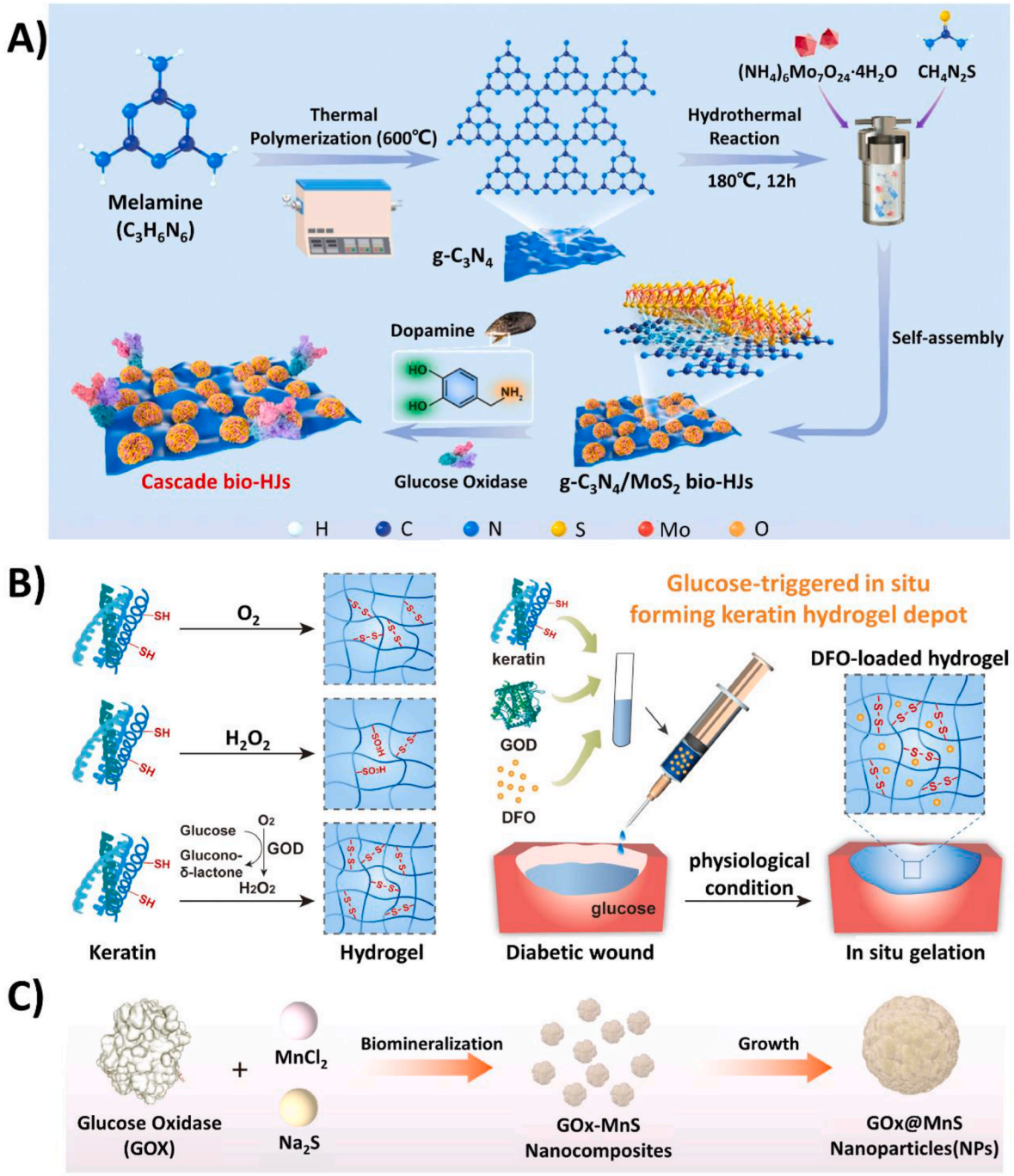

Fig. 7. Schematic representation of the scaffold material encapsulating GOx. A) Synthesis of the g-C_3N_4/MoS_2^-based C-bio-HJs. Reproduced with permission [24]. Copyright 2023, KeAi Communications Co. B) Schematic illustrations of gelation mechanisms by O_2 oxidation, direct addition of H_2O_2 solution, and indirect H_2O_2 supplement method via GOx-catalyzed glucose oxidation, and glucose-triggered in situ forming keratin hydrogel as a drug depot for the treatment of diabetic wounds. Reproduced with permission [142]. Copyright 2021, Elsevier BV. C) Synthesis of the GOx@MnS Nanoparticles. Reproduced with permission [85]. Copyright 2023, American Chemical Society.

loading of therapeutic drugs [149]; 2) Through metal coordination effects and the organic ligands of MOFs, some targeting molecules can be coupled to the MOF surface, endowing MOFs with the capability of targeted action; 3) The adjustable diameter endows MOFs with a certain degree of tissue penetration [150]; 4) Their degradability mediates the efficient excretion of MOFs, preserving the therapeutic effects while reducing the toxic effects of the metal framework [151].

Guangye Ge's team synthesized cobalt-based metal-organic frameworks (ZIF-67) in situ with $Na_2S_2O_8$ and electrostatically adsorbed GOx onto the porous surface of ZIF-67 to create NZG nanoparticles. When NZG nanoparticles are applied to infected wounds, the weakly acidic environment promotes the degradation of ZIF and the release of GOx. In this process, the degradation of ZIF releases Co^{2+} and $S_2O_8^{2-}$. Co^{2+} exhibits strong antibacterial activity, and $S_2O_8^{2-}$ is converted into highly toxic SO_4^-, which further forms hydroxyl radicals (·OH). Both Co^{2+} and $S_2O_8^{2-}$ act to disrupt bacterial membranes and organelle membranes, clearing biofilms from infected wound surfaces [152].

The "Two-Birds-with-One-Stone" Strategy of MOFs. The metal elements in MOFs, while forming the scaffold structure, can also serve as enzyme mimics to enhance the therapeutic performance of MOFs. Metal

elements are essential for many types of biological enzymes. The stability of the metal elements' binding to the enzyme proteins can be categorized into metalloenzymes and metal-activated enzymes [153]. In metalloenzymes, the metal is an indispensable component of the enzyme molecule and cannot be separated by dialysis. The metal ions are typically part of the active site [154]. In metal-activated enzymes, the metal ions are not tightly bound to the enzyme molecule and act as activators of enzyme activity by enhancing the enzyme's substrate selectivity or by directly participating in the catalytic reaction [155]. The intimate association between metal elements and biological enzymes endows some metal elements with the ability to mimic the activity of biological enzymes [156].

Xiaojuan Yu and colleagues utilized alendronate (AL) and 2-methylimidazole (HMIM) to form a dual-ligand molecule, which was then co-assembled driven by cerium (Ce^{3+}) to form nanoparticles CHA. Glucose oxidase (GOx) was embedded to create a nanozyme CHA@GOx with multiple enzymatic activities [89]. The Ce nanoparticles possess a rich array of enzymatic activities, with Ce^{3+}/Ce^{4+} coexisting on the surface of CHA@GOx. The tetravalent state is responsible for scavenging H_2O_2 and hydroxyl radicals, while the trivalent state scavenges superoxide radicals, endowing the CHA@GOx material with SOD-like and CAT-like activities [89]. MOFs can also mimic the enzymatic activity of GOx, serving as a substitute for relatively unstable protein enzymes [53,60]. Yang Li and colleagues loaded Au nanoparticles modified with bovine serum albumin (Au@BSA) onto molybdenum disulfide nanosheets (MoS_2@Au@BSA NSs) [53]. MoS_2@Au@BSA possesses activities similar to GOx, SOD, and POD, synergistically promoting the healing of diabetic wounds at multiple stages [53]. The GOx-like activity of Au catalyzes the oxidation of glucose to gluconic acid and H_2O_2. H_2O_2 is then converted into ·OH under POD-like activity, thereby eliminating bacteria. When the wound pH reaches an alkaline state, MoS_2@Au@BSA mimics SOD, converting superoxide anions into O_2 and H_2O_2, and through CAT-like activity, it decomposes endogenous and exogenous H_2O_2 into O_2, thereby alleviating oxidative stress, relieving hypoxia, and promoting glucose oxidation [53].

