International Journal of Nanomedicine

Dovepress
Taylor & Francis Group

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REVIEW

Multimodal Synergistic Strategies for Diabetic Wound Healing Using Glucose Oxidase Nanocomposites: Therapeutic Mechanisms and Nanomaterial Design

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Abstract: Diabetic wounds (DWs) are characterized by high blood glucose levels, and one of the primary strategies for regulating blood glucose is the use of glucose oxidase (GOx). This enzyme catalyzes the oxidation of glucose to produce D-gluconic acid, consuming oxygen and generating hydrogen peroxide (H_2O_2) in the process. In DWs, this reaction not only effectively reduces glucose concentrations at the wound site but also provides an antibacterial effect through the release of H_2O_2. Based on this principle, combining glucose oxidase with other therapeutic approaches to develop multimodal wound treatment strategies has garnered significant research attention. Additionally, the abundance of binding sites on the GOx molecular surface enables the construction of multifunctional GOx-based nanocomposites. This review uniquely integrates emerging nanomaterial designs with cascade therapeutic strategies, offering insights into overcoming challenges in diabetic wound healing. Recently, multifunctional nanocomposites have gained attention for integrating multiple therapeutic modalities, relying on cascade mechanisms of multimodal synergistic therapies to tackle complex challenges in DWs treatment. However, there is currently no systematic review that comprehensively elaborates on the construction of these nanocomposites and the specific applications of multimodal treatment strategies in DWs healing. To fill this gap in the field, this review provides a comprehensive overview of these nanomaterials, starting with a systematic exploration of cascade and synergistic therapeutic mechanisms centered on GOx-catalyzed reactions. It highlights applications in photothermal therapy (PTT), photodynamic therapy (PDT), and gas therapy (GT), summarizes the design of nanocarriers, and discusses challenges in DWs healing and future development directions. The findings discussed provide a pathway for the development of clinically viable, cost-effective therapies for chronic wounds.

Keywords: glucose oxidase, wound healing, synergistic strategies, nanocomposite, diabetic wounds

Introduction

Diabetes is a group of metabolic disorders characterized by hyperglycemia, primarily caused by insufficient insulin secretion or impaired insulin action.[1] Despite the development of numerous anti-diabetic drugs,[2] the prevalence of diabetes continues to rise worldwide. In 2022, global diabetes prevalence had reached 828 million adults, reflecting a concerning surge of 630 million cases since 1990. Specifically, India led with 212 million affected individuals, followed by China with 148 million cases.[3] By 2030, the number of adults with diabetes is projected to increase by 69% in developing countries and by 20% in developed countries.[4] This trend has made diabetes and its associated complications a significant public health concern. Among these, the management of diabetic wounds (DWs) imposes a heavy and costly

Received: 31 December 2024
Accepted: 21 April 2025
Published: 2 May 2025

burden on patients. As of 2022, approximately 2.5% of the population in the United States faced substantial healthcare costs due to chronic wounds related to diabetes.[5]

Wound healing is a complex biological process involving the coordinated actions of various cells and molecular pathways, including four typical key stages: platelet activation and hemostasis, inflammation, proliferation, and remodeling.[6] At every stage of wound healing, pathological disruptions can lead to delayed or stalled healing cycles, resulting in abnormal wound healing.[7] Every stage of wound healing, pathological disruptions can lead to Among these disruptions, hyperglycemia contributes to the formation of a pathological microenvironment through various underlying pathophysiological mechanisms, such as sustained inflammation and vascular endothelial damage, which further hinder the healing of DWs.[8,9] These mechanisms indicate that the delayed healing of DWs is closely associated with multiple interacting factors. These include the accumulation of AGEs (advanced glycation end products), activation of inflammatory responses, vascular dysfunction, increased risk of infection, and reduced cellular migration capacity. Together, these factors contribute to a vicious cycle that hinders DWs healing. To address these challenges, various therapeutic strategies have been explored, such as controlling blood glucose levels, mitigating oxidative stress, applying antimicrobial agents, restoring inflammatory responses to normal levels, and promoting cellular migration and proliferation through the use of growth factors.[10–13] However, the pathological microenvironment in diabetes exhibits marked complexity, characterized by chronic inflammation, impaired angiogenesis, oxidative stress, bacterial infections, and biofilm formation. This multifaceted pathological foundation renders monotherapeutic approaches inadequate to comprehensively address all dimensions of the disease.[14]

In recent years, numerous studies have focused on integrating the catalytic activity of glucose oxidase (GOx) with the unique properties of nanomaterials, leading to the development of multifunctional GOx-based nanocomposites for DWs treatment. A wide variety of nanomaterials have been utilized to construct such nanocomposites, including metal-organic frameworks (MOFs),[15] metal oxide nanoparticles,[16] bio- heterojunctions (Bio HJ)[17] and noble metal nanoparticles.[18] These nanocomposites primarily utilize the catalytic activity of GOx for glucose regulation. This natural enzyme catalyzes the reaction between glucose and oxygen, producing gluconic acid and H_2O_2.[19] GOx is primarily composed of two identical protein subunits, each containing a flavin adenine dinucleotide (FAD) cofactor, which is the critical structure for its catalytic activity.[20]

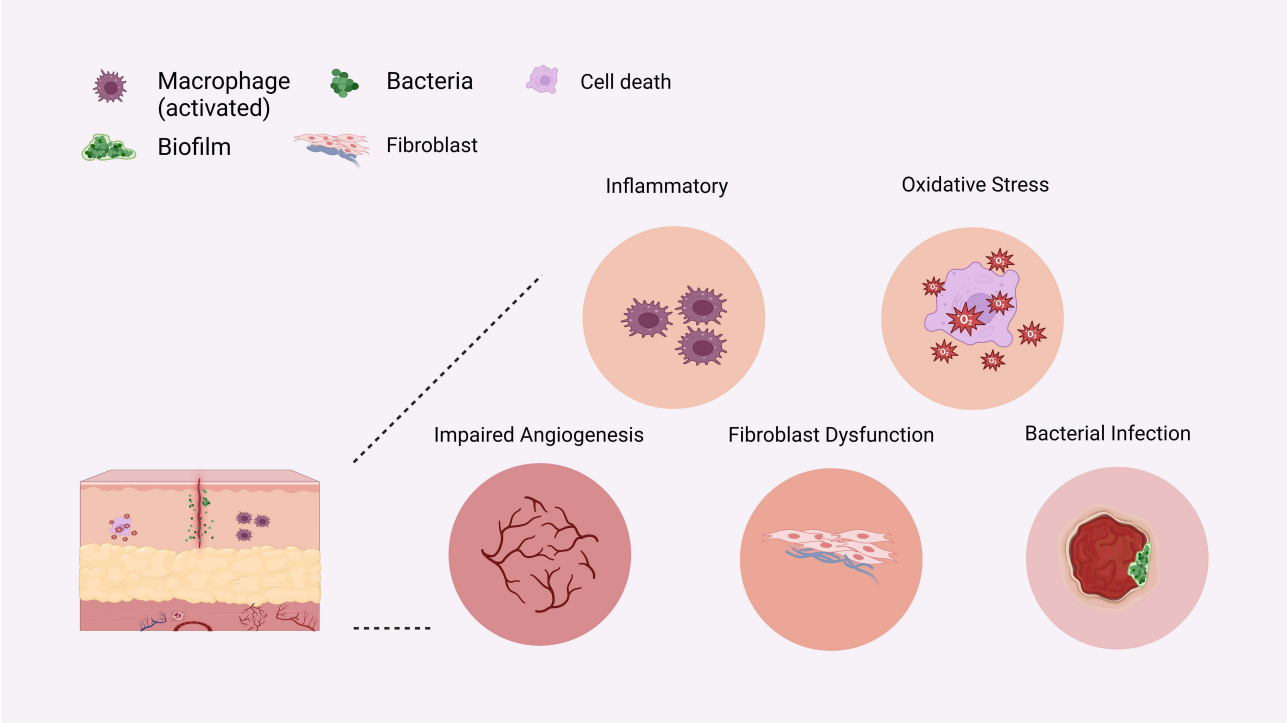
GOx has potential therapeutic value in the clinical treatment of diabetic wounds. Ilaria et al reported on a patient with diabetic wound ulcers who failed to heal completely after surgical debridement and systemic antibiotic treatment and was finally successfully treated with honey dressing containing GOx.[21] Furthermore, conjugation with nanomaterials provides GOx with multiple advantages, including enhanced stability,[22] improved enzymatic activity,[23] and the ability to achieve targeted delivery.[24] This endows GOx-based nanocomposites with significant value in wound treatment. Their applications extend beyond blood glucose regulation and have been utilized in eliminating bacterial infections,[25] mitigating oxidative stress,[26] and alleviating wound inflammation.[27] Nanocomposites based on transition metals can convert H_2O_2 in the microenvironment into highly oxidative substances, effectively eliminating pathogenic microorganisms in wounds and accelerating wound healing.[28] Moreover, these nanocomposites play a critical role in mitigating oxidative stress. DW are often accompanied by oxidative stress, where excessive free radicals cause cellular damage and hinder the healing process. Multienzyme-active nanocomposites have been developed to regulate redox balance, eliminate excess free radicals, reduce oxidative damage to cells, and alleviate inflammatory responses in the wound environment.[29] Every stage of wound healing, pathological disruptions can lead to Overall, GOx-based nanocomposites demonstrate remarkable synergistic effects between GOx and various nanomaterials: 1. Metal-based nanozymes utilize H_2O_2 generated by GOx to induce Fenton/Fenton-like reactions, producing hydroxyl radicals (•OH) for efficient antibacterial action;[30] 2, Catalase (CAT)/superoxide dismutase (SOD)-like catalysts leverage H_2O_2 generated by GOx to produce sustained oxygen (O_2), alleviating tissue hypoxia:[26] every stage of wound healing, pathological disruptions can lead to 3, GOx-mediated gluconic acid production creates an acidic environment that enhances nanozyme activity and improves therapeutic outcomes.[31] 4, GOx, as a glucose-responsive sensor, facilitates nanocarrier disintegration by providing an acidic environment or H_2O_2, triggering drug release.[32]

This review summarizes the mechanisms underlying the synergistic therapies enabled by various GOx-based nanocomposites for DWs treatment. It then elaborates on the specific applications of these nanocomposites in DWs

management. Additionally, the coupling processes of GOx with other nanomaterials and the types of nanomaterials utilized are discussed in detail. Finally, the challenges faced by these nanocomposites in DW treatment are analyzed, providing insights into future development.

Mechanisms of Impaired Wound Healing in Diabetes

The basic characteristics of DWs include excessive and prolonged inflammation, impaired healing, an increased risk of infection, and compromised tissue regeneration during the repair process (Scheme 1).[33] The complex pathological microenvironment in DWs is primarily driven by hyperglycemia, which serves as a critical initiating factor. Recent studies have identified the activation of the mtDNA-cGAS-STING pathway as a significant mechanism underlying the refractory nature of DWs healing. In a high glucose (HG) environment, excessive reactive oxygen species (ROS) promote the leakage of mitochondrial DNA (mtDNA) into the cytoplasm, leading to overactivation of the STING pathway. Macrophages, the most prominently upregulated factors in the STING pathway, polarize into a pro-inflammatory phenotype upon its activation. These macrophages continuously release various pro-inflammatory cytokines, such as Interleukin-1 beta(IL-1β), Interleukin-6(IL-6), and tumor necrosis factor-α (TNF-α), which further exacerbate the inflammatory response and impede wound healing.[34,35] At the same time, the excessive upregulation of tumor necrosis TNF-α induces the overexpression of tissue inhibitor of metalloproteinases-1 (TIMP-1) in keratinocytes, further reducing their migratory capacity and impeding the healing of DWs.[36] Geng et al used STING gene-edited macrophages for wound treatment, demonstrating their ability to induce polarization from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype. This transition promotes angiogenesis and collagen deposition, ultimately accelerating wound healing.[34] Prolonged exposure to a HG environment compromises endothelial cell proliferation and migratory capacity while inducing apoptosis, thereby impairing wound healing.[37] Studies have identified a key mechanism underlying vascular endothelial damage: the upregulation of proprotein convertase subtilisin/kexin type 9 (PCSK9).[38] PCSK9 promotes the binding of E3 ubiquitin ligase NEDD4 to vascular endothelial growth factor receptor 2 (VEGFR2), leading to VEGFR2 ubiquitination and degradation, which impairs angiogenesis. Additionally, PCSK9 suppresses the activation of AKT, endothelial nitric oxide synthase (eNOS), and ERK1/2, reducing nitric oxide (NO) production while increasing



Scheme 1 Mechanisms of Impaired Wound Healing in Diabetes. Created in BioRender. Sfds, D. (2025) https://BioRender.com/e43m843.

https://doi.org/10.2147/IJN.S515057

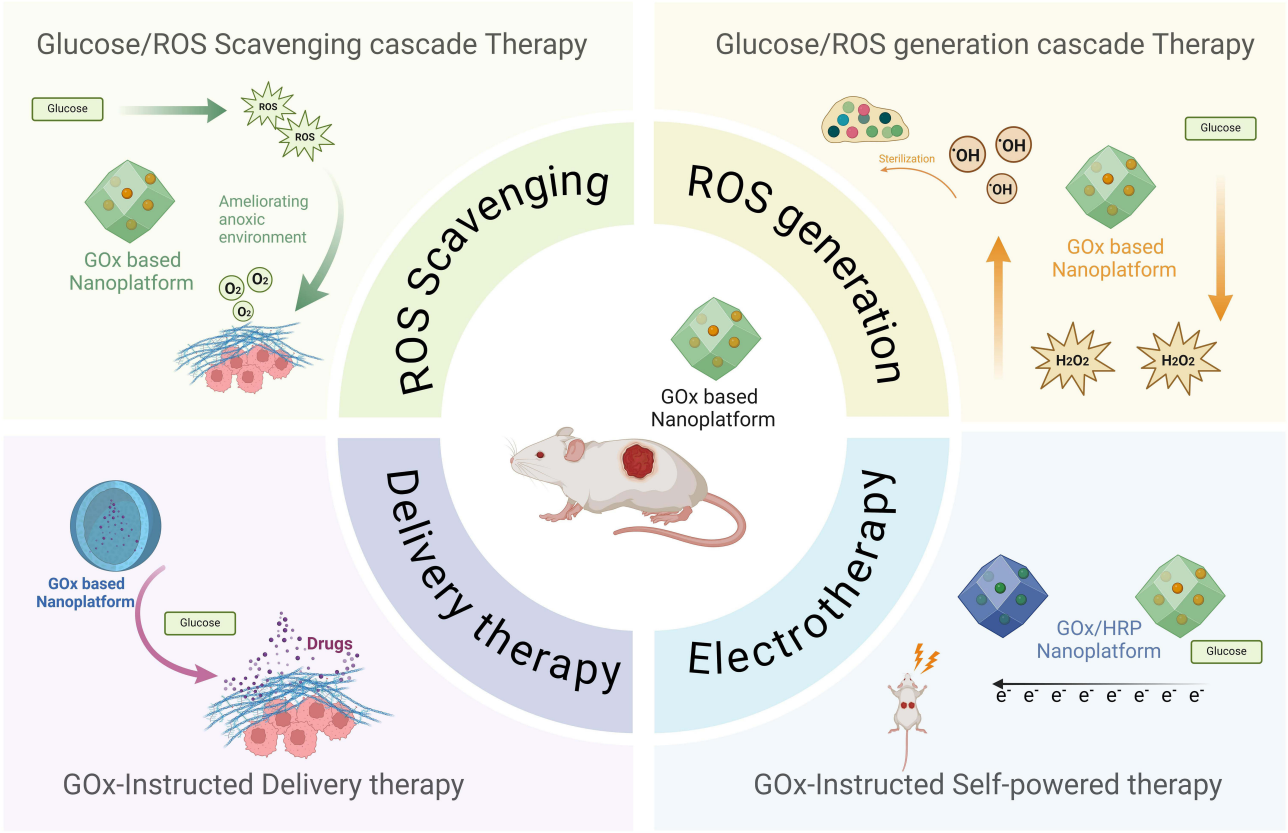
superoxide anion (O_2^-) generation. This exacerbates endothelial dysfunction and further impairs angiogenesis. Moreover, the hypoxic and nutrient-deprived wound environment aggravate these effects by diminishing the migratory and chemotactic capacities of essential repair cells, creating a vicious cycle that further delays diabetic wound (DW) healing.[37] In diabetic patients, persistent hyperglycemia enhances glycation reactions between glucose and proteins in the body, leading to the accumulation of advanced glycation end products (AGEs). AGEs exacerbate the inflammatory microenvironment by promoting the excessive activation of the NLRP3 inflammasome through increased ROS generation.[39] Additionally, AGEs can induce autophagy and polarize macrophages to the M1 phenotype by activating autophagy regulators such as IRF8, thereby impairing cutaneous wound healing.[40] Notably, the prolonged non-healing of DWs is often associated with an elevated risk of infection. Wound infections pose a significant challenge in DWs management, largely due to immune suppression, inadequate blood supply, and improper wound care caused by sensory nerve damage in the HG environment.[41,42] Furthermore, the abundance of glucose provides an optimal environment for bacterial proliferation, further elevating infection risks.[43] Conventional treatments for DWs infections include the use of topical antimicrobials, oral antibiotics, or intravenous antibiotic therapy.[44] However, due to immunosuppression and chronic inflammation caused by hyperglycemia, these traditional approaches often show limited efficacy.[45] Additionally, the prolonged use of antibiotics poses a significant risk of developing antimicrobial resistance. Decades of antibiotic overuse and misuse have altered bacterial genetics, leading to the emergence of resistant strains, including multidrug-resistant bacteria. Recent methicillin-resistant *Staphylococcus aureus* (MRSA) strains include HA-MRSA CC30 in North America and Europe, CA-MRSA USA300 in North America, and livestock-associated MRSA strains such as ST398 and ST93 in Australia.[46] Furthermore, bacterial biofilm formation complicates infection management. The extracellular polymeric substances (EPS) that constitute the biofilm matrix provide protective effects, making biofilm-associated bacteria approximately 10 to 1000 times more resistant to antibiotics than planktonic bacteria. This significantly increases the difficulty of managing DWs infections.[47]

