



Advancements in Gas-releasing Micro/ Nanoplatforms for Overcoming MDR Bacterial Infections in Diabetic Wounds*

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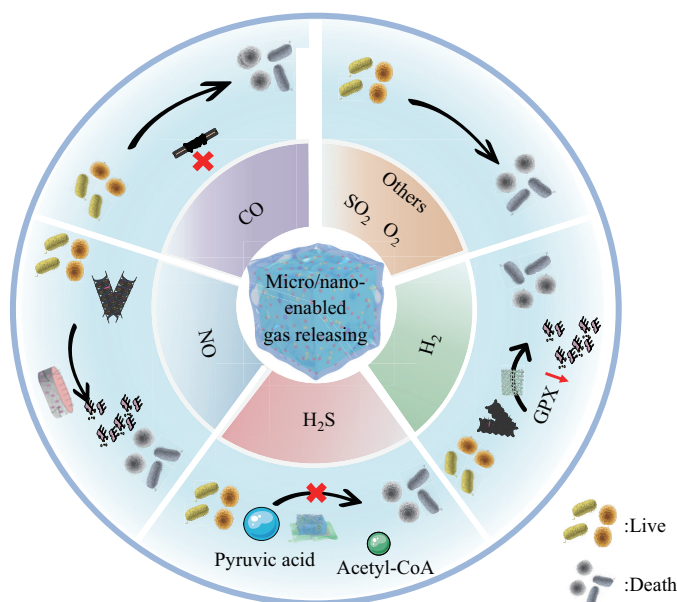
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Graphical abstract



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Abstract Chronic diabetic wounds, severely complicated by multidrug-resistant (MDR) bacterial infections, represent a profound and escalating global health crisis. The intrinsically hostile microenvironment of diabetic wounds, characterized by localized hypoxia, persistent oxidative stress, and poor vascularization, creates an ideal niche for opportunistic pathogens such as *Staphylococcus aureus* and *Pseudomonas aeruginosa*. These bacteria readily construct dense extracellular polymeric substance (EPS) biofilms, which not only physically shield the microbes from host immune responses but also actively trap the wound in a state of chronic, unresolved inflammation. Consequently, conventional systemic and topical antibiotic therapies are becoming increasingly futile, as poor perfusion at the wound site restricts drug bioavailability, while the rapid genetic evolution of bacteria and the impenetrable nature of biofilms lead to catastrophic treatment failures, often culminating in severe tissue necrosis and lower-extremity amputations. To circumvent the limitations of traditional antimicrobials, therapeutic gas delivery has emerged as a highly promising, paradigm-shifting strategy. Gaseous signaling molecules, particularly nitric oxide (NO), carbon monoxide (CO), hydrogen sulfide (H₂S), and hydrogen (H₂), possess unique physicochemical properties that allow them to seamlessly penetrate dense biofilm matrices and cellular membranes. Once inside, these gases operate *via* multi-targeted mechanisms that are incredibly difficult for bacteria to develop resistance against; for instance, NO induces severe lipid peroxidation and DNA cleavage in bacteria, CO downregulates pro-inflammatory cytokines, H₂S significantly accelerates endothelial cell migration for neovascularization, and H₂ acts as a powerful selective antioxidant to neutralize tissue-damaging reactive oxygen species (ROS). Together, these therapeutic gases not only exert broad-spectrum bactericidal effects but also actively reprogram the wound bed by promoting the critical M1-to-M2 macrophage polarization and stimulating angiogenesis. Despite their immense biological potential, the direct clinical translation of gas therapies is severely hindered by inherent physicochemical drawbacks, including extreme volatility, short physiological half-lives, poor aqueous solubility, and the high risk of off-target systemic toxicity, if applied indiscriminately. To conquer these immense pharmacokinetic barriers, cutting-edge advancements in materials science have driven the development of gas-releasing micro- and nanoplateforms. Utilizing sophisticated carriers such as metal-organic frameworks (MOFs), mesoporous silica, polymeric nanoparticles, liposomes, and injectable hydrogels, researchers can now encapsulate gas-donor molecules to achieve sustained, localized delivery. More importantly, these advanced nanoplateforms are ingeniously engineered to be stimuli-responsive. By exploiting the pathological hallmarks of the diabetic wound environment, such as elevated glucose concentrations, acidic pH, and overexpressed ROS, or by utilizing external triggers like near-infrared (NIR) light irradiation and ultrasound, these intelligent platforms ensure on-demand, precise spatio-temporal gas release. This often allows for powerful synergistic combinations, such as photothermal or photodynamic therapy coupled with gas release, thereby obliterating biofilms while sparing healthy tissue. While the therapeutic outcomes of these smart delivery systems in eradicating MDR infections and accelerating tissue repair are unprecedented, several critical challenges remain before widespread clinical adoption, as long-term biosafety profiles of the carrier nanomaterials, complexities in large-scale good manufacturing practice (GMP) production, and stringent regulatory hurdles must be rigorously addressed. Looking forward, the next frontier lies in the realm of precision medicine and theranostics, where future research must focus on the seamless integration of these gas-releasing platforms with flexible, wearable biosensors capable of continuously monitoring wound biomarkers (*e.g.*, pH, temperature, uric acid) in real-time. Coupled with artificial intelligence algorithms to govern automated, closed-loop adaptive dosing, these next-generation smart dressings hold the ultimate potential to comprehensively transform the clinical management of complex, infected diabetic wounds.

Key words multidrug-resistant infections, diabetic wounds, micro/nanoplateforms, gas therapy, controlled release

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Chronic diabetic wounds complicated by multidrug-resistant (MDR) bacterial infections are a growing global health concern, with increasing incidence rates attributed to the global rise in diabetes. According to the International Diabetes Federation (IDF), the number of individuals affected by diabetes is projected to reach 578.4 million by 2030^[1-2]. Diabetic wounds, particularly those that are slow-healing, contribute to significant morbidity, leading to non-traumatic amputations and severely impacting patients' quality of life^[3-4]. In the context of diabetic wound healing, normal physiological repair involves four overlapping stages: hemostasis, inflammation, proliferation, and tissue remodeling^[5-6]. However, in diabetic individuals, persistent hyperglycemia disrupts these processes, providing an ideal environment for bacterial colonization and biofilm formation^[7]. This

disruption exacerbates the difficulty of treating such wounds and significantly impairs angiogenesis. While antibiotics remain the cornerstone of treating infected diabetic wounds, their efficacy is increasingly compromised due to the development of antibiotic-resistant pathogens^[8].

A primary challenge in managing these infections is the formation of bacterial biofilms, which serve as protective barriers for bacteria, preventing the effective penetration of antibiotics. Biofilms not only hinder bacterial clearance by the host immune system but also promote the development of antibiotic resistance^[9-11]. Among the most problematic pathogens found in diabetic wound infections are multidrug-resistant strains, including Gram-positive bacteria such as *Staphylococcus aureus* (*S. aureus*), and Gram-negative bacteria like *Escherichia coli*

(*E. coli*) and *Pseudomonas aeruginosa* (*P. aeruginosa*), which are becoming increasingly resistant to conventional antibiotics^[10-11]. The persistent nature of these infections traps the wound in a chronic inflammatory state, promoting continuous tissue destruction and delaying healing. This cycle of infection and inflammation is further compounded by the hostile microenvironment, which includes dynamic changes in pH, high levels of reactive oxygen species (ROS), and altered matrix metalloproteinase (MMP) activity^[7, 12-14]. As such, the management of MDR bacterial infections in diabetic wounds has become a significant clinical challenge and represents a critical bottleneck in achieving effective wound healing.

Recent advancements in gas therapy have introduced a promising alternative to conventional treatments^[15-17]. Gaseous molecules such as nitric

oxide (NO), carbon monoxide (CO), hydrogen sulfide (H₂S), and hydrogen (H₂) are emerging as potent therapeutic agents (Figure 1). These gases have the unique ability to penetrate the dense extracellular polymeric substance (EPS) matrices of bacterial biofilms, disrupting bacterial metabolism and improving the permeability of antibiotics^[1, 18-21]. Gas therapy is not only effective in reducing bacterial load but also plays a role in modulating the immune response, particularly by promoting macrophage polarization and enhancing neovascularization^[22-28]. However, clinical applications of gas therapy face several limitations. The short half-lives, low solubility, and potential off-target toxicity of these gases pose significant challenges for their practical use^[23]. Additionally, achieving precise, controlled delivery and release of these gases remains an unresolved issue.