5.3. Supramolecular structures

The healing process of diabetic wounds also involves the dynamic remodeling of the local extracellular matrix (ECM). An ideal biomaterial should be capable of dynamically meeting the needs of local tissues to maximize wound healing [157]. Traditional hydrogels are typically formed by permanent and irreversible covalent reactions between polymer chains, lacking dynamism, and are unable to be reconstructed after structural damage [158]. The emergence of supramolecular chemistry has provided a way to construct dynamic hydrogels. Supramolecular structures are formed by non-covalent interactions, including hydrogen bonding, hydrophobic effects, and ionic interactions [159,160]. Compared to conventional hydrogels, supramolecular hydrogels possess dynamic reversibility and excellent self-healing properties, ensuring seamless adaptation to the complex structures of surrounding tissues [161].

Lei Chen's team designed a supramolecular photothermal cascade nanoreactor (CPNC@GOx-Fe^{2+}) in 2023 (Fig. 6A) [63]. The researchers based their design on palladium nanocubes (CPNC) with near-infrared absorption and excellent photothermal effects, and immobilized GOx and Fe^{2+} on chitosan. In an extraction wound model with biofilm presence, CPNC@GOx-Fe^{2+} and its mediated cascade reactions synergistically provided antibacterial action and wound protection, accelerating the healing of infected wounds without affecting the oral commensal flora [63]. Also from Lei Chen's team, in 2022, they reported a supramolecular cascade reactor constructed from chitosan (CS), sulfobutyl ether-β-cyclodextrin (SBE-β-CD), ferrous ions (Fe^{2+}), and GOx [64]。Within the supramolecular cascade reactor, GOx catalyzed the oxidation of glucose, and the produced H_2O_2 served as a substrate for Fe^{2+}, further generating ·OH radicals for antibacterial effects. Additionally, using a mixture of poly(ethylene glycol) diacrylate (PEGDA) and glucose as a precursor, the supramolecular cascade reactor could further initiate radical polymerization, forming a hydrogel structure in situ at the wound site [64]. Studies in diabetic wound models have shown that the in situ formation of the hydrogel and the antibacterial effect of ·OH radicals synergistically promoted the healing of diabetic wounds [64].

It should be noted that supramolecular structures do not necessarily exist in the form of hydrogels, which is also the reason why they are not included in the "Hydrogels" section. Siyuan Li's team reported an iron-protein mimetic supramolecular iron delivery system (SIDS) with a shuttle-like core-shell structure, where β-FeOOH serves as the core and a Fe^{3+}/polyamino acid network as the shell. This structure is achieved through the hydrolysis of $FeCl_3$, condensation of amino acids, and self-assembly of iron-containing components [61]. At room temperature, Fe^{3+} on the surface of SIDS is reduced to Fe^{2+}, and Au nanoparticles are deposited on its surface to construct FeOOH@Fe-Serine@Au NSs with dual nanozyme (GOx and POD) activities [61].

5.4. Heterojunctions

Heterojunctions are interfacial regions composed of two or more different semiconductor materials, often possessing superior optoelectronic properties that individual PN junctions of the constituent semiconductors cannot achieve [162]. In the field of biomaterials, research on heterojunctions is equally vibrant. By precisely controlling the stacking of different two-dimensional materials, entirely new electronic, mechanical, and optical properties can be generated [163].

Carbon nitride (CN) is a material of choice for a variety of photocatalytic reactions, including water splitting, CO_2 reduction, nitrogen reduction, and the degradation of organic pollutants [164]. Owing to its excellent thermal and chemical stability, tunable bandgap range, and level of surface functionalization, CN stands out among a series of two-dimensional materials with high specific surface areas [165,166]. Concurrently, individual photocatalysts often suffer from rapid recombination of photogenerated electrons and vacancies, leading to suboptimal catalytic efficiency. The construction of CN-based heterojunctions has been proven to mitigate charge-carrier recombination, thereby enhancing photocatalytic efficiency [167].

In GOx-based diabetic wound research, two studies have utilized CN-based heterojunctions. One study leveraged the photocatalytic water oxidation capability of CN, while the other harnessed its hydrogen evolution activity. Researchers have combined metal sulfides with CN to promote the separation of photoelectrons and enhance the catalytic efficiency of CN, while also mediating other strategies such as photothermal effects [24,57]. Yi Deng and colleagues constructed a cascade bioheterojunction (C-bio-HJs) composed of CN/MoS_2 and GOx (Fig. 7A) [24]. The suitable band edge position of MoS_2 and its good lattice matching with CN can enhance light absorption and facilitate the separation of photogenerated charges. The excellent photocatalytic water oxidation capability of CN/MoS_2 can provide substrates for GOx while alleviating the hypoxic environment of diabetic wounds. Furthermore, MoS_2 possesses photothermal effects and POD-like activity, and the combination of MoS_2 with CN can exert multimodal synergistic antibacterial functions, including PDT (photodynamic therapy), PTT (photothermal therapy), and CDT (chemodynamic therapy), avoiding the shortcomings of single-mode therapy [24]. Miaomiao He and colleagues constructed a CN/$Cu_{2-x}S$ heterojunction loaded with GOx [57]. CuS has an appropriate bandgap energy value and favorable pathogen-killing efficacy. Similar to MoS_2, CuS can also be combined with CN to improve the separation efficiency of photoelectrons and vacancies. The CN/$Cu_{2-x}S$ exhibited photocatalytic hydrogen evolution activity [57]. It is widely recognized that H_2 is an emerging therapeutic gas that can react with excessive ROS caused by endogenous H_2O_2, thereby improving inflammation.

The heterojunctions constructed by the teams of Yi Deng and

Miaomiao He exhibit differentiated photocatalytic activities of CN, leading to the production of either oxygen or hydrogen. Both teams have demonstrated the photocatalytic activity of these heterojunctions using sophisticated in situ atomic-scale characterization tools, including transmission electron microscopy (TEM), UV–Vis spectroscopy, X-ray diffraction (XRD), and small-angle X-ray scattering, yet they have not provided a thorough elucidation of the catalytic mechanisms. As a result, it remains challenging to discern the root cause of the differences in the catalytic activities of CN between the two studies. It is important to note that in photocatalytic reactions, uncontrolled oxidation of reactants can lead to poor selectivity, particularly within complex biological systems [168]. Given that organic molecules generally possess low redox potentials, photocatalytic reactions may cause damage to these molecules [169]. Additionally, inorganic semiconductors with larger band gaps can generate a multitude of highly oxidative free radicals, predominantly hydroxyl radicals, which can further disrupt the fragile microenvironment of diabetic wounds [170]. Therefore, we encourage researchers to utilize atomic-scale characterization tools to discuss or hypothesize the photocatalytic mechanisms, thereby bridging the gap between characterization results and catalytic activity and biocompatibility. This approach will enhance the credibility of the research and facilitate a deeper understanding for the readers [171].

5.5. Other carriers

Researchers have also employed other structures to load GOx to facilitate the healing of diabetic wounds, including silica nanoparticles, opal, GOx, and ion-covalent organic frameworks (iCOFs).