Mechanism of GOx Based Nanocomposite in Diabetic Wound Healing

The pathological microenvironment of diabetic wounds presents significant complexity, as monotherapy often fails to address its dynamic therapeutic requirements. Contemporary therapeutic strategies are undergoing a paradigm shift from single-target interventions to multimodal synergistic approaches in order to overcome the complex interplay of multiple pathological factors. These include persistent hyperglycemia, chronic hypoxia, sustained inflammatory responses, microbial biofilm formation, and dysregulated pH homeostasis, which collectively contribute to impaired wound healing processes.[48–51]

In this study, catalytic reaction induced by GOx is a central component of multimodal synergistic strategies. It effectively utilizes glucose in DWs by catalyzing its oxidation to produce H_2O_2 and create an acidic environment.[52] Notably, by combining GOx with different nanocarriers, this reaction can naturally cascade with other therapeutic modes, generating synergistic effects. The nanocomposites can effectively address various abnormal pathological microenvironments. In addition to regulating blood glucose levels, the nanocomposites can also modulate the pH of chronic wounds. Chronic diabetic wounds are typically weakly alkaline (pH: 7–9), which not only affects fibroblast activity but also promotes the colonization of pathogenic bacteria, thereby hindering wound healing. Catalyzed by GOx, glucose is oxidized to produce gluconic acid, which helps restore an ideal acidic environment that promotes wound healing. Moreover, some nanocomposites can effectively address wound biofilms, thereby exhibiting antibacterial effects. The nanocomposites can convert H_2O_2 into •OH, which react with fatty acids, amino acids, and sugars in the biofilm, triggering lipid peroxidation and eliminate the biofilm. Specifically, the primary therapeutic strategies of GOx-based nanocomposites include the following (Scheme 2):

1. Glucose/ROS Scavenging Cascade Therapy: GOx consumes glucose while nanocarriers with CAT/ SOD-like enzymes scavenge the excess ROS produced, thereby promoting wound healing.
2. Glucose/ROS Generation Cascade Therapy: GOx metabolizes glucose to generate H_2O_2, which is further catalyzed by metal catalysts within the nanocarriers to trigger Fenton or Fenton-like reactions. This produces hydroxyl radicals (•OH) with potent bactericidal and inflammation-regulating effects, facilitating wound healing.



Scheme 2 Four main mechanisms of the GOx based nanocomposites in DWs healing. Created in BioRender. Fan, z. (2025) https://BioRender.com/d38g314.

3. GOx-Instructed Self-Powered Therapy: Redox reactions are leveraged to convert high glucose levels in the wound into microcurrents, which enhance cell proliferation, migration, and tissue repair.
4. GOx-Instructed Delivery Therapy: The acidic or oxidative microenvironment generated by GOx metabolism triggers the precise release of therapeutic agents from drug-loaded nanocomposites, enabling targeted delivery and improving drug accumulation and efficacy at the wound site.

Glucose/ROS Scavenging Cascade Therapy

DWs are often accompanied by hypoxia, primarily caused by microcirculation disorders and impaired angiogenesis. The hypoxic environment hinders cell migration and proliferation, thereby delaying the wound healing process.[53] Oxidative stress is another critical mechanism triggered by hyperglycemia, where the accumulation of free radicals damages cells and tissues. Excessive oxidative stress leads to increased cell apoptosis and enhanced inflammatory responses, further impeding the wound healing process.[54] Additionally, hyperglycemic conditions create a favorable environment for pathogen growth, making it challenging for wounds in diabetic patients to heal.[55] An emerging therapeutic approach, Glucose/Reactive Oxygen Species (ROS) Scavenging Cascade Therapy, has shown promise in addressing these challenges. This strategy rapidly depletes glucose while simultaneously improving the inflammatory and hypoxic microenvironment by scavenging ROS within the wound.[26,56] The core of this therapy lies in utilizing GOx to catalyze the oxidation of glucose into gluconic acid and H_2O_2. Subsequently, H_2O_2 and ROS in the microenvironment are decomposed into oxygen by nano catalysts.[57] This dual-action approach not only mitigates hyperglycemia-induced damage but also enhances wound healing efficiency. The reaction proceeds as follows: [58]

$$\text{Glucose} + O_2 \xrightarrow{\text{GOx}} \text{Gluconic acid} + H_2O_2$$

https://doi.org/10.2147/IJN.S515057

$$2H_2O_2 \xrightarrow{\text{Catalase}} 2H_2O + O_2$$

Specifically, this strategy involves a two-step reaction: glucose consumption and oxygen delivery. In DWs, utilizing GOx to deplete local glucose remains an effective regulatory approach.[59,60] In the presence of O_2, GOx can rapidly consume glucose, producing gluconic acid and H_2O_2. However, due to microvascular complications and vascular dysfunction caused by diabetes, the hypoxic state in DW often persists, significantly limiting the activity of GOx.[61,62]

The second step of the Glucose/ROS Scavenging Cascade Therapy is oxygen delivery, which relies on nanocarriers with the antioxidant enzyme-like activity (NAEA) to overcome the limitation of GOx activity in hypoxic environments. Notably, this oxygen delivery therapy does not depend on exogenous O_2 donors; instead, it utilizes ROS in the environment to generate O_2. In the presence of NAEA, ROS in the microenvironment undergoes a series of reduction reactions, leading to the production of O_2. This process not only alleviates oxidative stress but also sustains oxygen delivery to the wound site.[63]

The Glucose/ROS Scavenging Cascade Therapy is based on the rational design of the interplay between GOx and NAEA, enabling them to complement each other effectively: 1. Mitigating H_2O_2 Accumulation: GOx alone often leads to excessive accumulation of H_2O_2 in the wound microenvironment, which can damage proteins, lipids, and DNA.[59] When NAEA is incorporated into the nanocomposite, GOx provides H_2O_2 as a substrate for NAEA and creates an acidic environment that enhances NAEA activity;[64] 2. Enhancing GOx Activity and Reducing Toxic Effects: NAEA boosts the activity of GOx while mitigating its cytotoxic side effects;[26] 3. In GOx-based nanocomposites, the close integration of GOx and NAEA significantly enhances substrate transfer efficiency, thereby accelerating the overall reaction rate.[63] Furthermore, the cascade therapy effectively mitigates ROS-related side effects through multi-mechanism synergy: Firstly, it utilizes NAEA to specifically scavenge excess •OH and H_2O_2 in the wound microenvironment, blocking their oxidative damage to proteins, lipids, and DNA, thereby reducing cell apoptosis and tissue damage;[27] Secondly, by clearing ROS, it suppresses the overactivation of related inflammatory pathways, improving the chronic inflammatory microenvironment. Simultaneously, the removal of ROS can restore vascular endothelial cell function, upregulate the expression of key angiogenic factors such as VEGF, and promote the formation of functional neovascularization.[65] This multi-target regulatory strategy synergistically promotes diabetic wound healing from multi-dimensions: oxidative damage, inflammatory response and angiogenesis. Overall, the Glucose/ROS Scavenging Cascade Therapy not only generates oxygen but also depletes excess glucose, thereby mitigating the adverse effects of hyperglycemia on wound healing. By regulating glucose levels, this therapy reduces bacterial growth and facilitates wound healing. Moreover, the generated O_2 enhances the catalytic activity of GOx while effectively alleviating hypoxia in the wound, thereby improving inflammation and promoting tissue repair and regeneration.[66]

Glucose/ROS Generation Cascade Therapy

Pathogenic microorganisms significantly hinder wound healing and treatment by affecting various stages of skin repair and increasing the risk of infection.[45] Currently, antibiotics remain an effective clinical measure for managing infected wounds.[67] However, the overuse and misuse of antibiotics have led to the gradual emergence of antibiotic-resistant pathogens.[68] Moreover, bacterial biofilms act as physical barriers, limiting antibiotic penetration and impairing the activation of immune cells.[47] To address these challenges, many studies in the field of biomaterials focus on innovative strategies such as photodynamic therapy (PDT),[69] chemodynamic therapy (CDT),[70] photothermal therapy (PTT)[71] photothermal therapy (PTT),[72] sonodynamic therapy (SDT)[73] and gas therapy (GT)[74] to combat resistant bacteria and biofilms. Studies have demonstrated that the GOx nanocomposites exhibit a significantly higher antibacterial effect compared to traditional therapeutic methods. Shi et al employed a crystal violet staining assay to evaluate the disruptive effects of different treatment groups against S. aureus biofilms. Experimental results demonstrated that hollow mesoporous silica nanoparticles loaded with azithromycin (HMSN-AZM) induced negligible changes to biofilms across tested concentrations. In contrast, GOx-HMSN (about 50%) and GOX-HMSN-AZM (85.3%) showed stronger biofilm eradication effects when the concentration of GOX reached 500ug/mL.[75] Among these strategies, glucose/ROS generation has emerged as an advanced and effective antibacterial approach. It enhances therapeutic efficacy by combining starvation therapy with ROS-mediated antibacterial effects. Starvation therapy, widely used in cancer treatment, inhibits tumor

growth by disrupting energy supply.[76] Recently, this strategy has shown promising therapeutic potential in DW as an adjunctive treatment. In the presence of oxygen, starvation therapy rapidly depletes glucose through GOx, cutting off bacterial nutrient sources while releasing H_2O_2, which possesses inherent antibacterial properties and inhibits bacterial growth.[77] Furthermore, studies suggest that starvation therapy can activate cellular protective mechanisms, minimizing ROS-induced damage to host cells while eliminating pathogens.[78]

In DW, the core mechanism of the glucose/ROS generation strategy is the production of antibacterial ROS, primarily leveraging CDT therapy. ROS are reactive oxygen species that include both free radicals and non-radical oxidants, such as O_2^-, H_2O_2, and •OH.[79] In infected wounds, ROS exhibit antibacterial effects through various mechanisms, including oxidizing bacterial membranes, damaging DNA and proteins, and disrupting biofilms.[80] Among these, CDT relies on Fenton and Fenton-like reactions to generate •OH, a highly reactive species capable of effectively killing bacteria. The specific reaction mechanism is as follows: [81]

$$Mn + 2H_2O_2 \rightarrow Mn^{n+1} + OH^- + \bullet OH$$

(Mn represents transition metal ions, and Mn^{n+1} refers to their oxidized forms).

However, the concentration of endogenous H_2O_2 is relatively low (approximately 10×10^{-6} M to 1×10^{-3} M), resulting in insufficient catalytic kinetics for CDT and limits the production of •OH.[82] Fortunately, ST therapy can supply additional H_2O_2 as a substrate for CDT, addressing the issue of endogenous H_2O_2 deficiency. Additionally, the gluconic acid generated by ST therapy can lower the local pH from neutral to 3–4, significantly activating nanocarriers with peroxidase-like activity and enhancing the efficiency of •OH production.[83]

GOx-Instructed Self-Powered Therapy

Electrotherapy (ES) is a treatment method that promotes wound healing by delivering low-intensity electrical currents.[84] By mimicking the endogenous injury current from the wound edge to its center, ES accelerates cell proliferation, migration, and angiogenesis, thereby facilitating wound closure and tissue repair.[85]

The GOx-guided self-powered therapy is based on a glucose enzymatic biofuel cell (GBFC) that utilizes glucose as a fuel to efficiently convert chemical energy into electrical energy. As an endogenous form of electrical stimulation, this enzyme-driven self-powered therapy overcomes the inconvenience of external power sources.[86] Specifically, this strategy involves constructing a GBFC system that uses HG levels in the wound as fuel. Through a cascade redox reaction between GOx at the anode and horseradish peroxidase (HRP) at the cathode, electrons are transferred from the GOx-containing anode to the HRP-containing cathode, generating endogenous biomimetic electrical currents.

The specific reactions at the anode and cathode in the GBFC system are as follows:[87]

Anode Reaction: GOx catalyzes the oxidation of glucose with oxygen, producing gluconic acid and H_2O_2.

$$\text{Glucose} + O_2 \xrightarrow{\text{GOx}} \text{Gluconic acid} + H_2O_2$$

Cathode Reaction: In the presence of H_2O_2 generated by GOx, HRP catalyzes a redox reaction, decomposing H_2O_2 into H_2O while oxidizing organic or inorganic reductants to produce ROS, such as •OH or other active compounds, for antibacterial purposes.[23]

$$H_2O_2 + AH_2 \xrightarrow{\text{HRP}} 2H_2O + A$$

(AH_2 represents a reductant, and A is the oxidized product)

The GOx-guided self-powered strategy offers three primary benefits for treating DW: 1. Provide biomimetic microcurrents to the wound area, promoting cell growth and migration; 2. Catalyze the oxidation of glucose, improving the HG conditions unfavorable for wound healing. 3. Decompose H_2O_2 through HRP catalysis, further generating strong oxidizing substances such as •OH, which exhibit potent antibacterial effects.[88] Additionally, the electric field generated by GBFC attracts negatively charged bacteria to the electrode surface, facilitating the precise antibacterial action of electrode-produced ROS.[89] In summary, the GOx-based self-powered strategy provides an innovative, non-invasive, sustained, and precise therapeutic approach for DW treatment. It not only eliminates pathogenic microorganisms on the

wound by generating electric fields and chemical antibacterial agents through glucose consumption but also promotes tissue regeneration via electric stimulation, preventing scar formation. This approach demonstrates significant potential for clinical applications.