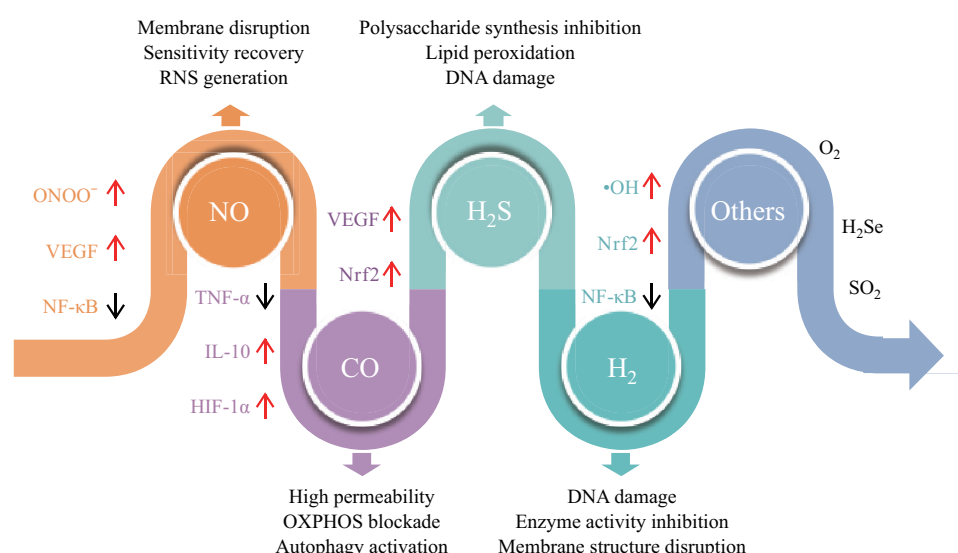


Fig. 1 Advances in the antibacterial mechanisms of therapeutic gases

This figure illustrates various mechanisms through which therapeutic gases such as NO, CO, H₂S, and H₂ exert their antimicrobial effects. Key molecules involved in these processes include reactive nitrogen species (RNS), peroxynitrite (ONOO⁻), vascular endothelial growth factor (VEGF), nuclear factor kappa-B (NF-κB), tumor necrosis factor-α (TNF-α), interleukin-10 (IL-10), oxidative phosphorylation (OXPHOS), nuclear factor E2-related factor 2 (Nrf2), and hydroxyl radicals (•OH).

To address these limitations, recent efforts have focused on the development of micro/nanoplatfoms that can efficiently release therapeutic gases in response to specific stimuli (Figure 2). These platfoms can be designed to release gases in response to various endogenous factors, such as hyperglycemia and acidic pH, or exogenous physical triggers, including light and ultrasound^[1]. The use of micro/nanoplatfoms enables enhanced accumulation of therapeutic gases at the wound site through mechanisms such as the enhanced permeability and

retention (EPR) effect or active targeting *via* surface modifications^[29-30]. These platfoms offer a more localized and controlled approach to gas delivery, reducing the risk of systemic toxicity and enhancing therapeutic outcomes. In addition to conventional nanocarriers, several gas-releasing living materials, including bacteria, cells, and algae, or their biomimetic derivatives, have been developed and are under investigation for their potential in treating MDR bacterial infections in diabetic wounds^[31-35]. Despite the progress, significant challenges remain,

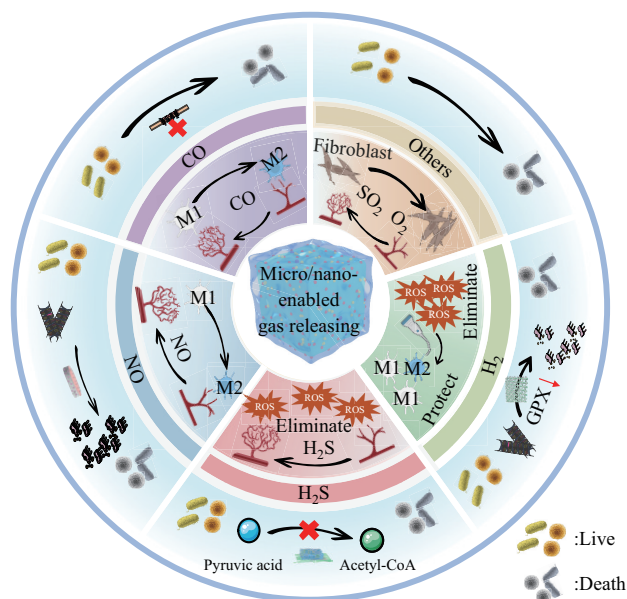


Fig. 2 Micro/nanoplatfroms-enabled gas release for MDR-infected chronic diabetic wound healing

This figure depicts the use of micro/nanoplatfroms for the controlled release of therapeutic gases (NO, CO, H₂S, and H₂) at the infection site to treat MDR bacterial infections in diabetic wounds, enhancing therapeutic efficacy against biofilm-protected bacteria and promoting wound healing.

particularly in terms of scalability, biosafety, and regulatory hurdles^[23]. This review aims to provide a comprehensive overview of recent advancements in gas-releasing micro/nanoplatfroms for the treatment of MDR bacterial infections in diabetic wounds. We will first elucidate the molecular mechanisms through which therapeutic gases, such as NO, CO, H₂S, and

H₂, contribute to both bacterial eradication and tissue repair. Next, we will examine the various strategies employed in the development of micro/nanoplatfroms that enable the precise and controlled release of these gases in response to both endogenous and exogenous stimuli. The review will also highlight the synergistic effects of these systems in promoting wound healing, with a particular focus on macrophage modulation and neovascularization. Finally, we will discuss the current limitations and challenges of these technologies, including issues related to delivery precision, scalability, and regulatory approval, and provide insights into potential future directions for overcoming these obstacles. By addressing these challenges, the integration of gas-releasing nanoplatfroms could become a transformative strategy in the management of MDR bacterial-infected diabetic wounds, ultimately improving patient outcomes.

1 Mechanisms of gas therapy in infected diabetic wounds

Chronic diabetic wounds are characterized by highly complex pathological mechanisms, with their persistent nature primarily driven by the vicious cycle between host metabolic dysfunction and pathogen infection (Figure 3)^[36-37]. Initially, hyperglycemia triggers abnormal activation of the glycolytic pathway and disrupts the tricarboxylic acid (TCA) cycle, resulting in significant energy metabolism disorders^[38]. This process accelerates the accumulation of advanced glycation end-products

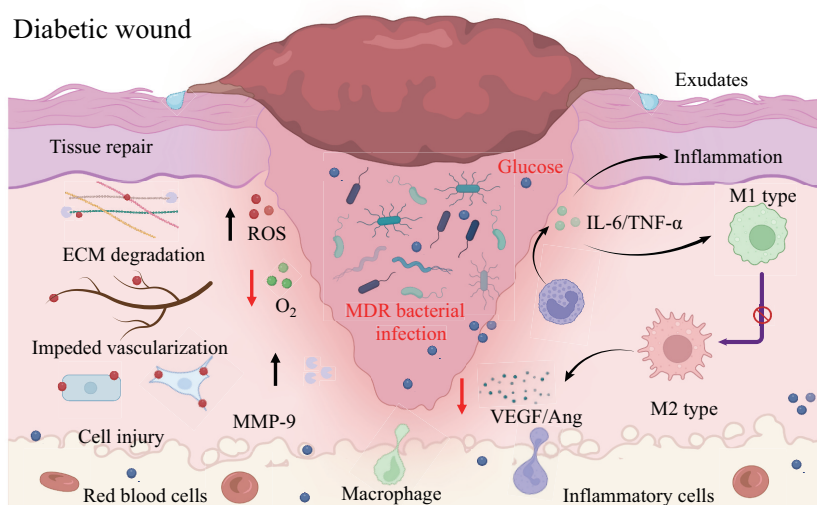


Fig. 3 Schematic illustration of the key features of the diabetic wound microenvironment

The diabetic wound microenvironment includes elevated glucose, acidic pH, high ROS, and altered MMP activity, which contribute to impaired wound healing, bacterial colonization, and biofilm formation.

(AGEs) and matrix metalloproteinase-9 (MMP-9), while also inducing mitochondrial dysfunction, thereby exacerbating oxidative stress^[39-40]. Excessive ROS, as key signaling molecules, recruit macrophages to the wound site, stimulating the sustained secretion of pro-inflammatory cytokines such as tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6). This inflammatory response not only damages the extracellular matrix (ECM) but also causes vascular endothelial injury and neuropathy, impairing blood supply and sensory perception^[41-42]. Furthermore, hyperglycemic tissue exudates increase susceptibility to bacterial infections, while the emergence of MDR bacteria due to antibiotic overuse worsens the situation. MDR bacteria form dense biofilms, establishing a physical barrier against antibiotic penetration and immune clearance, while also releasing virulence factors that further deteriorate the wound microenvironment^[8]. More critically, persistent drug-resistant infections and AGEs trap macrophages in the pro-inflammatory M1 phenotype, preventing their transition to the reparative M2 phenotype, which is vital for tissue repair through the secretion of growth factors like vascular endothelial growth factor (VEGF) and angiopoietin (Ang)^[43-45]. Therefore,

MDR bacterial infection exacerbates the vicious cycle in diabetic wounds, leading to prolonged healing stagnation, which can result in severe outcomes such as amputation, reduced quality of life, or death.

