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REVIEW

Recent Advances in Nanozymes for Bacteria-Infected Wound Therapy

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Abstract: Bacterial-infected wounds are a serious threat to public health. Bacterial invasion can easily delay the wound healing process and even cause more serious damage. Therefore, effective new methods or drugs are needed to treat wounds. Nanozyme is an artificial enzyme that mimics the activity of a natural enzyme, and a substitute for natural enzymes by mimicking the coordination environment of the catalytic site. Due to the numerous excellent properties of nanozymes, the generation of drug-resistant bacteria can be avoided while treating bacterial infection wounds by catalyzing the sterilization mechanism of generating reactive oxygen species (ROS). Notably, there are still some defects in the nanozyme antibacterial agents, and the design direction is to realize the multifunctionalization and intelligence of a single system. In this review, we first discuss the pathophysiology of bacteria infected wound healing, the formation of bacterial infection wounds, and the strategies for treating bacterially infected wounds. In addition, the antibacterial advantages and mechanism of nanozymes for bacteria-infected wounds are also described. Importantly, a series of nanomaterials based on nanozyme synthesis for the treatment of infected wounds are emphasized. Finally, the challenges and prospects of nanozymes for treating bacterial infection wounds are proposed for future research in this field.

Keywords: nanozyme, wound healing, bacterial infections, antibacterial, antibiofilms

Introduction

Bacteria exist in all corners of the human skin and do not cause infection under normal circumstances. When the skin and mucous barriers are damaged, they invade, grow, reproduce and secrete toxins, which gradually leads to the formation of acute/chronic infectious wounds with the passage of healing time.[1–3] Wound healing is one of the most important biological processes in the human body, and naturally restores the structural integrity of the skin through granulation tissue proliferation and the formation of scar tissue when exposed to external injuries such as cuts, lacerations, and stab wounds.[4,5] It is usually divided into acute trauma and chronic trauma based on recovery time. Acute wounds can complete the repair of anatomical and functional tissues within three weeks, while the healing time of chronic wounds is extended to three months after the formation of the wound. Bacterial infection is one of the important reasons for the formation of chronic wounds.[6,7] All organs and tissues of the body may be infected by bacteria, which can manifest as inflammation,[8] sepsis,[9] etc. In addition, chronic wounds in the form of diabetic ulcers, pressure, and vascular ulcers are common in clinical practice, and they always face the possibility of infectious complications.[10,11] Until the discovery and popularization of antibiotics known as bacterial infection terminating factors, the trend of bacterial infections was effectively controlled.[12,13]

However, decades of overuse and misuse of antibiotics have altered the genes of bacteria, leading to the emergence of drug-resistant strains and even multidrug resistance.[14] Moreover, when bacteria aggregate into biofilms, they acquire drug resistance approximately 10–1000 times that of the corresponding free bacteria due to the protective effect of extracellular polymers, which constitute the main component of biofilms.[15] Currently, approximately 700,000 people die each year due to drug-resistant bacterial infections, and this number is expected to rise to 10 million by 2050, with a resource cost of 100 trillion dollars.[16] Therefore, there is an urgent need to develop new antibacterial agents to address the growing problem of bacterial infections. The

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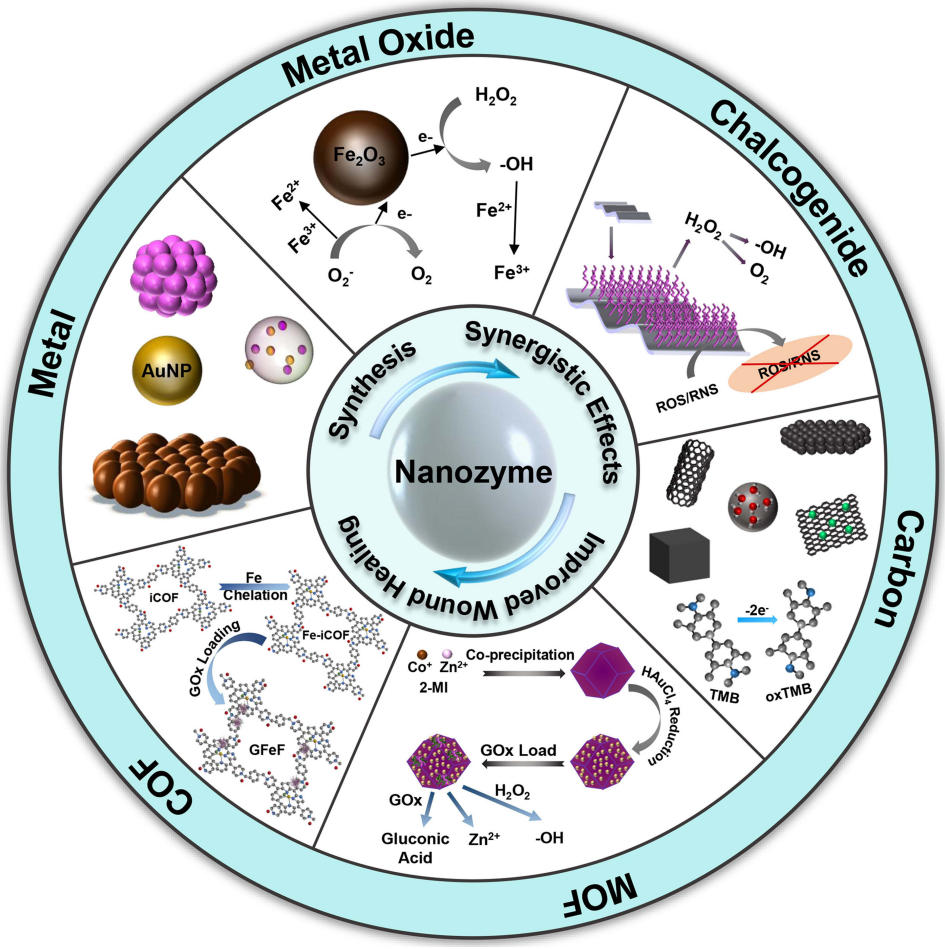
Graphical Abstract



development of nanotechnology has brought feasible ways for this. Most of the various nanoplatforms that have been developed at present show certain bactericidal properties, but they also have limitations such as a narrow antibacterial spectrum, low efficiency, high toxicity, and short-term effects (silver nanomaterials).[17–19]

Enzymes are biomaterials with excellent catalytic efficiency, substrate specificity, and environmental friendliness.[20,21] After the neutrophils of the human immune system engulf bacteria, their myeloperoxidase can catalyze hydrogen peroxide (H_2O_2) to generate highly toxic ROS to attack the bacterial cell membrane.[22] In practical applications, natural enzymes are subject to many limitations. Inspired by natural enzymes, researchers have focused on how to construct artificial nanozymes with enzyme-like activity to kill bacteria or disrupt biofilms.[23,24] As a substitute for natural enzymes, nanozymes can be applied in more fields due to their high surface energy and good photoelectron transport ability.[25] Excitingly, due to the excellent physicochemical properties of most nanomaterials, design adjustments can be made according to practical needs,[26] such as surface modification to improve biocompatibility,[27–29] and control of synthesis conditions to tune the catalytic efficiency.[30] Moreover, it usually has more robust stability and robustness in extreme environments.[31,32] In practical applications, artificial nanozymes have more advantages than natural enzymes, consisting of low cost, high stability, mass production, etc.[33]

Bacterial infection not only easily delays the wound healing process, but also easily causes severe tissue and cell damage, and even threatens life. In recent years, among the known nanomaterials researched, there are currently more researched metal nanoparticles (Au, Ag, Pd, and Cu),[34–37] nanoalloys (gold silver, gold copper, and iron platinum),[38–40]

compounds (cerium oxide, iron oxide, silicon dioxide, and cadmium selenide),[41–45] carbon-based materials (graphene, carbon nanotubes, fullerenes),[46–48] etc. Different materials are used for the development of nanozyme antibacterial agents, which tend to be multifunctional and intelligent in a single system. In this review, we aim to highlight the significant advances of nanozymes for improving bacterial-infected wound healing. First, we briefly describe the pathophysiology and information of bacteria infected wound healing. Second, cover the treatment strategies for bacterially infected wounds of nanozymes. The application of nanozymes in infected wounds is mainly reviewed. Finally, the future challenges and prospects of nanozymes in bacterially infected wounds are also discussed.

Bacteria-Infected Wound Healing and Treatment

Bacteria-infected wound healing is common in daily life and in the occurrence of diseases, and many factors affect wound healing.[49] Wound types are divided into acute wounds and chronic wounds according to the length of healing time. Although both types of wounds go through the same repair process, the former can take longer to heal than three months to develop into a chronic wound that may be accompanied by pathological changes involving infection or increased protease activity.[50,51] Acute wounds are common in cuts, lacerations, abrasions, burns, and incisions caused by surgery or accidental injury. All stages of wound healing are completed within a certain time frame, but infection may occur.[52,53] Chronic wounds are often caused by chronic diseases and complications caused by their care, and even acute wounds caused by improper treatment or infection (such as diabetic foot ulcers, acute orthopedic wounds, venous leg ulcers, ischemic ulcers, pressure ulcers, etc.).[54–57]

In chronic wounds, common features are usually depicted compared with normal wound healing, including nonmigrating epidermis, unresolved inflammation, fibrosis, presence of infection, and biofilm formation (Figure 1). Although there is an increase in neutrophils and macrophages, not all are properly functioning. Some fibroblasts become senescent

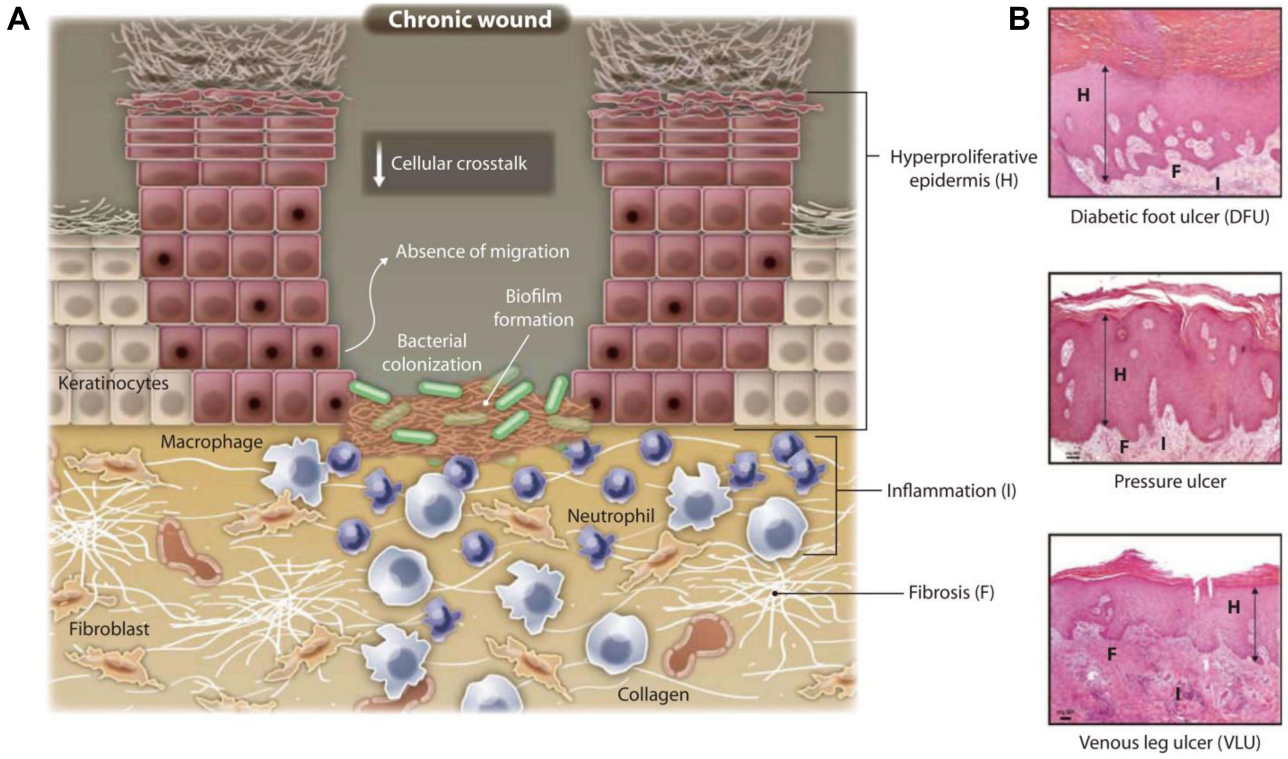


Figure 1 Molecular pathology of chronic wounds. Illustrations show molecular and cellular mechanisms that are impaired in chronic wounds. (**A**) Chronic wounds show hyperproliferative and nonmigratory epidermis, unresolved inflammation, presence of infection, and biofilm formation. (**B**) Histologies represent characteristics of a diabetic foot (DFU), venous stasis (VLU), and pressure ulcers. Although different in etiology, these chronic wounds show common cellular features: H, hyperproliferative epidermis; F, fibrosis; I, increased cellular infiltrate (inflammation). Reprinted from Eming SA, Martin P, Tomic-Canic M. Wound repair and regeneration: mechanisms, signaling, and translation. *Sci. Transl. Med.* 2014;6(265):265sr6. Copyright 2014, Wiley. Reprinted with permission from AAAS.[60]

and uncontrolled proteases interfere with essential repair mechanisms. Then, the healing time is gradually prolonged, eventually leading to the formation of a chronic wound.[58,59]

Pathophysiology and Formation of Bacteria-Infected Wounds

Pathophysiology of Bacteria-Infected Wound Healing

Wounds are most commonly colonized by a variety of microorganisms, including many potentially pathogenic microorganisms.[61,62] Therefore, wounds have a high risk of infection during the healing process. For normal wounds, the healing process is a succession and overlap of several multidimensional phases of hemostasis, inflammation, proliferation, and remodeling (Figure 2A).[63,64] In the dynamic process of wound healing, once the wound is formed, the damaged blood vessels rapidly constrict to initiate hemostasis.[65] Then, the platelets are activated upon contact with the subendothelial matrix, rapidly recruiting and secreting growth factors and chemokines to promote the recruitment of inflammatory cells, forming a blood clot as a temporary barrier to protect the wound (Figure 2B). Blood clots can also store cytokines and growth factors and provide a scaffold for the entry of immune cells, which are released as platelets activate, leading to early wound repair.[66]

The inflammatory phase represents the second stage of wound healing. During this phase, the accumulation of macrophages, lymphocytes, monocytes, mast cells, and polymorphonuclear neutrophils (PMNs) leads to inflammation.[67,68] Among them, macrophages are generally considered to be the predominant inflammatory cells in wound healing, and they play a role in phagocytosis of microorganisms, stimulation of granulation tissue and vascular formation, and gradually take over 3–5 days after wound formation.[69] Immune cells such as mast cells are also activated early in inflammation to recruit neutrophils by releasing histamine, which is beneficial for wound healing.[70,71] Moreover, PMNs play a central role in delayed wounding. In healthy individuals, PMNs flow freely in a resting state, called the dormant state. After wound infection, the activation of inflammatory mediators and complement released by various cells induces changes in the endothelial properties of the blood vessels. The endothelium sends signals to PMNs to migrate across the endothelial barrier toward the site of infection along a gradient of inflammatory factors and chemotactic agents (tumor necrosis factor-α, interleukin 8, platelet activating factor, leukotriene B4, and bacterial chemotactic peptides).[72,73] Upon exposure to pathogens, PMNs first recognize "pathogen-associated molecular patterns" that are widespread in microorganisms through cell surface pattern recognition receptors (Toll-like receptors).[74] Then, it binds and phagocytoses the pathogen. Phagocytosis triggers the PMN activation program by activating nicotinamide adenine dinucleotide phosphate oxidase (NADPH), leading to the release of superoxide anions, antimicrobial peptides, myeloperoxidases, and proteases.[75,76] This process is called "respiratory burst" (Figure 3). However, bacterial infection leads to excessive ROS production continuously and the wound remains in the inflammatory phase for a long time. Therefore, the prolonged healing time does not allow smooth entry into the proliferative and remodeling phases.[77]

Primary functions of normal intact skin, include control of microbial populations living on the skin surface and prevention of colonization and invasion of underlying tissues by potential pathogens.[78] Because the deep dermis is less repaired than the functioning epidermis in the later stages of healing, improperly healed wounds may lead to ulcerative skin abnormalities or excessive scar formation.[60] Ultimately, prolonged barrier defects may provide warm, moist, and nutritious conditions for bacteria to invade the underlying tissues of the skin, especially resistant bacteria that can further render antibiotics ineffective or even ineffective by forming biofilms, altering numbers and virulence, such as *Staphylococcus aureus* (*S. aureus*) and *Pseudomonas aeruginosa* (*P. aeruginosa*).[79] In addition, factors affecting infected wound healing include age, sex hormones, oxygenation, comorbidities (diabetes, obesity, nutrition), medication use (nonsteroidal anti-inflammatory drugs, steroids, anti-rejection drugs), lifestyle (alcoholism, smoking), and tumor treatment (chemotherapy, radiotherapy).[80,81] Meanwhile, different wound care methods and techniques can lead to different event outcomes.[11]

Formation of Bacterial Infection Wounds

Bacteria are ubiquitous in nature and in the human body, and colonize different body parts, such as the skin, gut, stomach, mouth, lungs, reproductive tract, and conjunctiva.[82] The bacterial microbiome plays a crucial role in human health, such as nutrient acquisition, control of cell proliferation and differentiation, molecular metabolism, and