GOx-Instructed Delivery Therapy

Drug therapy remains an effective approach for treating DW.[90] Given that DW healing is a dynamic, staged process, precise targeting and intelligent release of drugs are of critical importance.[91] To address this, many responsive delivery strategies have been developed for DW healing.[92] Among these, glucose-responsive delivery systems offer significant advantages, especially for DW characterized by HG levels.[93]

The GOx-guided drug delivery strategy exhibits glucose responsiveness. Centered on GOx, it converts glucose into gluconic acid and H_2O_2 in an HG environment, which subsequently triggers drug release,[94] including metal ions,[95] gaseous molecules,[96] and antimicrobial drugs.[59] The key advantage of this approach lies in its close correlation between drug release and the HG level in the wound environment. This ensures that therapeutic agents are released timely and effectively when glucose levels are high. Once blood glucose levels are regulated to normal by GOx, the drug release rate decreases correspondingly, thereby preventing unnecessary drug waste and reducing side effects.[97]

This delivery strategy primarily relies on two signals to trigger drug release: 1. The acidic environment generated by the GOx-catalyzed reaction induces the decomposition of pH-responsive carrier materials, enabling responsive drug release. For instance, Yang et al developed a nanocomposite combining GOx and metal-organic frameworks (such as ZIF-8) that demonstrated excellent antibacterial activity in DW treatment. These materials degrade in an HG environment, releasing Zn^{2+} and deferoxamine mesylate. This approach not only exhibits remarkable efficacy in treating wound infections but also promotes angiogenesis, accelerating wound healing;[59] 2. The H_2O_2 signal generated by GOx can stimulate structural changes in drug-loaded smart carriers, facilitating drug release. Zhou et al designed an antibacterial hydrogel by modifying GOx and L-arginine onto hyaluronic acid and chitosan, respectively. These components were in situ crosslinked via Schiff base reactions. The H_2O_2 produced by GOx oxidizes the L-arginine-modified chitosan, inducing the release of nitric oxide (NO). NO enhances wound healing by exerting antibacterial and anti-inflammatory effects while promoting angiogenesis and collagen deposition.[98]

In summary, the GOx-guided drug delivery strategy shows promising potential in DWs treatment. By leveraging the characteristics of enzymatic catalysis, it not only removes excess glucose but also enables responsive drug release tailored to the wound environment.

Design and Construction of GOx-Based Nanocomposite

Coupling Strategy of GOx-Based Nanoplatform

As a natural enzyme, GOx is prone to inactivation under biological conditions. Combining GOx with various carriers effectively enhances its stability.[99] Moreover, rational design and construction can minimize the spatial distance between GOx and its carrier, thereby improving synergistic effects.[100] In GOx-based nanocomposites materials, GOx can bind to carriers in two primary ways: physical binding and chemical binding. Table 1 lists the categories of nanocomposites combined with GOx and the combination methods.

Physical binding refers to the non-chemical attachment of GOx to a carrier. This binding method relies on weak interactions or physical barriers without forming stable chemical bonds and primarily includes physical adsorption and physical encapsulation. Physical adsorption utilizes weak interaction forces (such as van der Waals forces, hydrogen bonds, and electrostatic forces) to attach substances to a surface, without the formation of chemical bonds.[112] For example, a study mentioned the combination of GOx with Fe2(MoO4)3 through electrostatic interactions, forming a composite material called Fe2(MoO4)3@GOx. This electrostatic adsorption method effectively anchored GOx on the surface of Fe2(MoO4)3, stabilizing the material structure and demonstrating excellent catalytic performance in treating DWs infections.[28] Physical encapsulation involves embedding GOx within the pores or interior of a carrier. For example, Wang et al encapsulated GOx, HRP and single-walled carbon nanotubes (SWCNTs) within MAF-7, forming a nanocomposite named MAF-7-SWCNT-GOD/HRP through this physical encapsulation method.[88] Self-assembly

Table 1 Design and Construction of GOx Based Nanocomposites

Nanocomposites Types	Nanocarrier	Combination Method	Ref
Bio-HJ nanocomposite	Fe2O3/Ti3C2-MXene	Physical adsorption	[78]
	g-C3N4/MoS2	Adsorption of PDA coating	[101]
	CN/$Cu_{2-x}S$	Adsorption of PDA coating	[102]
MOF nanocomposite	ZIF-8	Physical encapsulation	[86,94,95,103]
	Fe-iCOF	Surface adsorption	[104]
	Fe-COF	Covalent connection	[105]
	Cu-MOF	Physical adsorption	[106]
	MAF-7	Physical encapsulation	[88]
	GOx–GA–Fe nanozyme	Physical encapsulation	[31]
	Zn-MOF	Electrostatic interaction	[15]
	Co-MOF	Physical encapsulation	[107]
Metallic inorganic nanocomposite	Fe_3O_4 NPs	PAH coating and covalent connection	[108]
	$Fe_2(MoO_4)_3$ NPs	Electrostatic interaction	[28]
	MnO2 nanoshells	/	[109]
Biomineralizing nanocomposite	MnS NPs	Biomineralizing	[96]
	OsNCs	Biomineralizing	[110]
	FexSy	Biomineralizing	[22]
	Cu-GMP/GODNF	Biomineralizing	[111]
Self-assembling Nanoreactor	Supramolecular nanoconfined catalytic system	Physical encapsulation	[112]
	AHQO-MV Self-Assembled Nanoreactor	Physical encapsulation	[113]
	Ce-driven coassembly Nanoreactor	Physical encapsulation	[26]
Polymers	Unimolecular enzyme–polymer conjugates	Glycan-initiated polymerization	[27]
	GOx-CAT nanogel	Polymerization	[100]
	Chitosan NPs	/	[65]
	Mesoporous bowl-shaped PDA NPs	Covalent connection	[114]
	Hyaluronic acid (HA) shell	Physical encapsulation	[115]
	Mesoporous PDA nanoparticles	Glutaraldehyde cross-linking	[116]
Other	HMSN	Covalent connection	[75]
	BP nanosheet	/	[117]
	Kaolinite nanoclay	/	[118]
	Camelina lipid droplets	Electrostatic interaction	[119]
	GOx–CAT nanoenzyme composite	/	[63]

Note: "/" indicates not described in detail in the reference.

technology is a classic drug delivery scheme that encapsulates therapeutic drugs and precisely delivers them to target sites for effective treatment. In recent years, this technology has been widely applied in the treatment of DWs. Yu Xiaojuan et al studied a dual-ligand molecule composed of alendronate (AL) and 2-methylimidazole (HMIM), and successfully used Ce-driven co-assembly technology to prepare nanoparticles (CHA).[26] During this process, GOx was embedded within the CHA particles, ultimately forming a nanocatalytic system (CHA@GOx) with multiple enzyme activities.

Chemical Binding refers to the stable attachment of GOx to a carrier through the formation of strong chemical bonds. This method primarily involves the formation of covalent or ionic bonds, which are generally more stable than physical binding, thereby better preserving the activity and stability of GOx. Chemical binding mainly includes covalent coupling and biomineralization. Covalent coupling refers to the formation of stable covalent bonds between GOx and a carrier through chemical reactions, ensuring the robust attachment of GOx to the carrier. For example, Zhu et al covalently coupled GOx to Fe-COF nanoparticle by EDC/NHS reaction to obtain Fe-COF/GOx.[105] Additionally, another study employed a glutaraldehyde cross-linking method to immobilize GOx on the surface of mesoporous bowl-shaped

nanoparticles, thereby forming a glucose-fueled cationic nanomotors.[114] Covalent coupling ensures the stability of GOx on the nanocarrier and maintains the synergistic effects between GOx and the nanocarrier.[120] Biomineralization refers to a natural or biomimetic process where minerals deposit under the guidance of organic templates (such as proteins or enzymes) to form stable inorganic-organic composite structures. This process involves chemical reactions that create chemical bonds, tightly binding target molecules to minerals and enhancing their stability and functionality.[121] For example, Deng et al constructed a GOx@FexSy composite material using a biomimetic mineralization approach. In this process, GOx was immobilized onto iron sulfide (FexSy) nanostructures through deposition on the FexSy nanoparticles.[22] This method effectively preserved the activity of GOx while leveraging the properties of iron sulfide to enhance the catalytic activity of the composite material.

Various Categories of GOx-Based Nanocomposites

The multimodal therapeutic strategy of GOx nanocomposites is primarily attributed to the conjugation of GOx with other nanomaterials. These nanomaterials possess diverse functionalities, playing multiple roles in enhancing the therapeutic effects. To achieve these functions, suitable nanocarriers are required. Based on the categories of nanocarrier, they can be divided into the following mainstream types (Scheme 3): 1, GOx/bio-HJ nanocomposite; 2, GOx/MOFnanocomposite; 3, GOx/Metallic inorganic nanocomposite; 4, GOx/Biomineralizing nanocomposite; 5, GOx/ Self-assembling nanoreactor; 6, GOx/polymer nanocomposite; 7, GOx/Other nanocomposite. The diversity of these GOx-based nanocarriers enables various therapeutic applications, leveraging the unique properties of each nanomaterial to enhance GOx stability,

Scheme 3 Different nanocarriers in the GOx based nanoplatform. Created in BioRender. Fan, z. (2025) https://BioRender.com/h98u539.

facilitate targeted delivery, and improve the overall therapeutic outcomes in the treatment of hyperglycemic diabetic wounds.

GOx/Bio-HJ Nanocomposite

Bio HJs refers to interfaces composed of two or more biocompatible materials (such as semiconductors, metals, or inorganic substances) with different energy levels and band structures.[122] In photocatalytic processes, these interface structures effectively facilitate the separation of electron-hole pairs via band differences or Schottky barriers, thereby enhancing the efficiency of photocatalytic reactions.[123]

In the treatment of DWs, rational construction of bio-heterojunctions and the integration of additional functional components enable the development of photocatalysis-centered multimodal synergistic therapeutic strategies.[102] Specifically, bio-heterojunctions absorb light energy and rapidly generate heat, leading to localized high temperatures that disrupt bacterial cell membranes. Meanwhile, during photocatalysis, the interface structure promotes the separation of electron-hole pairs, producing ROS with antibacterial effects. Excited electrons (e^-) reduce oxygen molecules to form superoxide anions (O_2^-), while holes (h^+) react with water molecules to generate •OH.[101] Furthermore, bio-heterojunctions can integrate other functional components into the interface structure, making them an ideal platform for multimodal therapies.[124]

Dai et al designed a bio-heterojunction FMG composed of Fe_2O_3, Ti_3C_2-MXene, and GOx, which exhibited additional PTT, PDT, and CDT effects.[78] Under near-infrared (NIR) irradiation, this combination not only catalyzed redox reactions to generate abundant ROS for bacterial attack but also synchronously released Fe^{2+} and Fe^{3+}, further increasing intracellular and extracellular iron overload (Figure 1a). This induced bacterial lipid peroxidation through ferroptosis pathways. Moreover, FMG reduced the risk of ferroptosis in normal cells by depleting glucose via GOx, thereby achieving a "starvation protection" function. This allowed FMG to selectively target bacteria via ferroptosis while protecting normal cells from harm.

Experimental results showed that lipid peroxidation in *S. aureus* treated with the FMG group was the highest (Figure 1b), and the antibacterial effect was inhibited by the iron chelator EDTA (Figure 1c and d). This confirmed that FMG oxidized bacterial cell membranes via ferroptosis to achieve a bactericidal effect. Additionally, the FM group (Fe_2O_3/Ti_3C_2-MXene without GOx) increased lipid peroxidation in infected cells, whereas the FMG group (FM + GOx) did not induce significant lipid peroxidation (Figure 1e). Meanwhile, phosphorylation of AMPK and SLC7A11 /xCT of RAW 264.7 cells treated with FMG were significantly increased (Figure 1f and g). This indicated that the FMG group activated the AMPK pathway through starvation protection, helping host cells evade ferroptosis. Based on PDT/CDT therapy, such nanocomposites can achieve efficient generation of ROS and have synergistic antibacterial effects to promote tissue regeneration. However, there are some limitations such as complex synthesis process and photoresponsivity dependence (insufficient deep tissue penetration).

GOx/MOF Nanocomposite

Metal-Organic Frameworks (MOFs) are a class of porous materials formed by the coordination of metal ions or metal clusters with organic ligands through coordination bonds. They are characterized by high specific surface area, structural tunability, and abundant functional sites. Due to the challenging healing and high infection risk of DWs, MOFs have garnered significant attention for their roles in providing antibacterial properties and accelerating wound healing.

From the perspective of their roles in wound healing, MOFs can be categorized into three types: a. ZIF-type MOFs: These provide antibacterial effects and controlled drug release; b. Fenton and Fenton-like active MOFs: These generate •OH for antibacterial purposes; c. Protective MOFs: These stabilize enzyme activity, thereby prolonging the antibacterial effects.

Zeolitic Imidazolate Frameworks (ZIFs)

ZIFs are a special subclass of MOFs, typically composed of transition metals (such as zinc or cobalt) coordinated with imidazolate ligands, forming a zeolite-like topology.[125] Due to their unique acid-responsive degradation properties, ZIFs are often combined with GOx. In the acidic environment provided by GOx, ZIFs gradually degrade, enabling precise antibacterial action and controlled drug release.[103] Furthermore, ZIF materials possess inherent antibacterial properties that can directly inhibit pathogens, effectively reducing the risk of wound infection.

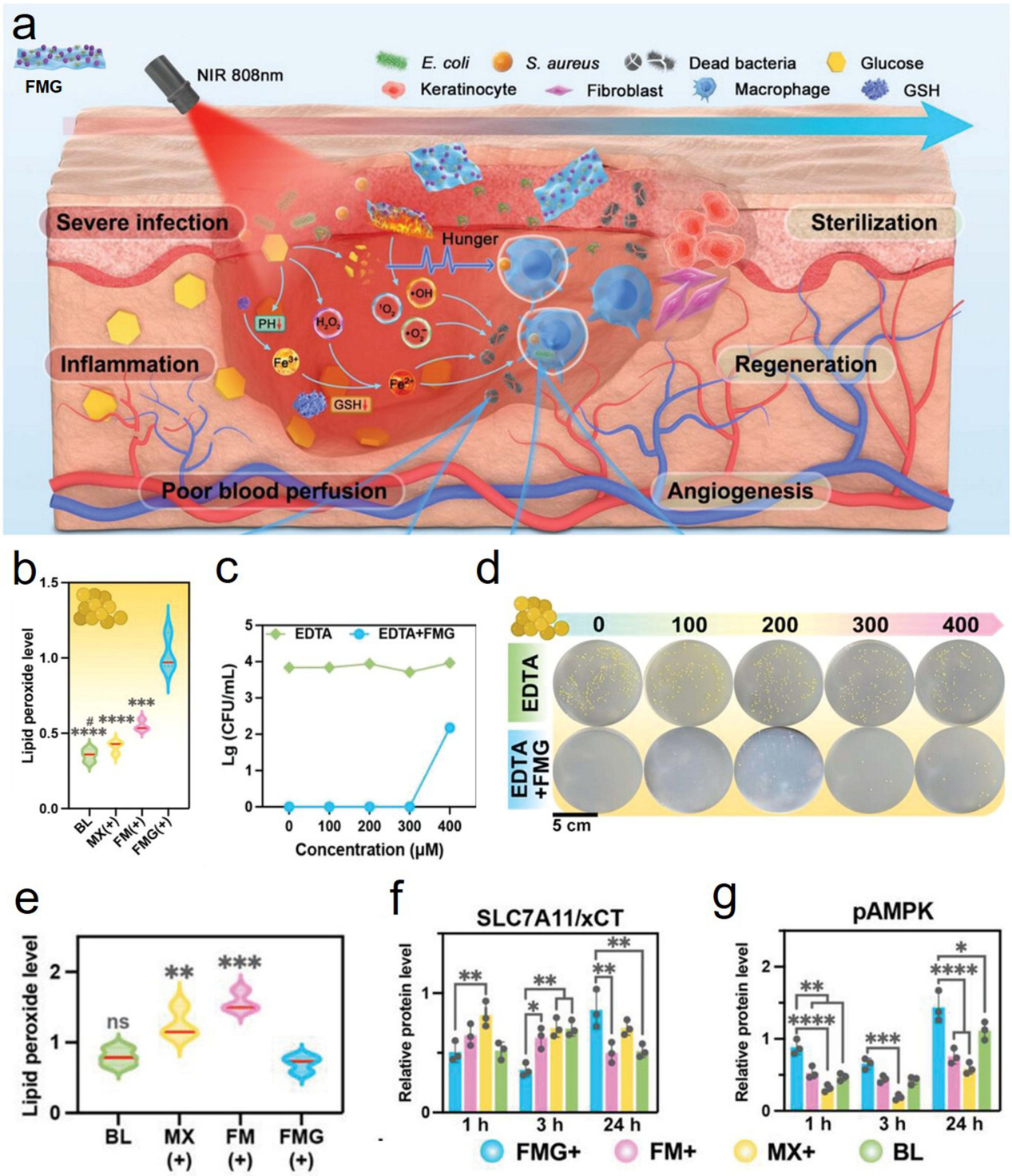


Figure 1 (**a**) Schematic diagram of ferroptosis bio-heterojunction (F-bio-HJs). (**b**) Lipid peroxide level in Staphylococcus aureus (S. aureus) with PBS, MX, FM, and FMG under near-infrared (NIR) irradiation. (**c**) Ethylenediaminetetraacetic acid (EDTA) inhibit the antibacterial property of FMG. (**d**) Photograph of culture plates of S. aureus treated with EDTA and FMG under NIR irradiation. (**e**) Lipid peroxide level in bacteria-invaded RAW264.7 cells with PBS, MX, FM, and FMG under NIR. (**f** and **g**) Immunoblotting of pAMPK and SLC7A11/xCT expression. Significance between two groups was calculated using one-way ANOVA and Tukey's multiple comparisons test (**e**–**g**). *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001. Adapted from Dai W, Shu R, Yang F, et al. Engineered bio-heterojunction confers extra- and intracellular bacterial ferroptosis and hunger-triggered cell protection for diabetic wound repair. *Adv Mater.* 2024;36(9):e2305277. © 2024 Wiley-VCH GmbH.[78]

Deng et al designed composite nanoparticles (F-GZ) composed of Fe_2O_3, ZIF-8, and GOx, exhibiting cascade enzyme catalytic activity and multifunctionality to address the complex microenvironment of diabetic bacterial-infected wounds.[95] Transmission electron microscopy revealed that F-GZ nanoparticles gradually degrade in glucose solutions

over time, releasing Zn^{2+} in a time-dependent manner. This is attributed to the pH reduction induced by GOx and the pH-sensitive properties of ZIF-8. Under acidic and glucose-rich conditions, this property exposes the GOx enzyme and Fe_2O_3, enhancing catalytic activity to produce •OH, which exhibit significant antibacterial effects. TMB chromogenic reactions demonstrated that at pH 5.5 (infection-associated wound conditions), the nanoparticles generate hydroxyl radicals in a concentration-dependent manner. In neutral environments, however, the composite nanoparticles catalyze H_2O_2 using Fe_2O_3 to continuously produce oxygen. Overall, under hyperglycemic conditions, GOx in F-GZ catalyzes glucose to acidify the environment, facilitating the release of Zn^{2+}, GOx, and Fe_2O_3. The H_2O_2 generated by GOx is oxidized by Fe_2O_3 to produce •OH, thereby enhancing antibacterial efficacy. During the wound healing phase, F-GZ catalyzes H_2O_2 to produce O_2, alleviating hypoxia and promoting tissue repair. Additionally, F-GZ was loaded into an injectable self-healing hydrogel (F-GZ@G) to reduce side effects and improve stability.