Minqi Shi and colleagues used hollow mesoporous silica nanoparticles (HMSN) as a nanocarrier to load and deliver azithromycin and GOx, achieving significant therapeutic effects in chronic diabetic wounds [172]. Brunauer-Emmett-Teller (BET) measurements indicated that HMSN has a relatively large surface area (617 m^2/g) and a pore size of 3.76 nm. TEM also revealed that the synthesized HMSN has a large cavity, which is conducive to the effective loading of drug molecules [172].

Yuxuan Ge and colleagues have constructed an intriguing set of nanoparticles [85]. Instead of employing additional scaffold materials, they opted to use GOx itself as a nano carrier, allowing the deposition of water-insoluble MnS on GOx through biomineralization to form GOx@MnS nanoparticles (Fig. 7C) [85].

Li Wang utilized an inverse opal structure to load GOx and metal bioinorganics (Fig. 6C) [112]. The inverse opal is a porous scaffold that is widely used in the biomedical field [173–175]. In most techniques, the formation of structures such as hydrogels, supramolecular particles, and porous scaffolds relies on the random connection of chemical bonds, leading to uncontrollable sizes and microstructures [147]. In contrast, the inverse opal structure scaffold possesses uniform dimensions, porosity, and connectivity, which can be maintained consistently across different samples [147]. This advantage of the inverse opal structure stems from its fabrication process, where these pores are inherited from a template composed of monodisperse microsphere lattices [174,176].

Covalent organic frameworks (COFs) possess a large specific surface area, regularly distributed active sites, and framework-enhanced functionalities, and exhibit strong mechanical flexibility and biocompatibility [177]. Ionic covalent organic frameworks (iCOFs), which are formed by modifying the target COFs with ionic organic molecules, have been widely applied across various fields, including carbon dioxide capture, electrochemistry, ion conduction, photodynamic therapy, and photothermal therapy [178,179]. Similar to two-dimensional graphene, COFs can also form covalent organic nanosheets with a thickness of just a few layers to achieve highly sensitive sensing and efficient drug delivery [180]. Yite Li and colleagues introduced porphyrin derivatives into COFs to prepare iron-chelating porphyrin-based iCOFs with photothermal characteristics and peroxidase activity [77]. The iCOF was further loaded with GOx via electrostatic interactions to form the GOx-on-Fe-iCOF nanozyme, which is encapsulated in an injectable hydrogel for the treatment of infected wounds [77].

5.5.1. Challenges and prospects

In recent years, with the advancement of material science and nanotechnology, multifunctional biomaterials with GOx-like activity have made significant research and development progress. These biomaterials have not only successfully addressed pathological challenges in diabetic wounds, such as angiogenesis obstacles, excessive oxidative stress, and high levels of inflammation, but more importantly, they have directly improved the hyperglycemic microenvironment at the wound site, thereby resolving the etiology of the aforementioned pathological processes. Consequently, multifunctional biomaterials with GOx-like activity have demonstrated substantial application potential and value in diabetic wound treatment. This article systematically reviews and summarizes the construction methods and application strategies of these biomaterials based on current research findings.

Currently, there is a paucity of clinical trial results related to GOx in wound treatment. We conducted a search on ClinicalTrials.gov using "Condition/disease = wound" and "Intervention/treatment = Glucose oxidase," identifying three clinical studies that met the criteria, as shown in Table 5. Only one study was dedicated to the treatment of diabetic wounds, in which a GAT@F nanozyme hydrogel complex was utilized, integrating a GOx and CAT treatment system. Medihoney, a blend of two types of honey from Australia and New Zealand, contains GOx and Leptospermum compounds, and has been used in clinical studies to promote the healing of palatal wounds. E−101 solution, composed of active components of GOx and porcine myeloperoxidase (pMPO), has been applied in the prevention of incisional infections in patients undergoing colorectal surgery.

The ultimate goal of biomaterials research is clinical translation, aimed at providing tangible benefits to patients (Fig. 8). We believe that before facilitating the translation of these biomaterials into clinical applications, the following key issues still need to be resolved.

1) Maintenance of GOx-Like Activity. When discussing the stability of GOx in wound healing, we must recognize its fundamental characteristics as a protein. Given the presence of various proteolytic enzymes in the wound environment that can decompose proteins, native GOx is prone to inactivation under such conditions. To enhance its stability for clinical applications, we might consider strategies such as enzyme immobilization, protein engineering, and chemical modification. Additionally, it is worth noting that both natural GOx and nanozymes can lead to the accumulation of gluconic acid during the catalytic process, gradually acidifying the local microenvironment. Should the pH exceed the enzyme's optimal range, a significant decrease in enzymatic activity will occur. Therefore, to sustain enzymatic activity and optimize therapeutic outcomes, it is essential to construct a glucose-driven cascade reaction system and regulate and utilize the degradation products of glucose rationally.

Table 5
Clinical studies of GOx for wound treatment, data from *ClinicalTrials.gov*.

Condition or disease	Phase[a]	Intervention/ Treatment	Enrollment	*ClinicalTrial.gov* ID
Diabetic Wound	Phase 2	GAT@F nanoenzyme hydrogel complex	49 (Estimated)	NCT06492811
Healing Wound	Phase 4	Medihoney dressing	20 (Estimated)	NCT04269694
Infections	Phase 3	E−101 Solution 300 GU/ml	503 (Actual)	NCT01297959

[a] Phase: The clinical trial phase of a study drug or biological product according to the definition established by the US Food and Drug Administration (FDA). There are five stages: early stage 1 (stage 0), stage 1, stage 2, stage 3, and stage 4.

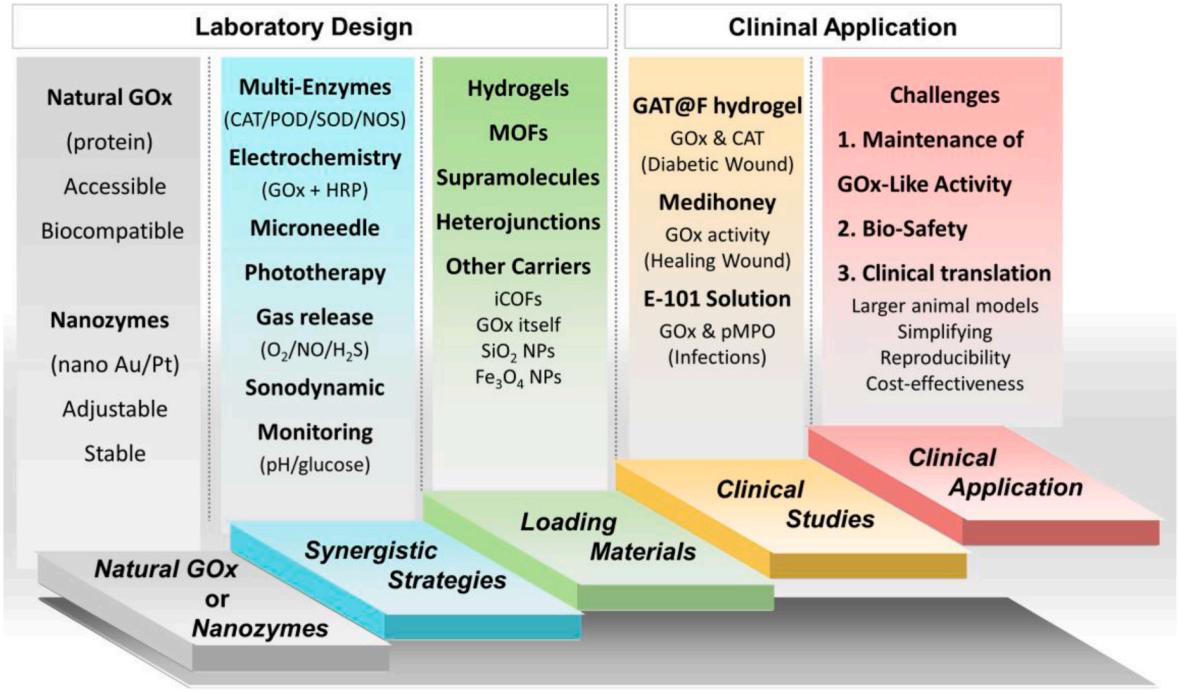

Fig. 8. GOx applied to diabetic wound treatment: from laboratory design to clinical application.