To counteract this complex and vicious pathological cycle, therapeutic gases have emerged as a highly effective intervention strategy. These gaseous signaling molecules uniquely penetrate dense bacterial biofilms to directly eradicate MDR strains, while simultaneously exerting profound immunomodulatory and angiogenic effects^[46-47]. By selectively neutralizing excessive ROS and inducing the polarization of macrophages from the proinflammatory M1 phenotype toward the reparative M2 phenotype, gas therapy systematically remodels the hostile wound microenvironment. A comprehensive summary detailing the mechanisms by which different gases eradicate bacteria and promote diabetic wound healing is presented in Table 1. The following subsections will systematically elaborate on the specific molecular mechanisms by which different therapeutic gases, including NO, CO, H₂S and H₂, facilitate the healing process of infected diabetic wounds.

Table 1 Functions and mechanisms of different gases in diabetic wound treatment

Gas types	Main function	Mechanisms	Reference
NO	Broad-spectrum antibacterial	Induce nitrosation and oxidative stress to oxidative DNA damage and lipid peroxidation	[48]
	Inflammation resolution	NF- κ B related pathways regulation; induce M2 polarization of macrophages through VASP signaling pathway	[49-50]
	Cell proliferation and tissue remodeling	Promote the secretion of VEGF and TGF- β	[51]
CO	Broad-spectrum antimicrobial	Induce ROS production and damages bacterial cell membranes	[52]
	Anti-inflammatory efficacy	Enhance cGMP production; suppress pro-inflammatory cytokine release; activate the heme oxygenase-1/CO system to alleviate RONS and cfDNA, inhibit macrophage activation	[53-54]
	Limited tissue repair	Interaction with heme-binding proteins and the activation of downstream signaling pathways, including sGC-mediated cGMP production and the p38 MAPK pathway	[55-56]
H ₂ S	Significant efficacy against <i>S. aureus</i> , <i>E. coli</i> , and MRSA	Disrupt the structure of biofilms	[57]
	Resistance to oxidation and immune regulatory properties	Enhance the expression of antioxidant molecules, decrease the secretion of Inflammatory factors, reduce P65 NF- κ B by up-regulating and sulfurizing SIRT1 to prevent macrophage inflammatory polarization	[58-59]
	Angiogenesis promotion	Increases VEGF, HIF-1 α , and the transcription of eNOS	[60]
H ₂	Limited antimicrobial efficacy	Disrupt the phospholipid bilayer structure of bacterial cell membranes; inhibit the activity of essential enzymes in the electron transport chain; interfere with DNA helicase and ribosomal functions	[61]
	Attenuate the inflammatory response	Neutralize ROS and ONOO ⁻	[48, 62]
	Promote vessel angiogenesis	Up-regulation of the VEGF/VEGFR2 signaling pathway	[63]

1.1 The role of NO in treating bacterial-infected diabetic wounds

NO, an endogenous gaseous signaling molecule, plays a central role in maintaining human physiological homeostasis^[3]. Under normal physiological conditions, NO is synthesized from L-arginine by the nitric oxide synthase (NOS) family, including the neuronal (nNOS), inducible (iNOS), and endothelial (eNOS) isoforms^[64-65]. In the pathological microenvironment of chronic diabetic wounds, hyperglycemia impairs NOS activity, resulting in a severe deficiency in NO synthesis^[66]. This NO deficit not only weakens the host's antimicrobial defense but also hinders angiogenesis and delays inflammation resolution. As a result, exogenous NO supplementation has emerged as a promising strategy to accelerate wound healing, particularly in the context of MDR bacterial infections. NO exerts its therapeutic effects through three mechanisms: broad-spectrum bactericidal activity, biofilm dispersal, and immune microenvironment remodeling. NO reacts with superoxide anions (O_2^-) produced during bacterial respiration to generate RNS like ONOO⁻ and dinitrogen trioxide (N_2O_3)^[67-68]. These RNS induce oxidative and nitrosative stress, targeting bacterial DNA, cell membranes, and proteins, which disrupts bacterial viability^[23]. Due to its non-specific cytotoxicity across multiple metabolic pathways, bacteria are less likely to develop resistance through single-gene mutations, making NO effective against MDR strains such as methicillin-resistant *Staphylococcus aureus* (MRSA) and *P. aeruginosa*^[20, 50]. Moreover, NO functions as a biofilm dispersal agent by downregulating cyclic dimeric guanosine monophosphate (c-di-GMP), a secondary messenger responsible for maintaining biofilm formation. This promotes the transition of bacteria from a sessile biofilm state to a planktonic form, enhancing antibiotic efficacy and immune system activity^[69]. Furthermore, NO influences macrophage polarization^[20, 70], switching M1 pro-inflammatory macrophages to M2 reparative macrophages, which secrete VEGF and other growth factors critical for angiogenesis and tissue repair^[71].

1.2 The role of CO in bacterial-infected diabetic wounds

CO is a versatile endogenous gaseous signaling molecule that is primarily produced through the heme degradation by heme oxygenase (HO) enzymes, including the inducible HO-1 and constitutive HO-2 isoforms^[72]. Initially known for its toxicity, CO has now been recognized as a significant modulator of cell metabolism, inflammation, and tissue repair.

CO's high chemical stability and lipophilicity allow it to diffuse easily across biological membranes and penetrate complex tissue structures, making it particularly effective for treating diabetic wounds complicated by MDR bacterial infections and biofilm formation^[21]. CO's antibacterial effects arise from its strong affinity for metal-containing proteins in bacterial cells, particularly cytochrome c oxidase in the bacterial respiratory chain, inhibiting aerobic respiration and oxidative phosphorylation^[65, 73]. This disruption leads to ATP depletion and metabolic collapse in bacteria. CO also induces oxidative stress, further enhancing bacterial damage^[74-75]. Importantly, CO can diffuse through the EPS matrix of biofilms, effectively targeting sessile and metabolically dormant bacteria, which are typically more resistant to conventional antibiotics^[76-77]. In addition to its direct antibacterial effects, CO modulates the immune response by regulating innate immune signaling and promoting macrophage phagocytosis, enhancing bacterial clearance^[55, 73]. CO's therapeutic window is concentration-dependent, showing mild bactericidal effects at low concentrations (10–50 $\mu\text{mol/L}$) but increased efficacy at higher concentrations (50–100 $\mu\text{mol/L}$) without affecting macrophage viability^[23, 78-79]. Moreover, CO helps resolve chronic inflammation by promoting macrophage polarization from the M1 to M2 phenotype^[80-81], which is essential for tissue repair. CO achieves these effects through the activation of pathways such as c-di-GMP production and the p38 mitogen-activated protein kinase pathway^[55-56].

1.3 The therapeutic effects of H₂S in diabetic wound infections

H₂S, the third endogenous gasotransmitter after NO and CO, plays a key role in cellular regulation and the pathophysiology of various diseases^[23, 82]. In endothelial cells, H₂S is synthesized by cystathionine- β -synthase (CBS), cystathionine- γ -lyase (CSE), and 3-mercaptopyruvate sulfurtransferase (3-MST), with a notable role in angiogenesis^[20, 48, 83]. In diabetic wounds, metabolic dysregulation significantly reduces endogenous H₂S production, impairing angiogenesis and contributing to chronic inflammation. Exogenous H₂S supplementation has emerged as a promising therapeutic strategy that not only promotes tissue repair but also targets MDR bacterial infections. H₂S stabilizes hypoxia-inducible factor 1 alpha (HIF-1 α) and upregulates miR-126-3p, which promotes vascular remodeling and angiogenesis in diabetic tissues^[84]. H₂S also exerts cytoprotective effects by inducing S-sulfhydration in key proteins, enhancing antioxidant defense systems, and inhibiting pro-

inflammatory pathways like NF- κ B^[85]. In terms of antimicrobial activity, H₂S induces oxidative stress within bacteria, causing lipid peroxidation and DNA damage, leading to bacterial death^[86-87]. H₂S also disrupts biofilms by degrading extracellular DNA and inhibiting polysaccharide synthesis, rendering bacteria more susceptible to treatment^[86-87]. However, due to its narrow therapeutic window (concentrations of ≥ 100 μ mol/L may become toxic, particularly in eukaryotic cells)^[88], H₂S requires controlled release systems to avoid toxicity, and recent advancements focus on designing micro/nanoplatfoms capable of sustained and on-demand release, ensuring therapeutic efficacy while minimizing systemic toxicity^[23]. These systems facilitate a synergistic integration of vascular restoration, immune modulation, and antibiofilm activity, effectively treating MDR bacterial-infected diabetic wounds while avoiding excessive toxicity.

