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Nanocatalytic medicine enabled next-generation therapeutics for bacterial infections

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ABSTRACT

The rapid rise of antibiotic-resistant strains and the persistence of biofilm-associated infections have significantly challenged global public health. Unfortunately, current clinical high-dose antibiotic regimens and combination therapies often fail to completely eradicate these infections, which can lead to adverse side effects and further drug resistance. Amidst this challenge, however, the burgeoning development in nanotechnology and nanomaterials brings hopes. This review provides a comprehensive summary of recent advancements in nanomaterials for treating bacterial infections. Firstly, the research progress of catalytic therapies in the field of antimicrobials is comprehensively discussed. Thereafter, we systematically discuss the strategies of nanomaterials for anti-bacterial infection therapies, including endogenous response catalytic therapy, exogenous stimulation catalytic therapy, and catalytic immunotherapy, in order to elucidate the mechanism of nanocatalytic anti-infections. Based on the current state of the art, we conclude with insights on the remaining challenges and future prospects in this rapidly emerging field.

1. Introduction

Bacterial infections pose a significant global public health challenge due to the rise of antibiotic-resistant strains and persistent biofilm-associated infections. [1–4]. The World Health Organization (WHO) identifies antibiotic resistance as a major threat to global health, food security, and development [5]. Pathogens like Methicillin-resistant *Staphylococcus aureus* (MRSA) and multidrug-resistant (MDR) Gram-negative bacteria have developed resistance to multiple antibiotics, making standard treatments ineffective [6–8]. Additionally, bacteria can form biofilms, structured communities encased in extracellular polymeric substances (EPS), which enhance their resistance to antibiotics [9–11]. The EPS matrix acts as a barrier, preventing antimicrobial agents and immune cells from penetrating, leading to chronic and recurrent infections [12]. Current therapeutic strategies, including high-dose antibiotic regimens and combination therapies, often fail to completely eradicate these infections and may cause adverse side effects and further resistance. Consequently, there is an urgent need for novel antimicrobial strategies to effectively address these complex bacterial infections.

Nanocatalytic therapy (NCT) has emerged as a groundbreaking approach against bacterial infections [13–15]. This strategy employs nanoscale catalysts to generate reactive oxygen species (ROS) and other intermediates to kill bacteria [16]. These nanocatalysts can interact with endogenous H_2O_2 through mechanisms such as chemical and nanozyme catalysis, or can be activated by external stimuli, including light (photocatalysis), ultrasound (sonocatalysis), and electric fields (electrocatalysis). The ROS produced, including hydroxyl radicals ($\cdot$OH), superoxide anions ($\cdot O_2^-$), and singlet oxygen ($^1O_2$), are highly effective at damaging bacterial cell membranes, proteins, and DNA, leading to bacterial cell death [17]. NCT provides advantages over traditional antibiotics by targeting bacteria *via* oxidative stress, thereby reducing

the potential for resistance development. Additionally, the versatility of nanocatalysts allows for precise control over their antimicrobial activity and can be engineered to possess additional functionalities, such as targeted delivery, enhanced permeability, and the ability to modulate the host immune response [18,19]. This multifunctionality makes NCT a versatile and powerful tool in the fight against bacterial infections.

The design and optimization of nanocatalysts are essential for enhancing their therapeutic efficacy [20,21]. Various metal-based nanocatalysts and metal oxides have shown exceptional catalytic properties. Hybrid structures like metal-organic frameworks (MOFs) and covalent organic frameworks (COFs) enable precise customization of catalytic activity and biocompatibility [22–24]. Functionalizing these materials with targeting ligands enhances specificity and minimizes off-target effects. Moreover, integrating nanocatalytic therapy with other treatment modalities, such as photothermal therapy and immunotherapy, can provide synergistic effects, significantly boosting overall antimicrobial efficacy [25,26].