Fenton and Fenton-Like Active MOFs

Some MOFs containing transition metals (such as iron or copper) exhibit Fenton and Fenton-like activity, enabling them to catalyze H_2O_2 in wound environments to generate highly reactive •OH.[126,127] With H_2O_2 provided by GOx as a substrate, these MOFs serve dual functions in the treatment of DW: On one hand, the released •OH can directly attack bacteria, exerting potent antibacterial effects;[128] On the other hand, the ROS generated by the Fenton reaction can regulate the redox state of the wound and reshape the spatial inflammation pattern, thereby accelerating wound healing.[129]

Li et al synthesized an ionic covalent-organic framework (Fe-iCOF) by chelating iron ions with porphyrin groups.[104] This Fe-iCOF nanozyme exhibited excellent peroxidase-mimicking activity, capable of converting H_2O_2 into highly toxic •OH. Additionally, the two-dimensional structure of Fe-iCOF provided a high specific surface area and uniformly distributed active sites, which enhanced its catalytic efficiency.

Subsequently, Li et al loaded GOx onto the surface of Fe-iCOF through electrostatic interactions to form a composite nanozyme (GFeF) (Figure 2a). GOx acted as the initial catalyst in GFeF, converting glucose into gluconic acid and H_2O_2, which provided both substrates and an acidic environment for the subsequent Fe-iCOF catalysis. This significantly improved the peroxidase-like activity of the system, generating more •OH for antibacterial purposes. To verify the generation of •OH, the research team employed ABTS as oxidation indicators to assess the catalytic activity of Fe-iCOF and GFeF. The results demonstrated that Fe-iCOF significantly increased the typical absorption peak of $ABTS^+$ in the presence of H_2O_2 (Figure 2b and c). After introducing glucose into GFeF, the absorption peak intensity further increased, indicating that GFeF generated more •OH through the glucose-triggered cascade reaction. Likewise, fluorescence probe DCFH-DA detected significantly enhanced fluorescence signals with GFeF in the presence of glucose at the bacterial level, further confirming its potent •OH generation capability. Plate counting method was used to detect the antibacterial activity of GFeF against *E. coli* and *S. aureus*. The results showed that compared with PBS, Fe-iCOF, GFeF, glucose and glucose + Fe-iCOF, glucose + GFeF treatment had the highest antibacterial activity, as indicated by plate photographs and colony counts (Figure 2e-h) of Escherichia coli and Staphylococcus aureus. Histological analysis revealed that compared to the control group, the GFeF-treated group showed higher collagen deposition and faster angiogenesis in wound tissues.

Protective MOFs

Some MOFs can provide protective effects, maintaining the stability of active components in harsh wound environments. Furthermore, the unique structure of these MOFs allows for the isolation of different active components, preventing mutual interference, enabling their independent functionality, and enhancing the efficiency of synergistic reactions.[130]

Li et al successfully synthesized a novel composite material, GOx@Co-MOF, by embedding GOx into the Co-MOF framework during its formation process.[107] The synthesis involved mixing a sodium squarate solution with a cobalt nitrate solution, followed by the addition of GOx to integrate the enzyme into the MOF structure. The reaction was conducted at room temperature for 30 minutes, and the resulting product was isolated via centrifugation, washed, and dried to yield the GOx@Co-MOF composite.

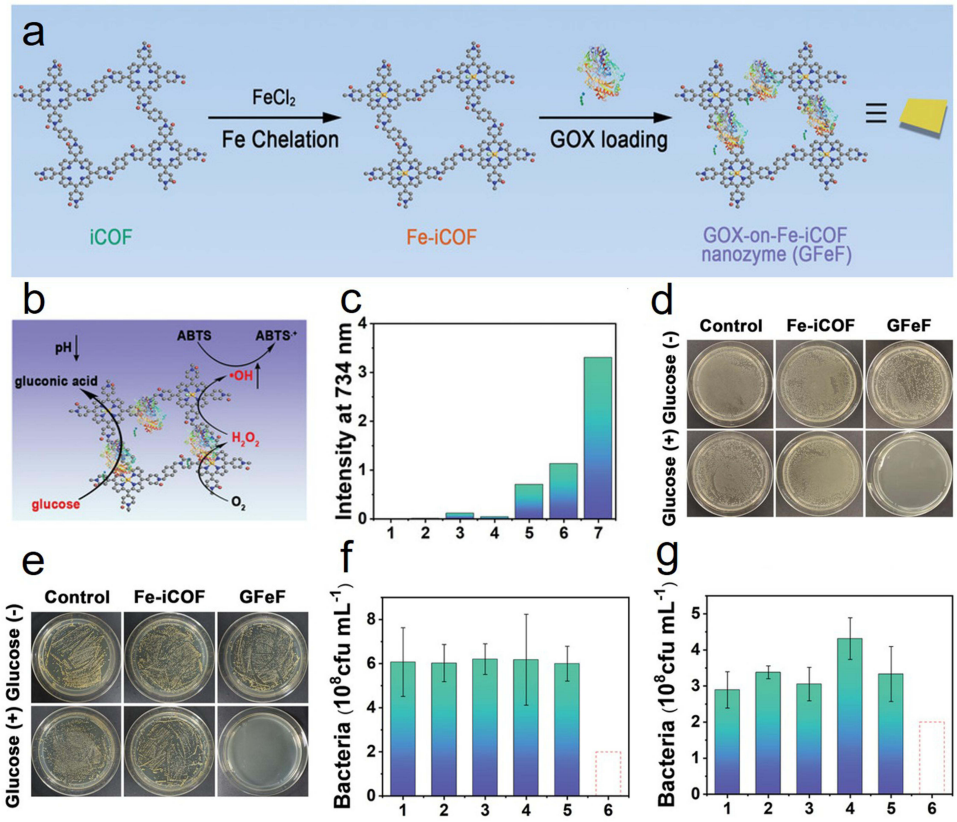


Figure 2 (**a**) Schematic representation of preparation of GOX-on-Fe-iCOF (GFeF) nanozyme. (**b**) Schematic illustration of the cascade reaction of GFeF nanozyme to the catalytic transformation of ABTS detection into ABTS radicals. (**c**) UV–vis absorption intensity at 734 nm of solution containing ABTS with 1) PBS, 2) glucose, 3) glucose + Fe-iCOF, 4) GFeF, 5) glucose + GOX, 6) glucose + Fe-iCOF + GOX, and 7) glucose + GFeF. (**d**) E. coli and (**e**) S. aureus after treatment of PBS, Fe-iCOF, GFeF, Glucose, Glucose + Fe-iCOF, and Glucose + GFeF. (**f**) E. coli and (**g**) S. aureus colonies after co-incubation with 1) PBS, 2) Fe-iCOF, 3) GFeF, 4) 15 mm Glucose, 5) 15 mm Glucose + Fe-iCOF, and 6) 15 mm Glucose + GFeF. Adapted from Li Y, Wang L, Liu H, et al. Ionic covalent-organic framework nanozyme as effective cascade catalyst against bacterial wound infection. *Small.* 2021;17(32):e2100756. © 2021 Wiley-VCH GmbH.[104]

GOx was effectively immobilized within the Co-MOF framework through strong coordination interactions, providing a stable environment that protected the enzyme. This design allowed GOx to maintain its enzymatic activity even in challenging conditions, such as those rich in proteins or reactive substances. Characterization techniques including FTIR, XPS, and SEM confirmed the successful integration of GOx within the Co-MOF and its uniform distribution. The Co-MOF framework not only stabilized GOx activity by preventing enzyme denaturation but also enhanced antibacterial efficacy through the gradual release of cobalt ions, which synergized with the hydrogen peroxide produced during glucose oxidation. This dual functionality resulted in significantly improved antibacterial performance compared to systems lacking MOF protection. Subsequently, the composite material was incorporated into a chitosan-based hydrogel, further enhancing its mechanical properties and biocompatibility for promoting wound healing. The protective effect of Co-MOF ensured sustained GOx activity, demonstrating the material's promising potential for advanced biomedical applications in wound care and infection control.

This type of nanocomposite can deliver drugs and achieve controlled drug release to promote wound healing. Additionally, it can exert bactericidal effects through Fenton-like reactions. However, despite the good antimicrobial properties of MOFs, the short diffusion distance of ROS limits their antibacterial activity. This becomes particularly problematic in deeper wounds, as ROS generated on the surface may not effectively reach deeper tissues. In some applications, the efficiency of ROS generation is still insufficient. This inefficiency may limit its antibacterial effects and its ability to accelerate wound healing.

GOx/Metallic Inorganic nanocomposite

Metallic inorganic nanocomposite refers to a functional material system built on metals and their compounds, such as metal oxides,[108] noble metal nanozymes.[115] Through nanoscale design and construction, it exhibits diverse physico-chemical properties for applications across various fields. These nanocarriers possess unique physical and chemical properties, such as semiconductor characteristics,[96] catalytic activity,[131] and the ability to regulate the release of therapeutic gases[132] and metalions.[42] These features give Metallic inorganic nanomaterials broad potential in various biomedical applications, especially in DW, where they are often used in conjunction with GOx.

Metal Oxides

$Fe_2(MoO_4)_3$ exhibits POD-like activity, enabling it to catalyze the decomposition of H_2O_2 into ROS, particularly •OH. Recently, Zhang et al developed a cascaded nanozyme system ($Fe_2(MoO_4)_3$@GOx) based on the synergistic interaction of `$Fe_2(MoO_4)_3$ and GOx for diabetic wound treatment.[28] This novel therapeutic strategy utilizes GOx to convert glucose into gluconic acid and generate H_2O_2 at diabetic wound sites. GOx not only lowers the local pH but also enhances the catalytic activity of $Fe_2(MoO_4)_3$ by providing substrates, continuously producing highly effective antibacterial molecules, such as •OH. This system takes full advantage of the high glucose concentration in diabetic wounds, providing a continuous substrate supply without the need for external H_2O_2 addition, thereby avoiding the instability of H_2O_2 in traditional treatments.

Experimental results show that the antibacterial effect of the $Fe_2(MoO_4)_3$@GOx system is significantly superior to the use of GOx or $Fe_2(MoO_4)_3$ alone. In antibacterial tests against ESBL-producing *E. coli* and MRSA, the $Fe_2(MoO_4)_3$@GOx complex exhibited excellent bacteriostatic effects (approximately 98.776% on MRSA and 98.396% on ESBL-producing *E. coli*), whereas the bactericidal rates of GOx or $Fe_2(MoO_4)_3$ alone ranged from 46.2% to 59.4%. The synergistic effect between GOx and $Fe_2(MoO_4)_3$ is particularly important in diabetic wound infections.

Noble Metal Nanozymes

Noble metal nanozymes are nanomaterials with surface catalytic properties that exhibit enzyme-like activities, making them widely applicable in the biomedical field. Common noble metal nanozymes include platinum (Pt), gold (Au), and silver (Ag), which typically display peroxidase-like activity, decomposing H_2O_2 into •OH with bactericidal effects, thereby demonstrating significant antibacterial functionality.[133]

Based on the peroxidase-like activity of noble metal nanozymes in acidic environments and the synergistic effect of GOx, researchers have developed a nanocapsule (APGH) (Figure 3a) composed of aptamer-functionalized platinum nanozymes (Apt-PtNZ), GOx, and hyaluronic acid (HA), providing a "bactericidal-anti-inflammatory" therapeutic strategy for diabetic wound infections.[115] This material is activated by hyaluronidase (HAase) secreted by pathogenic bacteria, releasing Apt-PtNZ and GOx. Apt-PtNZ targets bacteria through specific aptamers and catalyzes the localized production of H_2O_2, generating highly bactericidal hydroxyl radicals (•OH) that disrupt bacterial cell membranes and biofilm structures (Figure 3b).

Meanwhile, GOx oxidizes glucose into gluconic acid and produces H_2O_2, significantly lowering the pH of the wound microenvironment (Figure 3c), converting the alkaline environment into an acidic one more suitable for nanozyme activity, thereby enhancing the activity of PtNZ. To verify the nanozyme activity, methyl blue (MB) was used as an indicator in experiments. The results showed that after HAase activation, APGH significantly reduced MB absorbance, indicating that its peroxidase-like activity was significantly enhanced in acidic environments (Figure 3d). Furthermore, tests on pH and H_2O_2 production confirmed that GOx effectively lowered the local pH and generated sufficient H_2O_2 under high-glucose conditions in diabetic wounds, providing optimal conditions for the catalytic activity of Apt-PtNZ.

In vivo studies, APGH demonstrated wound-healing promotion in diabetic wounds. It not only effectively reduced bacterial infections but also inhibited inflammatory cell infiltration and promoted collagen production, accelerating wound closure. This strategy, which regulates the local microenvironment to overcome the limitations of traditional nanozymes, not only achieves efficient bactericidal effects for infection treatment but also lays a foundation for subsequent anti-inflammatory repair, showing broad application prospects for the treatment of complex infectious wounds.