2) Bio-Safety. Firstly, native GOx itself carries immunogenicity, and the metal components in nanozymes also harbor potential toxicity risks. If these substances enter the circulatory system through the wound's vasculature, they may adversely affect other organs or tissues. Therefore, clarifying the metabolic pathways of these substances and their degradation products in the body is crucial. Moreover, current bio-safety assessments are mostly limited to short-term observations of 2–4 weeks. To more comprehensively evaluate their long-term safety, future studies should conduct bio-safety research over extended periods. It is also important to consider the potential impacts of products like gluconic acid and H_2O_2 generated during glucose decomposition. We can utilize high-throughput sequencing technologies to deeply explore these potential impacts at the molecular level, ensuring the safety of this therapy in clinical applications.
3) Clinical Translation. In existing research, rodent animal models are widely used to evaluate GOx-based diabetic wound therapies. However, these animal models typically exhibit a strong tendency for self-healing, which may result in therapeutic effects observed in rodents not being entirely applicable to human patients. Therefore, before advancing to clinical trials, it is essential to use larger animal models that more closely resemble human physiological conditions, such as pigs or monkeys, for further functional validation. Additionally, although the multifunctionalization of biomaterials is a future trend, current research, in the pursuit of multifunctionalization, often employs complex multi-step reaction processes. This not only leads to high production costs but also, more critically, results in products with poor stability that are difficult to store long-term, thus limiting their widespread application. Therefore, in the future, while pursuing the multifunctionalization of biomaterials, it is imperative to place a high emphasis on simplifying the preparation methods, ensuring reproducibility, and cost-effectiveness, to guarantee that these advanced materials can maximize their value in practical applications.

In the future, biomaterials with GOx-like activity will have broad application prospects in the field of diabetic wound treatment. Future research directions will head towards simple preparation, multifunctionality, and the integration of diagnosis and therapy, with the ultimate goal of benefiting patients with diabetic wounds.

CRediT authorship contribution statement

Yuheng Liao: Writing – review & editing, Writing – original draft, Project administration, Investigation, Conceptualization. **Zhenhe Zhang:** Writing – original draft, Methodology, Conceptualization. **Yanzhi Zhao:** Writing – review & editing, Visualization, Software. **Shengming Zhang:** Writing – review & editing, Methodology, Investigation. **Kangkang Zha:** Visualization, Validation, Data curation. **Lizhi Ouyang:** Investigation, Formal analysis. **Weixian Hu:** Visualization, Investigation. **Wu Zhou:** Supervision, Resources. **Yun Sun:** Supervision, Resources. **Guohui Liu:** Supervision, Resources, Funding acquisition.

Ethics approval and consent to participate

The "Ethics approval and consent to paticipate" is not applicable.

Data availability

No data was used for the research described in the article.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Guohui Liu reports financial support was provided by the National Natural Science Foundation of China. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This work is supported by the National Natural Science Foundation of China (No. 82272491, No. 82072444).