In recent years, antibacterial treatments based on nanocatalytic medicine have garnered increasing research interest and achieved significant advancements. However, this research direction has yet to be comprehensively reviewed and discussed. Herein, we systematically overview and discuss the latest achievements in nanocatalytic medicine within the antibacterial field, providing a thorough review based on representative examples. This article classifies nanocatalytic therapies into endogenous stimulus-mediated (chemodynamic and nanozyme catalytic therapy) and external stimulus-mediated (photocatalytic, sonocatalytic, and electrocatalytic therapy) approaches, emphasizing the mechanisms, design principles, and benefits of each strategy (Fig. 1). Furthermore, we describe the latest applications of nanocatalytic medicine combined with immunotherapy in antibacterial treatment and their immunomodulatory mechanisms. Finally, we discuss the current challenges and clinical application prospects in this field, aiming to provide insights for its future development.
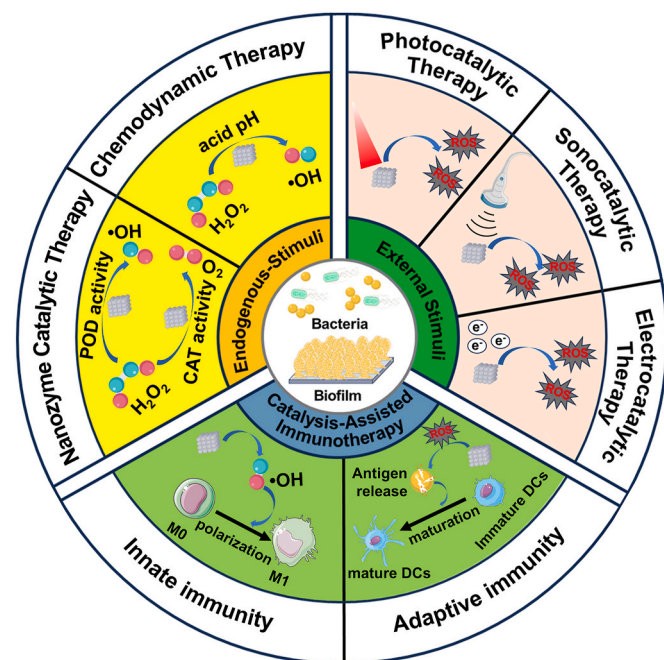

Fig. 1. Schematic diagram of nanocatalytic therapy for bacterial infections.

## 2. Endogenous-stimuli-mediated nanocatalytic medicine anti-infection

2.1. Chemodynamic therapy (CDT)

Shi *et al.* introduced CDT as a therapeutic approach where chemical stimulation induces ROS production in 2016 [27]. In acidic environments, it leverages Fenton and Fenton-like reactions to transform H_2O_2 into toxic $\cdot OH$ using Fe^{2+} or other transition metal ions such as Cu^{2+}, Co^{2+}, Mn^{2+}, achieving therapeutic outcomes without external physical stimulation. The typical reaction equation is as follows (M refers to Fe, Cu, Mn, Co, etc.):