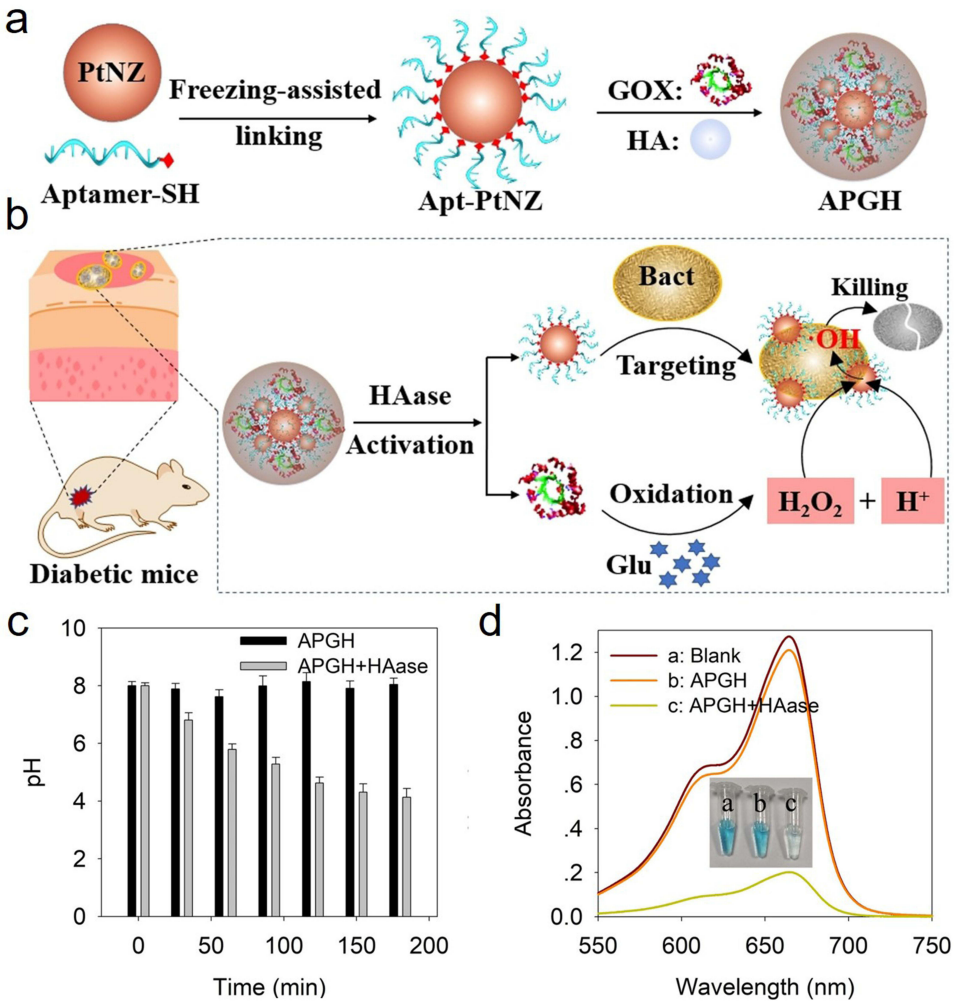


Figure 3 (**a**) The preparation route for the nanozyme capsule (APGH) with aptamer functionalized platinum nanozymes (Apt-PtNZ), GOX and hyaluronic acid (HA). (**b**) Schematic illustration of APGH activation, activity switching in the infected wound, and its application for chemodynamic sterilization through in situ generation of OH on bacteria surface. (**c**) APGH activation-induced pH change in the PBS buffer (pH 8.0) containing 10 mM Glu. (**d**) Absorbance and photo of MB solutions after different treatment to demonstrate APGH activation-dependent generation of •OH. Adapted from Chen L, Xing S, Lei Y, et al. A glucose-powered activatable nanozyme breaking pH and H(2) O(2) limitations for treating diabetic infections. *Angew Chem Int Ed Engl*. 2021;60(44):23534–23539. © 2021 Wiley-VCH GmbH.[115]

These nanocomposites mainly consist of metal oxides and certain noble metal-based nanomaterials, which exhibit good peroxidase-like activity which could provide a significant antibacterial ability. However, the synthesis and purification processes of some noble metal-based nanomaterials are complex, costly, and difficult to scale up for large-scale applications.

GOx/Biomineralizing Nanocomposite

Biomineralized-based materials are composite materials generated through the biomineralization process, typically mediated by organic templates or biomolecules. Under specific conditions, this process promotes the nucleation and growth of inorganic substances, resulting in materials with distinct structures and functions.[134] This process combines the advantages of biomolecules (such as proteins and enzymes) with inorganic materials, allowing the production of materials with high biocompatibility, stability, and functionality.[135] In the context of DWs treatment, biomineralized nanomaterials based on GOx have gained significant attention in recent years. GOx, an enzyme capable of catalyzing the oxidation of glucose to produce gluconic acid and H_2O_2, is often chosen as the organic template in biomineralization.[22] In the context of DWs treatment, biomineralized nanomaterials based on GOx have gained significant attention in recent years. GOx, an enzyme capable of catalyzing the oxidation of glucose to produce gluconic acid and H_2O_2, is often chosen as the organic template in biomineralization.

Metal sulfides readily react in acidic environments to release hydrogen sulfide (H_2S) gas. Based on this property, researchers developed a GOx@Fe_xS_y/AZM nanocomposite, providing an integrated "antibacterial-anti-inflammatory" therapeutic strategy for simultaneous infection control and inflammation regulation.[22] This material consists of iron sulfide nanoparticles (Fe_xS_y), glucose oxidase (GOx), and azithromycin (AZM), with GOx and AZM immobilized on the nanoparticles via biomimetic mineralization (Figure 4a). This design enables the controlled release of Fe^{2+} and H_2S gas in acidic environments (Figure 4b).

In hyperglycemic conditions, GOx converts glucose into H_2O_2, which, in the presence of Fe^{2+}, undergoes a Fenton reaction to generate highly bactericidal •OH. These reactive species effectively disrupt bacterial cell structures and biofilms, significantly enhancing antibacterial efficacy. During the anti-inflammatory phase, the synergy between AZM and low levels of H_2S effectively suppresses excessive inflammatory responses. AZM extends its activity within tissues to inhibit pro-inflammatory transcription factors AP-1 and NF-κB, while H_2S reduces inflammation through immune modulation, promoting the phenotypic shift of macrophages from pro-inflammatory M1 to anti-inflammatory M2 (Figure 4c-e). This phenotypic transformation not only aids in controlling wound infections but also supports tissue repair and regeneration, thereby accelerating the wound healing process. By combining "efficient antibacterial action during the infection phase" with "anti-inflammatory immune modulation during the healing phase", GOx@Fe_xS_y /AZM achieves dual functionality in diabetic wound management. It provides potent initial antibacterial effects while laying the foundation for subsequent anti-inflammatory repair, demonstrating significant therapeutic potential for complex infectious wounds.

Biomineralized Nanocomposites exhibit excellent biocompatibility and integrate the functionalities of organic biomolecules and inorganic substances. However, certain environmental conditions, such as pH and temperature, may influence the stability and activity of the incorporated biomolecules, potentially reducing the effectiveness of these nanomaterials in some applications.

GOx/Self-Assembling Nanoreactor

Self-assembly technology is a process that allows various molecular components to be combined through non-covalent interactions under specific conditions.[136] Based on this, researchers have developed many multifunctional self-assembled nanoreactors by assembling various materials (such as enzymes and catalytic materials), which are used for the treatment of diabetic wounds.[113]

Chen et al developed a glucose-activated supramolecular cascade reactor through self-assembly, which can be applied for the treatment of diabetic wounds.[112] The study first utilized the electrostatic interaction between chitosan (CS) and sulfobutylether-β-cyclodextrin (SBE-β-CD) to form a supramolecular assembly (CS@SBE-β-CD). Subsequently, ferrous ions (Fe^{2+}) were added to coordinate with the amino groups of chitosan, further stabilizing the assembly structure (CS@SBE-β-CD@Fe^{2+}). The particle size and morphological changes of the assemblies were confirmed using Fourier-transform infrared spectroscopy (FT-IR), dynamic light scattering (DLS), and transmission electron microscopy (TEM). Finally, glucose oxidase (GOx) was incorporated to form the final cascade reactor (CS@SBE-β-CD@Fe^{2+}-GOx). The catalytic capability of the reactor under high glucose conditions was validated using the TMB colorimetric assay and electron paramagnetic resonance (EPR), which confirmed the generation of •OH and their strong antibacterial activity.

Additionally, •OH can induce the rapid polymerization of vinyl monomers (eg, PEGDA) to form hydrogels in situ at the wound site. These hydrogels not only provide a moist environment for wound healing but also confine the activity of the reactor, enhancing its antibacterial effects. In a diabetic rat wound model, the supramolecular cascade reactor demonstrated significant antibacterial performance and promoted wound healing by effectively suppressing multidrug-resistant bacterial infections, reducing inflammatory responses, and accelerating collagen production and wound closure. This strategy combines antibacterial effects with in situ hydrogel formation by locally releasing •OH, offering a new approach for treating chronic diabetic wounds.

Self-assembling nanocomposites, typically composed of natural polymers, exhibit excellent biocompatibility. By modulating the assembly units, the functional properties of these nanocomposites (eg, responsive release) can be precisely designed, making them widely applicable in drug delivery and wound healing. However, the stability of these materials may be compromised under specific conditions, such as long-term storage or extreme environments,

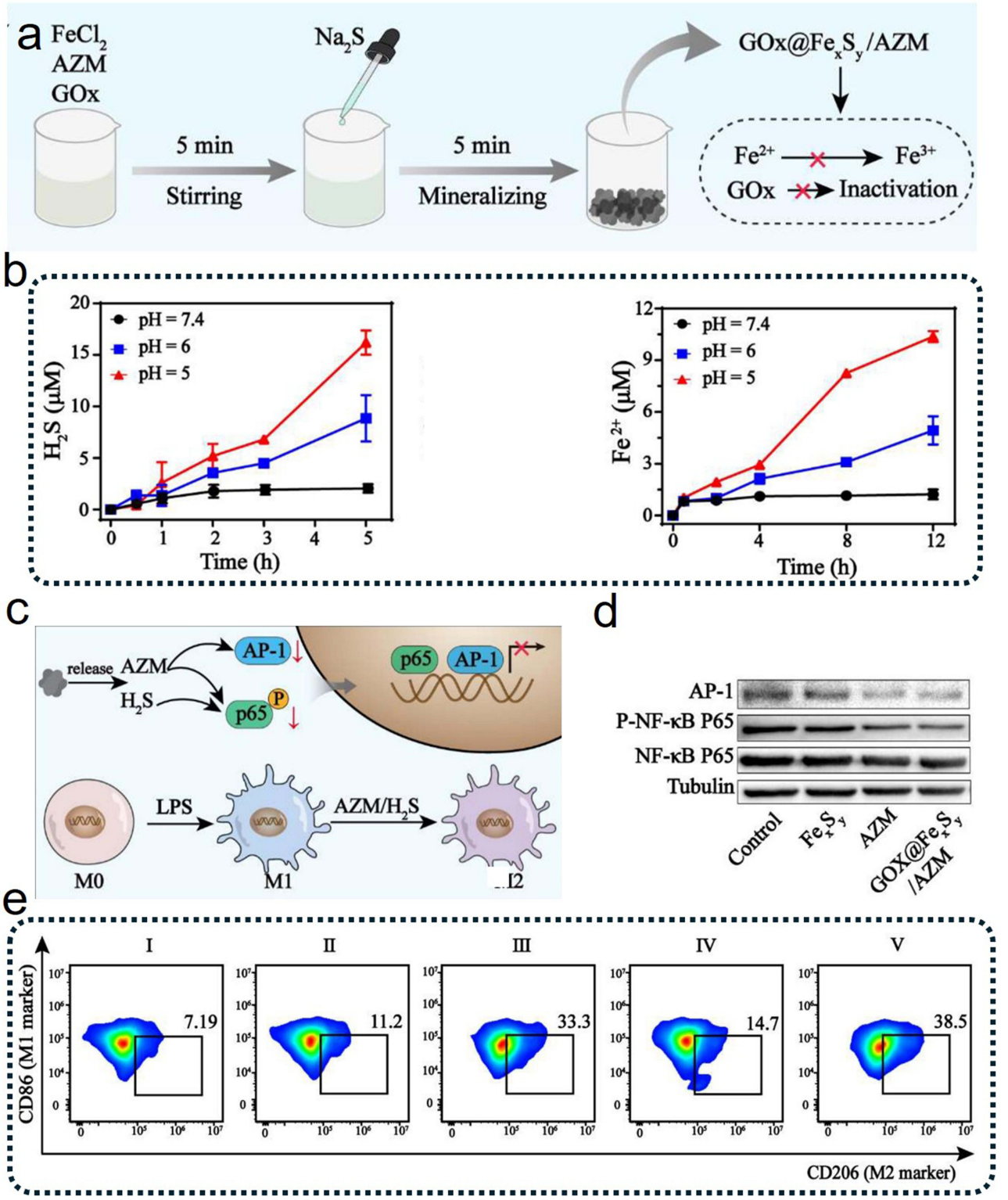


Figure 4 (**a**) The synthetic route of GOx@FexSy /AZM. (**b**) H2S gas and Fe2+ ions release of GOx@ FexSy/AZM in buffer solutions with different pH values. (**c**) Scheme of GOx@ FexSy /AZM induced M2 polarization in macrophages. (**d**) Western blot of p-NF- κB P65, NF- κB P65 and AP-1 expression in LPS-induced RAW 264.7 macrophages upon various treatments. (**e**) Flow scatter diagrams of CD86 (M1 marker) and CD206 (M2 marker) expression after different treatments. Control, Fex Sy, AZM@ FexSy, GOx@ FexSy, and GOx@ FexSy /AZM are denoted as I, II, III, IV, and V groups. Adapted from *Acta Biomater*, volume 181, Deng S, Ou K, Zhang C, et al. A one-two punch strategy for diabetic wound management based on an antibiotic-hybrid biomineralized iron sulfide nanoparticle. 333–346, copyright © 2024, with permission from Elsevier.[22]

under which the self-assembled structures may disintegrate, leading to functional loss. 4.2.6 GOx/Polymers nanocomposite.

Polymer is a macromolecule composed of repeating monomer units. Due to its structural diversity, biocompatibility, and tunable functionality, it is widely used in various fields. Polymers (such as nanogels and single-molecule enzyme-polymer conjugates) can encapsulate GOx through physical encapsulation, providing a stable supportive matrix that promotes the healing process of chronic wounds, such as those in diabetes.[27]

There were researchers who developed a glucose oxidase-catalase nanogel (GOx-CAT Nanogel, GCN) system for the treatment of diabetic wounds.[100] The nanogel was synthesized through covalent polymerization, combining GOx and CAT to achieve efficient cascade catalytic activity. GOx oxidizes glucose into gluconic acid and H_2O_2, which is subsequently decomposed into O_2 by CAT, improving the local hypoxic environment. TEM revealed that the nanogel has a uniform circular structure of approximately 80 nm, while DLS measured a hydrated particle size of 123 nm. The neutral zeta potential (−0.178 mV) indicated its excellent biocompatibility and stability.

Experimental validation demonstrated that GCN could continuously generate oxygen under simulated diabetic wound conditions with high glucose and oxidative stress, thereby alleviating local hypoxia. Its remarkable antioxidant properties effectively scavenged ROS, reducing oxidative damage and promoting the survival and migration of human gingival fibroblasts (HGF-1). In a diabetic rat oral mucosa ulcer model, GCN showed significant therapeutic effects, including a notable increase in ulcer closure rates (82.69% within 14 days), reduced inflammation, and enhanced angiogenesis (verified by TNF-α and CD31 immunofluorescence staining). Histological analysis further confirmed that the ulcer tissue in the GCN group exhibited tightly arranged cells and significant fibroblast proliferation.

In summary, the GCN system effectively addresses the complex pathological environment of diabetic wounds through the cascade catalytic activities of GOx and CAT, simultaneously supplying oxygen, reducing oxidative stress, and promoting cell migration. This multifunctional nanogel demonstrates significant therapeutic potential, offering a novel strategy for chronic wound treatment and promising applications in the biomedical field.

Polymeric nanocomposites possess drug-loading capabilities and sustained-release properties, enabling the prolonged release of therapeutic agents. However, in certain cases, the size and distribution of polymeric nanoparticles may become non-uniform, leading to inconsistent drug release and compromised therapeutic efficacy.

GOx/Other Nanocomposite

In DWs, various GOx-conjugated nanocomposites have been developed to achieve multimodal synergistic therapy. In addition to the mainstream nanocomposites, several other materials (such as black phosphorus nanosheets, mesoporous silica nanoparticles, and nanoclay) have played unique roles. Mesoporous silica nanoparticles enable sustained drug release through adjustable pore structures, facilitating the combined administration of azithromycin and GOx.[75] Black phosphorus nanosheets, with their photothermal conversion capability, generate a thermal effect under near-infrared light, further enhancing antibacterial properties and accelerating healing.[117] Nanoclay, with its layered structure, offers drug delivery while modulating the acidic environment to promote wound repair.[118] Camelina lipid droplets, owing to their excellent biocompatibility and sustained-release properties, can serve as drug carriers, enhancing wound healing.[119] The synergistic effects of these nanocomposites provide innovative strategies for the treatment of DWs.