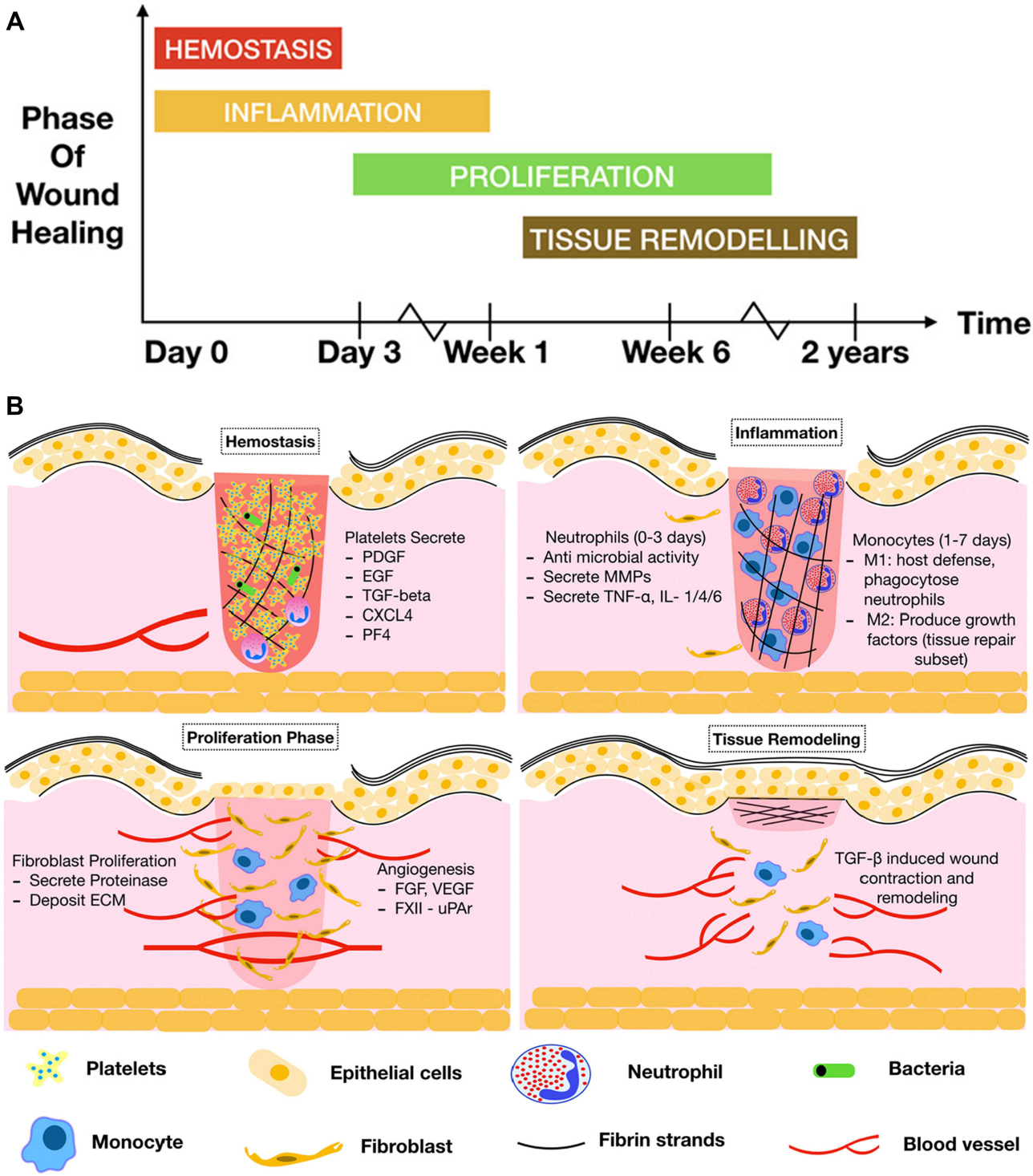


Figure 2 (**A**) Phases of wound healing. Timeline depicting the sequential yet overlapping phases of wound healing namely, hemostasis (red), inflammation (yellow), keratinocyte proliferation, angiogenesis (green) and tissue remodeling (brown). (**B**) Contribution of hematopoietic cells to wound healing. Reprinted from *Thromb. Res.* 179. pneja A, Kapoor S, Stavrou EX. Contribution of platelets, the coagulation and fibrinolytic systems to cutaneous wound healing. 179:56–63. Copyright 2019, with permission from Elsevier.[64]

Abbreviations: CXCL4, CXC chemokine ligand 4; ECM, extracellular matrix; EGF, epidermal growth factor; FGF, fibroblast growth factor; IL, interleukin; MMP, matrix metalloproteinase; PDGF, platelet derived growth factor; PF4, platelet factor 4; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor-α; uPAR, urokinase plasminogen activator receptor; VEGF, vascular endothelial growth factor.

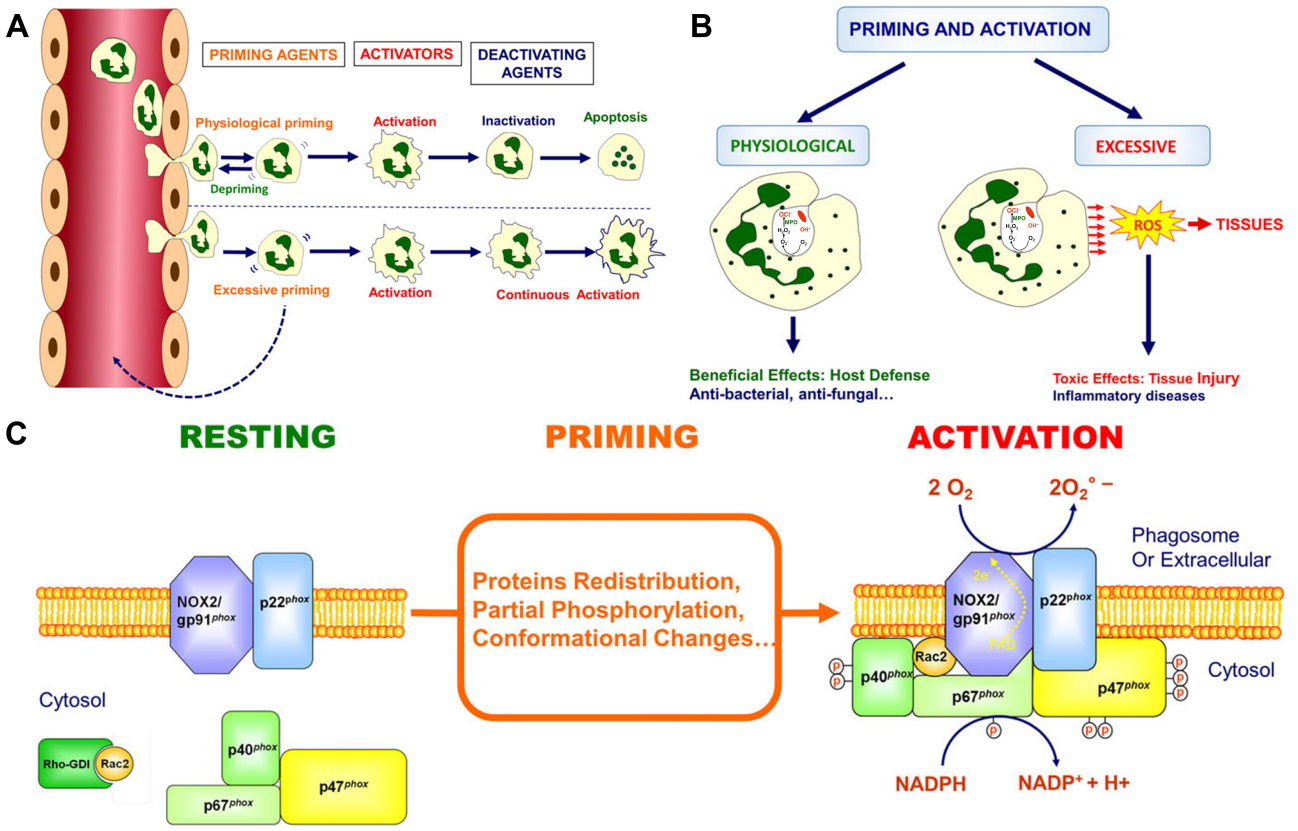


Figure 3 (**A**) Neutrophils from the circulation to the inflammation site. (**B**) Role of priming and activation of neutrophils in host defense and inflammation. (**C**) The NADPH oxidase in resting, primed and activated neutrophils. Reprinted with permission from J. El-Benna, M. Hurtado-Nedelec, V. Marzaioli, et al. Priming of the neutrophil respiratory burst: role in host defense and inflammation. *Immunol. Rev.* 2016;273(1):180–193. Copyright 2016, Wiley.[74]

development of the immune system.[3] However, when the living environment of the microbiome changes due to diet, low immunity, and the use of antibiotics, the diversity of the microbiome will be out of balance, thereby becoming opportunistic pathogens and leading to serious infections.[83,84] The skin, which is the organ with the second-highest number of microorganisms, is also at risk of infection if its integrity is compromised.[82]

The outcomes of wound healing may be related to the diversity of bacterial species.[85] Low levels of bacterial colonization do not affect wound healing; in contrast, high levels of colonization play a significant role in the formation of infectious chronic wounds.[86,87] Certain specific pathogenic microorganisms such as *S. aureus, P. aeruginosa*, and Group A Streptococcus are common types of infection. Bacterial infection wounds are formed due to their resistance to antibiotics and the formation of bacterial biofilms while secreting toxins and enzymes to aggravate wound damage.[88] Generally, bacterial biofilm is a viscous structure of polysaccharide matrix formed by autocrine after bacterial aggregation in a specific microenvironment. Most are produced in adversity, such as antibiotic use, and nutritional deficiencies.[89] Biofilms can be composed of single or multiple bacterial species.[90] Once biofilms are formed, it is difficult for immune cells to engulf them, which reduces the effectiveness of this type of infection.[91,92] Furthermore, biofilms are approximately 1000 times more resistant to fungicides than planktonic cells.[93]

The persistence of biofilms can cause an excessive inflammatory state, in which inflammatory cells produce oxidative free radicals and enzymes that further damage surrounding collateral tissue cells and are the main cause of bacterial infection wound formation.[94,95] After invading wounds, pathogenic microorganisms suppress the adaptive immunity of wound healing through quorum sensing (QS) signaling, making them unable to fully activate dendritic cells and macrophages.[96] It can also prevent the expression of endogenous antimicrobial peptides (AMPs) in wounds in innate immunity. AMPs can respond to trauma by macrophages, infiltrating granulocytes, and keratinocytes, and are part of the skin's innate immune response to defend against infection. For instance, S100A8/A9 is not expressed in human venous

chronic leg ulcers, but is expressed in actively healing wounds.[97–99] Moreover, some components of biofilms, such as rhamnolipids in *P. aeruginosa* biofilms, cause neutrophil death and cell necrosis.[100,101] Another possible underlying mechanism is that biofilms block the recognition of bacterial infections in the body through the Toll-like-receptor pathway. This results in reduced oxidative burst activity of neutrophils in wounds, insufficient stimulation of cytokines, and markedly slowed wound epithelialization.[102]

Treatment Strategies for Bacterially Infected Wounds

Traditional Strategies

The skin is a multilayered organ barrier that prevents the human body from dehydrating and invading pathogenic microorganisms. Repair after injury is a significant and complex biological process in the human body.[103,104] Due to the widespread use and even abuse of antibiotics, bacterial resistance is rising year by year.[105] Currently, to promote the rapid healing of wounds and avoid the formation of chronic wounds caused by infection, traditional treatments, and new application methods are researched and developed, and new modern treatments are also sought.

Traditional treatment strategies have a long history of development in developing countries such as Asia, Africa, Australia, and Latin America.[106] Common materials include herbs, plant extracts, compounds of animal origin, organisms, silver, and traditional dressings.[107–109] There are many kinds of plant extracts, such as sea buckthorn,[110,111] aloe,[112–114] angelica,[115] and periwinkle,[116] containing a wide variety of Bioactive compounds,[117,118] which have good antibacterial activities and anti-inflammatory effects in the treatment of wound healing. Frogskin and its secretions,[119,120] honey, and propolis[121,122] are products of animal origin; and are generally used as ointments or temporary dressings. In addition, leech therapy also has numerous applications in bacterial infection wound healing as an alternative therapy.[123,124] The antimicrobial properties of silver can also help effectively control and prevent wound infections.[125–127] Even at the current frontier of antimicrobial drug development, traditional therapies still have enormous exploratory value.

Numerous advanced therapies have been investigated to meet the care needs of bacteria-infected wounds. Modern treatments are more demanding and functionally diverse, including modern dressings, stem cells, growth factors, and skin replacement therapies.[128–132] The main goal is to improve the antibacterial activity of the material so that it can be fully developed and made harmless to the human body. The combination of traditional therapy with modern technology is a new approach, for example, the use of honey combined with gelatin and chitosan (CS) to construct a hydrogel dressing for the treatment of burns, which has significant antibacterial activity and biosecurity against *Escherichia. coli* (*E. coli*) and *S. aureus*.[133] In addition, there are also hydrogel dressings loaded with bacteriophages for research against certain drug-resistant infections.[134] Negative pressure wound therapy has changed the way acute and chronic wounds are treated, especially in the management of infected wounds, it can shrink wound edges, remove inflammatory and infectious Substances, reduce edema and promote the formation of blood vessels and granulation tissue.[135] Hyperbaric oxygen therapy utilizes the binding mechanism of oxygen and hemoglobin to improve the oxygen content of ischemic tissue, enhance the activity of fibroblasts, promote angiogenesis and the clearance of some bacteria, downregulate inflammatory factors, and upregulate growth factors, and is generally used to treat intractable or complex ulcers.[136–138]

Traditional dry gauze dressings used in the clinic have difficulty creating an environment of low oxygen tension, which is not conducive to the activation of hypoxia-inducible factors and the accelerated rate of re-epithelialization.[139,140] Therefore, many new dressings have been developed to promote wound tissue regeneration by improving the microenvironment of the wound. The materials used include the antioxidants polyurethane, collagen, bacterial cellulose, CS, silica gel, HA, alginate, etc.[141–148] In recent years, studies have found that lasers and tissue-engineered alternatives can shorten the healing time of leg ulcers, pressure ulcers, diabetes, and wounds at high risk of infection.[15]

Compared with traditional treatment methods, modern treatment methods have solved the problems of dosage, safety, formulation, cost, production method, batch, and efficacy to a certain extent.[106,149,150] For instance, honey is one of the representative natural substances in traditional remedies. Differences in antibacterial activity are affected by differences in ingredients, with an incomplete understanding of the mechanism of action of active ingredients and lack of standardization of antibacterial activity being the main reasons for its limitation.[121,151,152] Moreover, while various treatment methods promote wound healing, they also have side effects that cannot be ignored. Including glucocorticoids

with powerful anti-inflammatory effects, long-term use can lead to osteoporosis, muscle atrophy, eye diseases, central nervous system diseases, hyperglycemia, etc.[153] Worryingly, new antibiotics are always effective initially, but inevitably develop resistance over time into clinical use, which means that limited shelf life needs to be extended by the continuous development of new drugs and strategies.[154]

Nanozyme Strategies

Nanozymes as emerging materials have more advantages than traditional antibacterial agents. Currently, the synthetic route of nanozymes is mainly chemical synthesis, and manual intervention is the basis for the realization of the controllable design. The advantages of nanozymes mainly include the following aspects (Figure 4): (1) They are less susceptible to drug resistance than other materials. For instance, antibiotics target the basic cellular functions of bacteria, and bacteria can acquire compensatory mutations in adverse environments to reduce the adverse effects of resistance mutations.[155] Resistant plasmids and gene cassettes accumulate continuously and gradually form multiple drug resistance through self-transmission among bacteria, manifested as inactivated enzymes or changes in cell membrane permeability, making it difficult for drugs to bind to bacteria.[156] However, the bactericidal mechanism of nanozymes is mainly to catalyze the substrate through its oxidoreductase activity to generate highly toxic ROS, while it is difficult for bacteria to deal with the damage caused by ROS. (2) Enables the construction of nanozymes with targeting capabilities. Even though the selectivity of the nanozyme itself is relatively weak, its structural advantage enables it to form other components (aptamers, peptides, nucleic acid probes, antibodies, antibiotics) to achieve selective antibacterial effects. For instance, through the surface-binding properties and endocytosis of ROS, nanozymes selectively act on bacteria rather than normal tissue cells.[157] In addition, a selective antigram system was constructed based on photoacid molecules and MoS_2 for the differences in the structural composition of the cell walls of different bacteria. Charge switching is regulated by controlling the duration of UV light irradiation, with shorter durations focusing on Gram-positive bacteria and longer durations on Gram-negative bacteria.[158] (3) Nanozymes can modulate catalytic performance by changing various conditions. The catalytic performance of nanozymes is affected by ambient temperature, pH, light, activators, and inhibitors, therefore, ROS generation can be indirectly regulated by controlling the influencing factors.[159] In addition, size, morphology, components, and surface modification will also directly affect the catalytic activity of nanozymes.[160–162] (4) Multifunctional antimicrobial agent design is a future trend. Nanozymes in monotherapy mode are often ineffective in practical applications. In addition to enzyme-like catalytic activity, nanozymes can also combine photodynamic, physical cleavage, magnetic, fluorescence, and other capabilities at the same time, or construct multienzyme systems.[163–165] The synergy of multiple functions enables nanozymes to remove bacteria and biofilms more efficiently. (5) Furthermore, most of the preparation methods of nanozymes are relatively simple chemical syntheses, with obvious cost advantages and excellent stability, so they are suitable for mass production and in line with clinical application research.[166]

There are many types of nanozymes, and there have been many studies on different types of materials, such as metal-based nanozymes, metal oxide-based nanozymes, carbon-based nanozymes, and metal-organic framework (MOF) @covalent-organic framework (COF)-based nanozymes. In general, the antibacterial design of nanozymes mainly revolves around two aspects: first, how to destroy the biofilm so that it can come into contact with bacteria, and then how to ensure the effectiveness and maintenance of antibacterial ingredients after contact with bacteria. Most nanozymes utilize intrinsic enzyme-like and physicochemical activities, such as common peroxidase (POD)-like and oxidase (OXD)-like activities, to catalyze the production of abundant highly toxic free radicals in a short time, and regulate the level of ROS to achieve antibacterial activity.[167] Nanozymes mainly carry out antibacterial activity in the following ways.