$$M^{n+} + H_2O_2 \rightarrow M^{(n+1)+} + \cdot OH + OH^- \tag{1}$$

$$M^{(n+1)+} + H_2O_2 \rightarrow M^{(n)+} + \cdot O_2H + H^+ \tag{2}$$
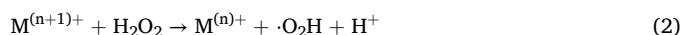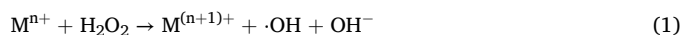
CDT is frequently utilized in the development of nanomaterials for cancer therapy due to the mild acidity and elevated H_2O_2 levels in the tumor microenvironment (TME) [28–31]. Given that the infection microenvironment, particularly the biofilm microenvironment (BME), shares similar characteristics with the tumor microenvironment, namely higher levels of glutathione (GSH) and H_2O_2 as well as an acidic pH compared to normal tissues, CDT has gained attention as a promising strategy for infection treatment [32]. This approach can induce endogenous chemical reactions at infection sites, generating ROS to eliminate pathogens while sparing normal tissues, thereby enhancing therapeutic specificity and reducing side effects. Li and co-workers synthesized $FePS_3$ nanosheets using Fe, P, and S powders as raw materials through a high-temperature solid-state reaction (Fig. 2A–C) [33]. Under the acidic pH conditions of the infection microenvironment, $FePS_3$ nanosheets release Fe^{2+}, which decomposes H_2O_2 into toxic ROS *via* the Fenton reaction, thereby achieving antimicrobial effects. Additionally, the reductive $[P_2S_6]^{4-}$ can reduce Fe^{3+} to Fe^{2+}, further enhancing the efficacy of CDT. However, bacteria can protect themselves from the host immune system and antibiotics by forming biofilms. Especially in implant-associated infections (IAIs), biofilm is a major cause of refractory and chronic infection. Therefore, eliminating bacterial biofilms is one of the key goals in anti-infective therapy. Bacterial biofilms are intricate assemblies of bacteria and their secreted EPS, serving as physical and chemical shields for the enclosed bacteria. EPS in biofilm primarily consists of polysaccharides, proteins, and extracellular DNA (eDNA), with eDNA being essential for biofilm formation, maturation, and structural stability. The $\cdot OH$ produced by CDT, with a redox potential of 2.80 eV, can effectively damage DNA structure. Based on this, Guo *et al.* proposed a space-selective CDT strategy for treating IAIs. Using iron oleate $[Fe(OA)_3]$ and copper oleate $[Cu(OA)_2]$ complexes, $CuFe_5O_8$ nanocubes (NCs) were synthesized. These $CuFe_5O_8$ NCs were shown to generate high levels of $\cdot OH$ *via* the Fenton reaction within biofilms, disrupting eDNA and degrading the biofilm, thus compromising its barrier function (Fig. 2D–H) [34]. Outside the biofilm, the $CuFe_5O_8$ NCs catalyzed the production of low levels of $\cdot OH$, which promoted macrophage polarization toward the M1 phenotype, reversing the immunosuppressive microenvironment of the biofilm.