References

[1] J.Y. Ding, et al., Mesenchymal stem cell-derived extracellular vesicles in skin wound healing: roles, opportunities and challenges, Mil Med Res 10 (1) (2023) 36.
[2] Y. Xiong, et al., Reactive oxygen species-scavenging nanosystems in the treatment of diabetic wounds, Adv. Healthcare Mater. 12 (25) (2023) e2300779.
[3] N.C. Nowak, et al., Cutaneous innervation in impaired diabetic wound healing, Transl. Res. 236 (2021) 87–108.
[4] Y. Li, et al., Exosomes: compositions, biogenesis, and mechanisms in diabetic wound healing, J. Nanobiotechnol. 22 (1) (2024), 398.
[5] H.J. Kang, et al., Self-assembled elastin-like polypeptide fusion protein coacervates as competitive inhibitors of advanced glycation end-products enhance diabetic wound healing, J. Contr. Release 333 (2021) 176–187.
[6] H.N. Wilkinson, M.J. Hardman, Cellular senescence in acute and chronic wound repair, Cold Spring Harbor Perspect. Biol. 14 (11) (2022).
[7] L. Wan, et al., The advanced glycation end-products (AGEs)/ROS/NLRP3 inflammasome axis contributes to delayed diabetic corneal wound healing and nerve regeneration, Int. J. Biol. Sci. 18 (2) (2022) 809–825.
[8] S.T. Krishnan, et al., Neurovascular factors in wound healing in the foot skin of type 2 diabetic subjects, Diabetes Care 30 (12) (2007) 3058–3062.
[9] W. Zhou, et al., Glucose and MMP-9 dual-responsive hydrogel with temperature sensitive self-adaptive shape and controlled drug release accelerates diabetic wound healing, Bioact. Mater. 17 (2022) 1–17.
[10] B. Lan, et al., Sustained delivery of MMP-9 siRNA via thermosensitive hydrogel accelerates diabetic wound healing, J. Nanobiotechnol. 19 (1) (2021) 130.
[11] H. Maranna, et al., Negative pressure wound therapy in grade 1 and 2 diabetic foot ulcers: a randomized controlled study, Diabetes Metabol. Syndr.: Clin. Res. Rev. 15 (1) (2021) 365–371.
[12] L.A. Lavery, et al., Diabetic Foot Syndrome: evaluating the prevalence and incidence of foot pathology in Mexican Americans and non-Hispanic whites from a diabetes disease management cohort, Diabetes Care 26 (5) (2003) 1435–1438.
[13] N.H. Cho, et al., IDF Diabetes Atlas: global estimates of diabetes prevalence for 2017 and projections for 2045, Diabetes Res. Clin. Pract. 138 (2018) 271–281.
[14] Y. Hu, et al., Stimuli-responsive therapeutic systems for the treatment of diabetic infected wounds, Nanoscale 14 (36) (2022) 12967–12983.
[15] J. Jiang, et al., Recent progress in nanozymes for the treatment of diabetic wounds, J. Mater. Chem. B 11 (29) (2023) 6746–6761.
[16] Y. Liao, et al., Engineered extracellular vesicles in wound healing: design, paradigms, and clinical application, Small 20 (7) (2024) e2307058.
[17] Z. Zhang, et al., Copper incorporated biomaterial-based technologies for multifunctional wound repair, Theranostics 14 (2) (2024) 547–570.
[18] C.M. Wong, K.H. Wong, X.D. Chen, Glucose oxidase: natural occurrence, function, properties and industrial applications, Appl. Microbiol. Biotechnol. 78 (6) (2008) 927–938.
[19] L.H. Fu, et al., Catalytic chemistry of glucose oxidase in cancer diagnosis and treatment, Chem. Soc. Rev. 47 (17) (2018) 6454–6472.
[20] S.B. Bankar, et al., Glucose oxidase–an overview, Biotechnol. Adv. 27 (4) (2009) 489–501.
[21] F. Duan, et al., Thermo-pH-Sensitive polymer conjugated glucose oxidase for tumor-selective starvation-oxidation-immune therapy, Adv. Mater. 35 (17) (2023) e2209765.
[22] Y. Fu, et al., Glucose oxidase and metal catalysts combined tumor synergistic therapy: mechanism, advance and nanodelivery system, J. Nanobiotechnol. 21 (1) (2023) 400.
[23] M. Sharifiaghdam, et al., Macrophages as a therapeutic target to promote diabetic wound healing, Mol. Ther. 30 (9) (2022) 2891–2908.
[24] Y. Deng, et al., Rapid sterilisation and diabetic cutaneous regeneration using cascade bio-heterojunctions through glucose oxidase-primed therapy, Bioact. Mater. 25 (2023) 748–765.
[25] Y. Yang, et al., Ubiquitination flow repressors: enhancing wound healing of infectious diabetic ulcers through stabilization of polyubiquitinated hypoxia-inducible factor-1α by theranostic nitric oxide nanogenerators, Adv. Mater. 33 (45) (2021) e2103593.
[26] M. Zubair, J. Ahmad, Role of growth factors and cytokines in diabetic foot ulcer healing: a detailed review, Rev. Endocr. Metab. Disord. 20 (2) (2019) 207–217.
[27] Z. Lu, et al., Porous Pt nanospheres incorporated with GOx to enable synergistic oxygen-inductive starvation/electrodynamic tumor therapy, Adv. Sci. 7 (17) (2020) 2001223.
[28] Q. Li, et al., Enhancing diabetic wound healing with a pH-responsive nanozyme hydrogel featuring multi-enzyme-like activities and oxygen self-supply, J. Contr. Release (2023).
[29] J. Yang, et al., Glucose-responsive multifunctional metal-organic drug-loaded hydrogel for diabetic wound healing, Acta Biomater. 140 (2022) 206–218.
[30] S. Li, et al., Microneedle patches with antimicrobial and immunomodulating properties for infected wound healing, Adv. Sci. 10 (22) (2023) e2300576.
[31] S.H. Kuo, et al., Role of pH value in clinically relevant diagnosis, Diagnostics 10 (2) (2020).
[32] M.H. Pipelzadeh, I.L. Naylor, The in vitro enhancement of rat myofibroblast contractility by alterations to the pH of the physiological solution, Eur. J. Pharmacol. 357 (2–3) (1998) 257–259.
[33] C.B. Keragala, R.L. Medcalf, Plasminogen: an enigmatic zymogen, Blood 137 (21) (2021) 2881–2889.
[34] J.S. Chin, et al., Drug therapies and delivery mechanisms to treat perturbed skin wound healing, Adv. Drug Deliv. Rev. 149–150 (2019) 2–18.
[35] T.K. Hunt, et al., Respiratory gas tensions and pH in healing wounds, Am. J. Surg. 114 (2) (1967) 302–307.