Chen et al developed a drug-free bioclay enzyme (Bio-Clayzyme) composed of Fe^{2+}-tannic acid (TA) network-coated kaolinite nanoclay and GOx, designed to treat diabetic and infected wounds through bimetallic antibacterial therapy.[118] The assembly process involved coating kaolinite (Kaol) nanoclay with an Fe^{2+}-TA network, followed by the incorporation of GOx to form the final Bio-Clayzyme structure (Kaol@GOx@Fe-TA).

Bio-Clayzyme exhibited glucose-triggered catalytic activity, where GOx facilitated the conversion of glucose into gluconic acid and H_2O_2, leading to a localized drop in pH. The acidic environment triggered the release of Al^{3+} from the kaolinite, which disrupted bacterial membranes and enhanced the intracellular transport of Fe^{2+}. The production of •OH through the Fe^{2+}-mediated Fenton reaction was significantly enhanced, as confirmed by TMB detection and ESR spectroscopy.

In addition to its potent antibacterial activity, Bio-Clayzyme demonstrated hemostatic and anti-inflammatory properties. Kaol accelerated coagulation by physically adsorbing erythrocytes and platelets, while TA suppressed inflammatory

cytokines such as IL-6 and TNF-α, thereby promoting wound healing. In a diabetic mouse wound model, Bio-Clayzyme significantly promoted wound closure and collagen deposition due to its synergistic antibacterial, hemostatic, and anti-inflammatory effects.

Multimodal Synergistic Therapy in Diabetic Wound Healing with GOx-Based Nanocomposite

The healing process of DW is complex and dynamic, influenced by multiple factors. These include bacterial infections, macrophage dysfunction, excessive pro-inflammatory cytokines, elevated ROS, and persistent hypoxia, which collectively hinder cellular behavior and the overall healing process.[137] This has led to the recognition that single therapies are insufficient to meet the demands of DW treatment. Instead, multimodal synergistic therapeutic strategies hold greater promise for overcoming the complexities of DW management. Among these strategies, GOx-based nanocomposites have garnered significant attention, primarily leveraging cascade reactions centered on GOx catalytic activity to integrate with various therapeutic modalities. Currently, a range of rationally designed GOx-based nanocomposites has been developed, offering multimodal synergistic treatments for DWs. Table 2 outlines the mechanisms and recent advances in these synergistic therapies. Moreover, GOx-based nanocomposite can be integrated with targeted delivery strategies to achieve localized enrichment of therapeutic agents at the wound site. This approach not only enhances therapeutic efficacy but also minimizes biological toxicity, making it a highly promising direction in DW treatment.

Glucose/ROS Scavenging Cascade Synergistic Therapy

Glucose/ROS scavenging cascade therapy promotes the healing of DW by consuming glucose and generating oxygen. However, with elevated blood glucose levels, the risk of wound infection also increases, and this single strategy alone is insufficient to address the complex pathological conditions of DWs. To overcome these challenges, researchers in recent years have incorporated PDT and CDT into this approach, enabling multimodal treatments that integrate antibacterial and anti-inflammatory effects.

PDT Synergized with Glucose/ROS Scavenging

PDT is an innovative treatment technique that utilizes photosensitizers, specific wavelength light sources, and oxygen molecules within tissues. Upon stimulation by specific light irradiation, PDT activates the photosensitizer to produce ROS, selectively destroying pathological tissues.[138] In the treatment of DW, PDT achieves efficient antibacterial effects by generating ROS without inducing bacterial resistance.[139] However, the hypoxic environment within the wound limits the bactericidal efficacy of PDT. To address this, many researchers have developed oxygen-generating systems based on glucose/ROS scavenging strategies, significantly enhancing PDT's antibacterial performance in hypoxic conditions.[109]

Table 2 Progress and Mechanisms of Different Types of Synergistic Therapy

GOx-Guided Therapeutic Strategies	Therapeutic Mechanism	Synergistic Therapies and Functions	Ref
Glucose/ROS Scavenging therapy	Depleting Glucose While Alleviating Oxidative Stress	GT, Antibacterial and Anti-Inflammatory	[102]
		PDT, Antibacterial	[109]
		CDT, Antibacterial	[29,108,110]
Glucose/ROS generation therapy	H_2O_2 Generated from Glucose Depletion Catalytically Produces •OH for Antibacterial Action	PTT, Antibacterial	[32,116,117]
		PTT\PDT, Antibacterial	[78,101]
		Immunomodulation, Anti-Inflammatory	[96]
		Antibiotic, Antibacterial	[75]
GOx-Instructed Self-powered therapy	Harnessing Glucose as Fuel to Generate Microcurrent for Tissue Repair	CDT, Antibacterial	[88]
GOx-Instructed Delivery therapy	Leveraging GOx-Catalyzed Reactions to Trigger Precise Drug Release	GT, Antibacterial and Anti-Inflammatory	[15]
		CDT\GT, Antibacterial and Anti-Inflammatory	[22,113]

Recent studies[109] have described a BEMGNPs nano-drug delivery system, which integrates berberine (BBR) and epigallocatechin gallate (EGCG)-derived self-assembled photosensitizer nanoparticles (BENPs) with MnO_2 nanoshells and GOx. In DW, this material first catalyzes glucose through GOx, producing gluconic acid and H_2O_2, thereby reducing localized hyperglycemia. Subsequently, the generated H_2O_2 is decomposed by MnO_2 nanoshells, releasing O_2. Oxygen, as a critical substrate for PDT, not only alleviates the hypoxic environment at the wound site but also provides a sufficient oxygen supply for the subsequent photosensitization reaction. Finally, under light irradiation, BENPs act as photosensitizers, generating large amounts of ROS (Figure 5a). The synergy between ROS and oxygen further enhances the antibacterial efficacy, particularly against multidrug-resistant bacterial infections (Figure 5d).

The generation of ROS under light irradiation was assessed using DCFH-DA. In the experimental group, with both glucose and light exposure, fluorescence intensity increased significantly, indicating a marked rise in ROS production (Figure 5b). In contrast, control groups lacking either light or glucose showed minimal changes in fluorescence intensity. After filling with O_2, ROS production in the experimental group was 6 times higher than in the controls (Figure 5c), demonstrating that oxygen generation effectively enhances PDT-induced ROS production, thereby improving the antibacterial performance of the material.

CDT Synergized with Glucose/ROS Scavenging

Based on the unique characteristics of the DW microenvironment, CDT has been further optimized in recent years to achieve efficient antibacterial effects. By utilizing self-supplied H_2O_2 and acidic conditions, CDT catalytically generates •OH, effectively eradicating bacteria.[140] Researchers have integrated this therapy with the Glucose/ROS scavenging strategy to create a switchable dual-cascade reaction mechanism: In acidic environments, the system generates •OH to eliminate biofilms effectively; In neutral environments, the system produces oxygen to promote tissue regeneration and wound healing.[29]

Du et al proposed a pH-switchable nanozyme cascade catalysis (PNCC) strategy based on Fe_3O_4-GOx nanozymes, aiming to optimize the therapeutic effects on DW by combining CDT with glucose/ROS scavenging mechanisms.[108] This system leverages the acidic and neutral microenvironments within DWs to trigger distinct reaction pathways under different pH conditions, thereby achieving dual cascade reactions. In acidic environments (eg, biofilm regions, pH ~5.5), the Fe_3O_4-GOx system utilizes a GOx/POD cascade reaction to catalyze the production of •OH, effectively eradicating bacteria within biofilms and shortening the inflammatory phase of wound healing. Meanwhile, in the more neutral wound environment (pH 7.4), the system initiates a GOx/CAT cascade reaction, decomposing glucose-oxidation-generated H_2O_2 into O_2. The generated oxygen alleviates hypoxia in the wound area and provides an oxygen-rich environment conducive to tissue regeneration, thereby accelerating healing during the proliferation and remodeling phases. Experimental analysis demonstrated the occurrence of the GOx/CAT cascade reaction under neutral conditions, as indicated by high oxygen production when Fe_3O_4-GOx nanozymes were mixed with glucose and H_2O_2 solutions. Under acidic conditions, the Fe_3O_4-GOx system produced substantial amounts of •OH through the GOx/POD cascade reaction, which was confirmed by methylene blue (MB) degradation and terephthalic acid (TA) fluorescence assays. Antibacterial experiments showed that Fe_3O_4-GOx nanozymes exhibited significant bactericidal activity under acidic conditions. Additionally, scanning electron microscopy and staining experiments revealed bacterial structural damage, including membrane disruption and cell death, caused by the nanozyme in acidic environments. Moreover, Fe_3O_4-GOx effectively inhibited and eradicated biofilms, demonstrating its potential for treating biofilm-associated infections.

These findings suggest that the pH-switchable catalytic functions of Fe_3O_4-GOx nanozymes effectively address the multifaceted pathological challenges of DWs, thereby significantly enhancing wound healing efficacy and speed.

Glucose/ROS Generation Cascade Synergistic Therapy

Bacterial biofilms are structures composed of EPS secreted by bacteria, consisting of polysaccharides, proteins, lipids, and DNA.[141] Biofilms provide a physical barrier that shields bacteria from antibiotics and host immune system attacks, making biofilm-associated infections particularly challenging to treat.[142]

The core mechanism of glucose/ROS cascade therapy involves leveraging the strong oxidative properties of ROS to directly target and degrade the EPS components, such as polysaccharides, proteins, and lipids, thereby overcoming the

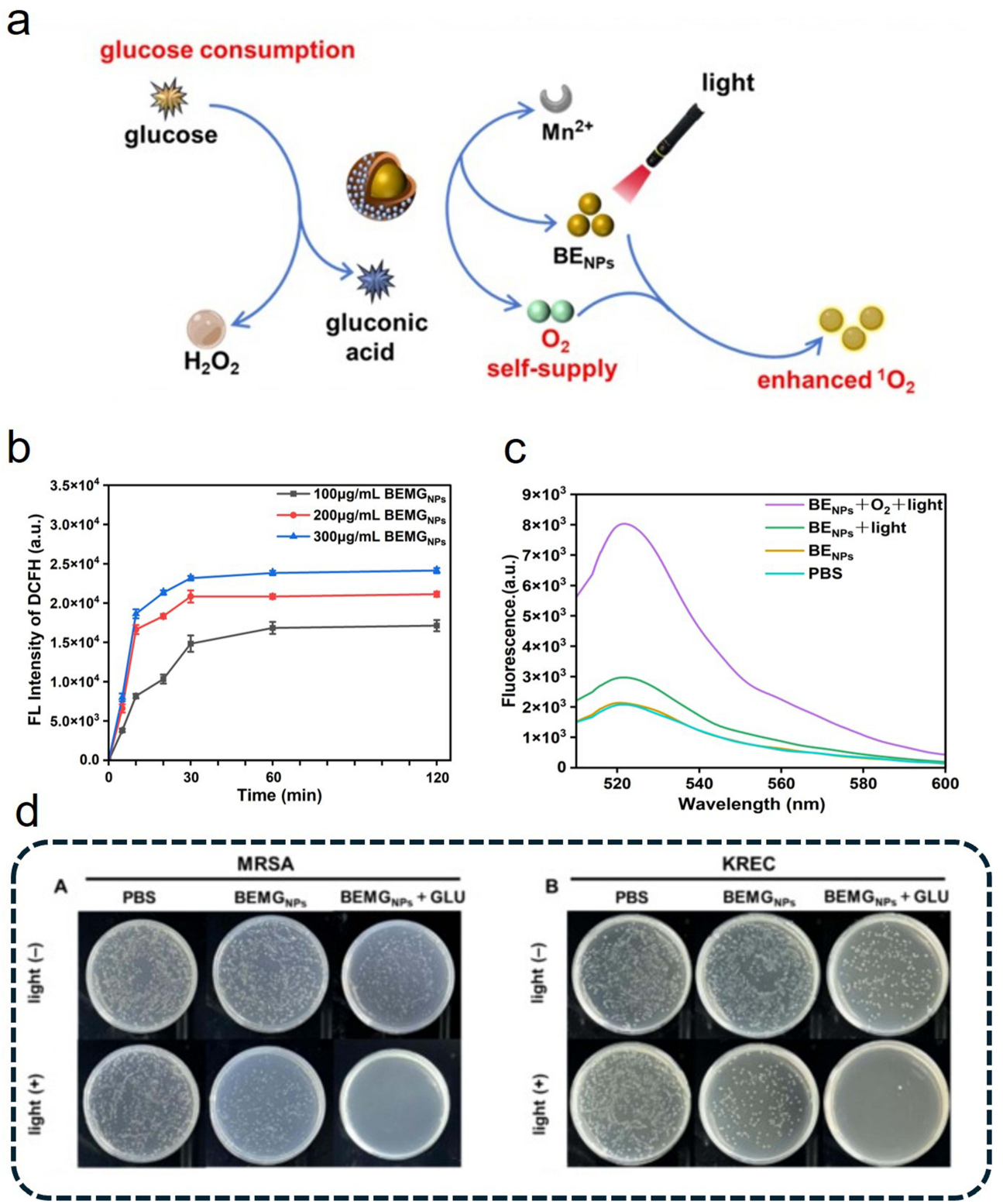


Figure 5 (**a**) The therapeutic mechanism of BEMGNPs based on the glucose-driven cascade reaction. (**b**) ROS generation of BEMGNPs at different concentrations under light irradiation (100 mW cm−2) measured by DCFH fluorescence change at 530 nm (n=3). (**c**) Improved ROS generation from BENPs under the assistance of O2. (**d**) Images of bacterial colonies of MRSA and KREC with various treatments. Adapted from J Colloid Interface Sci, volume 672, Zhang J, Li W, Tao Z, et al. Endogenous glucose-driven cascade reaction of nano-drug delivery for boosting multidrug-resistant bacteria-infected diabetic wound healing. 63–74, copyright © 2024, with permission from Elsevier.[109]

protective barrier of biofilms.[143] However, this therapy has certain limitations. First, high concentrations of ROS may pose toxic risks to host tissues.[144] Second, infections with dual resistance to ROS and immune cell attacks may not be eradicated solely by exogenous oxidative stimulation.[145]

To address the shortcomings of glucose/ROS cascade therapy, its combination with other therapies has become a key research focus. PTT through localized thermal effect, accelerates bacterial membrane disruption and apoptosis, thereby enhancing the antibacterial efficacy of ROS.[117] PDT utilizes light to activate photosensitizers, generating additional ROS.[146] Additionally, immunomodulatory therapy (IMT) can synergize with glucose/ROS cascade therapy by mobilizing the host immune system to eliminate residual pathogens and promote wound healing.[147] The combined application of multiple therapies not only enhances antibacterial efficacy but also mitigates the potential side effects of standalone treatments, demonstrating the synergistic and amplified therapeutic effects of integrated strategies.

PTT Synergized with Glucose/ROS Generation

PTT is a non-invasive technique that utilizes specific wavelengths of light to convert light energy into heat energy via photothermal materials, thereby achieving therapeutic effects.[148] This therapy primarily relies on photothermal materials such as carbon nanotubes, gold nanoparticles, and black phosphorus[149–151] Upon light irradiation, these materials absorb light energy and convert it into heat, leading to a localized temperature increase. This thermal effect exhibits multiple therapeutic benefits, including antibacterial activity, anti-inflammatory effects, promotion of macrophage M2 polarization, and angiogenesis.[152] When PTT is combined with glucose depletion and ROS generation, its photothermal effect raises the local temperature, enhancing bacterial membrane permeability and further amplifying the bactericidal efficacy of •OH. Moreover, this combined therapy achieves effective bacterial eradication at moderate temperatures, minimizing the risk of thermal damage to healthy tissues. This makes it particularly effective against drug-resistant strains and biofilm-associated infections, highlighting its significant potential for clinical applications.[116]

Shen Yizhong et al designed a Fe-driven multifunctional cascade nano-reactor, GOX/MPDA/Fe@CDs, for synergistic photothermal and chemodynamic antibacterial therapy.[116] This system integrates GOX, Fe-doped carbon dots (Fe@CDs), and mesoporous polydopamine (MPDA), enabling the generation of large amounts of ROS in high-glucose environments. Additionally, the photothermal effect increases the temperature of the affected area (~45°C), enhancing bacterial membrane permeability and biofilm disruption. Specifically, the GOX/MPDA/Fe@CDs nanozyme induces localized temperature elevation under near-infrared (808 nm) laser irradiation, facilitating GOX-catalyzed glucose conversion into H_2O_2, which is further utilized in the Fenton reaction to produce •OH for potent antibacterial effects. In the presence of 10 mm glucose, the survival rate of methicillin-resistant MRSA significantly decreased, demonstrating the system's efficient utilization of endogenous glucose and its successful synergistic catalytic and antibacterial performance. Moreover, GOX/MPDA/Fe@CDs exhibited excellent anti-biofilm activity, effectively removing bacterial biofilms through cascade catalytic reactions and significantly enhancing antibacterial treatment outcomes. Notably, the system performed exceptionally well in high-glucose, hypoxic, and mildly acidic environments. When combined with laser irradiation, biofilm removal efficiency dramatically increased from 57.05% with standalone treatment to 97.14%, confirming the enhancement of the glucose/ROS generation strategy by photothermal therapy. Live/dead bacterial staining further revealed that most bacteria within the biofilm were successfully eliminated following the combined treatment, underscoring the high efficiency of this synergistic therapeutic strategy in eradicating biofilms and killing bacteria.