The efficacy of using CDT strategies to treat bacterial infections depends on the activity of the Fenton reaction. The activity of the Fenton reaction is closely related to the concentrations of catalytic ions and H_2O_2, as well as local pH and temperature conditions. Additionally, excessively high local concentrations of GSH can weaken the bactericidal ability of the $\cdot OH$ produced by the Fenton reaction. Despite the acidic pH (6.5–7.0) and overexpression of H_2O_2 at bacterial infection sites compared to normal tissues, these conditions are still insufficient to efficiently initiate the Fenton reaction to produce an adequate amount of $\cdot OH$. Excessive GSH production at the infection site can neutralize $\cdot OH$, reducing the antimicrobial efficacy of the CDT strategy. In view of this, researchers have adopted various strategies in recent years to enhance the efficacy of CDT. These strategies mainly include increasing the H_2O_2
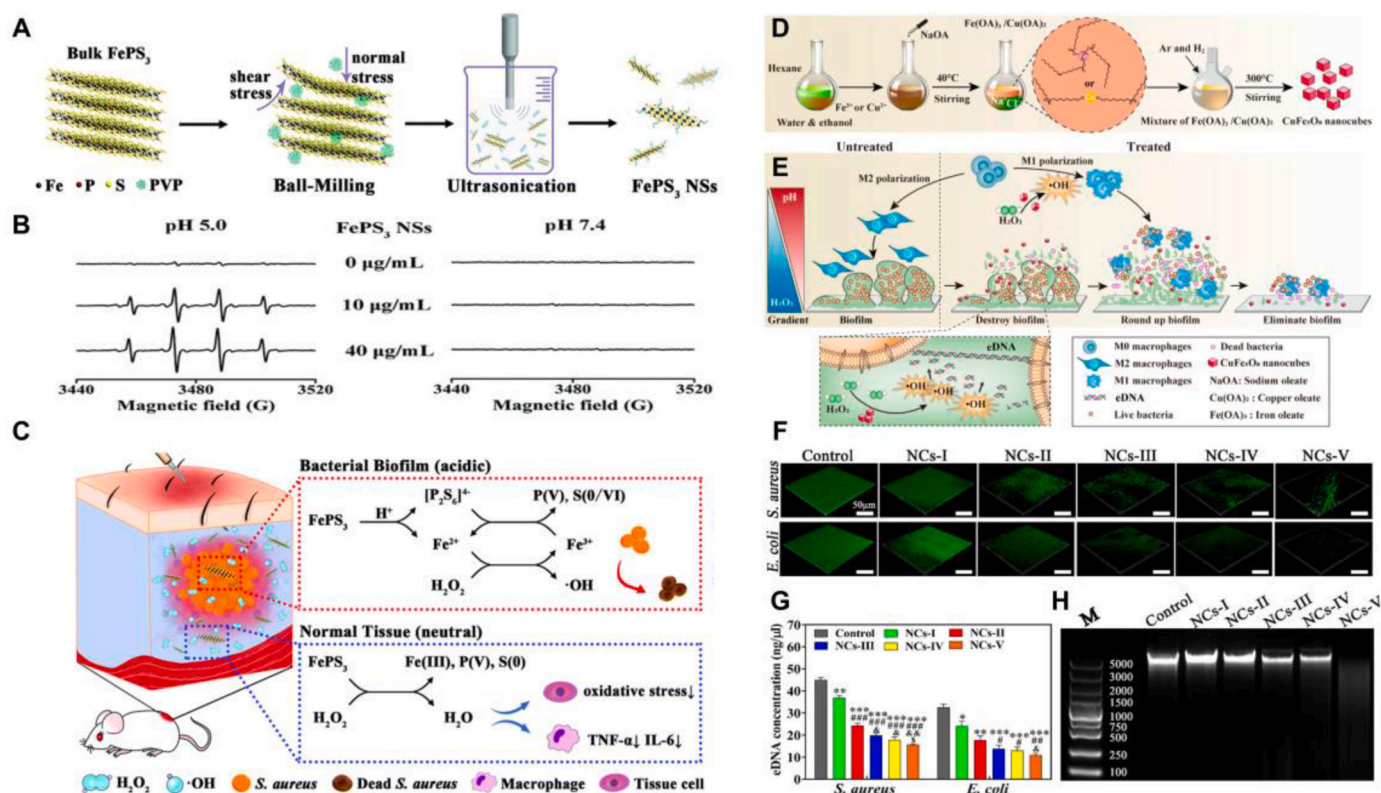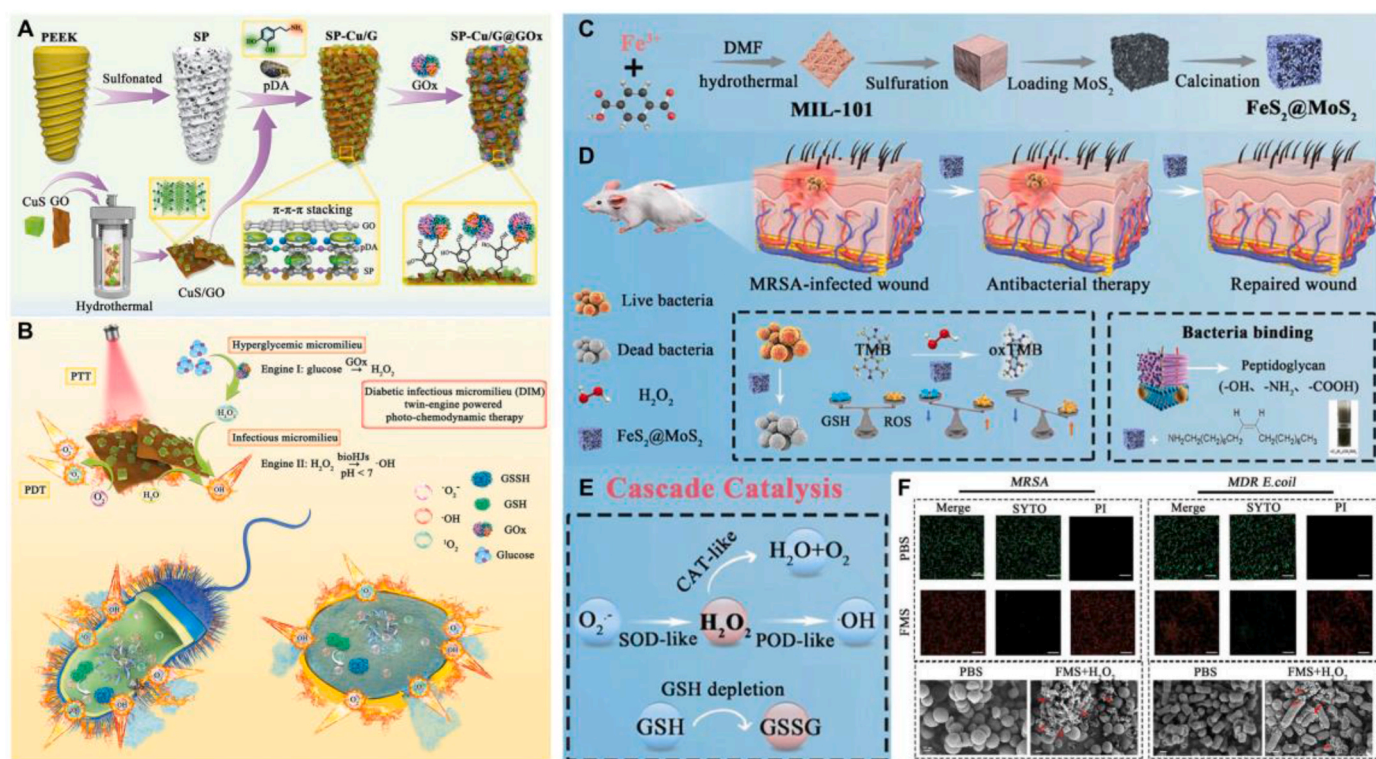
Fig. 2. Nanomaterials using CDT strategies to combat bacterial infections. **A)** The schematic illustration of the strategy and process for constructing FePS$_3$ nanosheets (FePS$_3$ NSs). **B)** EPR spectra of FePS$_3$ NSs under different pH and concentration conditions in the presence of H$_2$O$_2$. **C)** FePS$_3$ NSs exhibit self-enhanced Fenton activity in acidic infection environments, generating ROS to eliminate the infection. **D)** The synthesis process of CuFe$_5$O$_8$ NCs. **E)** Schematic illustration of CuFe$_5$O$_8$ NCs using CDT strategy to generate ·OH *via* Fenton reaction to disrupt biofilm structure and modulate immunity. **F)** 3D reconstructed images of *S. aureus* and *E. coli* biofilms after treatment with CuFe$_5$O$_8$ NCs. **G)** Results of eDNA content in the biofilms of *S. aureus* and *E. coli* after treatment with CuFe$_5$O$_8$ NCs. **H)** Agarose gel electrophoresis images showing DNA damage by ·OH generated through the Fenton reaction with CuFe$_5$O$_8$ NCs. A-C) Reproduced with permission [33]. Copyright 2021, The Royal Society of Chemistry. D-H) Reproduced with permission [34]. Copyright 2020, ACS Publications.