[36] A.J. Bullock, et al., Bacteria induced pH changes in tissue-engineered human skin detected non-invasively using Raman confocal spectroscopy, Appl. Spectrosc. Rev. 55 (2) (2020) 158–171.
[37] T.A. Krulwich, G. Sachs, E. Padan, Molecular aspects of bacterial pH sensing and homeostasis, Nat. Rev. Microbiol. 9 (5) (2011) 330–343.
[38] J. Yan, B.L. Bassler, Surviving as a community: antibiotic tolerance and persistence in bacterial biofilms, Cell Host Microbe 26 (1) (2019) 15–21.
[39] H. Lambers, et al., Natural skin surface pH is on average below 5, which is beneficial for its resident flora, Int. J. Cosmet. Sci. 28 (5) (2006) 359–370.
[40] J.C. Berkmann, et al., Early pH changes in musculoskeletal tissues upon injury-aerobic catabolic pathway activity linked to inter-individual differences in local pH, Int. J. Mol. Sci. 21 (7) (2020).
[41] Z.Y. Han, et al., pH-Responsive wound dressings: advances and prospects, Nanoscale Horizons 8 (4) (2023) 422–440.
[42] C. Sun, et al., An integrated therapeutic and preventive nanozyme-based microneedle for biofilm-infected diabetic wound healing, Adv. Healthcare Mater. 12 (30) (2023) e2301474.
[43] R. Derwin, et al., The effect of inflammation management on pH, temperature, and bacterial burden, Int. Wound J. 20 (4) (2023) 1118–1129.
[44] S. Wang, et al., Triple cross-linked dynamic responsive hydrogel loaded with selenium nanoparticles for modulating the inflammatory microenvironment via PI3K/akt/NF-κB and MAPK signaling pathways, Adv. Sci. 10 (31) (2023) e2303167.
[45] Y. Liang, et al., pH/glucose dual responsive metformin release hydrogel dressings with adhesion and self-healing via dual-dynamic bonding for athletic diabetic foot wound healing, ACS Nano 16 (2) (2022) 3194–3207.
[46] X. Du, et al., pH-switchable nanozyme cascade catalysis: a strategy for spatial-temporal modulation of pathological wound microenvironment to rescue stalled healing in diabetic ulcer, J. Nanobiotechnol. 20 (1) (2022) 12.
[47] Y. Zhou, et al., Multifunctional nanoreactors-integrated microneedles for cascade reaction-enhanced cancer therapy, J. Contr. Release 339 (2021) 335–349.
[48] R. Hao, et al., Ultrasmall Au/Pt-loaded biocompatible albumin nanospheres to enhance photodynamic/catalytic therapy via triple amplification of glucose-oxidase/catalase/peroxidase, J. Colloid Interface Sci. 654 (Pt A) (2024) 212–223.
[49] Y. Shen, et al., A multifunctional cascade nanoreactor based on Fe-driven carbon nanozymes for synergistic photothermal/chemodynamic antibacterial therapy, Acta Biomater. 168 (2023) 580–592.
[50] Y. Ahmed, et al., Roles of reactive oxygen species in antibiotic resistant bacteria inactivation and micropollutant degradation in Fenton and photo-Fenton processes, J. Hazard Mater. 430 (2022) 128408.
[51] Z. Li, et al., A tumor cell membrane-coated self-amplified nanosystem as a nanovaccine to boost the therapeutic effect of anti-PD-L1 antibody, Bioact. Mater. 21 (2023) 299–312.
[52] Y.Y. Liu, et al., Photodegradation of carbon dots cause cytotoxicity, Nat. Commun. 12 (1) (2021) 812.
[53] Y. Li, et al., Injectable hydrogel based on defect-rich multi-nanozymes for diabetic wound healing via an oxygen self-supplying cascade reaction, Small 18 (18) (2022) e2200165.
[54] X. Zhang, et al., Guanosine-driven hyaluronic acid-based supramolecular hydrogels with peroxidase-like activity for chronic diabetic wound treatment, Acta Biomater. 172 (2023) 206–217.
[55] J.S. Barroso-Martínez, et al., Real-time detection of hydroxyl radical generated at operating electrodes via redox-active adduct formation using scanning electrochemical microscopy, J. Am. Chem. Soc. 144 (41) (2022) 18896–18907.
[56] K.B. Dickson, J. Zhou, Role of reactive oxygen species and iron in host defense against infection, Front Biosci (Landmark Ed) 25 (8) (2020) 1600–1616.
[57] M. He, et al., Multi-functional bio-HJzyme: revolutionizing diabetic skin regeneration with its glucose-unlocked sterilization and programmed anti-inflammatory effects, Adv. Sci. 10 (21) (2023) e2300986.
[58] M. Wang, et al., Recent advances in glucose-oxidase-based nanocomposites for tumor therapy, Small 15 (51) (2019) e1903895.
[59] L. Shang, et al., Ultrasound-Augmented multienzyme-like nanozyme hydrogel spray for promoting diabetic wound healing, ACS Nano 17 (16) (2023) 15962–15977.
[60] J. Shan, et al., Glucose metabolism-inspired catalytic patches for NIR-II phototherapy of diabetic wound infection, Acta Biomater. 157 (2023) 200–209.
[61] S. Li, et al., Biomimetic dual-nanozymes with catalytic cascade reactions against diabetic wound infection, J. Colloid Interface Sci. 651 (2023) 319–333.
[62] Z. Zhou, et al., Nanohybrid double network hydrogels based on a platinum nanozyme composite for antimicrobial and diabetic wound healing, ACS Appl. Mater. Interfaces 15 (14) (2023) 17612–17626.
[63] L. Chen, et al., Supramolecular photothermal cascade nano-reactor enables photothermal effect, cascade reaction, and in situ hydrogelation for biofilm-associated tooth-extraction wound healing, Adv. Mater. 35 (31) (2023) e2301664.
[64] L. Chen, et al., Glucose-activated nanoconfinement supramolecular cascade reaction in situ for diabetic wound healing, ACS Nano 16 (6) (2022) 9929–9937.
[65] Z. Zhong, et al., γ-Fe(2) O(3) loading mitoxantrone and glucose oxidase for pH-responsive chemo/chemodynamic/photothermal synergistic cancer therapy, Adv. Healthcare Mater. 11 (11) (2022) e2102632.
[66] B.L. Greene, et al., Applications of photogating and time resolved spectroscopy to mechanistic studies of hydrogenases, Acc. Chem. Res. 50 (11) (2017) 2718–2726.