Animal experiments demonstrated a significant synergistic effect of combining PTT and CDT in accelerating DW healing. The combined treatment group achieved nearly complete wound closure within 9 days, whereas the group treated with GOX/MPDA/Fe@CDs alone required 12 days to reach partial wound closure. Control groups and laser-only treatment groups showed the least effective results. These findings validate the efficacy of the combined treatment in improving therapeutic outcomes and expediting wound healing.

PTT/PDT Synergized with Glucose/ROS Generation

In wound therapy, multimodal synergistic therapies have shown great potential due to their ability to address the limitations of single therapies and integrate multiple treatment modalities.[153] Among these, the combination of PTT,

PDT, glucose depletion, and ROS generation has attracted significant attention.[154] PTT utilizes near-infrared light to produce localized thermal effects, effectively killing bacteria and inhibiting biofilm formation;[155] PDT, through photosensitizer activation, generates ROS (eg, singlet oxygen) with high selectivity and minimal damage to surrounding tissues;[156] CDT relies on chemical reactions to release ROS, effectively targeting drug-resistant bacteria.[157] The synergy of these three approaches not only enhances antibacterial efficacy but also reduces side effects, providing a more efficient and comprehensive antibacterial strategy. This is particularly suitable for the treatment of refractory bacterial infections in wound care.[158]

Researchers have developed an innovative C-bio-HJs that integrates PTT, PDT and CDT to synergistically promote DW healing.[101] This system leverages the photothermal effects and Fenton-like catalytic properties of MoS_2 combined with the photocatalytic characteristics of g-C_3N_4, achieving multimodal therapy under near-infrared (808 nm laser) irradiation (Figure 6a). Specifically, MoS_2 serves as the primary photothermal conversion material, rapidly heating to 47.5°C under laser irradiation. This localized temperature increase significantly enhances bacterial membrane permeability and disruption. Concurrently, g-C_3N_4 facilitates the separation of photo-induced electron-hole pairs under light exposure, promoting the generation of ROS, including singlet oxygen ($^1O_2$) and $\cdot O_2^-$ (Figure 6b), then synergizing the PTT effect. In this system, GOx catalyzes the conversion of glucose in DWs into H_2O_2, inducing a "starvation therapy" effect that depletes bacterial energy supply. MoS_2 further converts H_2O_2 into •OH via the Fenton reaction. These highly reactive ROS effectively eradicate drug-resistant bacteria and disrupt bacterial biofilms, substantially improving CDT efficacy. Experiments demonstrated that the nanosystem achieved over 95% bactericidal efficiency against methicillin-resistant MRSA and *E. coli* within 10 minutes, particularly under dual-light (Xe lamp and 808 nm laser) irradiation (Figure 6d). The enhanced antibacterial performance was attributed to the synergy among PTT, PDT, and CDT. The local hyperthermia induced by PTT not only increased bacterial sensitivity to ROS but also accelerated the catalytic activity of GOx, facilitating rapid ROS production. In vivo experiments demonstrated the superior wound-healing efficacy of C-bio-HJs in diabetic mouse models. Compared to single-therapy groups, the synergistic treatment group exhibited significant wound contraction and healing within 7 days (Figure 6c). This study highlights the potential of C-bio-HJs for synergistic PTT, PDT, and CDT antibacterial therapy, offering an efficient and safe strategy for treating refractory diabetic wounds.

This multimodal synergistic therapy (PTT/ PDT/CDT) primarily achieves antibacterial effects through the generation of ROS. However, the excessive production of ROS inevitably causes oxidative damage to healthy cells and tissues. To address this critical issue, the development of functional nanomaterials with precise targeting capabilities is an effective solution. For example, surface modification with specific ligands (such as bacterial membrane-targeting peptides) can significantly enhance the selectivity of the nanocomposites toward pathogenic microorganisms, thereby reducing non-specific damage to host tissues.[159]

In the combined application of PTT and PDT, the localized high temperatures generated during the photothermal conversion process may lead to the inactivation of the photosensitizers used in PDT, thereby diminishing their photodynamic efficacy. Therefore, it is crucial to screen novel photosensitizers with excellent thermal stability (such as metalloporphyrin derivatives), which can maintain stable photosensitizing performance within the PTT treatment temperature range (typically 45–50°C).[160] Additionally, the excessive thermal effects induced by PTT may cause thermal damage to surrounding tissues and delay the healing process. Thus, photothermal materials with precise photothermal conversion properties and real-time temperature monitoring systems can help mitigate this risk.

By addressing the challenges, researchers are expected to develop more efficient and safer combined PTT/PDT therapeutic strategies, significantly improving diabetic wound healing outcomes and patient prognosis.

IMS Synergized with Glucose/ROS Generation

DW typically exhibit spatial differences in inflammatory patterns: early-stage wounds lack an acute inflammatory response, while chronic non-healing wounds often develop an excessive and prolonged chronic inflammatory state due to delayed immune cell infiltration.[129] Immunomodulatory Strategy (IMS) involves the flexible application of anti-inflammatory and pro-inflammatory regulation methods, tailored to the dynamic changes during the wound healing process. This approach aims to facilitate a smooth transition of the wound from the inflammatory phase to the proliferative and remodeling phases.[161,162]

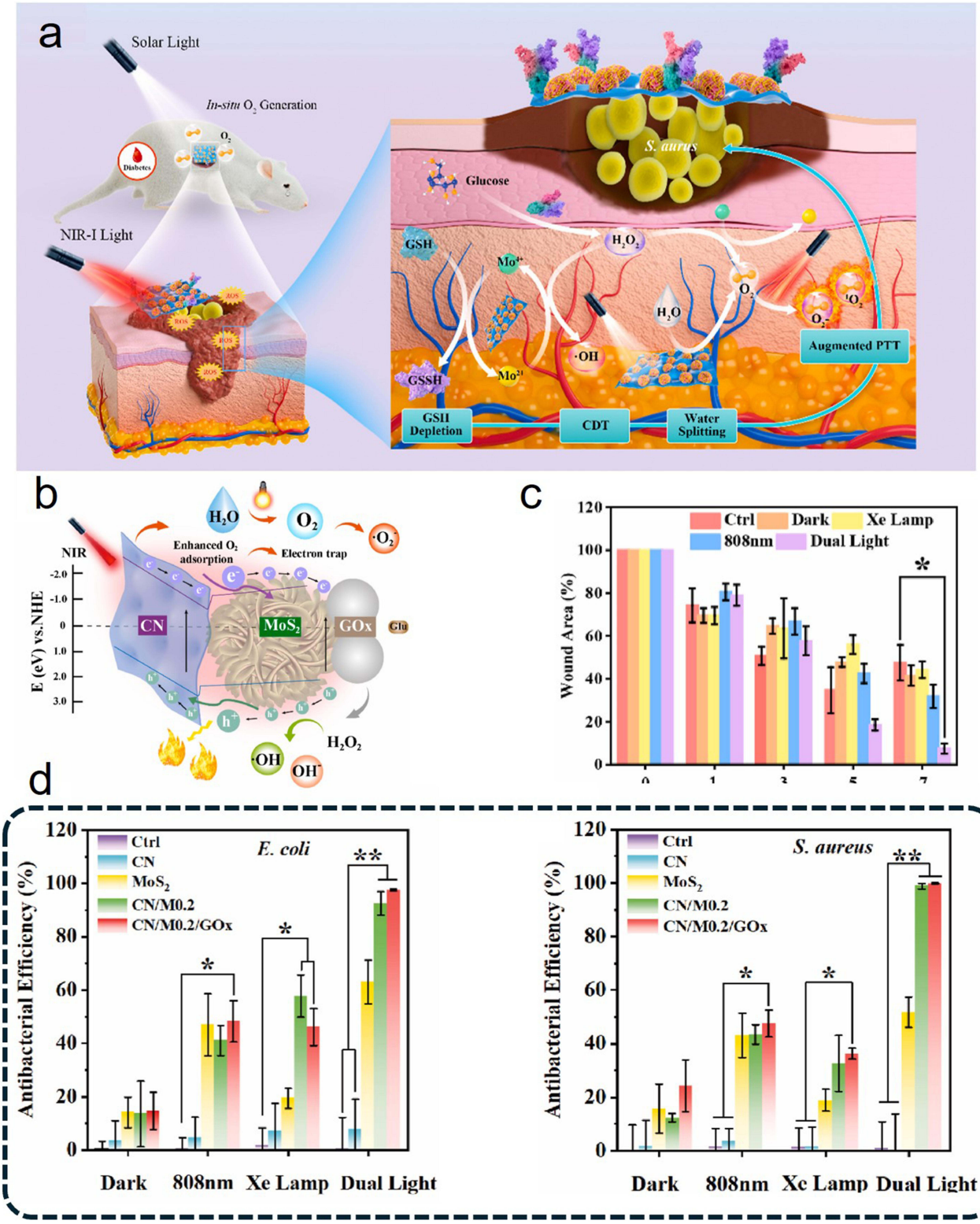


Figure 6 (**a**) The schematic diagram of GOx-induced cascade antimicrobial action for the treatment of infected cutaneous regeneration. (**b**) The schematic diagram of the electron transfer process between CN and MoS2 based on DFT calculation and the synergistic treatment mechanism of CN/M/GOx C-bio-HJs. (**c**) Quantitative data of the wound area of mice during treatment. (**d**) After 10 min of treatment in the dark or in light, the antimicrobial efficiency against E. coli and S. aureus was measured with different samples. (* represents $p < 0.05$, ** represents $p < 0.01$). Adapted with permission from Deng Y, Ouyang X, Sun J, et al. Rapid sterilisation and diabetic cutaneous regeneration using cascade bio-heterojunctions through glucose oxidase-primed therapy. *Bioact Mater.* 2023;25:748–765. © 2022 The Authors. Publishing services by Elsevier B.V. on behalf of KeAi Communications Co. Ltd.[101]

https://doi.org/10.2147/IJN.S515057

Researchers have designed a GOx-driven H_2S-releasing nanosystem, GOx@MnS, as an innovative strategy for DW treatment, integrating immunomodulation and CDT.[96] In high-glucose environments, this system catalyzes the conversion of glucose into H_2O_2, initiating a Fenton-like reaction to generate •OH, achieving efficient broad-spectrum antibacterial activity. Simultaneously, MnS releases H_2S in the acidic microenvironment, which possesses anti-inflammatory properties and induces macrophage polarization from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype. This effectively alleviates chronic inflammation and promotes wound healing. In vitro antibacterial experiments demonstrated that GOx@MnS nanoparticles exhibit potent bactericidal activity against various pathogens, including methicillin-resistant MRSA and *E. coli*. The antibacterial efficacy was significantly enhanced in high-glucose environments through •OH generation. Fluorescence staining and scanning electron microscopy analyses confirmed that this system effectively disrupted bacterial membrane structures and eradicated biofilms. In terms of immunomodulation, GOx@MnS nanoparticles showed excellent performance. In murine macrophage experiments, the system significantly upregulated M2 macrophage markers (CD206), downregulated M1 macrophage markers (CD86), reduced the expression of pro-inflammatory cytokines (eg, TNF-α and IL-6), and enhanced the secretion of anti-inflammatory cytokines (eg, IL-10) through sustained H_2S release. These effects contributed to the remodeling of the immune microenvironment.

In vivo studies using a diabetic mouse model revealed that the GOx@MnS combined system exhibited superior synergistic antibacterial and anti-inflammatory effects compared to single-component treatments with GOx or MnS. Ultimately, the system achieved better tissue regeneration outcomes, highlighting its potential as a highly effective strategy for DW management.

GOx- Instructed Self-Powered Synergistic Therapy

Glucose-guided self-powered synergistic therapy utilizes the high glucose concentration in diabetic wounds as fuel to GBFCs for energy conversion. By combining bioelectrical stimulation, glucose depletion, this approach achieves a synergistic wound treatment effect.[88]

Xiangli Zhang developed a self-powered enzyme-linked microneedle patch based on GOx and HRP for DW treatment.[86] This system leverages an enzyme-coupled cascade reaction to catalyze glucose and consume excess local glucose, generating a stable microcurrent in hyperglycemic environments. The generated microcurrent not only activates bioelectrical stimulation effects but also significantly reduces localized hyperglycemia, thereby accelerating wound healing (Figure 7a).

In in vitro antibacterial experiments, ZIF-8 nanoparticles demonstrated significant antibacterial activity against various pathogens (eg, Escherichia coli and S. aureus) (Figure 7c). In vitro, the microneedle patch exhibited measurable electrical output in glucose solutions of varying concentrations, with the current reaching ± 3.53 μA in a high-glucose environment (26 mm) (Figure 7d). In vivo experiments demonstrated that the current at the wound site in diabetic rats was higher than in normal wounds, as detected by a high-precision digital multimeter. This finding further validated the self-powered system's responsiveness to hyperglycemic conditions. The microcurrent generated by the microneedle patch reduced the expression of pro-inflammatory cytokines (eg, IL-6, TNF-α) while enhancing the secretion of anti-inflammatory cytokines (IL-4, IL-13) (Figure 7b). This resulted in the remodeling of the immune microenvironment and effective suppression of chronic inflammation. By harnessing the immunomodulatory effects of electrical stimulation, this system significantly improved wound healing outcomes, opening new avenues for the design and application of wound treatment materials in the future.