concentration, lowering the pH of the reaction condition, raising the local temperature, and reducing the GSH levels in the infection microenvironment. All these approaches have successfully amplified the Fenton reaction and improved the antibacterial efficiency of nanomaterials. Li and co-workers developed a polyetheretherketone (PEEK) implant incorporating copper sulfide/graphene oxide (CuS/GO) bioheterojunctions (bioHJs) and glucose oxidase (GOx) for treating diabetic wound infections (Fig. 3A and B) [35]. In the diabetic infectious microenvironment (DIM), GOx catalyzes the conversion of glucose into H$_2$O$_2$, initiating the reaction. Subsequently, Cu^{2+} released from bioHJs decomposes H$_2$O$_2$ into highly toxic ·OH through the Fenton reaction, serving as the second step of the reaction. Additionally, this PEEK material exhibits excellent photothermal and photodynamic properties, capable of generating abundant singlet oxygen (^{1}O$_2$) and superoxide (·O$_2^-$) under laser irradiation. This dual-engine strategy has been shown to enhance the Fenton reaction, producing numerous toxic ROS that can cause bacterial cell membrane rupture and intracellular content leakage, ultimately leading to bacterial death. Sun *et al.* utilized MIL-101 (Fe)-derived cascade nano-enzymes to kill multidrug-resistant bacteria and accelerate the healing of infected wounds by enhancing CDT strategy (Fig. 3C–F) [36]. The engineered FeS$_2$@MoS$_2$ nanocubes exhibit POD-, CAT-, SOD-like activities, and the ability to deplete GSH. In the acidic infection microenvironment, the FeS$_2$@MoS$_2$ NPS exhibit SOD-like activities, promoting the conversion of superoxide anions (·O$_2^-$) into H$_2$O$_2$. Subsequently, the generated H$_2$O$_2$ serves as a substrate for the Fenton reaction with the FeS$_2$@MoS$_2$ NPS, producing ·OH radicals capable of killing bacteria. FeS$_2$@MoS$_2$ NPS can lower GSH levels at infection sites and catalyze nicotinamide adenine dinucleotide