ROS possess a powerful oxidative capacity and play a crucial role in the body's defense against pathogen invasion (Figure 5). Redox nanozymes can exhibit an intrinsic ROS generation ability to kill bacteria. For instance, a nanomaterial with POD-like activity can convert H_2O_2 to hydroxyl radicals (-OH), which inactivate the biological components of bacteria and biofilms (such as proteins, nucleic acids, lipids, and polysaccharides) (Figure 6A).[168] Namely, increasing ROS levels can lead to genetic and structural damage to bacteria and biofilms, making it difficult to develop drug resistance.[169]

In general, elevated concentrations (1–6%) are required to exert the antibacterial effect of H_2O_2, which can cause damage to healthy tissue surrounding an infected wound.[170] For instance, nanomaterials mimic vanadium chloroperoxidase, when halide ions and H_2O_2 coexist, the catalytic reaction produces abundant singlet oxygen ($^1O_2$) and hypochlorous acid to destroy

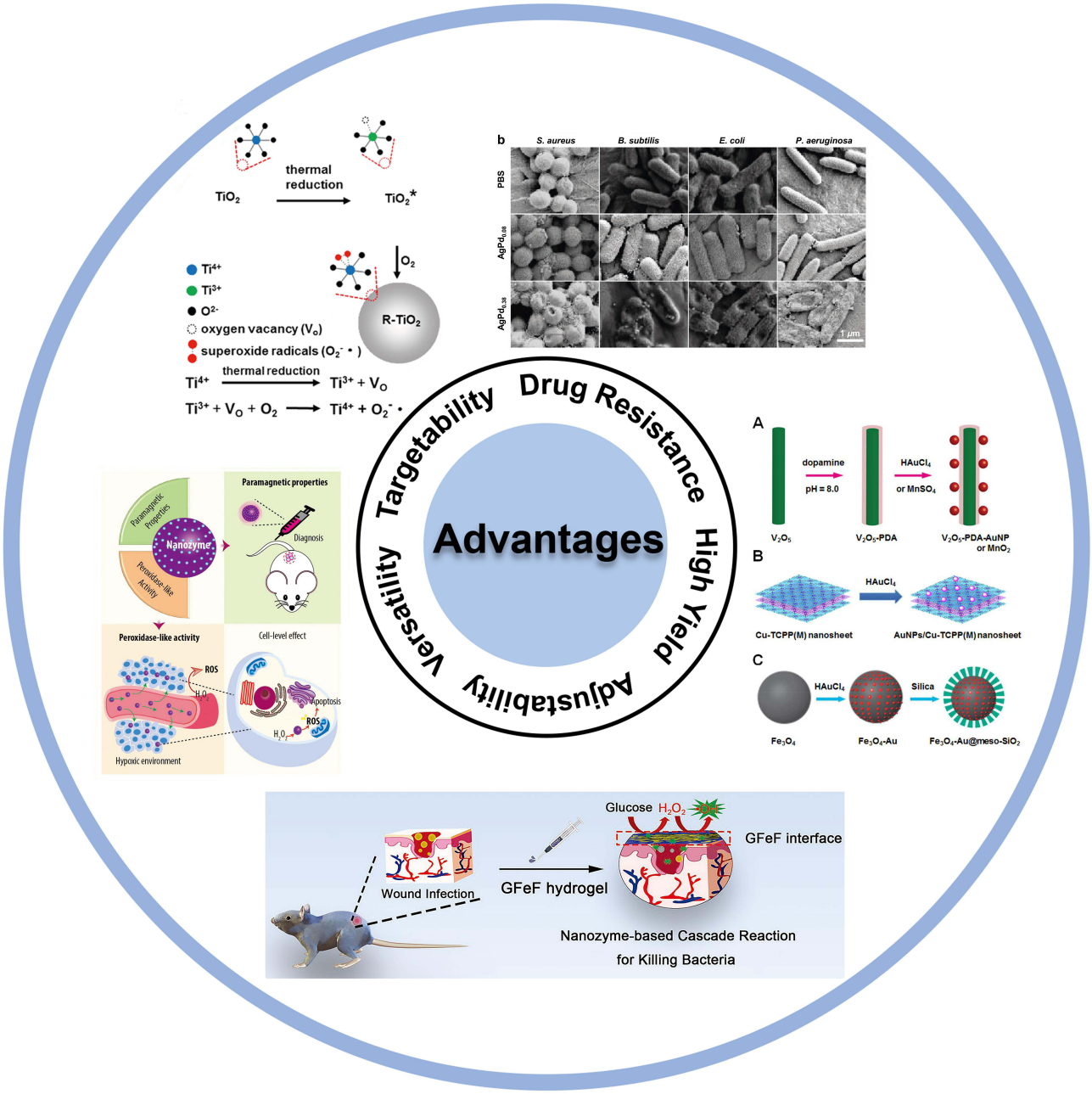


Figure 4 Schematic diagram of the antibacterial advantages of nanozymes. Reprinted with permissions from Liu X, Gao Y, Chandrawati R, et al. Therapeutic applications of multifunctional nanozymes. *Nanoscale*. 2019;11(44):21046–21060. Copyright 2019, The Royal Society of Chemistry, permission conveyed through Copyright Clearance Center, Inc.[165] Wu J, Li S, Wei H. Integrated nanozymes: facile preparation and biomedical applications. *Chem. Commun. (Camb)*. 2018;54(50):6520–6530. Copyright 2018, The Royal Society of Chemistry.[166] 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.[364] And F. Gao, T. Shao, Y. Yu, et al. Surface-bound reactive oxygen species generating nanozymes for selective antibacterial action. *Nat. Commun*. 2021;12(1):745. Creative Commons license and disclaimer available from: https://doi.org/10.1038/s41467-021-20965-3.[157]

bacteria and biofilms.[171] However, nanozymes are mostly pH-dependent, and relatively high doses of ROS may cause unnecessary damage. Therefore, one study encapsulated glucose oxidase (GOx) in MOF. Gluconic acid is produced by consuming glucose in the wound by GOx, which regulates the pH microenvironment suitable for the antimicrobial activity of the nanozyme and achieves a glucose-H_2O_2-hydroxyl radical cascade catalytic reaction (Figure 6B).[172]

The ROS generation performance of some nanozymes sensitive to external stimuli can be enhanced with additional light. For instance, TiO_2 nanotubes and black phosphorus are candidates for photoactivated enhancement therapy due to their excellent electron transportability and electronic band structure.[173,174] The composite material composed of these

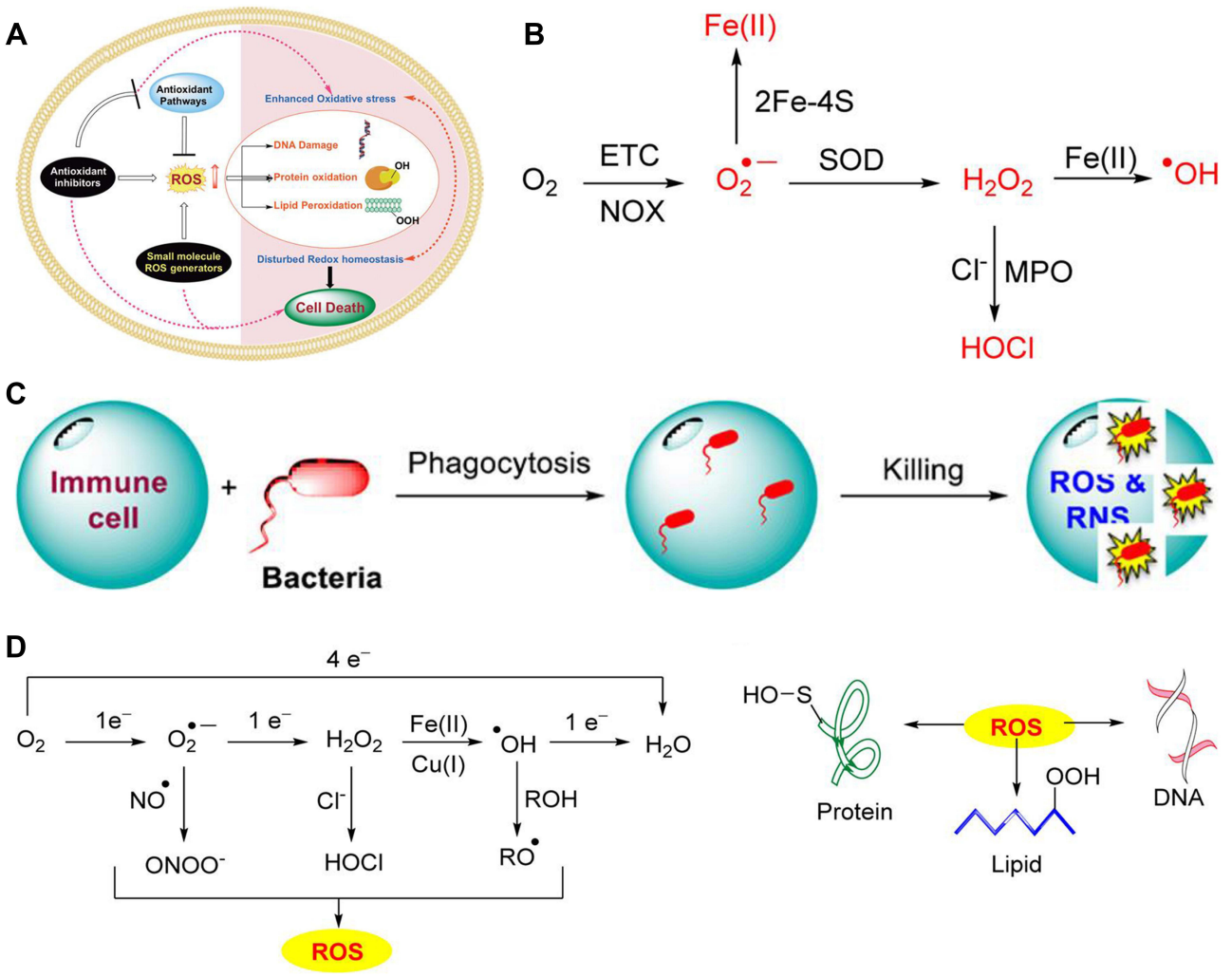


Figure 5 (**A**) Schematic illustration of ROS causing cell death. (**B**) ROS generation is induced by cellular enzymes. (**C**) Phagocytosis of bacteria during immune response in cells. (**D**) General scheme for ROS production and damaging effects of ROS to biomacromolecules. Reprinted with permission from Dharmaraja AT. Role of Reactive Oxygen Species (ROS) in Therapeutics and Drug Resistance in Cancer and Bacteria. *J. Med. Chem*. 2017;60(8):3221–3240. Copyright 2017, American Chemical Society.[169]

materials can actively catalyze the generation of ROS under light irradiation, and enhance the original enzyme-like activity of the binding component.[175] A modality of synergistic energy conversion to stimulate therapy can more precisely control the course of treatment and reduce the probability of resistance to a single antibacterial modality.[176,177]

Biofilms are a barrier to the effective functioning of antibacterial agents, in which environmental DNA (eDNA) is believed to play a Key role in maintaining membrane integrity. According to reports, some nanozymes with deoxyribonuclease (DNase)-like enzymes can hydrolyze eDNA to destroy biofilms.[178] In addition, hydroperoxidase-like nanozymes can block bacterial QS, impeding biofilm formation by inhibiting autoinduction such as N-acyl homoserine lactones.[179] The biofilm microenvironment (BME) has also received increasing attention from scholars in recent years. Utilizing the characteristics of the BME: (negative charge, low pH, and high concentration of reduced glutathione (GSH)), pH or GSH-dependent nanozyme design was carried out, and these characteristics were used to assist high-efficiency antibacterials.[180,181]

Nanozyme-Based Treating for Bacterial Infection Wounds

With the rapid development in nanotechnology and computer science, many synthetic methods have been proposed for the fabrication of new nanozymes, and possible catalytic mechanisms can be revealed through theoretical calculations. Benefiting from the advantages of materials synthesis, it is possible to modify the structure, morphology and size to

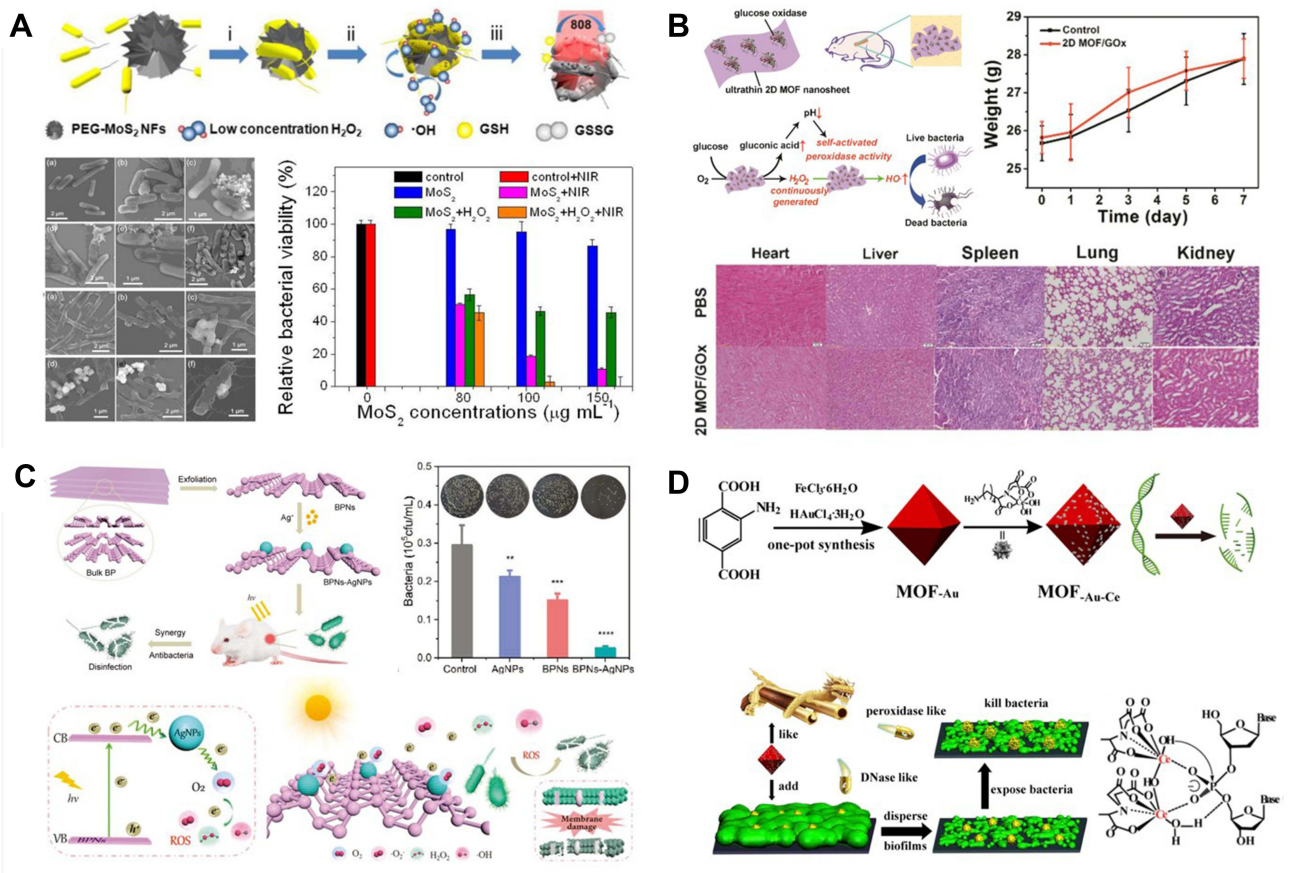


Figure 6 (**A**) Schematic illustration of PEG-MoS_2 as a combined system for POD catalyst-photothermal synergistic eliminating of bacteria. (i) PEG-MoS_2 was captured by bacteria; (ii) PEG-MoS_2 catalyze decomposition low concentrated H_2O_2 to generate OH to damage the cell walls integrity; (iii) 808 nm laser irradiation causes hyperthermia, which accelerates GSH oxidation. Reprinted with permission from Yin W, Yu J, Lv F, et al. Functionalized Nano-MoS(2) with Peroxidase Catalytic and Near-Infrared Photothermal Activities for Safe and Synergetic Wound Antibacterial Applications. *ACS nano*. 2016;10(12):11000–11011. Copyright 2016, American Chemical Society.[168] (**B**) GOx encapsulation in MOF to construct a Band-Aid dressing and its toxicity test. Scale bars: 50 μm. Reprinted with permission from Liu X, Yan Z, Zhang Y, et al. Two-Dimensional Metal-Organic Framework/Enzyme Hybrid Nanocatalyst as a Benign and Self-Activated Cascade Reagent for in Vivo Wound Healing. *ACS nano*. 2019;13(5):-5222–5230. Copyright 2019, American Chemical Society.[172] (**C**) Preparation of silver-loaded black phosphorus nanosheets (BPN-AgNPs) by facile BPN-mediated reduction of Ag^+ precursors and their antibacterial effect under light irradiation. Reprinted with permission from Wiley, Liang M, Zhang M, Yu S, et al. Silver-Laden Black Phosphorus Nanosheets for an Efficient In Vivo Antimicrobial Application. *Small*. 2020;16(13):e1905938. © 2020 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.[173] (**D**) Schematic diagram of the synthesis of MOF-Au-Ce by attaching cerium complexes to the surface of MOF-Au, which catalyzes DNA cleavage through DNase-like enzyme activity. Reprinted from *Biomaterials*. 208. Liu Z, Wang F, Ren J, et al. A series of MOF/Ce-based nanozymes with dual enzyme-like activity disrupting biofilms and hindering recolonization of bacteria. 21–31. Copyright 2019, with permission from Elsevier.[178]

confer enzymatic activity to nanomaterials.[182] The well-defined structure facilitates the elucidation of the active catalytic center, and the location of the active site means that it may have different catalytic properties. For example. noble metal nanoparticles, the distribution of active atoms may be located at the edges, corners, and tips. In wound antimicrobial therapy, numerous synthetic strategies have been used to synthesize and design nanomaterials with excellent intrinsic enzymatic activity, such as metals, metal oxides, sulfur generics, carbon-based nanoparticles, MOFs, and covalent metal organic frameworks (Table 1).