1.4 The mechanism of H₂ in managing bacterial-infected diabetic wounds

H₂, once considered physiologically inert, has emerged as a therapeutic agent with significant potential in treating chronic diabetic wounds, primarily due to its superior biological safety and unique physicochemical properties^[63, 89]. Its therapeutic effects involve two main dimensions: host microenvironment remodeling and selective pathogen eradication. In terms of regulating the host microenvironment, H₂ exhibits a selective antioxidant effect, scavenging highly cytotoxic ROS such as $\bullet$ OH and ONOO⁻, while preserving the physiological ROS that are necessary for cellular signaling^[90]. This targeted antioxidant activity alleviates excessive inflammation, protecting vascular endothelial cells and surrounding tissues from oxidative damage^[91]. Furthermore, due to its small molecular size, H₂ possesses exceptional tissue permeability, allowing rapid diffusion into deeper cellular layers to promote re-epithelialization by enhancing epidermal stem cell proliferation and extracellular matrix deposition^[20]. Regarding bacterial infections, H₂ functions not only as an antioxidant but also as an energy modulator, disrupting bacterial survival homeostasis. It exerts bactericidal effects by disrupting bacterial cell membrane integrity, inhibiting essential enzyme activities in the electron transport chain, and interfering with DNA helicase and ribosome function, leading to programmed bacterial death^[92-93]. H₂ effectively addresses a major challenge in wound infection management by penetrating biofilms, which are dense bacterial clusters resistant to traditional antibiotics^[94]. Its high diffusion rate ensures the gas reaches and destroys bacteria shielded within the

biofilm structure. To overcome the challenges of low water solubility and poor retention of H₂ at the wound site, current research is focused on functionalized micro/nanomaterials designed for sustained local release of H₂. This strategy establishes a dynamic ROS regulation system that induces oxidative stress imbalance within bacteria while maintaining redox homeostasis in host cells to facilitate tissue repair. This bidirectional regulatory mechanism not only enhances the antibacterial activity of H₂ but also prevents excessive ROS-induced damage to surrounding tissues, thus facilitating both the eradication of MDR bacterial infections and wound healing.

2 Advances in gas-releasing micro/nanoplatfoms for MDR bacterial-infected diabetic wound healing

2.1 NO releasing micro/nanoplatfoms

NO has been shown to possess significant antibacterial and biofilm-disrupting capabilities, along with its ability to accelerate wound healing by mitigating inflammation and promoting cell migration^[24, 95]. However, the endogenous NO concentration in diabetic wounds is often insufficient to meet therapeutic needs, making exogenous NO supplementation an effective alternative. Various NO-releasing micro/nanoplatfoms have been developed, including metal-organic frameworks (MOFs)^[96], inorganic nanomaterials^[97-98], hydrogels^[99-101], and microneedle patches^[102]. These platfoms can be classified into endogenous- and exogenous-stimuli-responsive systems, based on their responsiveness to the diabetic wound microenvironment. Endogenous-stimuli-responsive platfoms target specific features such as hyperglycemia. For instance, Hu *et al.*^[103] developed a glucose-responsive biohybrid cryogel (GOA@HG) composed of methacrylated gelatin (GelMA), aldehyde-functionalized hyaluronic acid methacrylate (HAAMA), glucose oxidase (GO_x), and L-arginine (Figure 4a). This cryogel absorbs wound exudate and converts glucose into hydrogen peroxide (H₂O₂) via GO_x, which then oxidizes L-arginine to release NO, significantly inhibiting MRSA growth and promoting healing. Another study by Ma and colleagues^[66] reported a hydrogel dressing incorporating artificial multi-enzyme nanoflowers (COH-GB), which modulate the wound microenvironment by reducing glucose and pH, leading to NO generation and enhanced wound healing.

Exogenous-stimuli-responsive platfoms offer

precise spatiotemporal control over NO release. For example, Lin *et al.* [104] developed a deep-red light-responsive small-molecule prodrug (RhB-NO-2), which combines NO therapy with photodynamic therapy (PDT) to treat MDR bacterial infections (Figure 4b). Upon activation by light, NO and ROS are generated, which synergistically kill bacteria and reduce inflammation by inhibiting NF- κ B pathway.

Additionally, Chen *et al.* [105] introduced a heat-responsive NO-releasing nanostructure (mCu-SAE@BNN6@PEG-Van), which integrates NO release with photothermal therapy (PTT) and catalysis to eradicate biofilms and accelerate diabetic wound healing (Figure 4c). These studies highlight the potential of controlled NO delivery systems for treating MDR bacterial-infected diabetic wounds.

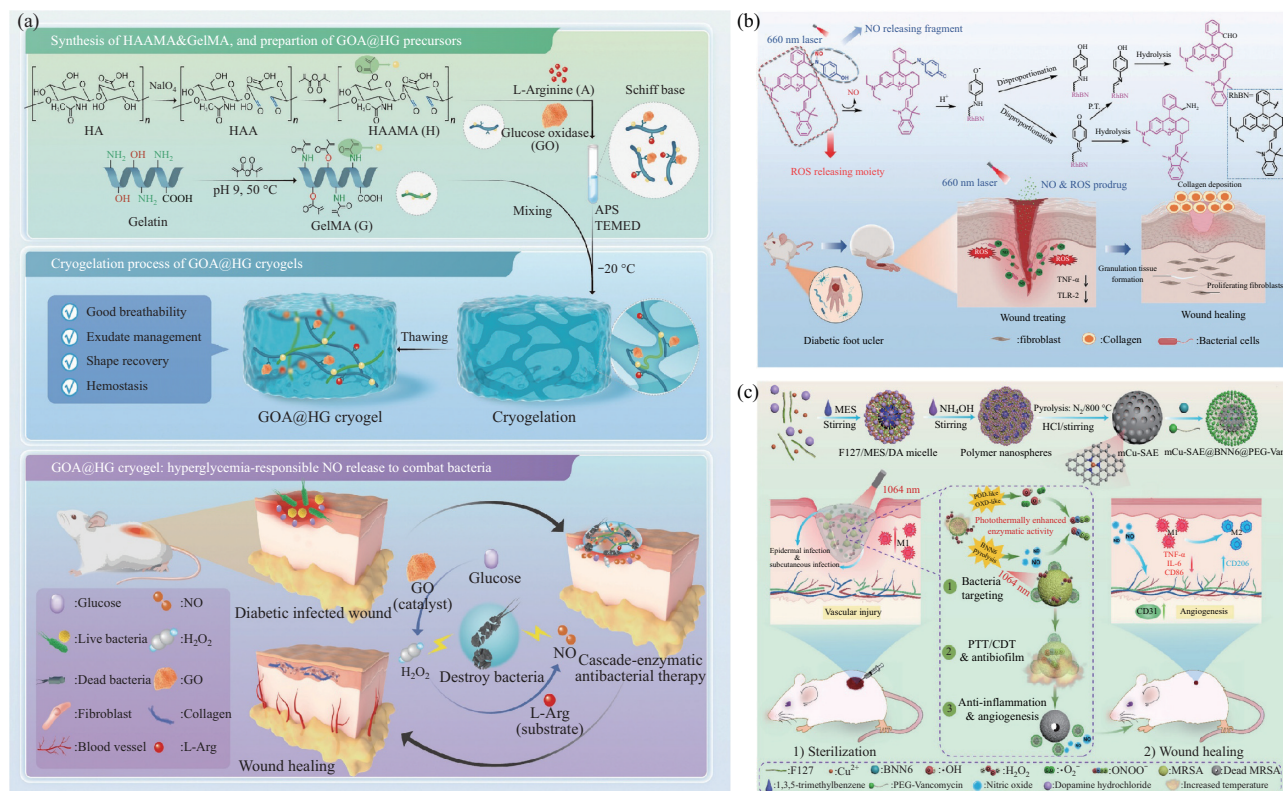


Fig. 4 NO-releasing micro/nanoplatforams for healing diabetic wounds infected with MDR bacteria

(a) Preparation of glucose-responsive NO-releasing GOA@HG cryogels and their mechanism for treating MRSA-infected diabetic wounds [103]. (b) Schematic depiction of the synthesis of deep red light-activated NO-releasing/PDT prodrugs and their wound healing effects against drug-resistant bacterial infections [104]. (c) Construction of NIR-II light-enhanced NO/PTT/CDT nanostructures and their application in treating MDR bacterial infection-induced diabetic wounds and subcutaneous cysts [105].

2.2 CO releasing micro/nanoplatforams

Previous studies have demonstrated CO's beneficial role in both anti-inflammatory and antibacterial therapies [73, 75, 106]. Traditional CO therapies primarily rely on gaseous CO inhalation, which faces limitations due to the gas's low solubility and the difficulty in controlling dosage [107]. To overcome these challenges, researchers developed CO-releasing molecules (CORMs), such as tricarbonyldichlororuthenium (II) dimer (CORM-2), tricarbonylchloro(glycinato)ruthenium (II) (CORM-3), and CORM-401, which have shown efficacy in eradicating MDR bacteria [108]. However, these CORMs often release CO too rapidly, leading to

tissue damage [20, 109]. To address this, Zou *et al.* [110] engineered a near-infrared (NIR)-triggered nanotank (MXene@MOF@CORM-401, MMC) (Figure 5a), which releases CO in a controlled "gas bomb"-like manner under NIR irradiation, significantly accelerating wound healing in MRSA-infected diabetic mice. In a similar vein, Zhao *et al.* [111] developed an aggregation-induced emission luminogen (AIEgen)-based microneedle patch (T/MnCO@AMOF MN) that enhances wound healing by modulating the wound microenvironment and promoting angiogenesis (Figure 5b). This system effectively delivers CO to the infected tissue, improving wound closure and promoting macrophage

polarization and angiogenesis.