GOx- Instructed Delivery Synergistic Therapy

The GOx-Instructed Delivery Synergistic Therapy integrates various therapeutic agents with CDT to enhance antibacterial, anti-inflammatory, and wound healing effects. This approach utilizes the acidic environment and H_2O_2 generated by the glucose oxidation reaction for the intelligent release of therapeutic agents. The accumulated H_2O_2 further triggers Fenton or Fenton-like reactions, generating•OH to achieve CDT's bactericidal effects.[163]

The drug release rate of this therapy is closely correlated with the HG environment of the wound. Under elevated glucose levels, the GOx-catalyzed reaction is accelerated, leading to increased H_2O_2 production and rapid drug release. Conversely, when glucose levels decrease, the release rate of the drug slows accordingly, minimizing drug waste and

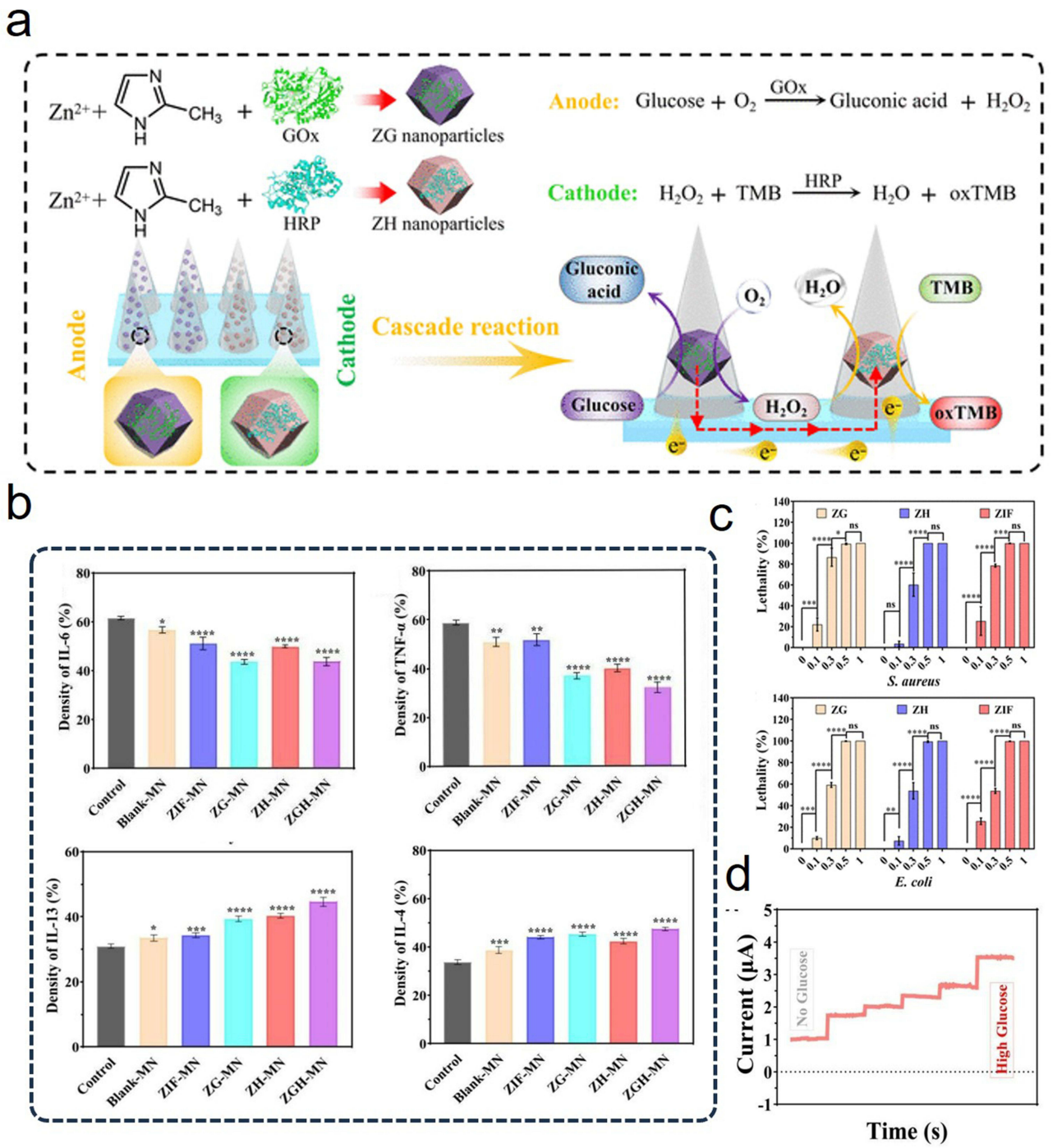


Figure 7 (**a**) Schematic of the enzyme cascade reaction generated by the self-powered MN patch. (**b**) Quantitative analysis of immunohistochemistry staining for IL-6, TNF-α, IL-13, and IL-4 on days 7. (**c**) Statistics of the mortality of S. aureus and E. coli with different nanoparticle concentrations. (**d**) In vitro test: current response of the prepared MNs to 0, 18, 20, 22, 24, and 26 mmol/L glucose. (significances are presented by *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$; ns, not significant). Adapted from Zhang X, Wang Z, Jiang H, et al. Self-powered enzyme-linked microneedle patch for scar-prevention healing of diabetic wounds. *Sci Adv.* 2023;9(28):eadh1415. Creative Commons.[86]

potential side effects.[113] Additionally, the multimodal synergistic effects of CDT combined with various therapeutic agents can exert comprehensive benefits during different therapeutic stages. This enables effective infection control, immune regulation, and tissue regeneration, ultimately accelerating the healing process of DW.[104]

Researchers have developed a supramolecular self-assembly strategy based on cucur[8]bituril (CB[8]) to construct a nanoreactor encapsulating GOx, Fe_3O_4 nanozymes, and L-Arg.[113] In hyperglycemic environments, GOx catalyzes

glucose to produce gluconic acid (GA) and H_2O_2. The H_2O_2 generated is utilized by Fe_3O_4 nanozymes to trigger a Fenton reaction, producing highly reactive •OH for oxidative antibacterial effects. Simultaneously, H_2O_2 oxidizes L-Arg to generate NO, which not only enhances antibacterial efficacy but also acts as a gaseous signaling molecule to regulate the local immune microenvironment and mitigate inflammation.

This nanoreactor exhibits self-regulated permeability, with its membrane undergoing expansion-contraction behaviors in acidic environments, enabling precise control over the enzymatic reactions within. Under acidic conditions, the membrane permeability increases, facilitating the influx of small substrates like glucose and the efflux of products like H_2O_2. As the reaction progresses and H_2O_2 concentrations rise, the efficiency of the Fenton reaction is further enhanced, generating more •OH and significantly improving antibacterial performance. Additionally, L-Arg oxidation under low pH conditions produces NO, whose release is pH- and H_2O_2-dependent. This responsive release mechanism ensures intelligent drug delivery, minimizing side effects and reducing drug wastage.

In in vitro antibacterial tests, the GOx/Fe_3O_4 nanoreactor demonstrated minimum inhibitory concentrations (MICs) of 25 μg/mL for *Escherichia coli* and 50 μg/mL for *S.aureus*, compared to 100 μg/mL and 300 μg/mL, respectively, for GOx alone, confirming the enhanced antibacterial effect of multimodal synergism. In vivo, the nanoreactor exhibited remarkable wound healing efficacy on infected diabetic wound models in mice. It effectively suppressed local bacterial infections while modulating the immune microenvironment through NO release, promoting the polarization of macrophages from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype. This transition significantly reduced pro-inflammatory cytokines (eg, TNF-α, IL-6) and increased anti-inflammatory cytokines (eg, IL-10, IL-4), accelerating wound healing and reducing chronic inflammation.

By integrating multi-enzyme cascade reactions with responsive drug release, this nanoreactor combines CDT, NO gas therapy, and immunomodulation into a synergistic multimodal therapeutic platform. This approach exerts comprehensive effects at various stages of DW treatment, effectively controlling infections and significantly accelerating tissue regeneration and wound repair.

Conclusion

DWs present a complex and dynamic pathological microenvironment, posing significant challenges to effective treatment. GOx-based nanocomposites, with their multimodal synergistic therapeutic capabilities, have emerged as highly promising tools for addressing these challenges. This review systematically summarizes the construction methods and application strategies of such nanocomposites in DW treatment. By integrating the catalytic activity of GOx with the unique properties of various nanomaterials, these composite achieve multifaceted regulation of the wound environment and demonstrate remarkable therapeutic outcomes. Overall, these nanocomposites accelerate DW healing through four primary strategies: 1, Consuming excess glucose and scavenging ROS to alleviate oxidative stress and promote healing; 2, Catalyzing glucose to produce H_2O_2, which triggers Fenton or Fenton-like reactions for antibacterial effects and inflammation modulation to expedite healing; 3, Converting elevated glucose levels at the wound site into microelectric currents to enhance tissue repair; 4, Utilizing GOx-catalyzed reactions to trigger precise drug release for targeted therapy. Currently, GOx can be combined with various nanocarriers through methods such as physical adsorption, encapsulation, covalent conjugation, and biomineralization. These carriers include metal-organic frameworks, noble metal nanoparticles, bio-heterojunctions, carbon dots, Metallic inorganics, and biomineralized nanoparticles, among others. They significantly enhance the stability, targeting capability, and therapeutic efficacy of GOx, making it a focal point in DW treatment research.

Perspective and Challenge

In DWs, GOx has been widely studied for its excellent ability to regulate glucose. Current research mainly focuses on natural GOx, while some studies have developed artificial nanozymes with GOx-like activity.[164] From the enzyme catalytic mechanism, natural and GOx-like enzymes show similar catalytic efficiencies in Michaelis-Menten kinetic, yet differ greatly in applications: 1. GOx has highly specific catalytic selectivity, and its enzymatic reaction strictly follows the oxidative metabolic pathway of glucose. Artificial nanozymes, in contrast, have great chemical stability, staying active long in complex wound microenvironments. However, their multi-enzymatic nature may cause side reactions. 2.

Biological enzymes, with natural protein structures, have good tissue compatibility and are mass-produced. Existing artificial enzyme systems, mainly based on noble metals like gold and platinum,[165] pose bio - toxicity risks and high - cost challenges for large - scale production. Still, the multi - enzymatic features of artificial enzymes can be turned into therapeutic benefits through precise control. For instance, multienzymatic artificial enzymes can be designed to reduce glucose and ROS damage simultaneously. With nano catalytic medicine's progress, GOx - like artificial enzymes are likely to be the future mainstream for blood glucose regulation.

Recently, some drug delivery systems (such as electrospun nanofibers, hydrogels, microneedles, etc.),[106,166,167] hydrogels,[95] microneedles,[86] etc.) can precisely regulate the spatial, temporal, and dosage distribution of drugs in vivo, thereby further enhancing the therapeutic efficacy of GOx-based nanocomposites. Notably, certain biomaterials with complex structure have demonstrated significant advantages in wound healing. Their specialized structural designs can be strategically integrated with catalytic nanocomposites to achieve therapeutic synergism. For instance, core-sheath nanostructures[168] allow spatial segregation of the nanocomposites and auxiliary drugs within distinct sheath and core compartments. Controlled sheath degradation[169] could then orchestrate stage-specific drug release profiles aligned with the pathophysiological progression of wound healing. Additionally, the Janus interface can provide a multi-chamber structure[170] to ensure that the loading unit can contact the surrounding environment directly, a key feature to improve catalytic efficiency. Composite materials based on complex nanostructures and GOx-based nanocomposites have broad prospects in wound care. Additionally, studies have shown that GOx-based nanocomposites exhibit excellent biocompatibility, providing a possibility for clinical translation. The HA-Ru NFs/GOx nanosystem developed by Liu et al has shown remarkable safety profiles.[24] In vitro hemolytic activity revealed no significant erythrocyte damage even at concentrations as high as 250 μg/mL (10 times the effective antibacterial concentration), indicating excellent hemocompatibility. MTT assay and CCK-8 assay further confirmed that HA-Ru NFs/GOx exhibited negligible cytotoxicity at 250 μg/mL. In vivo experiments showed that BALB/c mice administered with HA-Ru NFs/GOx via tail vein injection displayed no significant body weight changes, and serum liver function markers (ALT and AST) showed no significant differences compared to the untreated group. Histopathological examination of major organs through H&E staining revealed no tissue damage.

However, the clinical application of such nanocomposites still face considerable challenges, requiring further optimization and exploration.

(1) Before the clinical translation of GOx nanocomposites, further in-depth investigations are required to thoroughly evaluate their potential toxicity, long-term biocompatibility, and metabolic pathways in vivo. Long-term exposure to GOx-based nanocomposites may induce potential adverse effects through multiple biological pathways. Primarily, their antibacterial efficacy fundamentally relies on ROS generation. While endogenous antioxidant defense mechanisms typically maintain redox homeostasis under physiological conditions, prolonged exposure to nanocomposites could potentially overwhelm this regulatory mechanism. This imbalance may precipitate a state of chronic oxidative stress, disrupting cellular metabolic processes. Moreover, the nanoscale dimensions inherent to these nanocomposites render them susceptible to recognition as foreign bodies by the immune system. Persistent exposure could consequently initiate sustained immune surveillance, potentially leading to chronic inflammatory responses through continuous activation of immunoregulatory pathways. Additionally, some nanomaterials may accumulate in the body over extended periods, particularly in metabolic organs such as the liver and kidneys, potentially leading to adverse effects. Therefore, the development of nanocomposites with both high catalytic activity and excellent biodegradability has become an urgent priority. To address this challenge, future research should focus on optimizing material composition and surface modifications to minimize toxicity and enhance safety. Additionally, it is critical to establish comprehensive in vitro and in vivo evaluation systems to ensure their long-term safety in practical applications.

(2) The pathological features of diabetic wounds are often highly complex, involving factors such as hyperglycemic environments, persistent chronic infections, increased oxidative stress, and tissue hypoxia. While various GOx-based nanocomposites have been developed for synergistic treatments, most current strategies predominantly focus on antibacterial mechanisms, neglecting other pathological aspects requiring simultaneous therapeutic intervention. In the future, it is essential to develop multifunctional nanocomposites integrating capabilities such as antibacterial, antioxidative, tissue regeneration, and angiogenesis-promoting functions to achieve multimodal therapeutic effects. Designing

multifunctional materials and optimizing their synergistic mechanisms could significantly enhance therapeutic efficiency and accelerate wound healing.(3) GOx-based nanocomposites used in antibacterial treatments may inadvertently damage normal cells. The catalytic action of GOx produces hydrogen peroxide (H_2O_2) and other reactive oxygen species (ROS), which, while effective in eradicating pathogens, can cause oxidative damage to healthy cells and further impair tissue healing. Enhancing the targeted selectivity of GOx nanocomposites to avoid nonspecific toxicity is, therefore, a major challenge requiring urgent attention.

(4) As a natural enzyme, GOx faces significant stability challenges in biological environments. Although its stability can be partially improved by loading it onto nanomaterial surfaces or embedding it within nanocarriers, it remains prone to inactivation under complex physiological conditions. This stability issue directly impacts the sustained catalytic efficiency of GOx, thereby limiting its practical clinical applications. Future strategies could address this limitation through two approaches: 1) optimizing carrier designs to further enhance enzyme protection; 2) developing novel GOx-mimicking artificial enzymes as substitutes for natural GOx. Such artificial enzymes typically exhibit higher stability and more versatile catalytic properties.

(5) The clinical translation of GOx-based nanocomposites faces several challenges, including regulatory hurdles, cost constraints, and manufacturing scalability. Regulatory concerns primarily center on the safety and long-term biocompatibility of nanomaterials, such as the potential accumulation of iron-based nanoparticles in metabolic organs and the stability of GOx in complex biological environments. To facilitate clinical implementation, it is essential to establish a rigorous safety evaluation framework and real-time activity monitoring system. Cost-related challenges stem from the high synthesis expenses of noble metal nanozymes, which can be alleviated by adopting cost-effective alternatives, such as biomineralized iron sulfides. Additionally, manufacturing scalability is limited by the intricate nature of nanocomposite synthesis. By overcoming these obstacles, GOx-based nanoplatforms can move closer to clinical application, offering innovative and effective solutions for diabetic wound healing.

Abbreviations

DWs, Diabetic wounds; GOx, glucose oxidase; H_2O_2, hydrogen peroxide; PTT, photothermal therapy; PDT, photodynamic therapy; GT, gas therapy; SDT, sonodynamic therapy; HG, high glucose; ROS, reactive oxygen species; mtDNA, mitochondrial DNA; IL-1β, Interleukin-1 beta; IL-6, Interleukin-6; TNF-α, tumor necrosis factor-α; TIMP-1, tissue inhibitor of metalloproteinases-1; PCSK9, proprotein convertase subtilisin/kexin type 9; VEGFR2, vascular endothelial growth factor receptor 2; eNOS, endothelial nitric oxide synthase; NO, nitric oxide; O_2^-, superoxide anion; AGEs, advanced glycation end products; MRSA, Staphylococcus aureus; EPS, extracellular polymeric substances; MOFs, metal-organic frameworks; FAD, flavin adenine dinucleotide; Bio HJ, bio- heterojunctions; OH, hydroxyl radicals; CAT, Catalase; SOD, superoxide dismutase; O_2, oxygen; NAEA, antioxidant enzyme-like activity; OH, hydroxyl radicals; GBFC, glucose enzymatic biofuel cell; ES, Electrotherapy; HRP, horseradish peroxidase; AL, alendronate; HMIM, 2-methylimidazole; NIR, near-infrared irradiation; HAase, hyaluronidase; HGF-1, human gingival fibroblasts; AZM, azithromycin; SWCNTs, single-walled carbon nanotubes; HMSN, hollow mesoporous silica nanoparticles.

Consent for Publication

All authors consent to publication.

Author Contributions

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

Funding

This project was funded by the National Natural Science Foundation of China (82260426, 82460419) and Jiangxi Province Training Project for Academic and Technical Leaders in Key Disciplines (20243BCE51023).

Disclosure

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

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