Metal-Based Nanozymes

In recent years, many researchers have made efforts to find new nanozyme antibacterial agents for bacterial infection wound treatment and have achieved important research results (Table 2). Metals are one of the most common constituent materials of nanozymes.[183] Metal nanomaterials have excellent electronic properties, which are derived from their rich charge coverage.[184] In addition, there are characteristics such as facile preparation, high surface energy, and excellent photothermal conversion performance,[185,186] which suggest that relevant adjustments (such as surface modification) can

Table 1 Summary of the Strategy, Synthesis Methods, Activity, Kinetic Parameters, and Healing Effect of Nanozymes

Strategy	Synthesis Method	Nanozyme	Activity	Substrate, Km (mM), Vmax (μM s^{-1})	Wound Healing Days	Ref.
Synthesis and surface modification	Modified Hummers method	GQD	POD	H_2O_2 (2.288, 0.1563)	3	[272]
	Soft-template strategy	Fe-NC SAzyme	POD	H_2O_2 (4.48, 0.118)	4	[266]
	AuNPs modification	AuNPs/Cu-MOFNs	POD	H_2O_2 (0.65, 0.225), TMB (0.29, 0.396)	8	[29]
	"Sequential growth" strategy	NMC_{TP-TTA}	POD	H_2O_2 (0.458, 0.57), TMB (0.291, 0.7351)	5	[369]
One-step solvothermal/hydrothermal reaction	One-step bottom-up ethanol-thermal method	VOx NDs	POD, OXD	H_2O_2 (0.077, 2.876), TMB (0.21352, 2.669)	6	[226]
	One-pot solvothermal method	MoO_{3-x} NDs	POD	H_2O_2 (0.26, 0.152), TMB (2.65, 0.00152)	6	[227]
	Solvothermal method	nFeS	POD, CAT	H_2O_2 (172.3, 0.4191), TMB (1.807, 9.113)	6	[241]
	Facile one-pot hydrothermal route	PEG-MoS_2 NFs	POD	H_2O_2 (2.812, 0.0801), TMB (0.537, 0.0388)	5	[168]
Precipitation	Deposition-precipitation	gC_3N_4@AuNPs	POD	H_2O_2 (0.222, 1.508), TMB (0.295, 0.86)	3	[200]
	Co-precipitation process	GOx-Hb MRs	POD, GOx	GOx (2.6, 0.0294)	/	[300]
Exfoliation	Sonication exfoliation	N-MoS_2, N-WS_2 NSs	POD	/	8	[247]
Pyrolysis	"Encapsulated-pyrolysis" strategy	SAF NCs	POD	H_2O_2 (0.01195, 0.234)	13	[263]
	Pyrolysis of colloidal silica/polyaniline assemblies	N-SCSs	POD, OXD, SOD, CAT	H_2O_2 (81.53, 0.2327), TMB (0.15, 0.2205)	9	[262]
	Mesoporous silica protected pyrolysis strategy	PMCS	POD	H_2O_2 (40.16, 0.1215), TMB (0.224, 0.1066)	6	[25]
	Pyrolysis	PEG@Zn/Pt-CN	POD	H_2O_2 (0.067, 0.0511)	12	[325]
Reduction	In situ reduction of AgNPs by TA	TA-Ag	POD	H_2O_2 (180.53, /), TMB (2.28, /)	21	[216]
	Via in situ reduction	UsAuNPs/MOFs	POD	H_2O_2 (7.94, /), TMB (0.101, /)	5	[310]
Others	A solution-based approach	CuO NRs	POD	H_2O_2 (3.4, 0.109), ABTS (0.04, 0.111)	/	[224]
	1, Ice bath 2, Vacuum drying	UNMS NCs	POD	H_2O_2 (0.23, 0.157), TMB (2.35, 0.00157)	5	[375]
	1, Fe chelation 2, GOx loading	GFeF	POD, GOx	H_2O_2 (3.35, 0.588), GOx (20, 0.01136)	9	[364]

Table 2 Metal-Based Nanozymes and Metal Oxide-Based Nanozymes for Improving Bacterial Infectious Wound Healing

Type	Materials	Substrate	Synthesis Procedure	Microbial Type	Antibacterial Mechanism	Antimicrobial Activity	Special Characteristics	Ref.
Metal-based	gC_3N_4@AuNPs	H_2O_2 (100 μM)	Deposition-precipitation	*S. aureus, E. coli*	Generates ROS, AuNPs stabilize -OH through partial electron exchange interactions, damage biofilm	>97% inactive bacteria in the presence of 20 μg/mL, SEM: Bacterial surface roughening and wrinkling	Avoid the injury caused by the use of high concentration H_2O_2 and maintain high activity in the pH (5.0–7.4) environment of the wound	[200]
	Cu-HCSs and CuO-HCSs	H_2O_2 (Gram-positive: 10 mM, Gram-negative: 1 mM)	Thermal decomposition	*Sphingomonas typhimurium (S. typhimurium), P. aeruginosa, Streptococcus mutans (S. mutans), E. coli and S. aureus*	Releases Cu ions and generates ROS, leading to membrane damage, enzymatic inhibition and possible DNA degradation	Sterilization decreased logarithmically	Kill bacteria and inhibit inflammation effectively, exhibited copper state-dependent peroxidase, catalase, and superoxide dismutase-like activities	[204]
	$AgPd_{0.38}$	O_2	1, Electro-displacement reaction 2, An ice-water bath	*S. aureus, B. subtilis, E. coli and P. aeruginosa*	Destroys the cell wall and cytoplasmic membrane	MBC = 4–64 μg/mL	ROS production is material dose-dependent, independent of pH, temperature and buffers, surface binding properties, inhibits biofilm formation	[157]
	TA-Ag	H_2O_2 (1 mM)	In situ reduction of AgNPs by TA	*Staphylococcus epidermidis (S. epidermidis), E. coli*	Electron transfer between Ag NPs and TA maintains the dynamic redox balance of phenol-quinone, high POD-like activity	In the presence of H_2O_2, the bacteriostatic rate within 2 hours: *S. epidermidis* (90%), *E. coli* (89%)	Rapid ROS production, bacterial adhesion, repeatability	[216]

(*Continued*)

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Table 2 (Continued).

Type	Materials	Substrate	Synthesis Procedure	Microbial Type	Antibacterial Mechanism	Antimicrobial Activity	Special Characteristics	Ref.
Metal oxide-based	CuO NRs	H_2O_2 (under visible light)	A solution-based facile approach under ambient conditions	*E. coli*	Generates ROS, CuO photoexcite the charge carriers to enhance the generation of -OH radicals, POD-like activity	Reduction of viability = 92% (pH 6.0 and visible light), TEM: Bacterial surface roughening and wrinkling	Sterilization; H_2O_2 production rate increased by 20 times under visible light, ~60% of the activity is retained at pH 6 and ~80% of the activity is retained at 37 °C	[224]
	CeO_2/BG	H_2O_2 (50 mM)	1, Liquid-feed flame spray pyrolysis 2, One-step synthesis	*S. aureus, E. coli, and Candida albicans*	Promotes intracellular ROS	Reduction of viability = ~ 90%	Antioxidant protection cell, synthesis controllable, different antibacterial activities of materials containing Ce^{4+} or Ce^{3+} in different phosphate environments	[225]
	ZnO/graphene oxide	/	Solution precipitation	*B. subtilis, Enterococcus faecalis (E. faecalis), E. coli and S. typhimurium*	Oxidizes cellular lipids and damages cell membranes, generates ROS	MIC = 6.25 μg/mL (*E. coli* and *S. typhimurium*), MIC = 12.5 μg/mL (*B. subtilis*) MIC = 25 μg/mL (*E. faecalis*)	ZnO particles and graphene oxide complement each other to enhance antibacterial properties, simple and fast synthesis	[230]
	Fe_3O_4 MNPs	H_2O_2, DNA, BSA	One-step in a solvothermal system	*E. coli, P. aeruginosa*	Oxidative cleavage of nucleic acids, proteins and oligosaccharides, generates ROS	98% inactive bacteria in the presence of 0.01% H_2O_2 and 20 μg /mL MNP	Wide pH range (4.5–9), significant biofilm cleavage ability	[231]
	VOx NDs	H_2O_2 (50 μM), O_2	One-step bottom-up ethanol-thermal method	*Extended spectrum β-lactamases producing (ESBL-producing) E. coli*, MRSA, *kanamycin-resistant E. coli*	Oxidizes cellular lipids and damages cell membranes, generates ROS	SEM: Bacterial surface roughening and wrinkling	Bienzymatic synergism, concentration of H_2O_2 decreased by about 2–4 orders, broad-spectrum antibacterial	[226]
	MoO_{3-x} NDs	H_2O_2 (100 μM)	One-pot solvothermal method	*ESBL-producing E. coli*, MRSA	Generates ROS, photothermal effect, damage biofilm	SEM: Bacterial surface roughening and wrinkling	POD/PTT/Photodynamic triple-therapy, broad-spectrum antibacterial, steady	[227]

be made according to practical applications. For instance, increasing the biocompatibility or changing the catalytic efficiency; is expected to be extended in biomedical applications.[27] Certainly, metals such as silver, cobalt, and copper have certain toxicity in the antibacterial treatment of infected wounds, and metal nanozymes face the challenge of how to enhance selectivity and improve biosafety.[187,188]

The morphology of nanoparticles is one of the parameters affecting catalytic performance. For example, gold nanozymes have excellent and stable catalytic, optical, electronic, supramolecular, and biological properties, manifested in different sizes and shapes (spheres, cubes, stars, prisms, etc.).[189] In general, smaller gold nanoparticles have better catalytic activity due to the higher number of angular sites.[190] However, the size dependence of the catalytic performance is not applicable to different shapes of gold nanoparticles.[191] McVey et al observed that smaller AuNSs (14 nm diameter) showed higher catalytic efficiency.[192] However, Biswa et al found that gold nanorods (AuNRs) with an aspect ratio of 2.8 were slightly more efficient than 34 nm gold nanorods (AuNSs) for the oxidation of 3,3',5,5'-tetramethylbenzidine.[193] Gold nanozymes are able to catalyze the production of ROS through POD activity for application in infected wounds. Ultrathin graphitic carbon nitride (gC_3N_4) is a nontoxic conjugated polymer with good thermal stability, chemical stability, and natural enzyme-like catalytic activity.[194,195] It has a wide range of applications in photocatalysis, sensors, biomedicine, and other fields. Although gC_3N_4 alone cannot be directly used for wound anti-infection, the use of gC_3N_4 combined with other antibacterial materials provides the possibility for the treatment of wound infection.[196–199] Wang et al prepared a g-C_3N_4@AuNPs (CNA) nanocomposite by a deposition-precipitation method.[200] AuNPs stabilize the -OH generated by CNA catalyzed by H_2O_2 through the interaction of electron exchange, and the two work synergistically. CNAs are capable of POD-like catalysis in the presence of ultralow concentrations of H_2O_2 (10 μM) to generate highly toxic -OH to destroy biofilms and even kill individual bacteria shed on biofilms. It not only avoids tissue damage and persistent inflammation caused by the use of high concentrations of H_2O_2, but also maintains high activity in the pH environment in the wound. Animal experiments showed that CNA could efficiently decompose gram-positive bacteria and gram-negative bacteria. In addition, it can also inhibit the formation of new biofilms and reduce the inflammation of lung infections caused by methicillin-resistant *S. aureus* (MRSA). These characteristics indicate that CNA can be used in clinical research. In addition, Zhang et al combined gold nanoparticles with α-FeOOH/porous carbon as an enzyme-Fenton bionanocatalyst.[201] The GOx activity of gold nanoparticles catalyzes the generation of gluconic acid from glucose and regulates the pH while inducing the reaction of H_2O_2 with Fe^{2+} to produce -OH. Crucially, the above synergy can achieve the target sterilization effect at near physiological concentrations of H_2O_2. Despite the lack of further studies to exploring different shapes to obtain empirical information, as a general rule, higher surface-to-volume ratios are expected to show enhanced catalytic performance.

The activity of nanozymes is related to their composition and structure.[202,203] Some metal-based nanozymes exhibit metal valence-dependent catalytic activity, and materials with different sterilization mechanisms are often designed by adjusting the metal valence. For instance, Xi et al compared two copper/carbon nanozymes (Cu-HCSs and CuO-HCSs) with metal valence states of Cu^0 and Cu^{2+}, respectively (Figure 7A–E).[204] Interestingly, the two nanozymes have completely different antibacterial mechanisms. The Cu-modified copper/carbon nanozyme catalyzes the generation of ROS for sterilization through POD activity, while the CuO-modified copper/carbon nanozyme directly releases Cu^{2+}. The experimental results show, that although both enzymes have significant antibacterial effects, the enzyme-like activity of Cu^0 is higher than that of Cu^{2+}.

The variable particle size of metal-based nanozymes makes it possible to further explore. The endocytosis of mammalian cells is not possessed by bacteria, and the internalized substances are captured in endocytic vesicles in the cytoplasm. Due to the abundance of endocytic vesicles, partial disruption does not necessarily lead to cell death.[205] Developing antibacterial agents that target bacteria without damaging normal cells has always been a challenge. Gao et al designed silver-palladium bimetallic alloy nanocages AgPd, which can be catalyzed by the oxidase activity possessed by Pd to generate highly toxic $^1O_2$ (Figure 7F–K).[157] The material exploits clathrin-mediated endocytosis in mammalian cells to protect cells from $AgPd_{0.38}$ and the surface-bound nature of ROS to preferentially target bacteria. Biosafety and antibacterial experiments also show that it can effectively kill gram-positive and gram-negative bacteria by destroying cell walls and cytoplasmic membranes while maintaining low toxicity, even for MRSA. In contrast, $AgPd_{0.08}$ does not have the antibacterial properties of $AgPd_{0.38}$. In addition, $AgPd_{0.38}$ is stable at different pH values and temperatures, and

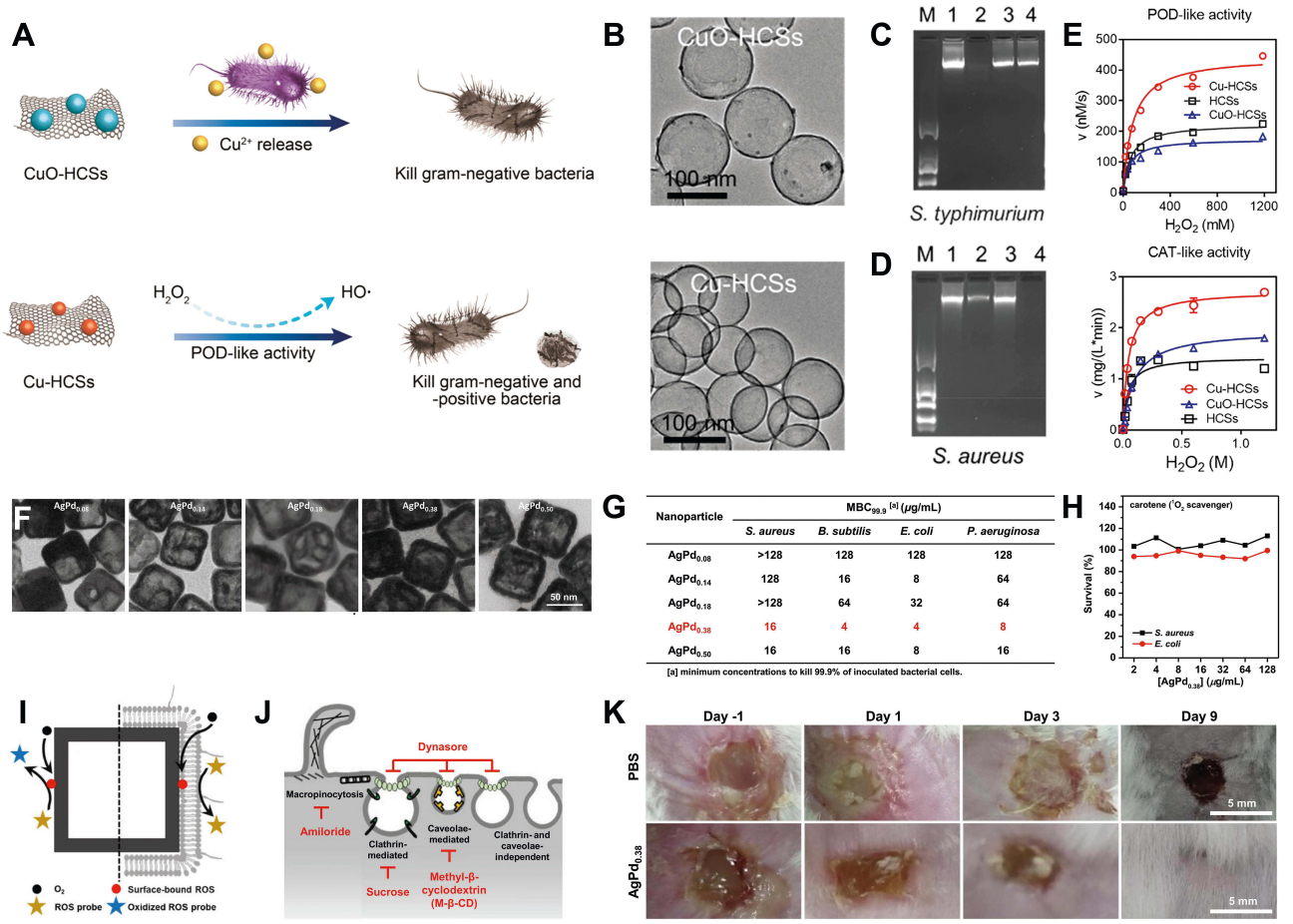

Figure 7 Metal-based nanozymes. (**A**) Schematic representation of antibacterial activity of CuO-HCSs and Cu-HCSs. (**B**) TEM images of copper/carbon nanozymes. (**C**) Genomic DNA degradation of treated with copper/carbon nanozymes. M, DNA marker; 1, control; 2, CuO-HCSs; 3, Cu-HCSs; 4, HCSs. (**D**) Genomic DNA degradation of *S. aureus* treated with Cu-HCSs and H_2O_2. M, DNA marker; 1, control; 2, Cu-HCSs; 3, H_2O_2; 4, Cu-HCSs/H_2O_2. (**E**) Steady-state kinetic assay of POD-like activity and CAT-like activity of copper/carbon nanozymes with varied [H_2O_2], respectively. Reprinted with permission from Xi J, Wei G, An L, et al. Copper/Carbon Hybrid Nanozyme: Tuning Catalytic Activity by the Copper State for Antibacterial Therapy. *Nano letters*. 2019;19(11):7645–7654. Copyright 2019, American Chemical Society.[204] (**F**) Transmission electron microscopy (TEM) images of AgPd nanocages with different Pd content. (**G**) In vitro antibacterial potentials of AgPd nanocages. (**H**) Plate-killing assays of $AgPd_{0.38}$ in the presence of carotene. (**I**) Schematic illustration of the strikingly suppressed oxidation of ROS probes in the bulk solution by $AgPd_{0.38}$@lipid, as compared to that by $AgPd_{0.38}$, indicative of effective separation of the ROS generated by $AgPd_{0.38}$ from the ROS probes in the bulk solution due to the presence of the lipid bilayer coating, suggesting that the ROS on $AgPd_{0.38}$ is surface-bound. (**J**) Schematic illustration of endocytosis pathways and their respective inhibitors. (**K**) Photographs of wounds from the two treatment groups throughout the observation window. Reprinted with permission from Gao F, Shao T, Yu Y, et al. Surface-bound reactive oxygen species generating nanozymes for selective antibacterial action. *Nat. Commun*. 2021;12(1):745. Creative Commons license and disclaimer available from: https://doi.org/10.1038/s41467-021-20965-3.[157]

when used as a coating additive, it can enable inert substrates to inhibit biofilm formation, which may be an anti-genetically encoded and phenotypic antimicrobial resistance. The size of the endocytosed substances has a certain range, which can be considered for the improvement of nanozymes with low toxicity, high antibacterial, and high metabolic properties.[206]

Toxicity is an unavoidable primary challenge for metal nanomaterials. Excessive use of AgNPs can lead to the danger of poisoning and even death, and exposed AgNPs are prone to aggregation after contact with bacteria, thereby reducing the antibacterial efficiency and biocompatibility.[207,208] Liang et al used the binding affinity of phosphorus and metal atoms to load AgNPs into ultrathin two-dimensional (2D) black phosphorus nanosheets (BPNs) to form nanohybrids (BPN-AgNPs).[173] As new ideal photocatalysts, BPNs not only possess tunable bandgaps and high carrier mobility, but also possess unique in-plane anisotropy, which provides a significant stable scaffold. The advantage of hybrid materials lies in the use of BPNs to ensure the slow release of Ag ions and reduce toxicity. In addition, the addition of AgNPs as

electron acceptors solves the problem that the photocatalytic activity of BPNs is limited by light-induced electron-hole recombination and the narrow spectrum of light absorption.