phosphate (NADPH) decomposition, inhibiting glutathione regeneration and enhancing the antimicrobial efficacy of ·OH radicals. Owing to the multiple nanozyme activities of FeS$_2$@MoS$_2$ NPS, which effectively eliminate MDR *E. coli* and MRSA infections, this nanomaterial provides a strategy for designing cascade nanozyme platforms combined with CDT for the treatment of bacterial infections.

Given that antimicrobial therapy using CDT strategies alone is sometimes not therapeutically effective, more researchers have recently begun employing combined treatment strategies based on CDT to address bacterial infection challenges. Localized high temperatures have been shown to enhance the Fenton reaction, making the combination of CDT and photothermal therapy (PTT) an ideal synergistic strategy for antibacterial treatment. Zhang *et al.* created a two-stage nanosheet-structured iron hydroxide composite coating on Mg alloy, followed by thermal reduction to disrupt surface Fe-OH bonds [37]. This process improved photothermal conversion efficiency and increased Fe^{2+} content, enhancing Fenton reaction activity. Consequently, this multifunctional Mg-based implant coating material exhibited synergistic photothermal/chemodynamic antibacterial efficacy against bacterial infections. Considering the deep tissue penetration advantage of NIR-II laser, He *et al.* attached Pt nanoparticles (Pt NPs) to V$_2$C MXene to form an artificial nanoplatform (Pt@V$_2$C) [38]. They demonstrated that under NIR-II laser irradiation, Pt@V$_2$C exhibited enhanced CDT activity and photothermal activity, effectively eliminating methicillin-resistant *Staphylococcus aureus* (MRSA) from deep tissues within subcutaneous abscesses and bacterial keratitis. Through the synergistic action of PTT/CDT, this approach accelerated abscess resolution and promoted wound and corneal healing. Deng *et al.* designed and developed a