The blood glucose level in diabetic mice is typically maintained at approximately 25 mmol/L, nearly five times higher than that of normal mice^[1, 112]. Persistent hyperglycemia is the primary cause of impaired healing in diabetic wounds, and consequently, developing micro/nanoplatfroms that integrate CO therapy with glucose-lowering capabilities is crucial for treating diabetic wounds complicated by MDR bacterial infections. Liu's team^[113] reported an ultrasound-responsive microneedle patch (MN@GOx@TiO_{2-x}@CO) designed to achieve simultaneous glucose consumption and CO gas delivery (Figure 5c). This patch consists of a sonosensitizer (TiO_{2-x}), a hydroxyl radical (•OH)-triggered CO prodrug (MPA-CO), GO_x, and a HA matrix. Upon application, the HA matrix dissolves into a semi-fluid state at the wound site, facilitating the release of the encapsulated

components into the infected tissue. Initially, GO_x catalyzes the oxidation of glucose to gluconic acid and H₂O₂, significantly reducing the glycemic load at the wound site. Under ultrasound stimulation, the electrons generated by TiO_{2-x} facilitate the conversion of H₂O₂ to •OH. This oxidative capacity is synergistically enhanced by Ti³⁺ ions, which catalyze a Fenton-like reaction to maximize •OH yield. These abundant •OH then triggers MPA-CO to release CO gas. This glucose-driven cascade reaction not only effectively inhibits *S. aureus* and MRSA infections but also promotes angiogenesis by upregulating VEGF expression and stimulating fibroblast migration, thereby accelerating wound healing in diabetic mice. The development of such a stimuli-responsive CO-releasing microneedle patch offers a promising therapeutic strategy for CO-based management of infected diabetic wounds.

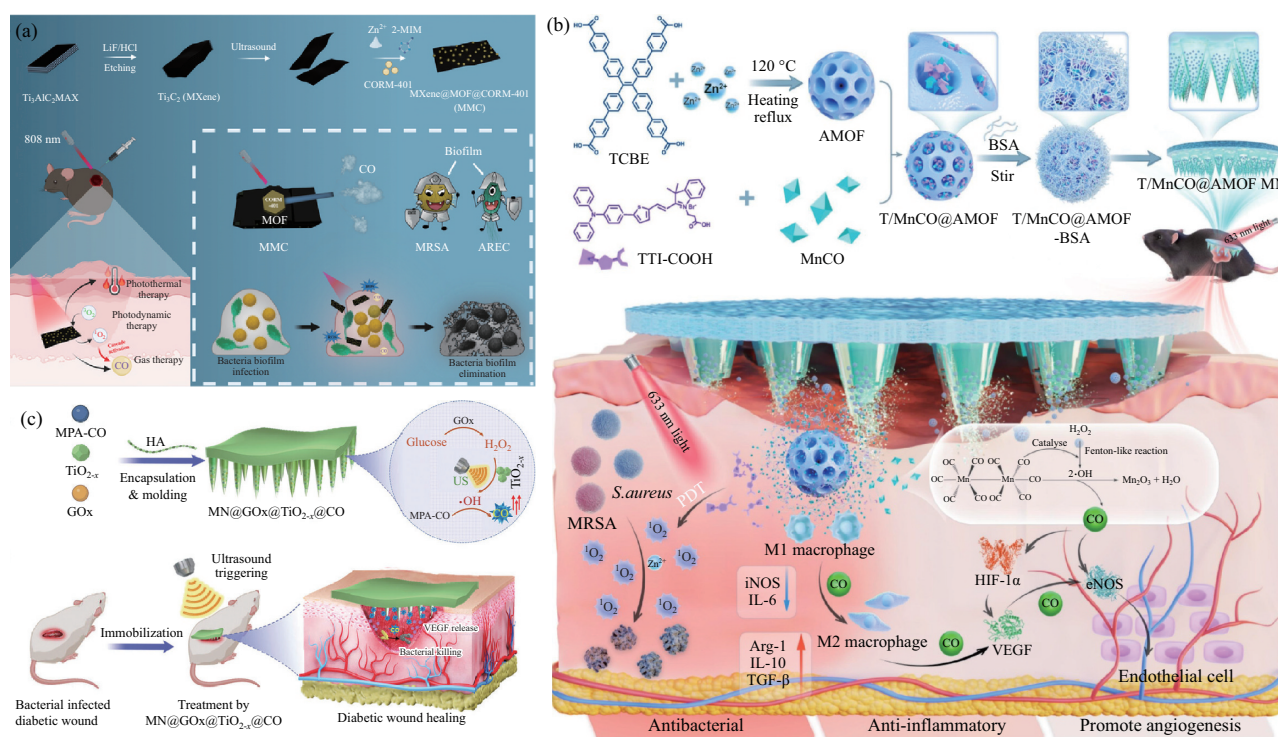


Fig. 5 CO-releasing micro/nanoplatfroms for healing diabetic wounds infected with MDR bacteria

(a) NIR-triggered nanotanks MMC initiate CO release in a gas bomb-like manner, enabling effective antibacterial activity and accelerated healing in MRSA-infected diabetic wounds^[110]. (b) Schematic depiction of the synthesis of AIEgen-based engineered frameworks with CO-releasing properties and their therapeutic mechanism in treating MDR bacterial-infected diabetic wounds^[111]. (c) Synthetic route of ultrasound-responsive CO-releasing microneedles and their application in healing MRSA-infected diabetic wounds^[113].

2.3 H₂S releasing micro/nanoplatfroms

H₂S has gained attention for its biofilm-eradicating properties, anti-inflammatory effects, and ability to promote angiogenesis^[114-115]. However, the therapeutic potential of H₂S is often limited by its

uncontrolled release. To overcome this limitation, Ge *et al.*^[116] developed a glucose-responsive H₂S-releasing nanosystem (GOx@MnS) for treating MDR bacterial-infected diabetic wounds (Figure 6a). This system catalyzes glucose oxidation, lowering the local

pH and triggering the release of H_2S , which exhibits bactericidal effects and modulates macrophage polarization toward the M2 phenotype.

Nanozymes with robust catalytic activities, such as blood glucose regulation, ROS generation, and free radical scavenging, have emerged as stable alternatives to natural enzymes in the treatment of diabetic wounds^[117-120]. In this context, Yin *et al.*^[121] engineered a cascade nanozyme system with H_2S -releasing capabilities (FeS@Au), which consists of ultra-small gold nanoclusters (Au NCs) loaded onto ferrous sulfide nanoparticles (FeS NPs) (Figure 6b). The Au NCs exhibit GO_x -mimicking activity, converting glucose into gluconic acid and H_2O_2 , thereby increasing local wound acidity. This acidity enhances the peroxidase (POD)-like activity of FeS NPs, which converts H_2O_2 into $\cdot\text{OH}$, thereby inducing ferroptosis in drug-resistant bacteria. Simultaneously, the acidic microenvironment triggers a slow release of H_2S from FeS@Au . The released H_2S upregulates hypoxia-inducible factor-1 α (HIF-1 α) levels, promoting the proliferation, migration, and tube formation of human umbilical vein endothelial cells (HUVECs).

In vitro and *in vivo* studies confirmed that FeS@Au possesses broad-spectrum antibacterial activity against various pathogens, including MRSA, and delivers superior therapeutic outcomes in full-thickness diabetic wounds. This strategy, combining nanozyme catalysis with H_2S -mediated gas therapy, offers a promising approach for treating infected diabetic wounds, by simultaneously promoting bacterial sterilization and tissue regeneration.

While H_2S functions as a reductive gas that scavenges ROS in the wound microenvironment, aiding inflammation resolution and tissue repair, its antioxidative function may conflict with the therapeutic need for elevated ROS levels required to eradicate bacteria in the early stages of infection. To overcome this challenge, a programmable gas-releasing nanosystem responsive to the infection microenvironment was developed, known as PB-SNP@ SiO_2 (PSS) (Figure 6c)^[3]. This system uses Prussian blue (PB) nanoparticles loaded with sodium nitroprusside (SNP), a NO donor, and coated with a silica shell that incorporates a glutathione (GSH)-responsive H_2S donor, bis[3-(triethoxysilyl)propyl]