Dressings are powerful candidates as carriers, providing a stable platform for metal nanozymes to function. Hydrogels are 3D hydrophilic polymer networks that retain and absorb water, creating a moist environment suitable for wound healing.[209] In recent years, the construction of stable and effective nanobiocomposites based on hydrogels (carboxymethyl cellulose, lignin-agarose, sodium alginate, CS, etc.) has received extensive attention.[210–215] Jia et al simulated the viscosity of mussel secretions and reduced tannic acid (TA) on Ag nanoparticles in situ to construct an ultra-small self-coagulating hydrogel nanozyme with POD-like activity.[216] The resulting nanozymes are rich in phenolic hydroxyl groups, which not only support the long-term reproducible existence of adhesion, but also enable the nanozymes to be uniformly distributed in the hydrogel to improve mechanical properties and electrical conductivity, and shorten the distance for free radicals to reach bacteria. The POD-like activity can catalyze H_2O_2 in the wound to generate -OH, and synergize with the inherent antibacterial properties of Ag to kill bacteria. In the antibacterial experiment with *E. coli* as the target strain, the hydrogel achieved an excellent bactericidal effect, and promoted the formation of granulation tissue and collagen deposition. In addition, there are others such as supramolecular-based adhesives, lignin-based hydrogels, and topologically adhesive hydrogels that are also under development, which may be potential candidates for wound antimicrobial therapy delivery platforms.[217–219]

Metal Oxide-Based Nanozymes

Metal oxide nanomaterials have unique redox and optoelectronic properties.[220] Compared with antibacterial agents such as traditional antibiotics, quaternary ammonium ions, and metal ions, metal oxide nanozymes, like other artificial enzymes, can use enzyme-like activity to catalyze H_2O_2 to exert an antibacterial effect.[171,221] Nanozymes based on metal oxides such as Fe_3O_4,[222,223] CuO,[224] CeO_2,[225] VCl_3,[226] $MoCl_3$,[227] V_2O_5,[228] Tb_4O_7,[229] and ZnO[230] have been studied in antibacterial aspects, and the construction of multifunctional antibacterial agents from multiple perspectives (Table 2).

The ROS that catalyzes the production of H_2O_2 can effectively decompose the protein, polysaccharide, and nucleic acid components of bacterial biofilms.[22] It has been studied to decompose H_2O_2 by the POD-like activity of Fe_3O_4 metal nanoparticles (MNPs) for cleaning and disinfection.[231] However, in practical applications, ROS are not specific to bacteria, and the survival cycle of ROS is very short. Therefore, shortening the time required for ROS to reach bacteria is a feasible means to improve sterilization efficiency. Ji et al utilized Fe_3O_4 MNPs as catalysts and HA-encapsulated graphene-mesoporous silica nanosheets (GS) as drug carriers to constitute a targeted "on-demand" prodrug ascorbic acid (AA) delivery material (AA@GS@HA-MNPs).[223] The choice of AA as the prodrug is based on the characteristics of non-toxicity and anti-oxidation, which can avoid the generation of free radicals and destroy itself at the same time. Additionally, the light absorption ability brought by GS is used to synergize with the ROS catalyzed by Fe_3O_4 nanoparticles for effective sterilization. The material can effectively destroy the biofilm in situ, significantly shorten the action distance of ROS, and solve the problem of massive inactivation of ROS during the transfer process.

For the infected wound environment, it is a more precise method to adjust the external conditions to activate nanozymes to control the action process, such as light and pH, which can also enhance the activity of some light and nanozymes suitable for acidic conditions.[232,233] Karim et al used visible light as a trigger for semiconducting CuO nanorods (NRs) with POD-like activity (Figure 8).[224] Experiments showed that the affinity of CuO NRs for H_2O_2 under visible light irradiation was increased by 4 times compared with the nonirradiated condition, and the further result was that the rate of ROS generation was increased by 20 times. Therefore, the antibacterial efficiency of CuO NRs triggered by visible light against *E. coli* can be enhanced even at ultralow H_2O_2 concentrations. Studies have demonstrated that the catalytic activity of nanozymes is pH-dependent, which limits their application in infected wounds. Vallabani et al took advantage of the fact that adenosine triphosphate (ATP) can interact with Fe ions,[234] using ATP as a modulator to improve the enzymatic activity of citrate-modified Fe_3O_4 nanozymes.[235] The experimental results show that the nanozyme can catalyze H_2O_2 in a neutral pH environment under the regulation of ATP, and the killing effect on *E. coli* and *Bacillus subtilis* (*B. subtilis*) is improved.

Adjusting the internal conditions of nanozymes is an effective way to control their activity. Martin et al controlled the oxidation state during the synthesis of cerium oxide nanomaterials by liquid feed flame spray pyrolysis, and then

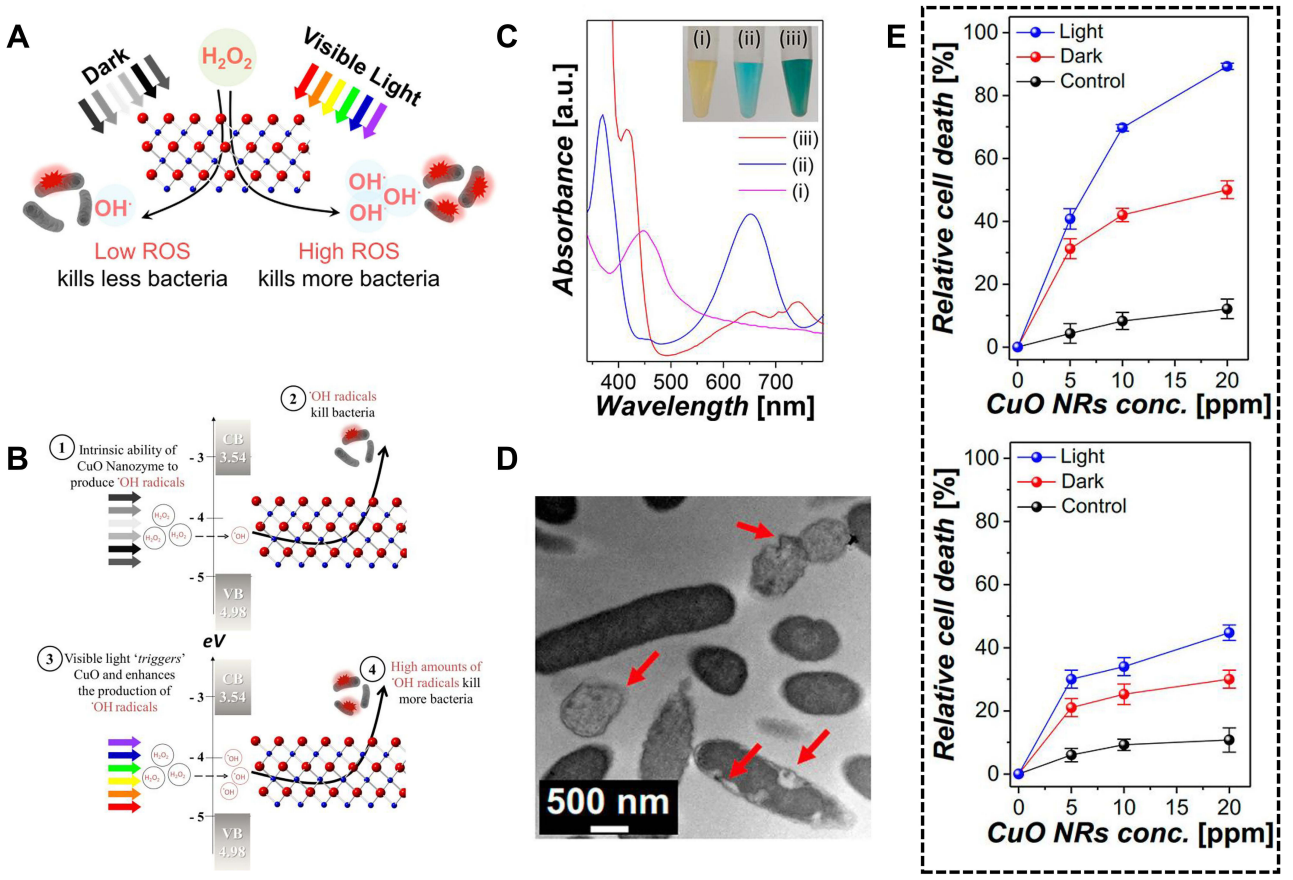

Figure 8 Metal oxide-based nanozymes. (**A**) Schematic diagram of the action of CuO nanorods (NRS) under dark and visible light illumination. (**B**) Mechanism of Nanozyme-catalysed antibacterial performance of CuO NRs. (**C**) UV-visible absorbance spectra of different peroxidase substrates using CuO NRs in the presence of H_2O_2: (i) OPD, (ii) TMB, and (iii) ABTS. Insets show the color of post-reaction solutions. (**D**) CuO NRs + H_2O_2 with visible light irradiation. Red arrows showed physical damage of ROS to bacterial cells. (**E**) Light triggered antibacterial performance of CuO NRs at pH 6.0 and pH 7.0, respectively. Reprinted with permission from Karim MN, Singh M, Weerathung P, et al. Visible-Light-Triggered Reactive-Oxygen-Species-Mediated Antibacterial Activity of Peroxidase-Mimic CuO Nanorods. *ACS Appl. Nano Mater.* 2018;1-(4):1694–1704. Copyright 2018, American Chemical Society.[224]

combined them with bioglass to form CeO_2/bioglass hybrid nanozymes.[225] Attempts were made to control the size, oxidation state, and Ce^{3+}/Ce^{4+} ratio of the nanoparticles, thereby directly changing the catalytic activity of the nanozyme and balancing the antioxidative and antibacterial behavior of the nanozyme. Antibacterial experiments show that CeO_2 rich in Ce^{3+} has higher antibacterial activity than CeO_2 rich in Ce^{4+} in a phosphorus-poor environment, but the opposite is true in a phosphorus-rich environment. Therefore, the property that the ratio of metal oxidation states in metal oxide nanozymes affects the enzymatic activity can be a feasible way to design nanozymes adapted to the wound environment.

A single enzyme-like activity is easily limited to the infectious wound microenvironment, and the multifunctional construction of nanozymes is an effective means to improve antibacterial efficiency. Ma et al prepared dual-enzyme active vanadium oxide nanodots (VO_xNDs) by a one-step ethanol thermal method using VCl_3 as a precursor, which exhibited significant performance against both nonresistant and drug-resistant *S. aureus* and *E. coli*.[226] The POD-like and oxidase-like activities act synergistically in the presence of 50 μM H_2O_2, the former induces the decomposition of external H_2O_2 to generate -OH, and the latter decomposes O_2 to generate superoxide anion radical (O^{2-}). Compared with the H_2O_2 concentration with the same effect, the H_2O_2 concentration catalyzed by VO_xNDs was reduced by four orders of magnitude. The material has excellent biocompatibility and can be applied to the research of infected wounds. In addition, combining multiple therapies is also an important means to prevent drug-resistant bacteria and promote wound healing. For instance, photothermal therapy (PTT) can be used to adjust the temperature, and photodynamic therapy (PDT) can be used to increase ROS generation.[236,237] Zhang et al constructed MoO_3-xND nanozymes by a one-pot hydrothermal method using $MoCl_3$ as a precursor with POD-like catalysis, photodynamic and photothermal adsorption

capabilities.[227] During the antibacterial process, the enzyme-like activity decomposes H_2O_2, the photodynamic effect mediated by negative ions induces the generation of ROS, and the photothermal effect stimulated by photothermal adsorption adjusts the temperature of the material to 50 °C (the optimal enzymatic temperature). Experiments show that MoO_3-xNDs have excellent broad-spectrum antibacterial properties and can play a role in low concentrations of H_2O_2 (100 μM).

Chalcogenide-Based Nanozymes

Nanomaterials constructed from metal sulfides offer considerable advantages in electron optics, physicochemistry, functional structure, and fabrication cost. When an enzyme-like active material is constructed, it can synergistically exert its excellent photodynamic properties, providing a feasible way for efficient and highly safe antibacterial materials.[238] For instance, 2D nanomaterials of metal sulfides are more environmentally and biosafety friendly than metals and metal oxides. Although most forms of sulfur are not toxic, the main safety issues of sulfide 2D nanomaterials focus on sulfide metal dissolution and concomitant heavy metal formation.[239] Therefore, it is necessary to pay attention to the detection of stability and safety in the application research of infected wounds. At present, MOS_2, CuS, and FeS_2 nanomaterials have been widely studied due to their intrinsic enzyme-like catalytic activity.[240,241] This section introduces the antimicrobial wound application of chalcogenide-based nanozymes (Table 3).

Because the enzyme-like catalytic activity of chalcogenide itself is not enough for the antibacterial treatment of wounds, most studies focus on how to improve its catalytic performance or synergize with other means. In situ photodynamic sterilization is an efficient antibacterial method, and the inherent optical properties of metal sulfides can exert excellent photocatalytic or photothermal properties.[242] Yi et al prepared polyethylene glycol functionalized molybdenum disulfide nanoflowers (PEG-MoS_2 NFs) with good biocompatibility by a one-pot hydrothermal method, and the antibacterial mechanism was to utilize POD activity to catalyze the generation of -OH to enhance the effect of PTT.[168] The POD activity decomposes the low concentration of H_2O_2 in the wound to generate -OH, and after the bacterial cell wall is destroyed, the permeability and thermal sensitivity are improved. When combined with the thermal effect of PEG-MoS_2 NFs under 808 nm laser induction, the treatment time is shortened. Compared with the separate use of the two antibacterial methods, the synergistic effect appears to be fast and efficient. Notably, the affinity of PEG-MoS_2 for H_2O_2 was better than that of horseradish peroxidase (HRP). X-ray photoelectron spectroscopy (XPS) and X-ray near-edge absorption spectra spectrum analysis proved that under the high temperature of light induction, nanozymes can promote the oxidation of GSH to destroy the cell defense system. It showed the ability to quickly kill ampicillin-resistant *E. coli* and endospore *B. subtilis*. Similarly, nanocomposites (UNMS NCs) synthesized by MOF-modified MoS_2 by Liao et al also possess the ability to promote GSH oxidation under photothermal conditions.[243] UNMS NCs can synergistically sterilize the three antibacterial abilities of photothermal, photodynamic, and POD activity in the presence of 808 nm near-infrared radiation.

Contrary to the above, Yu et al synthesized a photo catalytically enhanced enzyme-like activity nanomaterial TiO_2NTs@MoS_2.[174] MoS_2 nanoflowers serve as a coating for TiO_2 nanotubes, which have a high specific surface area and excellent electron transport ability,[244] and the layered structure of MoS_2 reduces the bandgap of TiO_2 from 3.2 eV to 2.97 eV, which undoubtedly extends the photoresponse scope. The combination of TiO_2 greatly improves the POD-like activity of MoS_2, and the two components work synergistically to generate abundant ROS for antibacterial treatment under visible light conditions. Meanwhile, bacterial experiments show that TiO_2NTs@MoS_2 has a good broad-spectrum antibacterial effect. Alleviating the hypoxia and inflammatory response of wound tissue plays a crucial role in promoting the healing of infected wounds. Thus, Yang et al immobilized TA-chelated Fe-modified molybdenum disulfide nanosheets (MoS_2@TA/Fe NSs) on multifunctional hydrogels, which exhibited excellent antibacterial properties.[245] This is due to the catalase (CAT) activity brought about by the TA/Fe complex, which can decompose H_2O_2 into O_2 in a neutral pH environment, thereby alleviating tissue hypoxia. The photothermal effect and POD-like activity are derived from MoS_2 NSs, which can catalyze the generation of -OH in an acidic environment. The combination of the two materials enables the hydrogel to acquire antioxidant capacity, and the hydrogel inhibits the release of inflammatory factors, which can effectively remove excess ROS and reactive nitrogen species to alleviate the inflammatory response. The phenolic hydroxyl group retained by TA chelation makes

Table 3 Chalcogenide-Based Nanozymes and Carbon-Based Nanozymes for Improving Bacterial Infectious Wound Healing