[67] C. Wang, et al., Hydrogen generation upon nanocatalyzed hydrolysis of hydrogen-rich boron derivatives: recent developments, Acc. Chem. Res. 53 (10) (2020) 2483–2493.
[68] Z. Su, et al., Enzymatic bionanocatalysts for combating peri-implant biofilm infections by specific heat-amplified chemodynamic therapy and innate immunomodulation, Drug Resist. Updates 67 (2023) 100917.
[69] C. Nie, et al., Engineered enzyme-loaded erythrocyte vesicles precisely deprive tumoral nutrients to induce synergistic near-infrared-II photothermal therapy and immune activation, ACS Nano 17 (14) (2023) 13211–13223.
[70] C. Deng, et al., Direct electrochemistry of glucose oxidase and biosensing for glucose based on boron-doped carbon nanotubes modified electrode, Biosens. Bioelectron. 23 (8) (2008) 1272–1277.
[71] Q. Liu, et al., Direct electrochemistry of glucose oxidase and electrochemical biosensing of glucose on quantum dots/carbon nanotubes electrodes, Biosens. Bioelectron. 22 (12) (2007) 3203–3209.
[72] R. Chen, et al., Highly sensitive surface plasmon resonance sensor with surface modified MoSe(2)/ZnO composite film for non-enzymatic glucose detection, Biosens. Bioelectron. 237 (2023) 115469.
[73] S. Cinti, et al., Novel bio-lab-on-a-tip for electrochemical glucose sensing in commercial beverages, Biosens. Bioelectron. 165 (2020) 112334.
[74] M. Zhao, et al., Multistage-responsive dual-enzyme nanocascades for synergistic radiosensitization-starvation cancer therapy, Adv. Healthcare Mater. 12 (21) (2023) e2300118.
[75] S.L. Wong, et al., Diabetes primes neutrophils to undergo NETosis, which impairs wound healing, Nat. Med. 21 (7) (2015) 815–819.
[76] X. Zhang, et al., Self-powered enzyme-linked microneedle patch for scar-prevention healing of diabetic wounds, Sci. Adv. 9 (28) (2023) eadh1415.
[77] Y. Li, et al., Ionic covalent-organic framework nanozyme as effective cascade catalyst against bacterial wound infection, Small 17 (32) (2021) e2100756.
[78] C. Jia, Y. Guo, F.G. Wu, Chemodynamic therapy via Fenton and fenton-like nanomaterials: strategies and recent advances, Small 18 (6) (2022) e2103868.
[79] M. Deng, et al., Diabetes immunity-modulated multifunctional hydrogel with cascade enzyme catalytic activity for bacterial wound treatment, Biomaterials 289 (2022) 121790.
[80] S. Zhang, et al., Luminescent MOF-based nanofibers with visual monitoring and antibacterial properties for diabetic wound healing, ACS Appl. Mater. Interfaces (2023).
[81] C. Wang, et al., Electrospun fibers integrating enzyme-functionalized metal-organic frameworks for postoperative tumor recurrence inhibition and simultaneously wound tissue healing, Int. J. Biol. Macromol. 248 (2023) 125876.
[82] D. Dong, et al., Acid-degradable nanocomposite hydrogel and glucose oxidase combination for killing bacterial with photothermal augmented chemodynamic therapy, Int. J. Biol. Macromol. 234 (2023) 123745.
[83] M. Tian, et al., Bimetal-organic framework/GOx-based hydrogel dressings with antibacterial and inflammatory modulation for wound healing, Acta Biomater. 158 (2023) 252–265.
[84] X. Liu, et al., Two-dimensional metal-organic framework/enzyme hybrid nanocatalyst as a benign and self-activated cascade reagent for in vivo wound healing, ACS Nano 13 (5) (2019) 5222–5230.
[85] Y. Ge, et al., Glucose oxidase driven hydrogen sulfide-releasing nanocascade for diabetic infection treatment, Nano Lett. 23 (14) (2023) 6610–6618.
[86] J. Song, et al., Novel chitosan based metal-organic polyhedrons/enzyme hybrid hydrogel with antibacterial activity to promote wound healing, Carbohydr. Polym. 291 (2022) 119522.
[87] Y. Li, et al., A guanosine-quadruplex hydrogel as cascade reaction container consuming endogenous glucose for infected wound treatment-A study in diabetic mice, Adv. Sci. 9 (7) (2022) e2103485.
[88] L. Wang, et al., A self-powered and drug-free diabetic wound healing patch breaking hyperglycemia and low H(2)O(2) limitations and precisely sterilizing driven by electricity, Chem. Sci. 13 (41) (2022) 12136–12143.
[89] X. Yu, et al., Glucose/ROS cascade-responsive ceria nanozymes for diabetic wound healing, Mater Today Bio 15 (2022) 100308.
[90] D. Li, et al., Spark" PtMnIr nanozymes for electrodynamic-boosted multienzymatic tumor immunotherapy, Adv. Mater. (2023) e2308747.
[91] M. Jain, B.J. Ravoo, Fuel-driven and enzyme-regulated redox-responsive supramolecular hydrogels, Angew Chem. Int. Ed. Engl. 60 (38) (2021) 21062–21068.
[92] Y. Yang, et al., Improved pharmacodynamics of epidermal growth factor via microneedles-based self-powered transcutaneous electrical stimulation, Nat. Commun. 13 (1) (2022) 6908.
[93] R. Wang, et al., Liposomal enzyme nanoreactors based on nanoconfinement for efficient antitumor therapy, Angew Chem. Int. Ed. Engl. 62 (44) (2023) e202308761.
[94] J. Bai, et al., Metal-organic framework-integrated enzymes as bioreactor for enhanced therapy against solid tumor via a cascade catalytic reaction, ACS Biomater. Sci. Eng. 5 (11) (2019) 6207–6215.
[95] S. Lyu, et al., Going below and beyond the surface: microneedle structure, materials, drugs, fabrication, and applications for wound healing and tissue regeneration, Bioact. Mater. 27 (2023) 303–326.
[96] X. Zhai, et al., Microneedle/CD-MOF-mediated transdural controlled release of methylprednisolone sodium succinate after spinal cord injury, J. Contr. Release 360 (2023) 236–248.
[97] W. Zhu, et al., Photothermal nanozyme-based microneedle patch against refractory bacterial biofilm infection via iron-actuated janus ion therapy, Adv. Mater. 34 (51) (2022) e2207961.
[98] J. Li, et al., Advances in the application of microneedles in the treatment of local organ diseases, Small (2023) e2306222.
[99] P. Wang, et al., Intelligent microneedle patch with prolonged local release of hydrogen and magnesium ions for diabetic wound healing, Bioact. Mater. 24 (2023) 463–476.
[100] X. Zhang, et al., Bioinspired adaptable indwelling microneedles for treatment of diabetic ulcers, Adv. Mater. 35 (23) (2023) e2210903.
[101] B. Zhao, et al., A conserved PLPLRT/SD motif of STING mediates the recruitment and activation of TBK1, Nature 569 (7758) (2019) 718–722.
[102] Q. Meng, et al., High-strength smart microneedles with "offensive and defensive" effects for intervertebral disc repair, Adv. Mater. 36 (2) (2024) e2305468.
[103] X. Zhang, et al., Immunomodulatory microneedle patch for periodontal tissue regeneration, Matter 5 (2) (2022) 666–682.
[104] P. Zhao, et al., Versatile hydrogel dressing with skin adaptiveness and mild photothermal antibacterial activity for methicillin-resistant Staphylococcus aureus-infected dynamic wound healing, Adv. Sci. 10 (11) (2023) e2206585.
[105] Z. Zhang, et al., Phototherapy techniques for the management of musculoskeletal disorders: strategies and recent advances, Biomater. Res. 27 (1) (2023) 123.
[106] Q.S. Deng, et al., Double-network hydrogel enhanced by SS31-loaded mesoporous polydopamine nanoparticles: symphonic collaboration of near-infrared photothermal antibacterial effect and mitochondrial maintenance for full-thickness wound healing in diabetes mellitus, Bioact. Mater. 27 (2023) 409–428.
[107] W. Li, et al., Development of an antiswelling hydrogel system incorporating M2-exosomes and photothermal effect for diabetic wound healing, ACS Nano 17 (21) (2023) 22106–22120.
[108] Y. Li, et al., Artificial nonenzymatic antioxidant MXene nanosheet-anchored injectable hydrogel as a mild photothermal-controlled oxygen release platform for diabetic wound healing, ACS Nano 16 (5) (2022) 7486–7502.
[109] C. Fan, et al., Multi-functional wound dressings based on silicate bioactive materials, Biomaterials 287 (2022) 121652.
[110] Y. Wang, et al., Graphene-based nanomaterials for cancer therapy and anti-infections, Bioact. Mater. 14 (2022) 335–349.
[111] X. Zhou, et al., A glucose-responsive nitric oxide release hydrogel for infected diabetic wounds treatment, J. Contr. Release 359 (2023) 147–160.
[112] L. Wang, et al., Biomimetic enzyme cascade structural color hydrogel microparticles for diabetic wound healing management, Adv. Sci. 10 (14) (2023) e2206900.
[113] Y. Kang, et al., Programmed microalgae-gel promotes chronic wound healing in diabetes, Nat. Commun. 15 (1) (2024) 1042.
[114] K.R. Olson, Y. Gao, Effects of inhibiting antioxidant pathways on cellular hydrogen sulfide and polysulfide metabolism, Free Radic. Biol. Med. 135 (2019) 1–14.
[115] P. Qiu, Y. Liu, J. Zhang, Recent advances in studies of molecular hydrogen against sepsis, Int. J. Biol. Sci. 15 (6) (2019) 1261–1275.
[116] X. Sun, et al., Novel controlled and targeted releasing hydrogen sulfide system exerts combinational cerebral and myocardial protection after cardiac arrest, J. Nanobiotechnol. 19 (1) (2021) 40.
[117] A. Liu, et al., Nitric oxide nanomotor driving exosomes-loaded microneedles for achilles tendinopathy healing, ACS Nano 15 (8) (2021) 13339–13350.
[118] H.H. Chen, et al., Two-pronged microbe delivery of nitric oxide and oxygen for diabetic wound healing, Nano Lett. 23 (12) (2023) 5595–5602.
[119] H. Chen, et al., Symbiotic algae-bacteria dressing for producing hydrogen to accelerate diabetic wound healing, Nano Lett. 22 (1) (2022) 229–237.
[120] Z. Cheng, R. Kishore, Potential role of hydrogen sulfide in diabetes-impaired angiogenesis and ischemic tissue repair, Redox Biol. 37 (2020) 101704.
[121] Z. Yuan, et al., Near-infrared light-triggered nitric-oxide-enhanced photodynamic therapy and low-temperature photothermal therapy for biofilm elimination, ACS Nano 14 (3) (2020) 3546–3562.
[122] Y. Cao, et al., Starch and chitosan-based antibacterial dressing for infected wound treatment via self-activated NO release strategy, Int. J. Biol. Macromol. 220 (2022) 1177–1187.
[123] S. Son, et al., Multifunctional sonosensitizers in sonodynamic cancer therapy, Chem. Soc. Rev. 49 (11) (2020) 3244–3261.
[124] X. Bi, et al., Silver peroxide nanoparticles for combined antibacterial sonodynamic and photothermal therapy, Small 18 (2) (2022) e2104160.
[125] D. Sun, et al., Ultrasound-Switchable nanozyme augments sonodynamic therapy against multidrug-resistant bacterial infection, ACS Nano 14 (2) (2020) 2063–2076.
[126] L. Cai, et al., Piezoelectric metal-organic frameworks based sonosensitizer for enhanced nanozyme catalytic and sonodynamic therapies, ACS Nano 17 (8) (2023) 7901–7910.
[127] D. Jiang, et al., Nanozyme: new horizons for responsive biomedical applications, Chem. Soc. Rev. 48 (14) (2019) 3683–3704.
[128] D.A. Jankowska, et al., Simultaneous detection of pH value and glucose concentrations for wound monitoring applications, Biosens. Bioelectron. 87 (2017) 312–319.
[129] H. Chen, et al., Hierarchically molecular imprinted porous particles for biomimetic kidney cleaning, Adv. Mater. 32 (52) (2020) e2005394.
[130] Y. Liu, et al., Responsive porous microcarriers with controllable oxygen delivery for wound healing, Small 15 (21) (2019) e1901254.
[131] Y. Shang, et al., Cardiomyocyte-driven structural color actuation in anisotropic inverse opals, ACS Nano 13 (1) (2019) 796–802.
[132] H. Wang, et al., Biomimetic enzyme cascade reaction system in microfluidic electrospray microcapsules, Sci. Adv. 4 (6) (2018) eaat2816.
[133] H.E. Talbott, et al., Wound healing, fibroblast heterogeneity, and fibrosis, Cell Stem Cell 29 (8) (2022) 1161–1180.