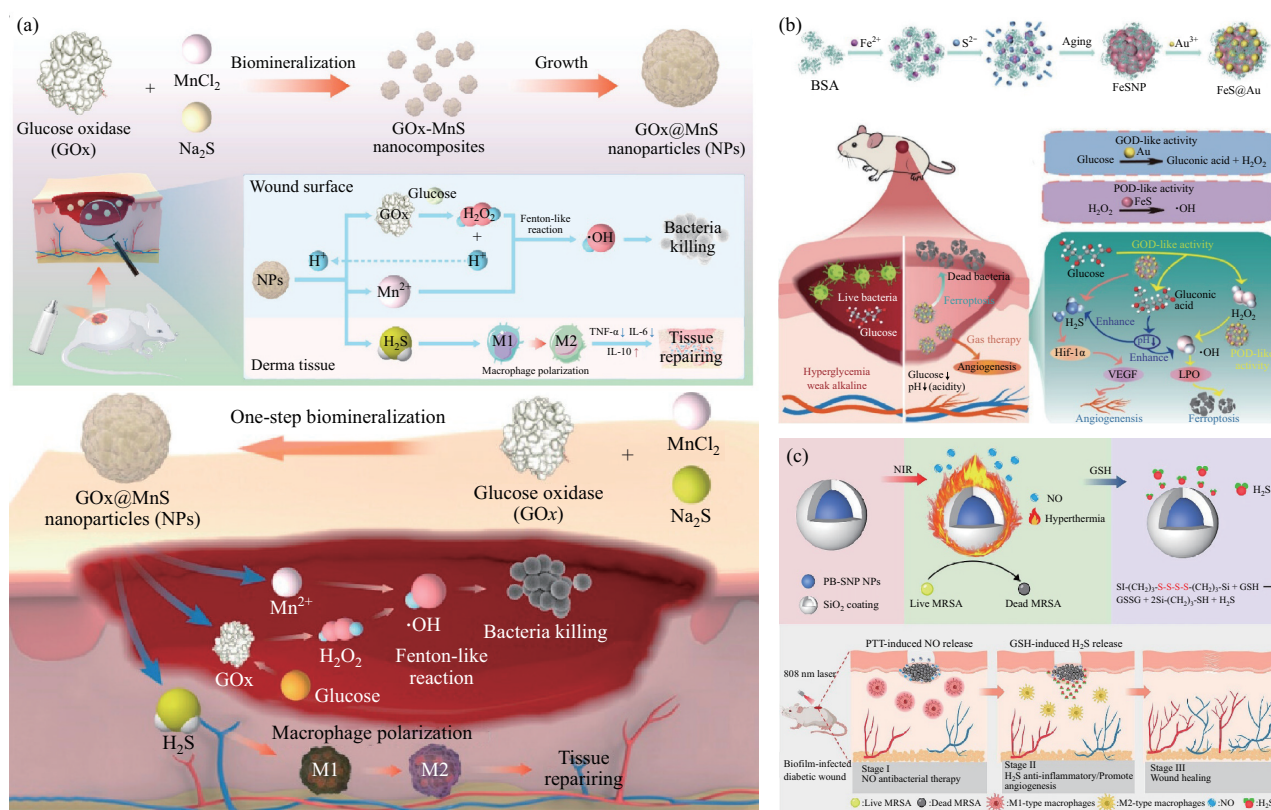


Fig. 6 H_2S -releasing micro/nanoplatforms for promoting MDR bacterial-infected diabetic wound healing

(a) Preparation of glucose-responsive H_2S -releasing nanoscale GOx@MnS nanoparticles and their therapeutic mechanism for treating MRSA-infected diabetic wounds^[116]. (b) Design and therapeutic mechanism of a glucose/pH dual-responsive nanozyme that promotes diabetic wound healing by triggering H_2S release to exert synergistic antibacterial and anti-inflammatory effects^[121]. (c) Schematic diagram of the synthesis and microenvironment-triggered NO/ H_2S release of PB-SNP@ SiO_2 -PSS nanomaterials for the programmed therapy of MDR biofilm-infected diabetic wounds^[3].

tetrasulfide. Upon NIR laser irradiation, the PSS nanoparticles release NO and generate hyperthermia, which effectively eradicates drug-resistant bacteria. Subsequently, the H₂S donor reacts with GSH within bacterial biofilms or tissues to release H₂S, mitigating excessive inflammation and promoting wound healing. This synergistic, multi-gas release strategy circumvents the limitations of single-gas therapies that cannot adapt to the dynamic stages of wound healing. Encapsulation within carriers such as liposomes, polymeric nanoparticles, and MOFs can shield labile donors from premature degradation in aqueous and oxidative physiological environments, thereby improving their chemical stability during delivery^[122]. Such nanocarrier-assisted loading creates an *in situ* depot, which enables controlled and sustained release at the target site rather than rapid and uncontrolled gas liberation. These nanoplatfroms offer significant potential for treating diabetic wounds complicated by MDR bacterial infections by providing controlled gas release tailored to the needs of different stages of wound healing.

2.4 H₂ releasing micro/nanoplatfroms

Traditional H₂ therapies, such as hydrogen-rich water (HRW) and hydrogen-rich saline (HRS), face limitations due to their low solubility and limited tissue penetration, which hinders their therapeutic efficacy in wound healing^[123]. Recently, a *Bacillus-Chlorella* (Bac-Chl) gel dressing was developed to continuously deliver H₂ to chronic diabetic wounds through photosynthesis^[62]. This system scavenges toxic free radicals, secretes IL-10, and promotes fibroblast proliferation and endothelial differentiation, directly mitigating inflammation and facilitating wound healing. However, excessive ROS, which is overproduced in diabetic wounds, exacerbates oxidative stress. Thus, a combination therapeutic approach targeting both oxidative stress and hyperglycemia is essential for improving diabetic wound healing.

Chen *et al.*^[124] designed photosensitive hydrogenated titanium oxide (HTON) nanorods, where H₂ incorporation significantly alters the band structure, enabling visible-light-driven photocatalytic H₂ generation using glucose as a sacrificial agent. The synergistic consumption of glucose and H₂ generation inhibits AGEs and their receptor (RAGE) pathways, thereby preventing skin cell apoptosis and promoting cell proliferation and migration. Despite its advantages, light-triggered strategies are limited by the shallow penetration depth of the light source. In contrast, Xu and colleagues^[125] described an ultrasound-responsive piezoelectric hydrogel

(C₃N₄@Gel) designed for treating bacteria-infected diabetic wounds. This system utilizes polysaccharides/NADH within biofilms as sacrificial agents for sonocatalytic H₂ production. The generated H₂ rapidly permeates the biofilm, disrupting bacterial energy metabolism and the electron transport chain to eradicate the biofilm. Notably, H₂'s high permeability allows it to reach deep-seated bacteria, which is often unattainable by conventional ROS antibacterial agents. In a *S. aureus*-infected diabetic mouse model, this combined internal-external strategy significantly reduced bacterial survival (97% inhibition rate) and shortened wound healing time by 26%.

Furthermore, an acid-responsive gel (LR&AB@CAH) that simultaneously consumes glucose and generates H₂ was developed to promote diabetic wound healing by scavenging ROS (Figure 7a)^[126]. The system encapsulates *Lactobacillus rhamnosus* and acid-responsive H₂-generating nanoparticles (AB@MSN) within a calcium alginate hydrogel. The *Lactobacilli* metabolize glucose into lactic acid, lowering the local pH, which triggers H₂ release from AB@MSN. This composite gel supports probiotic growth, reduces local glucose levels, enhances antioxidant enzyme activity, and alleviates oxidative stress, thereby promoting wound healing. Transcriptomic analysis further confirmed that this strategy restores the wound microenvironment by regulating genes related to transmembrane transport, inflammatory responses, and key signaling pathways such as PPAR, TNF, and adipocytokine signaling.

Diabetic wounds are typically characterized by an acidic microenvironment in the early stages of bacterial infection, which presents challenges for effective H₂ release and utilization. Zhang *et al.*^[63] reported an acid-responsive nanofibrous dressing (Fe@PLGA+GA) composed of poly (lactic-co-glycolic acid) (PLGA) loaded with citric acid (CA) and iron (Fe) nanoparticles (Figure 7b). The degradation of PLGA into lactic and glycolic acids helps maintain local acidity, while protons from CA intensify the acidity around the Fe nanoparticles, promoting sustained H₂ generation. In a MRSA-infected diabetic wound model, this dressing exhibited pronounced antibacterial effects and accelerated wound healing by downregulating matrix metalloproteinase-9 (MMP-9) and promoting fibroblast migration.

2.5 Other gas-releasing micro/nanoplatfroms in diabetic wound healing

In addition to NO, CO, H₂S, and H₂, other gases like oxygen (O₂) have also been explored for treating diabetic wounds infected with MDR bacteria.