Type	Materials	Substrate	Synthesis Procedure	Microbial Type	Antibacterial Mechanism	Antimicrobial Activity	Special Characteristics	Ref.
Chalcogenide-based	nFeS	H_2O_2 (50 mM)	Solvothermal method	*S. mutans, E. coli, P. aeruginosa, S. enteritidis, S. aureus and multidrug-resistant* (MDR) *S. aureus*	Nano-iron sulfides accelerate the release of hydrogen polysulfanes to inhibit enzyme activity, degrade DNA, and accelerate ROS generation	Kill bacteria with 3-log reduction of viability (from 107 to 104 CFU mL^{-1}) within 10 min	The main antibacterial ingredient is polysulfane, H_2O_2 improves release, broad-spectrum antibacterial	[241]
	PEG-MoS_2 NFs	H_2O_2 (100 mM), GSH	Facile one-pot hydrothermal route	*Ampicillin-resistant (Ampr) E. coli, B. subtilis*	Accelerates GSH oxidation to destroy cell protection system, generates ROS	Exposure to the 808 nm laser for 10 min, the bacteria inactivation percentages are 97% (*Ampr E. coli*) and 100% (*B. subtilis*), the statistical loss of GSH after 6h is 73.4%	Synergistic treatment of POD and PTT, low concentration H_2O_2, controllable	[168]
	UNMS NCs	H_2O_2 (140 μM)	1, Ice bath 2, Vacuum drying	*Ampr E. coli*, MRSA	Generates ROS, induce membrane stress and damage cell integrity, accelerate GSH oxidation	The capture efficiency of UNMS NCs was about 22.8% (AREC) and 35.4% (MRSA), in the presence of H_2O_2, reduce bacterial viability: AREC (99.7%), MRSA (96.7%)	Positive charge trapping, POD/PTT/ Photodynamic triple-therapy	[243]
	MoS_2@TA/ Fe	H_2O_2 (100 μM)	Temperature requirement: 220 °C	*S. aureus, E. coli*	Generates ROS, accelerates GSH oxidation, alleviates hypoxia removes excess ROS and reactive nitrogen species (RNS)	Reduction of survival = ~ 100% (*S. aureus* and *E. coli*), SEM: Bacterial surface roughening and wrinkling	Combine PTT, GSH loss, and POD/CAT-like activity, anti-inflammatory	[245]
	R-CMs	H_2O_2 (100 μM)	One-pot hydrothermal method	*S. aureus, E. coli*	Surface-adhering bacteria, generates ROS	SEM: Bacterial surface roughening and wrinkling	Rough surface increases the adhesion to bacteria, POD-like activity, PTT	[246]

Carbon-based	C-dots	O_2	1, Heating 2, Column chromatography	*E. coli, S. enteritidis*	Generates ROS	Inhibition efficiency: 92% (*E. coli*), 86% (*S. enteritidis*)	Synthetic controllability, excellent water solubility, PDT	[260]
	SAF NCs	H_2O_2 (100 × 10−6 M)	"Encapsulated-pyrolysis" strategy	*S. aureus, E. coli*	Generates ROS, thermal effect	MIC = 62.5 μg mL−1 (SAF NCs)	POD-like activity and PTT synergy	[263]
	N-SCSs	H_2O_2 (10 mM)	Pyrolysis of colloidal silica/ polyaniline assemblies	*S. aureus, E. coli*, MDR *S. aureus*	Generates ROS, disrupted cell membranes	SEM: Bacterial surface roughening and wrinkling	Larger surface area, good bacterial adsorption, photoexcitation, lower dose of H_2O_2, multienzyme activity	[262]
	o-CNTs	H_2O_2 (10 mM)	One-pot nitric-acid-assisted reflux method	*Ampr E. coli*, MRSA	"Competitive inhibition" effect of oxygen-containing groups weakens non-catalytic sites, generates ROS	SEM: Bacterial surface roughening and wrinkling	Synthetic adjustable, POD-like activity, competitive inhibitory effect	[268]
	GQD	H_2O_2 (1 mM: *E. coli*, 10 mM: *S. aureus*)	Modified Hummers method	*S. aureus, E. coli*	Generates ROS, oxidative lysis of biofilms	Inhibition efficiency = ~ 90%, SEM: Bacterial surface roughening and wrinkling	Lower dose of H_2O_2, best catalytic performance = 4 (pH), applied to antibacterial band-aid	[272]

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the hydrogel highly viscous, which can fill the wound defect and make close contact with it. Simultaneously, it can also promote the oxidation of GSH, and experiments show that the material has excellent clinical application value.

The roughness of the material surface can improve the adhesion of bacteria, thereby improving the antibacterial efficiency. Cao et al proposed a strategy to construct rough surfaces to expose more active sites and adhere to bacteria.[246] MoS_2 and Cu NWs were composited to construct nanozymes to destroy bacteria by enhancing the affinity for the cell wall and exposing the active site to increase the amount of -OH generation. Similar to the mechanism of action, Wang et al used an ultrasonic exfoliation strategy to fabricate defect-rich N-doped transition metal dichalcogenide nanosheets.[247] Both N-MoS_2 and N-WS_2 NSs exhibited enhanced enzyme-like activity in experiments.

Although natural organosulfur compounds have been used for the prevention of bacterial diseases for a long time, their poor water solubility and difficulty in mass production limit their biomedical applications.[248] Xu et al converted natural organosulfur compounds to inorganic sulfur compounds by a solvothermal method (Figure 9A), and the obtained nanomaterial (nFeS) has more than 500 times higher antibacterial ability than garlic-derived organosulfur compounds.[241] Synthetic nanozymes exhibit universal antimicrobial activity against Gram-positive and Gram-negative bacteria. The POD-like and CAT-like activities of nFeS are better than those of Fe_3O_4. The antibacterial activity comes from the rapid oxidation of the nFeS surface under the condition of H_2O_2, which accelerates the release of free sulfide (hydropolysulfane). In addition, CuS is also a common material for the sulfide construction of nanozymes. Nain et al prepared copper sulfide nanocrystals (BSA-CuS NCs) by heating an alkaline solution containing Cu^{2+} and bovine serum albumin (BSA), a facile method that does not require the addition of an additional sulfur source (Figure 9B).[249] BSA-CuS NCs possess abundant surface-active sites and can catalyze H_2O_2 in situ to generate $^1O_2$ and -OH. Moreover, under near infrared (NIR) laser irradiation, BSA-CuS NCs could eradicate 99% of bacteria in MASA-infected wounds within one minute, a more than 60-fold enhanced antibacterial response compared to nonirradiated conditions. Good biocompatibility is also one of the basic elements that BSA-CuS NCs are expected to be used in the clinic. In summary, nanozyme treatment platforms based on metal sulfides have many advantages. In addition to improving enzyme-like activity, the combination of other efficient antibacterial methods also brings more possibilities for wound treatment.[250]

Carbon-Based Nanozymes

Carbon-based nanomaterials, including carbon dots (CDs), carbon nanotubes, carbon nitride, fullerenes, and graphene, have been widely reported for nanozyme catalytic applications.[251,252] Due to their good biocompatibility, catalytic

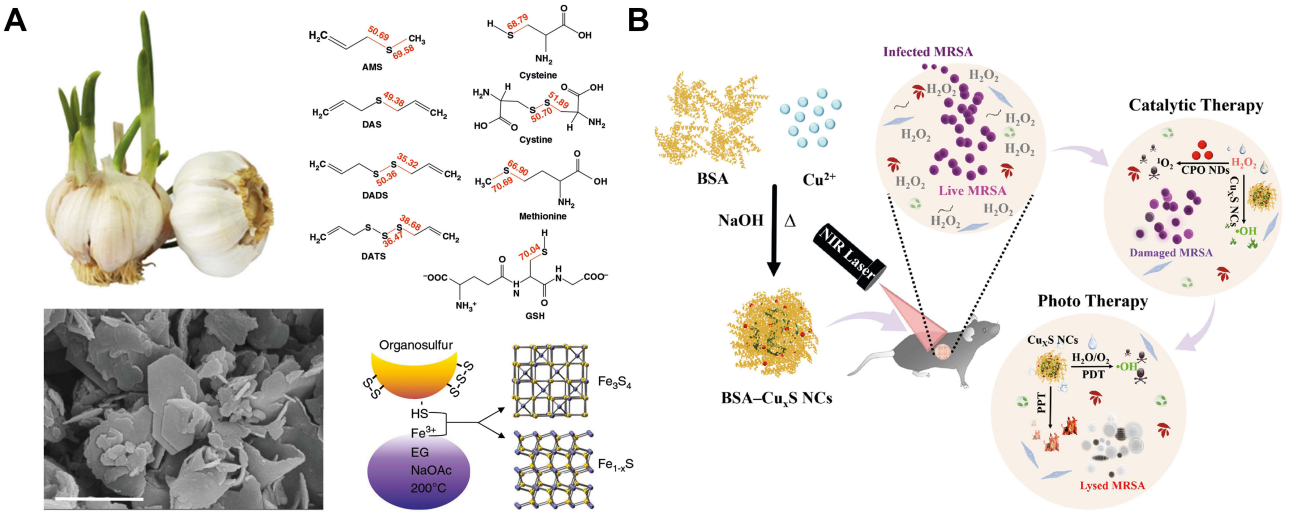

Figure 9 Chalcogenide-based nanozymes. (**A**) Converting organosulfur compounds into nano-iron sulfide (nFeS) by solvothermal synthesis. Reprinted with permission from Xu Z, Qiu Z, Liu Q, et al. Converting organosulfur compounds to inorganic polysulfides against resistant bacterial infections. *Nat. Commun.* 2018;9(1):3713. Copyright 2018, Open Access.[241] (**B**) Schematic representation of the synthesis of the BSA−Cu_xS NCs and their application for the treatment of bacterial wound infection coupled with NIR laser irradiation. Reprinted with permission from Nain A, Wei SC, Lin YF, et al. Copper Sulfide Nanoassemblies for Catalytic and Photoresponsive Eradication of Bacteria from Infected Wounds. *ACS Appl. Mater. Interfaces.* 2021;13(7):7865–7878. Copyright 2021, American Chemical Society.[249]

properties, and surface functionalization, carbon materials often exhibit intrinsic POD, CAT, hydrolase, and superoxide dismutase activities. The theoretical calculations and experiments helped to reveal that the enzymatic activity of carbon-based materials is derived from the abundant oxygen-containing functional groups on the surface, which has potential application value in the prevention and treatment of infected wounds[253] (Table 3).

CDs are a new type of carbon-based zero-dimensional material with excellent optical properties, stability, and biocompatibility, that have attracted much attention in the development of light-induced sterilization functions.[254,255] Gao et al used S. cerevisiae as the precursor-derived fluorescent CDs.[256] Under visible light, photogenerated electrons reacted with oxygen to form superoxide ions, and the bactericidal efficiency against *E. coli* was close to 100% at 120 min. The prepared CD surface is highly negatively charged, capable of selectively staining dead *E. coli* (positively charged) at different excitation wavelengths, and can also be used as a dye for assessing bacterial viability. In addition, the group also prepared novel CDs by a one-pot hydrothermal method using ampicillin as a precursor to generate ROS under visible light irradiation to disrupt the integrity of the cell membrane.[257] Low concentrations (0.7 mg/mL) can also inhibit Listeria monocytogenes and *S. aureus*, which are expected to be used in clinical research in infected wounds.

The properties of CDs allow modification of functional groups and doping of different elements.[258,259] Zhang et al synthesized a series of nitrogen-doped CDs related to phosphorescence quantum yield and photooxidative activity, showing higher activity than other carbon nanomaterials, mimicking oxidase production in seconds $^1O_2$ with excellent photosensitivity.[260] Under light irradiation conditions, the inhibition efficiency against *E. coli* and *Salmonella enteritidis* (*S. enteritidis*) was 92% and 86%, respectively. Tammina et al used glucosamine as a precursor to synthesize carbon dots (N, Zn-CDs) doped with N and Zn by microwave digestion, which could not only generate ROS under light conditions to kill *E. coli* and *S. aureus*, but also inhibit *E. coli* under dark conditions.[261] In addition, there are nitrogen-doped amorphous carbons (SAF NCs) and nitrogen-doped sponge-like carbon spheres (N-SCS) on bacterial infection, both of which are effective sterilization through POD-like activity synergistic with light effect.[262,263] The anti-infective strategy of synergistic photothermal/photocatalysis with enzymatic activity is currently the main direction in the development of carbon-based nanozymes.[264,265]

The low toxicity of carbon nanotubes (CNTs) makes them exhibit excellent potential in the biomedical field. Using the "competitive inhibition" effect, weakening the noncatalytic sites, and appropriately oxidizing CNTs to enhance the catalytic efficiency are feasible strategies.[266,267] Using pristine carbon nanotubes (p-CNTs) as precursors, Wang et al prepared a series of oxide-rich carbon nanotubes (o-CNTs) by one-pot oxidative reflux method (Figure 10).[268] Through experiments and theoretical calculations, it is found that -OH and -COOH on the surface of o-CNTs act as competing sites and inhibit catalysis, and carbonyl groups act as active sites. Due to the inherent hydrogen bonding interaction and high negative charge, -COOH exhibits stronger inhibitory ability. Therefore, by further preparing 2-bromo-1-acetophenone-modified o-CNTs (o-CNTs-BrPE), after weakening the effect of competitive inhibition, o-CNTs-BrPE in a series of o-CNTs shows the best POD activity. The results of antibacterial experiments showed that o-CNTs not only enhanced the efficiency of ROS generation, but also effectively reduced bacterial-induced purulent inflammation and edema.

Graphene-based nanozymes possess POD-like activity, and their antibacterial properties mainly depend on the number of layers, morphology, size, dispersibility, and electron transport capacity.[269] Notably, studies have shown that graphene quantum dots (GQDs) are less toxic than graphene oxide (GO).[270,271] Sun et al constructed an antibacterial system by combining GQDs and low-concentration H_2O_2.[272] During the reaction, the POD-like activity of GQDs converts H_2O_2 into -OH, which improves the antibacterial properties and avoids unnecessary damage caused by the use of high concentrations of H_2O_2. The bacterial experiments showed that the system could significantly inhibit *E. coli* and *S. aureus*. CS functionalization of graphene quantum dots enables synergistic sterilization under light irradiation via multivalent interactions and photothermal, photodynamic, and chemotherapy effects.[273] Furthermore, graphene quantum dots (C60-GQDs) prepared by breaking C60 cages may inherit a nonzero Gaussian curvature, which plays a significant role in association with proteins on bacterial surfaces.[274] Considering reducing toxicity as much as possible, Lin et al prepared tetraaminophthalocyanine-modified graphene oxide nanocomposites by noncovalent functionalization, which can inactivate bacteria at extremely low doses.[275] First, the phthalocyanine photosensitizer generates ROS under 680 nm light irradiation. The second is the physical cleavage of the cell membrane by graphene oxide. Eventually extensive destruction of bacterial morphology occurs, resulting in death.

MOF-Based Nanozymes

MOFs are highly permeable and crystalline porous coordination polymers formed by assembling organic ligands and metal ions/clusters using the principles of coordination chemistry.[276] MOFs with enzyme-like activity can be obtained by designing organic ligands and metal nodes.[277] As an emerging material, MOFs have emerged as substitutes for enzymes due to their broad coordination capabilities, tunable porosity, mesoporous structure, and customizable cavities and channels.[278,279] In recent years, applications in the fields of gas adsorption/separation, sensing, biomedicine, and catalysis have attracted much attention.[280–284] Compared with traditional antibacterial agents, using MOFs as materials has many advantages. For instance, some metal ions (such as iron ions, gold ions, silver ions, copper ions, zinc ions, and cobalt ions) and nanozymes formed by porphyrin/imidazole can slowly and continuously release toxic metal ions and ROS according to specific conditions (pH, light, temperature, etc.).[285–288] Easily modifiable organic components are beneficial to endow photocatalytic properties and enhance antibacterial ability.[289–291] The high porosity and high specific surface area not only facilitate the surface modification of the material, but also realize the high loading of the contents, and even obtains multieffect antibacterial properties.[292,293] The special structure of MOFs provides a feasible route for the design of more antibacterial agents.[294] In addition, good biocompatibility, dispersibility, and biodegradability are essential for in vivo studies. Numerous advantages have attracted much attention for the design of nanozymes based on MOFs, whose precise framework properties hold a bright future in the treatment of infected wounds[295] (Table 4).

Natural Enzyme-MOF Composite Nanozymes

The high porosity and surface area of MOFs are good platforms for directly doping natural enzymes. Generally, through the methods of encapsulation, pore penetration, chemical bond connection, and surface adsorption, it can act as an exoskeleton to wrap the natural enzyme and protect it from external stimuli, so the activity of the loaded enzyme can be directly obtained.[296–298] However, the pH of the optimal reaction environment for nanozymes is generally 3–4, and it is often difficult to optimize performance in the microenvironment of infected wounds, which severely limits their application.[299] In general, 2D MOFs have better catalytic activity than 3D MOFs due to their higher specific surface

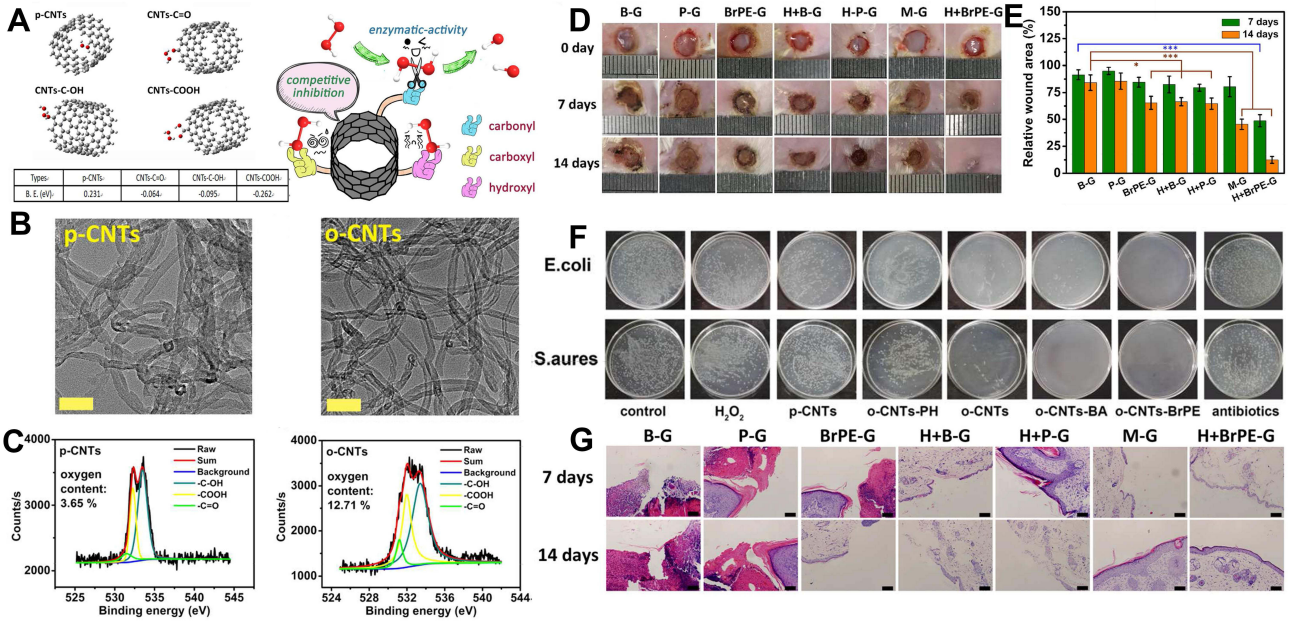

Figure 10 Carbon-based nanozymes. (**A**) Binding between H_2O_2 molecule and CNTs. (**B**) TEM images of p-CNTs and o-CNTs. Scale bars: 50 nm. (**C**) O1s XPS spectra of p-CNTs and o-CNTs. (**D**) Time-dependent photographs of wound healing on mouse backs upon different treatments. (**E**) Quantitative evaluation of wound healing by measuring wound areas. Error bars represent standard deviation from the mean (n = 3). Asterisks indicate statistically significant differences (*P < 0.05, **P < 0.01, ***P < 0.001). (**F**) Digital images of the corresponding colonies showed the influence of o-CNTs-based enzymatic activity on the growth of *E. coli* and *S. aureus*. (**G**) Histological analysis of skin tissues harvested from mice 7 and 14 days post-wounding. Scale bars: 50 μm. Reprinted with permission from Wang H, Li P, Yu D, et al. Unraveling the Enzymatic Activity of Oxygenated Carbon Nanotubes and Their Application in the Treatment of Bacterial Infections. *Nano letters*. 2018;18(6):3344–3351. Copyright 2018, American Chemical Society.[268]