Fig. 3. Enhancing CDT strategies to amplify the Fenton reaction and improve the antibacterial efficacy of nanomaterials. A) Schematic of the CuS/GO bioHJs-engineered and GOx-coated PEEK implant synthesis. **B)** Mechanism by which CuS/GO bioHJs-engineered and GOx-coated PEEK boosts the Fenton reaction and enhances bactericidal efficiency in infection microenvironments by increasing H_2O_2 concentration, lowering GSH levels, and raising reaction temperature. **C)** Synthesis of the $FeS_2@MoS_2$ cascade nano-system. **D)** $FeS_2@MoS_2$ NPs enhance the Fenton reaction to combat multidrug-resistant bacteria and aid infected wound healing. **E)** Schematic of $FeS_2@MoS_2$ nanozymes with POD-, CAT-, and SOD-like activities and their catalytic mechanisms. **F)** Live/dead staining and SEM images of bacteria after $FeS_2@MoS_2$ nanozyme treatment. A-B) Reproduced with permission [35]. Copyright 2022, Wiley-VCH. C-F) Reproduced with permission [36]. Copyright 2024, Wiley-VCH.

photoactivated cascaded bio-heterojunction, which under dual-light conditions can generate ·OH and ·O_2^- through CDT synergizing with PDT for anti-infective therapy, while the material also exhibits good photothermal performance (Fig. 4A–F) [39]. They elucidated the excellent therapeutic effects of a CDT-based therapy combined with PDT/PTT on diabetic bacterial wound infections. In addition, Liu *et al.* innovatively composed a nanocomplex of poly-dopamine/hemoglobin/Fe^{2+} and loaded it with antimicrobial peptides, named PL@HPFTM nanoparticles [40]. These nanoparticles catalyze the generation of ·OH through the reaction between Fe^{2+} and H_2O_2 at the infection site, while the efficient photothermal conversion increases the temperature and the sustained release of antimicrobial peptides. This combined therapy strategy of CDT/PTT/antimicrobial peptides significantly enhances the bactericidal efficiency, eliminating bacterial infections. Sonodynamic therapy (SDT) is another treatment strategy that achieves therapeutic effects by generating ROS, showing excellent efficacy against bacterial infections as well. Huang *et al.* developed a multifunctional nanoreactor by integrating piezoelectric barium titanate with polydopamine and copper, utilizing spatiotemporal ultrasound-driven tandem catalysis to enhance sonodynamic and chemical dynamic therapy efficacy (Fig. 4G–K) [41]. This combined CDT and SDT strategy produces substantial ROS, disrupting bacterial membrane structure, damaging DNA, and inducing cuproptosis-like bacterial death. This strategy exhibits excellent antibacterial performance under ultrasound stimulation, significantly reducing IAIs caused by bacterial biofilm formation. CDT and CDT-based combination therapies have demonstrated efficacy against bacterial infections, including those caused by drug-resistant strains. In the future, more nanocatalytic platforms based on CDT strategies are expected to be designed and developed, further enhancing the efficiency of antimicrobial treatments

and reducing associated adverse effects.

Chemodynamic therapy for bacterial infections is an effective and promising treatment approach. Although it depends on the chemical conditions of the specific microenvironment, researchers are also focused on optimizing material design, reducing chemical toxicity and improving antibacterial efficiency based on chemokinetic therapy [42]. Additionally, combination therapy based on CDT is emerging as a key direction and trend in the future of nanocatalytic medical treatments for bacterial infections [38].