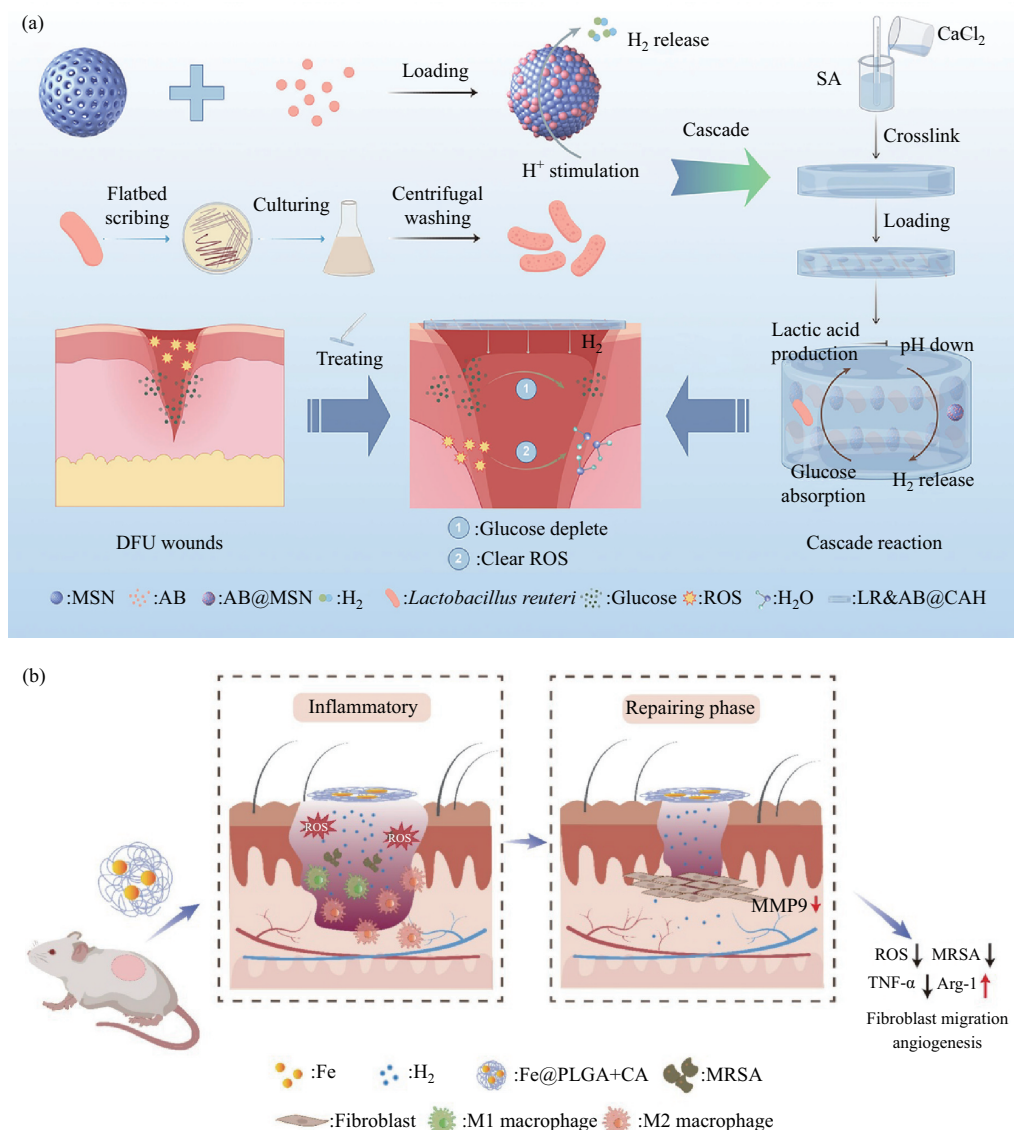


Fig. 7 H_2 -releasing micro/nanoplatforams for accelerated diabetic wound repair

(a) Schematic depiction of the construction of the glucose-driven probiotic active hydrogel LR&AB@CAH and its promotion of noninfected diabetic wound healing through enhanced H_2 production^[126]. (b) Schematic illustration of the Fe@PLGA+CA dressing with sustained H_2 release for accelerating the healing of MRSA-infected diabetic wounds^[63].

Hypoxia is a key pathological feature of these wounds, significantly hindering wound healing^[127-128]. While hyperbaric O_2 therapy is an established treatment, it requires long treatment durations and frequent sessions^[48, 129]. Traditional solid O_2 -generating materials, such as CaO_2 , MgO_2 , and $2Na_2CO_3 \cdot 3H_2O_2$, suffer from uncontrolled O_2 release and poor specificity, leading to suboptimal outcomes^[130]. To address this, Gao *et al.*^[130] developed a poly(ionic liquid) microneedle patch loaded with living *Chlorella* (PILMN-Chl) for treating chronic diabetic wounds infected with MRSA. Under light irradiation, the microneedles generated O_2

continuously for 30 h, providing antibacterial and anti-inflammatory effects *via* transdermal O_2 delivery. *In vivo* experiments confirmed that this strategy significantly enhanced wound healing in drug-resistant bacterial-infected diabetic wounds.

Moreover, enzymatic catalysis offers a promising approach to ameliorate hypoxic conditions. Xu *et al.*^[131] reported a glucose-activated cascade O_2 -releasing hydrogel (HP-LT/G/M) that consumes glucose, scavenges ROS, and releases O_2 to improve the wound microenvironment and accelerate wound healing. This hydrogel, constructed from phenylboronic acid-grafted hyaluronic acid (HP) and

lysozyme (LT), utilizes GOx and MnO₂ nanozymes to catalyze the production of H₂O₂ and convert it into O₂. In an MRSA-infected diabetic mouse model, this hydrogel significantly accelerated wound closure, reduced inflammation, and promoted collagen deposition and angiogenesis. This platform, integrating multi-enzyme catalytic cascades with microenvironmental responsiveness, underscores the potential of gas molecule release strategies for improving wound healing and eliminating drug-resistant infections.

In addition, unconventional gases such as hydrogen selenide (H₂Se) and sulfur dioxide (SO₂) have demonstrated multifaceted effects in treating drug-resistant bacterial infections or non-infected diabetic wounds. H₂Se induces oxidative stress by interfering with intracellular sulfur metabolism in bacteria, killing MDR bacteria embedded in biofilms and activating biofilm dispersal genes^[132]. H₂Se also enhances the activity of glutathione peroxidase 1 (GPx1) in epidermal cells, alleviating oxidative stress and suppressing post-infection inflammation^[133]. SO₂, an endogenous lipophilic gas derived from sulfur-containing amino acid metabolism, demonstrates broad-spectrum bactericidal efficacy against drug-resistant bacteria^[27]. It functions by depleting intracellular free thiols, thereby intensifying ROS-induced oxidative stress^[134]. Despite limited application in diabetic wound treatments, the antibacterial and anti-inflammatory properties of these gases hold great promise for future therapeutic strategies.

3 Challenges and limitations of gas-releasing platforms for diabetic wound healing

Gas-releasing micro/nanoplatforms have shown considerable promise in treating diabetic wounds complicated by MDR bacterial infections by leveraging the antimicrobial and biofilm-disrupting properties of specific gases. These therapies also accelerate wound healing through the modulation of inflammation, immune responses, and angiogenesis. However, the clinical translation of these technologies remains challenged by several factors, including insufficient mechanistic understanding, potential toxicity, and regulatory barriers. Despite the development of numerous strategies based on the properties of micro/nanomaterials and the unique features of the diabetic wound microenvironment, critical issues hinder their application in clinical settings. Future research efforts should focus on

deepening the mechanistic understanding of gas therapy, improving the precision of gas delivery, and advancing personalized treatment approaches to facilitate the transition from laboratory research to clinical application.

3.1 Gas consumption and biosafety concerns

The primary barrier to the clinical adoption of gas therapy lies in the dual nature of gaseous signaling molecules, which possess narrow therapeutic windows. This necessitates careful control of their dosage to avoid cytotoxicity while maintaining sufficient antimicrobial efficacy^[135]. For example, while high concentrations of CO are required to inhibit bacterial respiration effectively, excessive systemic absorption can lead to irreversible binding with hemoglobin, causing severe hypoxia^[75]. Similarly, uncontrolled NO release can react with superoxide anions to form ONOO⁻, a potent species that, although bactericidal, may induce significant oxidative damage to healthy host tissues and impair wound re-epithelialization^[136]. Moreover, gases' high volatility and the challenge of achieving precise spatiotemporal release within the dynamic diabetic wound environment often result in off-target leakage, leading to potential systemic toxicity. Furthermore, the long-term biocompatibility and metabolic fate of micro/nanomaterials used for gas delivery remain major concerns, as immune responses or tissue accumulation could compromise patient safety during prolonged treatment. Thus, overcoming these challenges requires the development of advanced delivery systems capable of precise, spatiotemporal control over gas release. Ideally, such systems should respond to specific pathological stimuli, such as pH, enzymes, or ROS levels, inherent to the diabetic wound microenvironment, allowing for on-demand gas release at the target site. This approach would minimize off-target effects and systemic toxicity while maximizing therapeutic efficacy. Additionally, the long-term biosafety of the micro/nanomaterials themselves must be rigorously evaluated, and strategies should focus on biodegradable carriers with clear metabolic pathways to mitigate immune responses. Ultimately, intelligent, stimulus-responsive platforms capable of balancing potent antibacterial action with minimal host tissue damage are crucial for the clinical translation of gas therapy for diabetic wounds.