Table 4 MOF-Based Nanozymes for Improving Bacterial Infectious Wound Healing

Type	Nanozymes	Substrate	Synthesis Procedure	Microbial Type	Antibacterial Mechanism	Antimicrobial Activity	Special Characteristics	Ref.
Natural enzyme-MOF	2D Cu-TCPP (Fe)	Glucose, H_2O_2	Under mild magnetic stirring	*S. aureus*, *E. coli*	Converts glucose to gluconic acid to stimulate POD-like activity, generates ROS	In the presence of glucose, reduce bacterial viability: *S. aureus* (90%), *E. coli* (88%), SEM: Bacterial surface roughening and wrinkling	Self-activating cascade system, pH adjustment (3–4)	[172]
	MIL@GOx-MIL NRs	Glucose, O_2, H_2O_2	Water bath	MRSA	Generates ROS, oxidizes glucose to cut off cellular energy supply, inhibits biofilm	Inhibition efficiency>99.9%	Self-activating cascade system, optimum pH = 4 (under 37 °C),	[299]
	GOx-Hb MRs	Glucose (12.5 mM), H_2O_2	Co-precipitation process	MRSA	Generates ROS, inhibits biofilm	K_m and V_{max} of GOx-Hb MRs were 2.60 mM and 2.94 × 10–8 M·s−1, respectively	Diabetic wound, action pH = 5	[300]
	l-Arg/GOx@CuBDC	Glucose (10 mM), H_2O_2	Package	*S. aureus*, *E. coli*	Generates ROS and RNS, Fenton-like effect, decomposition membrane structure	Bacterial inactivation≥97% (38 μg mL^{-1} for *E. coli* and 3.8 μg mL−1 for *S. aureus*), SEM: Bacterial surface roughening and wrinkling	Double-cascade reaction, adhesion properties, multienzyme activity	[305]
Metal-MOF	UsAuNPs/MOFs	H_2O_2 (100 × 10−6 M)	1, Hydrothermal 2, Ultrasonic exfoliation 3, In situ reduction	*S. aureus*, *E. coli*	Generates ROS	In the presence of H_2O_2, reduce bacterial viability: *S. aureus* (82%), *E. coli* (90%), SEM: Bacterial surface roughening and wrinkling	Lower dose of H_2O_2, POD-like activity, steady	[310]
	AuNPs/Cu-MOFNs	H_2O_2	AuNPs modification	*S. aureus*	Hot electrons on AuNPs under LSPR excitation activate H_2O_2 molecules into transition states	Antibacterial effect: close to vancomycin in eight days, SEM: Bacterial surface roughening and wrinkling	Localized surface plasmon resonance, photoexcitation, POD-like activity, the optimum temperature and pH are 60 °C and 6, respectively	[29]
	$MOF_{-2.5Au-Ce}$	H_2O_2 (0.5 mM), eDNA	1, One-pot hydrothermal method 2, Activated carboxylic acid group	*S. aureus*	Hydrolyzed eDNA, generates ROS	Complete DNA degradation: 0.5 mg mL^{-1}, 3D Confocal Laser Scanning Microscopy: in the Presence of H_2O_2, thinner biofilms (<5 μM), SEM: Bacterial surface roughening and wrinkling	Synergy of double enzyme activity, lower dose of H_2O_2	[178]

(*Continued*)

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Table 4 (Continued).

Type	Nanozymes	Substrate	Synthesis Procedure	Microbial Type	Antibacterial Mechanism	Antimicrobial Activity	Special Characteristics	Ref.
Derivatives of MOFs	PMCS	H_2O_2 ((100 μM)	Mesoporous silica protected pyrolysis strategy	*P. aeruginosa*	Generates ROS	Antibacterial effect: 99.87%	Surface defects, POD-like activity	[25]
	FeN_5SA/CNF	O_2	1, Package 2, One-step hydrothermal synthesis	*S. aureus, E. coli*	Generates ROS	The catalytic rate constant of FeN_5SA/CNF is 70 times greater than that of the commercial Pt/C	Good stability under strong acid and alkali, OXD-like activity	[322]
	PEG@Zn/Pt-CN	H_2O_2 (100 μM)	1, Solution coordination 2, Pyrolysis 3, Polyethylene glycol coating treatment	*S. aureus, E. coli*	Generates ROS, physical cleavage disrupts cell membranes, heat destroys cells	Antibacterial effect: 98.74% (*E. coli*) and 99.63% (*S. aureus*), SEM: Bacterial surface roughening and wrinkling	POD and PTT synergy, optimum pH = 3, photothermal conversion effect = 48%	[325]
Others	V-POD-M	H_2O_2 (0.1 × 10−3 M)	Single-channel oriented assembly method	*S. aureus, E. coli*	Virus-like spikes disrupt cell membranes, generates ROS, oxidized GSH	MIC ≈ 16 μg mL−1 MBC = 16 μg mL−1, antibacterial effect: close to vancomycin in fifteen days SEM: Bacterial surface roughening and wrinkling	Mesoporous silica-based spike structures trap bacteria, POD-like activity	[315]
	PEG@Zr-Fc MOF	H_2O_2 (10 × 10−4 M)	1, One-pot hydrothermal method 2, Covalent cross-linking	*S. aureus, E. coli*	Fenton reaction, generates ROS, photothermal effect	Bacterial inactivation: 91.4% (*E. coli*) and 94.7% (*S. aureus*), extinction coefficient at 808nm: 4.60 Lg−1cm−1, SEM: Bacterial surface roughening and wrinkling	POD and PTT synergy, best temperature: 35 °C	[312]

area. Liu et al encapsulated GOx in an ultrathin 2D MOF (2D Cu-TCPP(Fe)) to form a self-activating cascade employing physical adsorption.[172] In the wound environment, GOx was used to convert glucose into gluconic acid and H_2O_2 to reduce the pH microenvironment, and coupled with the POD-like activity of Cu-TCPP(Fe), H_2O_2 was catalyzed to generate highly toxic -OH. While killing bacteria in situ, avoiding the side effects caused by the use of high concentrations of H_2O_2, reduces the pH value, greatly improves the catalytic activity of nanozymes, and forms a virtuous cycle. Fluorescence experiments further confirmed the significant enhancement of the catalytic activity of Cu-TCPP(Fe) by gluconic acid, which also has better stability than free GOx. Similarly, Li et al used a coprecipitation method to form a multilayer film on the surface of $MnCO_3$ with GOx and Hb, and then removed $MnCO_3$ by slight crosslinking to obtain enzymatic cascade microreactors (GOx-Hb MRs).[300] The Michaelis-Menten constant (Km) was 2.60 mM according to by enzyme kinetics theory and method analysis. Compared with other GOx-containing cascade systems,[301,302] the Km value of GOx-Hb MRs is lower, which means a better affinity for glucose. Interestingly, GOx-Hb MRs can function in milder acidic environments. Experiments show that pH 5 is not optimal, but the cascade reaction activity remains at approximately 80% of the highest activity, and the intensity of -OH produced is significantly higher than that at pH = 7.4. At a lower concentration (2.4 μg/mL), it can effectively kill MRSA and inhibit the formation of biofilms. It is believed that the high antibacterial efficiency may come from the following two aspects. On the one hand, when bacterial infection occurs and produces mild acidic conditions, GOx-Hb MRs can efficiently catalyze the production of -OH. On the other hand, GOx consumes glucose to reduce the energy supply of bacteria.

Multienzyme nanoassembly is one of the future directions for carrying multiple functions.[303] Inspired by this, Chen et al published the first report of an enzymatic cross-linking reaction for the production of antimicrobial coatings.[304] Using HRP and GOx as catalysts, dendritic polyglycerol (dPG) was cross-linked to the glass surface to form an antibacterial coating l-Arg/GOx@CuBDC. Under extremely low bacterial concentrations (38 μg/L *E. coli*, 3.8 μg/L *S. aureus*), the material can still have an excellent inactivation effect (≥97%). Even with a high bacterial load (OD 540 = 1.0), cell viability can be reduced by more than 40%. Meanwhile, dPG, as a biologically inert polyhydroxy polymer, can reduce bacterial adhesion on the surface of modified objects.[305] The vivo biosafety experiments in mice proved that l-Arg/GOx@CuBDC has low toxicity and can be used in clinical research. The design of these enzymatic-MOFs, especially for targeted therapies, mainly considers the pore size of the MOFs, which affects diffusion and selectivity.[306] Therefore, in addition to maximizing catalytic performance, a fine balance should be considered in the selection of base materials for catalytic systems. In general, the combination of enzymes and MOFs can not only maintain the activity of the enzymes, but also provide high tolerance, enhanced stability under extreme conditions, and reusability, which is an ideal platform for the construction of nanozyme antibacterial agents.[307]

Metal-MOF Composite Nanozymes

Metal-based nanozymes have superior catalytic activity, but their application is limited by the aggregation phenomenon in the reaction process caused by biosafety and high surface energy.[187] Metals commonly used in the development of MOF antibacterial agents include Cu, Ag, and Ce.[308,309] Hu et al grew ultrasmall gold nanoparticles (UsAuNPs) on ultrathin 2D MOFs by in-situ reduction to prepare nanozyme UsAuNPs/MOFs.[310] Although UsAuNPs have a large surface energy, small diameter, and abundant active sites, they are prone to aggregation, so MOFs can provide an excellent reaction platform for them. UsAuNPs/MOFs have good stability, which can reduce the mass transfer resistance and improve the reaction speed, and play a role in cooperation with Au nanoparticles. The experimental results show that UsAuNPs/MOFs can catalyze the generation of -OH through POD-like activity at a safe dose of H_2O_2 (100×10^{-6} M), which can effectively sterilize *E. coli* and *S. aureus*. Metal nanoparticle surfaces have unique localized surface plasmon resonance (LSPR) properties. Yang et al took advantage of the LSPR excitation of AuNPs to enhance the intrinsic POD-like activity of copper metal-organic frameworks (Cu-MOFNs).[29] The prepared AuNPs/Cu-MOFN composite nanozyme effectively promotes the transfer of hot electrons due to the LSPR excitation and matching energy levels, further cleaving the chemical bonds of the substrate, and the reaction kinetics are 1.6 times faster than those under dark excitation. Thus, the enzyme-like activity of the composite material is greatly enhanced.

The use of Ag ions must carefully consider biological safety, and the combination with enzyme-like materials can reduce toxicity hazards to a certain extent. Zhang et al implanted Ag ions into NH_2-MIL-88B(Fe) material with POD-like

activity to construct NH_2-MIL-88B(Fe)-Ag.[41] In the reaction process, the synthesized material can effectively catalyze H_2O_2 to generate -OH, and release Ag ions at the same time, avoiding the damage caused by the use of high-concentration Ag ions and H_2O_2. To enable ROS catalyzed by nanozymes to efficiently sterilize, targeting the destruction of biofilms is an effective antibacterial strategy. Liu et al assembled the surface of a Ce nitrilotriacetic acid (NTA) complex and Au-doped MOF MIL-88B(Fe) by a one-pot hydrothermal method to obtain nanozyme MOF-Au-Ce.[178] The Ce center excites the phosphodiester bond after removing the electron from the phosphate, which leads to nucleophilic attack by -OH, and finally cleaves the P-O bond of the biofilm DNA. The introduction of Au enhanced the POD-like activity of the pristine MOFs. Different Au doping results in different changes in catalytic ability, among which MOF-2.5Au-Ce has the best catalytic ability. The ROS catalyzed by MOFs synergistically inhibited *S. aureus* by hydrolyzing the biofilm of eDNA by the Ce complex; while attenuating the inflammatory response. Although the current research on antibacterial nanozymes of metal-MOFs is not deep enough, it is expected to play a potential role in the application of infected wounds.

Other Composite Nanozymes

Targeting is an effective strategy for high-efficiency antibacterial activity. Metabolic biomarker technology can attach chemical functional groups to the surface of bacteria.[311] Mao et al loaded the in vivo metabolic marker molecule 3-azido-D-alanine (D-AzAla) onto MIL-100(Fe)NPs by coupling MOF and metabolic technology.[295] During the reaction, the iron (III) metal center of MIL-100(Fe) can catalyze H_2O_2. The dissociation of MIL-100 (Fe) occurs after the coordination cleavage of the melamine acid ligand with iron (III), thereby releasing D-AzAla. Using this principle of action, the material can specifically release D-AzAla in wounds with excessive secretion of H_2O_2, and then selectively integrate into the cell wall of bacteria to achieve metabolic labeling of bacteria in vivo. Animal and fluorescence experiments demonstrate that, with the assistance of MOFs, the synthetic material enables precise bacterial detection and PDT.

The ease of modification of MOF materials facilitates the synthesis of multi-therapeutic-conjugated nanozymes. Wang et al constructed a photothermal-nanozyme-hydrogel synergistic antibacterial platform.[312] First, 2D zirconium-ferrocene metal-organic framework nanosheets (Zr-Fc MOF) with enzymatic activity and photothermal properties were synthesized by a one-pot hydrothermal method, and then polyethylene glycol dicarboxylic acid (COOH-PEG-COOH) was used to functionalize the 2D Zr-Fc MOFs and then intercalate them into carrageenan-based hydrogels to form PEG@Zr-Fc MOF hydrogels. The intercalation of nanozymes modifies the pores of the carbon skeleton supported by carrageenan, and the encapsulation of hydrocolloids avoids the release of metal heteroatoms during the reaction process and reduces biological toxicity. In addition, the photothermal effect of Zr-Fc MOF enhanced the efficiency of catalyzing H_2O_2 to generate -OH, and wound infection model experiments also confirmed that the hydrogel can efficiently kill *E. coli* and *S. aureus*, and promote rapid tissue recovery. This strategy overcomes the dilemma of single PTT and single MOF catalysis limited by insufficient activity, light irradiation time, wound microenvironment, etc.[313]

Viral phages have spiny tails that enable them to trap and kill bacteria.[314] If artificial nanozymes mimic this behavior, they need to satisfy two structures, mesoporous and pointed; the former is used to load and release bactericidal substances, and the latter is used to trap bacteria. Inspired by this, Ye et al developed a peroxidase mimetic (V-POD-M) with a virus-like structure based on Cu-MOF.[315] The POD-M cascade catalytic center derived from MOF catalyzes the generation of -OH from H_2O_2 by simulating POD-like activity.[316] Density functional theory (DFT) calculation results show that MOF-supported MoO_3 acts as a peroxy complex intermediate, which promotes the Fenton-like catalytic activity of Cu (II) and reduces the free energy of catalyzing H_2O_2, thereby enhancing the productivity of ROS. In addition, the synergistic mesoporous silicon-based spiky structure has a nearly 100% inactivation effect at extremely low concentrations (16 μg/mL V-POD-M, 0.1×10^{-3} M H_2O_2), similar to the antibacterial effect of vancomycin. Biomimetic spiked structures have a promising future in the development of nonantibiotic antibacterial agents. Even for MOF materials with many properties, there are inevitably some inherent defects in exploration. Therefore, MOFs are formed into composites with other components to compensate for defects or even to obtain additional properties for synergistic antimicrobial activity.[317] In the future trend of multifunctional and intelligent treatment modes, MOF composites have bright prospects.