[134] B.R. Freedman, et al., Breakthrough treatments for accelerated wound healing, Sci. Adv. 9 (20) (2023) eade7007.
[135] M. Farahani, A. Shafiee, Wound healing: from passive to smart dressings, Adv. Healthcare Mater. 10 (16) (2021) e2100477.
[136] H. Roehrs, et al., Dressings and topical agents containing hyaluronic acid for chronic wound healing, Cochrane Database Syst. Rev. 7 (7) (2023) Cd012215.
[137] J. Li, et al., Moist-retaining, self-recoverable, bioadhesive, and transparent in situ forming hydrogels to accelerate wound healing, ACS Appl. Mater. Interfaces 12 (2) (2020) 2023–2038.
[138] S. Zhang, et al., Recent advances in responsive hydrogels for diabetic wound healing, Mater Today Bio 18 (2023) 100508.
[139] D. Hu, et al., Cellulose-based hydrogels regulated by supramolecular chemistry, SusMat 1 (2021).
[140] D.R. Griffin, et al., Activating an adaptive immune response from a hydrogel scaffold imparts regenerative wound healing, Nat. Mater. 20 (4) (2021) 560–569.
[141] X.X. Lei, et al., Multifunctional two-component in-situ hydrogel for esophageal submucosal dissection for mucosa uplift, postoperative wound closure and rapid healing, Bioact. Mater. 27 (2023) 461–473.
[142] Y. Chen, et al., Glucose-triggered in situ forming keratin hydrogel for the treatment of diabetic wounds, Acta Biomater. 125 (2021) 208–218.
[143] K. Huang, et al., Photothermal hydrogel encapsulating intelligently bacteria-capturing bio-MOF for infectious wound healing, ACS Nano 16 (11) (2022) 19491–19508.
[144] X. Qi, et al., Engineering robust Ag-decorated polydopamine nano-photothermal platforms to combat bacterial infection and prompt wound healing, Adv. Sci. 9 (11) (2022) e2106015.
[145] Y. Zhang, et al., Scarless wound healing programmed by core-shell microneedles, Nat. Commun. 14 (1) (2023) 3431.
[146] Q. Zhang, et al., Down-regulating scar formation by microneedles directly via a mechanical communication pathway, ACS Nano 16 (7) (2022) 10163–10178.
[147] Y.S. Zhang, C. Zhu, Y. Xia, Inverse opal scaffolds and their biomedical applications, Adv. Mater. 29 (33) (2017).
[148] J. Yang, et al., Multifunctional metal-organic framework (MOF)-based nanoplatforms for cancer therapy: from single to combination therapy, Theranostics 13 (1) (2023) 295–323.
[149] Q. Zhang, et al., Recent advances in metal-organic frameworks: Synthesis, application and toxicity, Sci. Total Environ. 902 (2023) 165944.
[150] Y. Zeng, et al., Multifunctional MOF-based microneedle patch with synergistic chemo-photodynamic antibacterial effect and sustained release of growth factor for chronic wound healing, Adv. Healthcare Mater. 12 (19) (2023) e2300250.
[151] J. Xiao, et al., Copper metal-organic framework nanoparticles stabilized with folic acid improve wound healing in diabetes, ACS Nano 12 (2) (2018) 1023–1032.
[152] G. Ge, et al., Na(2)S(2)O(4)@Co-metal organic framework (ZIF-67) @glucose oxidase for biofilm-infecting wound healing with immune activation, Int. J. Biol. Macromol. 226 (2023) 1533–1546.
[153] Y. Hua, et al., Composition-dependent enzyme mimicking activity and radiosensitizing effect of bimetallic clusters to modulate tumor hypoxia for enhanced cancer therapy, Adv. Mater. 34 (31) (2022) e2203734.
[154] W. Wang, et al., Cuproptosis: harnessing transition metal for cancer therapy, ACS Nano 17 (20) (2023) 19581–19599.
[155] H. Eom, et al., Underlying role of hydrophobic environments in tuning metal elements for efficient enzyme catalysis, J. Am. Chem. Soc. 145 (10) (2023) 5880–5887.
[156] R. Lai, Q. Cui, How to stabilize carbenes in enzyme active sites without metal ions, J. Am. Chem. Soc. 144 (45) (2022) 20739–20751.
[157] C. Chen, et al., Responsive and self-healing structural color supramolecular hydrogel patch for diabetic wound treatment, Bioact. Mater. 15 (2022) 194–202.
[158] J. Yang, et al., A programmable oxygenation device facilitates oxygen generation and replenishment to promote wound healing, Adv. Mater. 35 (52) (2023) e2305819.
[159] S. Zhuo, et al., Supramolecular hydrogels for wound repair and hemostasis, Mater. Horiz. 11 (1) (2024) 37–101.
[160] Z. Liu, W. Lin, Y. Liu, Macrocyclic supramolecular assemblies based on hyaluronic acid and their biological applications, Acc. Chem. Res. 55 (23) (2022) 3417–3429.
[161] G. Li, et al., Enhanced bacterial-infected wound healing by nitric oxide-releasing topological supramolecular nanocarriers with self-optimized cooperative multi-point anchoring, Adv. Sci. 10 (11) (2023) e2206959.
[162] J. Low, et al., Heterojunction photocatalysts, Adv. Mater. 29 (20) (2017).
[163] W. Dai, et al., Engineered bio-heterojunction confers extra- and intracellular bacterial ferroptosis and hunger-triggered cell protection for diabetic wound repair, Adv. Mater. 36 (9) (2024) e2305277.
[164] P. Kumar, et al., Multifunctional carbon nitride nanoarchitectures for catalysis, Chem. Soc. Rev. 52 (21) (2023) 7602–7664.
[165] A. Actis, et al., Singlet-triplet energy inversion in carbon nitride photocatalysts, Angew Chem. Int. Ed. Engl. 62 (48) (2023) e202313540.
[166] N.P. Dharmarajan, et al., Bio-Inspired supramolecular self-assembled carbon nitride nanostructures for photocatalytic water splitting, Adv. Mater. 36 (2) (2024) e2306895.
[167] X. Xu, et al., Efficient photocatalytic cleavage of lignin models by a soluble perylene diimide/carbon nitride S-scheme heterojunction, Angew Chem. Int. Ed. Engl. 62 (44) (2023) e202309066.
[168] D.S. Lee, V.K. Soni, E.J. Cho, N-O bond activation by energy transfer photocatalysis, Acc. Chem. Res. 55 (17) (2022) 2526–2541.
[169] Z.H. Zhu, et al., Porphyrin-based two-dimensional layered metal-organic framework with sono-/photocatalytic activity for water decontamination, ACS Nano 16 (1) (2022) 1346–1357.
[170] H.Y. Ma, et al., Roles of reactive oxygen species (ROS) in the photocatalytic degradation of pentachlorophenol and its main toxic intermediates by TiO(2)/UV, J. Hazard Mater. 369 (2019) 719–726.
[171] E. Zhao, et al., Transfer hydrogenation with a carbon-nitride-supported palladium single-atom photocatalyst and water as a proton source, Angew Chem. Int. Ed. Engl. 61 (40) (2022) e202207410.
[172] M. Shi, et al., Wound microenvironment-responsive glucose consumption and hydrogen peroxide generation synergistic with azithromycin for diabetic wounds healing, Theranostics 12 (6) (2022) 2658–2673.
[173] M. Lu, et al., Multifunctional inverse opal microneedle arrays for drug delivery and monitoring, Small 18 (27) (2022) e2201889.
[174] L. Wang, et al., Self-bonded hydrogel inverse opal particles as sprayed flexible patch for wound healing, ACS Nano 16 (2) (2022) 2640–2650.
[175] Z. Zhang, et al., Tailoring conductive inverse opal films with anisotropic elliptical porous patterns for nerve cell orientation, J. Nanobiotechnol. 20 (1) (2022) 117.
[176] D. Xu, et al., Living anisotropic structural color hydrogels for cardiotoxicity screening, ACS Nano 17 (15) (2023) 15180–15188.
[177] M. Feng, et al., Covalent organic framework based crosslinked porous microcapsules for enzymatic catalysis, Angew Chem. Int. Ed. Engl. 62 (33) (2023) e202306621.
[178] G. Das, et al., Fluorescence turn on amine detection in a cationic covalent organic framework, Nat. Commun. 13 (1) (2022) 3904.
[179] J. Wei, et al., Rapid and selective removal of aristolochic acid I in natural products by vinylene-linked iCOF resins, J. Hazard Mater. 461 (2024) 132140.
[180] W. Ji, et al., Synthesis of a covalent organic framework with hetero-environmental pores and its medicine co-delivery application, Nat. Commun. 14 (1) (2023) 6049.
[181] M. Tan, et al., Double-layer hydrogel with glucose-activated two-stage ROS regulating properties for programmed diabetic wound healing, ACS Appl. Mater. Interfaces (2023).
[182] W. Zhu, et al., Blood-glucose-depleting hydrogel dressing as an activatable photothermal/chemodynamic antibacterial agent for healing diabetic wounds, ACS Appl. Mater. Interfaces 15 (20) (2023) 24162–24174.
[183] D. Li, et al., Synergistical starvation and chemo-dynamic therapy for combating multidrug-resistant bacteria and accelerating diabetic wound healing, Adv. Healthcare Mater. 10 (18) (2021) e2100716.