3.2 Gaps in mechanistic understanding

Although gases such as NO, CO, and H₂S are known for their broad-spectrum bactericidal activity, the precise molecular mechanisms governing their interactions with both bacterial biofilms and the

diabetic host remain insufficiently understood. For example, bacterial sensitivity to gases varies significantly depending on their intrinsic antioxidant defenses and repair systems^[137]. Furthermore, pathogens within biofilms may upregulate adaptive mechanisms to resist oxidative stress induced by gases, a phenomenon that has yet to be fully characterized. Despite the high diffusivity of these gases, the dense EPS matrix of biofilms presents a substantial barrier to effective delivery, often allowing persistent bacteria in the basal layers to survive, which can lead to recurrent infections^[138]. Additionally, the heterogeneity of the diabetic microenvironment, with significant inter-patient variability in factors such as pH and glucose levels, introduces further unpredictability in the pharmacokinetics and effectiveness of gas-releasing therapeutic platforms across different patients^[139]. Another important mechanistic gap lies in the insufficient understanding of the temporal relationship between bacterial killing and tissue repair during different stages of wound healing. In infected diabetic wounds, inflammation is not uniformly detrimental; rather, an appropriate early inflammatory response is required for initial bacterial clearance, whereas prolonged and excessive inflammation can subsequently aggravate tissue injury and delay repair^[140]. Therefore, gas therapy should be understood as a dynamic and stage-adapted intervention rather than a static antibacterial treatment. Specifically, during the early phase of infection, gas-based platforms should prioritize rapid bacterial elimination and biofilm disruption to reduce pathogen burden and prevent persistent infection-driven inflammation. After initial infection control is achieved, the therapeutic focus should shift toward resolving excessive inflammation, limiting collateral tissue damage, and promoting angiogenesis, cell proliferation, and tissue remodeling in the later reparative phase. In this context, the key mechanistic question is not only whether a given gas can eradicate bacteria or support regeneration, but also when and in what sequence these effects should be activated. Rational gas therapy may therefore require a sequential intervention mode, in which an early-phase antimicrobial burst is followed by a later-phase immunomodulatory and pro-regenerative action. This time-resolved perspective may also explain why the same gas or gas-releasing platform can produce different biological outcomes depending on dose, release timing, and wound stage. To advance gas therapy, a deeper understanding of how gases interact with biofilm matrices, bacterial cells, and the evolving

wound microenvironment across different healing phases is essential. Molecular biology techniques, particularly multi-omics strategies, offer powerful tools for unraveling these complex mechanisms. By deciphering the synergistic pathways involved in bactericidal action, biofilm disruption, immune modulation, and tissue repair, these approaches can identify key biomarkers and potential therapeutic targets, thereby optimizing gas delivery systems for precise on-demand therapy and successful clinical translation.

3.3 Scalability, manufacturing, and regulatory challenges

The clinical translation of gas-releasing micro/nanoplatfoms faces additional challenges related to large-scale manufacturing, quality control, and regulatory approval. Multifunctional micro/nanoplatfoms typically involve complex synthesis processes, which create difficulties in maintaining structural consistency and functional reproducibility during industrial scale-up^[141]. Although MOFs offer high gas-loading capacity and highly tunable pore structures that facilitate controlled release, their application is often limited by inadequate long-term stability in complex wound exudates and by potential biosafety and toxicity concerns during industrial scale-up. In comparison, hydrogels generally exhibit lower absolute gas-loading capacity than MOFs, and their intrinsic swelling behavior may hinder precise and rapid on-demand release. Microneedles provide a distinct advantage by physically penetrating both thick mature biofilms and the stratum corneum, thereby improving local drug delivery to deeper infected tissues. However, their fabrication typically relies on highly precise micro-molding processes, which increases the difficulty of large-scale continuous manufacturing. Nanozymes, on the other hand, show strong potential for spatiotemporal control, but maintaining batch-to-batch structural consistency and catalytic uniformity remains a major challenge for large-scale industrial application. Gas therapy also occupies a unique regulatory category, blurring the line between pharmaceuticals and medical devices, particularly when non-traditional materials are used. The lack of standardized protocols for evaluating the pharmacokinetics, biodistribution, and long-term toxicology of gas-releasing nanomaterials complicates the regulatory approval process^[23]. As a result, rigorous safety assessments, including genotoxicity and immunotoxicity evaluations, are required before clinical trials can commence. Overcoming these limitations will necessitate the development of biodegradable, highly

specific, and controllable gas delivery systems, along with standardized protocols for evaluating the safety and efficacy of gas therapies in treating diabetic wounds.

3.4 Personalized treatment strategies and precision monitoring

Diabetic chronic wounds exhibit profound heterogeneity, characterized by varying microbial spectra, degrees of inflammation, and host metabolic conditions, which render standardized therapeutic protocols increasingly ineffective for treating MDR bacterial infections. Current clinical diagnostic methods, such as secretion cultures and drug susceptibility tests, fail to capture the dynamic changes in the wound environment and bacterial resistance in real time. Consequently, there is a critical need to establish a comprehensive, personalized treatment paradigm that integrates multidimensional wound assessment with adaptive therapeutic platform selection. This approach should go beyond bacterial identification to include tissue perfusion imaging and molecular profiling of inflammatory cytokines, enabling precise matching of gas-releasing agents to the wound's specific pathological features. For instance, CO and NO release systems could be prioritized for dismantling dense biofilms in MRSA infections^[139], while glucose-responsive hydrogen-generating nanohydrides (PdH) would be more appropriate for simultaneously addressing hyperglycemia and oxidative stress in highly inflamed wounds^[142-143]. The integration of intelligent sensing technologies with gas therapy offers a transformative pathway for precision monitoring. By embedding micro-sensors capable of detecting specific metabolites or resistance genes into gas-releasing hydrogels and utilizing artificial intelligence for real-time data analysis, clinicians can track infection dynamics and autonomously adjust therapeutic parameters. This adaptive approach optimizes treatment by transitioning from bactericidal phases to regenerative phases, ensuring maximum therapeutic efficacy while minimizing off-target toxicity in complex diabetic wounds.

4 Conclusion and future perspectives

Gas therapy's core value lies in its synergistic efficacy, combining antimicrobial, anti-inflammatory, and pro-healing properties to address the challenges posed by MDR bacterial infections in diabetic wounds. Specific gases, such as CO, H₂, and NO, exert distinct biological functions: CO promotes M₂ macrophage polarization, inhibits NF- κ B pathway

activation, and improves wound perfusion through VEGF expression; H₂ activates the NRF2-ARE pathway to provide antioxidant defense, regulate cytokine release, and preserve mitochondrial function; NO remodels the immune microenvironment and modulates Toll-like receptor signaling. These actions ameliorate conditions such as ischemia, hypoxia, and chronic inflammation, creating a stable environment for immune cells and overcoming the limitations of traditional therapies that focus solely on antibacterial effects.

The integration of micro/nanocarrier technology has propelled gas therapy from passive delivery to precise response, overcoming the issues of poor controllability and lack of targeting that hinder traditional gas treatments. Stimuli-responsive gas-releasing systems have been developed to respond to the diabetic wound features such as high glucose levels, pH changes, and elevated glutathione concentrations. These systems enable precise, spatiotemporal control over gas release, regulating timing, dosage, and range, thus avoiding gas overdose toxicity and aligning with the wound's pathological characteristics. Additionally, innovative carrier materials, such as biodegradable electrospun films and self-adhesive hydrogels, have improved patient compliance and safety, laying a solid foundation for clinical translation.

Gas therapy is transitioning from basic research to clinical application, with Phase II clinical trials confirming its safety and efficacy. Despite these advances, challenges remain, including gaps in mechanistic understanding, insufficient targeting efficiency, and a lack of standardized treatment protocols. Future research should focus on deepening the understanding of gas synergy, integrating resistance monitoring technologies, and establishing standardized protocols for personalized therapy. With continuous innovation in smart carrier technologies and a better understanding of gas mechanisms, gas therapy is poised to overcome current translational barriers and become a cornerstone treatment for MDR bacterial-infected diabetic wounds, ultimately improving patient outcomes and reducing amputation rates in the post-antibiotic era.

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释气微纳米平台用于多重耐药菌感染性糖尿病伤口治疗*

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摘要 慢性糖尿病伤口并发多药耐药 (MDR) 细菌感染对全球健康构成重大挑战, 通常导致持续炎症、生物膜形成和血管生成受损。由于细菌进化和不良的伤口环境, 传统抗生素越来越无效。利用一氧化氮 (NO)、一氧化碳 (CO)、硫化氢 (H₂S) 和氢气 (H₂) 等信号分子的气体疗法是一种很有前途的替代方案。这些气体可以穿透细胞外聚合物基质, 破坏细菌代谢, 促进巨噬细胞极化和新生血管。然而, 它们的临床应用受到半衰期短、溶解度低和脱靶毒性的限制。气体释放微/纳米平台的最新进展主要是通过控制释放机制来克服这些挑战。这些平台可以根据特定的刺激释放气体, 如高血糖、酸性pH值, 或物理触发, 如光和超声波。智能递送系统的发展是改善耐药感染治疗和组织修复治疗效果的关键。尽管取得了进展, 但挑战依然存在, 包括生物安全问题、可扩展性和监管障碍。未来应致力于精准监测和个性化治疗, 结合可穿戴传感技术和人工智能进行自适应给药, 推进气体释放平台在复杂糖尿病伤口治疗中的临床应用。

关键词 多重耐药感染, 糖尿病伤口, 微/纳米平台, 气体疗法, 控释

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