Derivatives of MOFs

Although nanozymes have catalytic activity comparable to that of natural enzymes, most nanozymes still have limited solubility and intrinsic catalytic activity under physiological conditions. For instance, metal oxide-based (Fe_3O_4, V_2O_5, CeO_2) nanozymes have a large number of internal atoms that are inert or cause unnecessary side reactions. Due to the versatility and postsynthesis modifiability of organic ligands and metal node linkages, MOF derivatives are one of the ideal alternatives to solve these difficulties.[182] The porous materials derived after calcination and their uniformly distributed atomic doping not only retain the excellent mesoporous properties of the precursor MOFs, but also the changes in structure and element valence further enhance the catalytic activity.[318]

In the research of antibacterial agents, single-atom nanozymes have become the research frontier because of their abundant active sites and high atom utilization, coupled with a clear definition of the coordination environment and electronic structure, so it is easier to analyze the catalytic mechanism and understand the structural properties.[319–321] Xu et al reported Zn-containing porphyrin-like structure carbon nanospheres (PMCS) derived from zeolite imidazolate framework 8 (ZIF-8) MOFs as precursors through a protective pyrolysis strategy (Figure 11A–D),[25] which not only have photosensitive properties, but also significant POD-like activity. The researchers believe that the coordinative unsaturation of the Zn-N_4 site is the reason for the high POD activity, which catalyzes the decomposition of H_2O_2 to generate -OH for sterilization. In the mouse wound model, the inhibition rate of *P. aeruginosa* was as high as 99.87%, which significantly promoted wound healing. In addition, Huang et al formed FeN_5SA/CNF single-atom nanozymes after pyrolysis of MOF-encapsulated iron phthalocyanine (FePc) (FePc@Zn-MOF) under N_2 at 900 °C.[322] During the pyrolysis process, the secondary building blocks of nitrogen-containing organic linkers are transformed into pyridine-

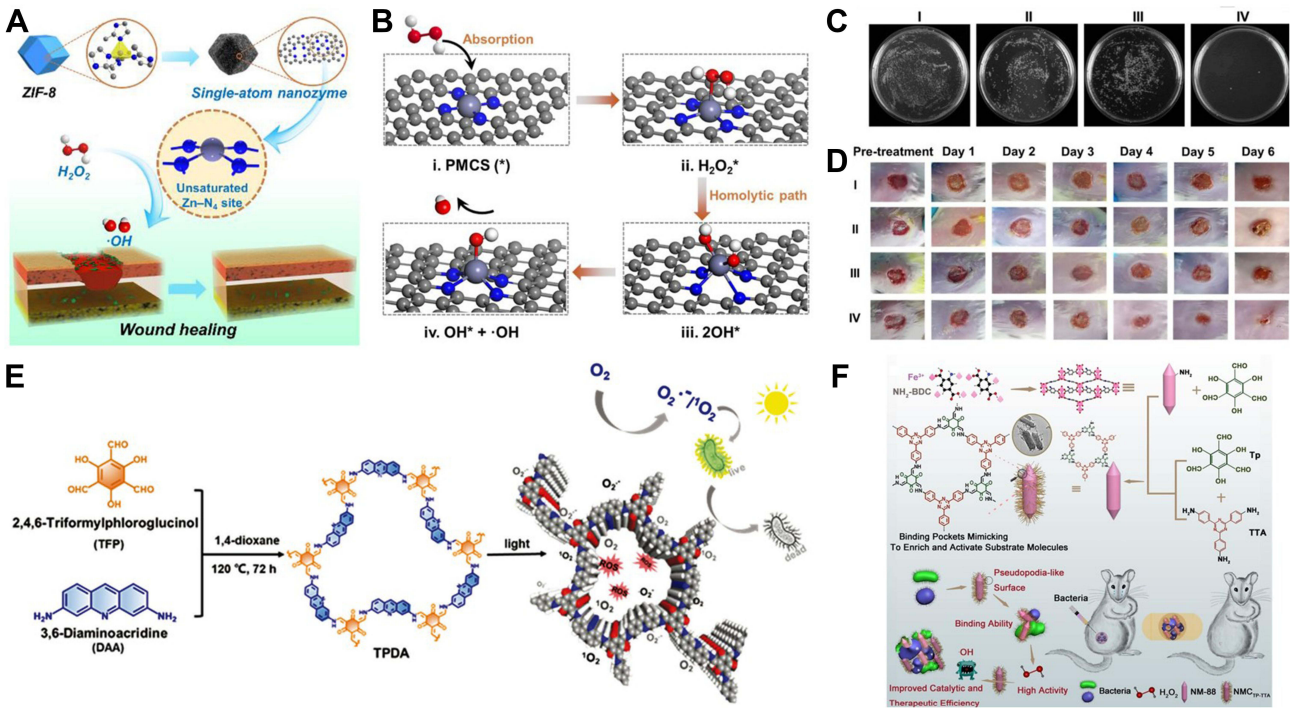

Figure 11 MOF-based nanozymes and COF-based nanozymes. (**A**) Schematic diagram of PMCs promoting wound healing. (**B**) Schematic diagram of catalytic mechanism. *Represents the active site on the PMCS (eg, H_2O_2 *Indicates that the H_2O_2 molecule binds to the Zn-N_4 active site on the PMCS). (**C**) Photographs of bacterial colonies formed by *P. aeruginosa* after exposed to (I) NaAc buffer, (II) NaAc buffer + H_2O_2, (III) PMCS and (IV) PMCS + H_2O_2, the final working concentrations for NaAc buffer, H_2O_2 and PMCS are 0.1 M, 100 μM and 100 μg mL^{-1}, respectively. (**D**) Photographs of *P. aeruginosa* infected wound treated with (I)-(IV) at different days. Reprinted with permission from Wiley, Xu B, Wang H, Wang W, et al. A Single-Atom Nanozyme for Wound Disinfection Applications. *Angew Chem Int Ed Engl.* 2019;58(15):4911–4916. © 2019 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.[25] (**E**) Schematic diagram of TPDA preparation and the mechanism of ROS generation. Reprinted with permission from Wiley, Zhang C, Guo J, Zou X, et al. Acridine-Based Covalent Organic Framework Photosensitizer with Broad-Spectrum Light Absorption for Antibacterial Photocatalytic Therapy. *Adv. Healthc. Mater.* 2021;10(19):e2100775. © 2021 Wiley-VCH GmbH.[361] (**F**) The synthesis of NMCTp-TTA hybrid nanozyme and their use for bacterial inhibition. Reprinted with permission from Wiley, Zhang L, Liu Z, Deng Q, et al. Nature-Inspired Construction of MOF@COF Nanozyme with Active Sites in Tailored Microenvironment and Pseudopodia-Like Surface for Enhanced Bacterial Inhibition. *Angew Chem Int Ed Engl.* 2021;60(7):3469–3474. © 2020 Wiley-VCH GmbH.[369]

type N carbon nanoframes and Zn ions after carbonization. The reconstitution sites within the confinement of the pyridine N substrate and the FeN_4 carbon nanoframe coordinate with each other to form FeN_5/C sites with better thermal stability. Through DFT calculations, the high oxidase catalytic activity is derived from the central metal atom and spatial configuration, and its active site is very similar to the heme coordinated by the axial ligands of natural oxidoreductases. Interestingly, due to the axial N coordination enhancing the catalytic activity, the enzymatic activity of FeN_5SA/CNF is 17 times higher than that of square-planar Fe-N_4. Despite the numerous advantages of single-atom nanozymes, the active site relies on a larger support. Therefore, it is easily cleared by the immune system and reduces the antibacterial efficiency in the body. Therefore, adjusting the size of the support and modifying the functional groups is a feasible way to achieve high antibacterial activity and excellent biocompatibility.[323]

As mimic enzymes, metal nanomaterials have unpredictable and nonuniform distributions and uncontrollable aggregation phenomena. When the size of metal atoms in M-N-C nanozymes increases to be similar to that of nanoparticles, MOFs are easily converted into porous carbon after calcination, and the derived metal/carbon nanozymes can prevent the aggregation of isolated MNPs and enhance the catalytic ability.[324] Wang et al constructed a hybrid nanozyme PEG@Zn/Pt-CN with photothermal, "nanoknife" and enzymatic catalysis through an MOF-derived strategy.[325] By effectively preventing the aggregation of Pt nanoparticles, the kinetic mass transfer resistance of the reaction process and the inhibition of photoelectron-hole complexation were reduced, which ultimately led to the improvement of the peroxidase-like catalytic and photothermal conversion performance of PEG@Zn/Pt-CN. The experimental results show that under the condition of a low concentration of H_2O_2, PEG@Zn/Pt-CN can generate a large amount of -OH and increase the permeability of the biofilm. In addition, when the NIR laser is introduced, it can also exert the effect of a "nano-knife" to physically damage bacteria. The bactericidal efficiencies against *E. coli* and *S. aureus* were 98.74% and 99.63%, respectively.

Metal oxide/carbon nanostructures constructed by immobilizing metal oxides on carbonaceous structures have stronger catalytic performance and make up for some shortcomings of traditional metal oxide nanoparticles, such as irregular distribution of active sites and aggregation.[326,327] Fan et al reported a MOF-derived 2D carbon nanosheet for anti-infective therapy.[328] The 2D nanomaterials (TRB-ZnO@G) were formed by anchoring carbon on MOF-derived ZnO-doped graphene (ZnO@G) with a phase-change thermally responsive brush via in-situ polymerization. The high photothermal activity and Zn ion release ability is synergistically antibacterial, and the sterilization rate is close to 100% under short time and low concentration conditions. The controllable porosity, good physical/chemical stability, high electrical conductivity, and high catalytic activity of MOF derivatives make them strong candidates for multifunctional materials. Simultaneously, it is also difficult to effectively control the properties (morphology, surface area, and composition) of calcined MOF materials due to various factors during the synthesis process. Achieving an effective controllable design in the development of antibacterial nanozymes is a future challenge.[33,318,329,330]

COF-Based Nanozymes

COFs are nontoxic, stable, green, low-cost, and tunable emerging porous crystalline materials.[331–334] The monomer design of COFs exploits the principles of directional bonding established by coordination polymers and supramolecular assemblies.[335,336] COF-based nanomaterials have a wide range of applied research in the medical field, including acting as carrier/ligand for antibiotics, tumor therapy, photodetectors, aptasensors, photodynamics, and photocatalysis.[337–341] Although there are few studies on the use of COFs to construct nanozymes for the treatment of bacterial infectious wounds, COFs have many characteristics that are suitable for designing nanozymes (Table 5). First, it is highly adjustable and can be used as a platform.[342–345] Second, structural ordering is conducive to catalysis, membrane construction, and material characterization.[346] Then, with high porosity and low density, COFs with uniform void distribution and composed of light elements are a potential basis for loaded drugs for targeted therapy and high gravimetric performance.[347–349] Finally, the stability is excellent. COFs linked by stable covalent bonds maintain a high degree of morphology in extreme pH, temperature, and solvent, with higher stability than most MOFs.[350–354]

Photosensitive fungicides have been studied in silver nanoparticles, copper, oxides, porphyrin derivatives, and phthalocyanines.[249,355–358] The key question is how to solve, and improve the absorption range of the spectrum, toxicity, and photostability.[359] In contrast, the rich pore structure and conjugated structure of COFs provide a possibility for the

Table 5 COF-Based Nanozymes for Improving Bacterial Infectious Wound Healing

Materials	Substrate	Synthesis Procedure	Microbial Type	Antibacterial Mechanism	Antimicrobial Activity	Special Characteristics	Ref.
GFeF	Glucose (15 mM), H_2O_2	1, Fe chelation 2, GOx loading	*E. coli*, *S. aureus*	Generates ROS	SEM: Bacterial surface roughening and wrinkling	Cascade reaction, optimum pH = 4, electrostatic adsorption	[364]
NMC_{TP-TTA}	H_2O_2 (10 mM)	Sequential growth	*E. coli*, MRSA	Generates ROS, surface pseudopodia tear at cell walls and deform structures	SEM: Bacterial surface roughening and wrinkling	Binding pocket structure to strengthen catalysis, COF pseudopodia surface catches bacteria, POD-like activity, in situ generations of –OH	[369]

design of antibacterial agents.[360] Zhang et al synthesized a photosensitizer (TPDA) with multiple active sites by condensing 2,4,4-triformylphloroglucinol (TFP) and 3.6-diaminoacridine (DAA) with Schiff bases (Figure 11E).[361] Due to the excellent light-harvesting ability of DAA and the increased conjugation effect brought by the COF framework, the light-converting ability of TPDA has been improved, and the high specific surface area exposes more active sites, which can be used in a short time (10 minutes) of light. This result showed the high killing effect of *S. aureus* and *E. coli* under irradiation. In addition, the abundant pore structure can facilitate the rapid arrival of ROS to the infection site. Although fish skin was selected for animal experiments, the good biocompatibility of TPDA makes it potentially applicable to humans.

The hyperglycemic microenvironment of diabetic wounds is an important factor leading to angiogenesis dysfunction and bacterial proliferation, and GOx is used to degrade excess glucose.[362,363] Li et al prepared an ionic COF nanozyme (GFeF) that indirectly generates H_2O_2 by a three-step method.[364] The loaded GOx produces gluconic acid and H_2O_2 in the wound, and then mimics the indirect production of H_2O_2 catalyzed by POD activity. Simultaneously, the positive charge characteristic of the composite material improves the adhesion of the synthetic material to the bacterial membrane and realizes the in-situ catalytic release of -OH. Therefore, the H_2O_2 indirectly generated by the cascade reaction triggered by glucose in the wound not only avoids direct damage to normal cells, but also has good antibacterial properties. Notably, the nanozyme can also be incorporated into injectable thermals to synergistically promote the healing of infected wounds. The same principle has also been studied in MOF-based nanozymes.[365]

The structure of the natural enzyme binding pocket can provide a friendly reaction microenvironment for the active center, which is beneficial to improve the catalytic efficiency.[366,367] Then COFs or MOFs can be used as the main framework, and then the functional groups on the surface can be adjusted to surround the active site to form a customized microenvironment.[333,368] Zhang et al constructed the MOF@COF nanozyme (NMCTP-TTA) for the first time (Figure 11F).[369] Surface COFTP-TTA was formed using ligands of phenol (weak acid) and triazine (basic functional) groups on amino-functionalized POD-like NH_2-MIL-88B(Fe)(NM-88) modified. Then, the COFTP-TTA-grown custom hierarchical nanocavities were used as enzyme-binding pockets to form pore microenvironments around the metal active sites of the MOF. The binding pocket structure enables the collection of substrate molecules for catalysis through noncovalent interactions. In addition, the pseudopod-like structures on the surface of COFs can effectively capture bacteria and kill them by in situ generated ROS, showing excellent antibacterial effects in antibacterial and animal experiments. The design of such multifunctional enzymes may provide new ideas for the treatment of infected wounds.

Currently, the antibacterial research of COF-based materials is more focused on photoexcitation and drug delivery, such as porphyrin-based and triazine-based materials, among which conjugation modulation is one of the new strategies to enhance photosensitivity.[370–374] However, the design of nanozymes is scarce, and it is expected that more antimicrobial agents can be derived by exploiting the advantages of COF.

Conclusion, Challenges, and Outlook

Wound healing is one of the great challenges facing modern medicine. Insufficient knowledge of pathophysiology and histiocyte recovery has limited the availability of medicinal materials for clinical infectious wound treatment. This means that new approaches are needed to make improvements to current treatment strategies. Currently, a series of artificial nanozymes is being developed with the advancement of biotechnology and nanotechnology. As potentially useful enzyme activity mimics, nanozymes not only show excellent performance in sensing, pollutant treatment, cancer treatment, ROS scavenging, and biopharmaceuticals, but also have the advantage of replacing antibiotic therapy in the clinical treatment of infected wounds. In this review, we address the pathophysiology of wound healing and the pitfalls of therapeutic approaches. The antibacterial advantages and antibacterial mechanisms of nanozymes and the research progress in the field of infected wounds are summarized. Current research on nanozymes has overcome many limitations of natural enzymes, such as complex preparation and storage, and poor stability. From our perspective, there are still challenges and obstacles that cannot be underestimated in future research.

1. Compared with most natural enzymes, the preparation price, stability, and reproducibility of nanozymes are well optimized. However, large-scale fabrication applications, such as the development of alternatives to noble metal nanozymes and further improving the physiological stability of pristine MOFs, should be considered. Simultaneously, antibacterial properties should be guaranteed.
2. At present, because of the lack of substrate specificity of nanozymes, their further application in wound healing is limited. Researchers have identified many factors that influence catalytic performance by positive and negative charge interactions, pH, GSH, and laser to confer the ability to target bacteria or biofilms with nanozymes. However, the complex composition of bacterial colonies and biofilms may attenuate these abilities. How to achieve substrate specificity and precise control of external conditions for multienzyme active nanozymes should receive more attention in the future.
3. In recent years of rapid development, research on nanozyme antimicrobial agents has been more focused on synthesis, treatment and application. The catalytic mechanism is fundamental to understanding the catalytic reactions of nanozymes, especially the relationship between catalytic performance and microstructure from the whole material to the atomic to the electronic structure. In contrast, in-depth studies and targeted mechanistic research strategies involving the mechanism of action are less available.
4. The pH of the optimal action environment for most nanozymes is acidic, which is not favorable for practical applications. It is worth exploring the physiological environment that can be stimulated in infected wounds to maintain excellent catalytic activity.
5. In the field of antimicrobial activity, POD-like nanozymes have received extensive attention. Therefore, other oxidoreductases (eg, OXD, CAT, SOD, GSH-Px) should also be promoted for utilization.
6. Due to the complex structure of nanozymes, some work affects the overall material properties only through the material surface. Other works precisely control the atomic distribution, content and structure of nanomaterials by adjusting the synthesis strategy. For example, MOFs with desirable catalytic activity are synthesized by the rational design of organic linkers and metal nodes to mimic the coordination environment of metal cofactors in natural enzymes. Currently, most MOF-derived nanozymes start from the ZIF series. Therefore, the development of other synthetic strategies and the discovery of other starting materials can provide new opportunities for nanozyme applications.
7. The long-term in vivo toxicity of nanozymes cannot be ignored in clinical applications. Although most nanozyme research involves biocompatibility, there is a lack of toxicity mechanism explanations and corresponding solutions. Attention should be paid to potential metabolic accumulation impairment and carcinogenicity, especially nanozymes that require in vivo administration and may favor accumulation in the liver and spleen. First, we can try to design nanomaterials of smaller sizes that can be metabolized through the kidneys and reduce retention. Second, nanozymes that can degrade in physiological environments should be constructed. Since there are currently few studies on renal metabolism and biodegradability, it would be valuable to conduct more in-depth studies.

8. Currently, there is no report of bacterial resistance to ROS. Considering the sustainability of the practical application of nanozymes, long-term observation of changes in this aspect is necessary. In this rapidly developing field, it is highly expected that the use of nanozymes in infected wounds will enable dazzling advances in medical antimicrobials.

Abbreviations

ROS, reactive oxygen species; H_2O_2, hydrogen peroxide; PMNs, polymorphonuclear neutrophils; NADPH, nicotinamide adenine dinucleotide phosphate; S. aureus, Staphylococcus aureus; P. aeruginosa, Pseudomonas aeruginosa; QS, dendritic cells; AMPs, antimicrobial peptides; CS, chitosan; E. coli, Escherichia. coli; HA, hyaluronic acid; MOF, metal-organic framework; COF, covalent-organic framework; POD, peroxide; -OH, hydroxyl radical; $^1O_2$, singlet oxygen; GOx, glucose oxidase; eDNA, environmental DNA; BME, biofilm microenvironment; GSH, glutathione; MRSA, methicillin-resistant Staphylococcus aureus; MNPs, metal nanoparticles; AA, ascorbic acid; NRs, nanorods; ATP, adenosine triphosphate; B. subtilis, Bacillus subtilis; O^{2-}, superoxide anion radical; PTT, photothermal therapy; PDT, photodynamic therapy; XPS, X-ray photoelectron spectroscopy; CAT, catalase; BSA, bovine serum albumin; NIR, near infrared; CDs, carbon dots; S. enteritidis, Salmonella enteritidis; CNTs, carbon nanotubes; p-CNTs, pristine carbon nanotubes; o-CNTs, oxide-rich carbon nanotubes; GQDs, graphene quantum dots; GO, graphene oxide; MRs, microreactors; Km, Michaelis-Menten constant; dPG, dendritic polyglycerol; LSPR, localized surface plasmon resonance; NTA, nitrilotriacetic acid; D-AzAla, 3-azido-D-alanine; DFT, density functional theory; ZIF-8, zeolite imidazolate framework 8; TFP, 2,4,4-triformylphloroglucinol; DAA, 3,6-diaminoacridine.

Ethics Approval and Consent to Participate

This manuscript is a review article that does not require prior approval.

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