2.2. Nanozyme catalytic therapy (NCT)

Nanozymes are artificial enzymes based on nanomaterials, first proposed by Scrimin and colleagues [43]. Nanozyme catalytic therapy is a method that uses nanomaterials with enzyme-like activities to treat diseases. These nanomaterials are typically designed to exhibit activities similar to natural enzymes, such as POD-like activity, CAT-like activity, and SOD -like activity. Enzyme catalysis is one of the most common catalytic reactions that maintain physiological homeostasis of biological systems [44]. Since the substrates of enzyme catalysis are biomolecules, these reactions typically occur under mild physical conditions. Despite natural enzymes having high substrate selectivity and catalytic efficiencies superior to synthetic catalysts, they are limited by high production costs, low yields, and susceptibility to denaturation and inactivation during transportation and storage, which restrict their applications in biological contexts [45,46]. As an alternative, nanozymes, composed of materials such as metal-organic compounds, inorganic crystals, or organic polymers, offer high stability and sustained enzyme reactions [47]. In the past, therapeutic strategies involving nanozyme-catalyzed ROS generation have been extensively studied in
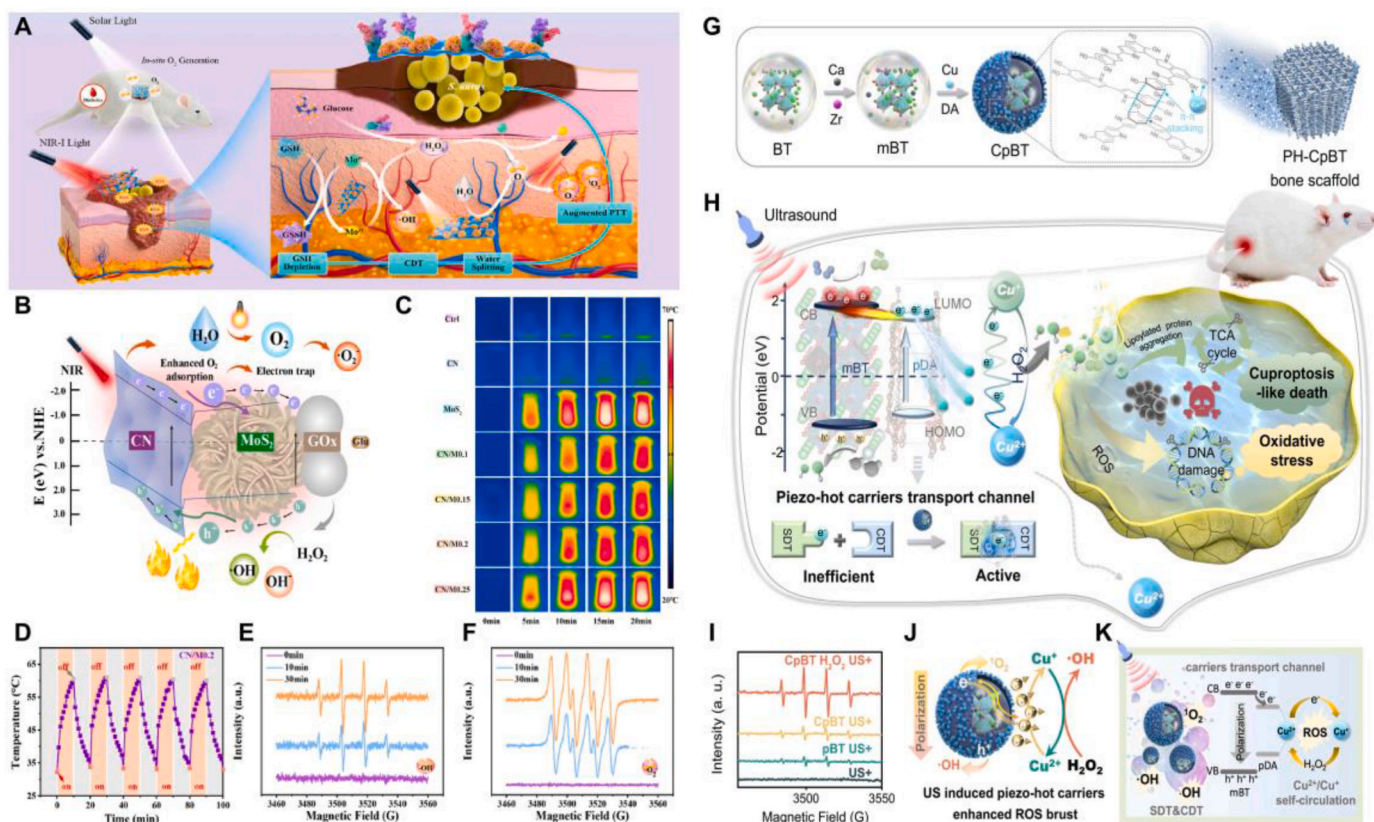
Fig. 4. CDT-based combined therapeutic strategies to tackle bacterial infection challenges. A) C-bio-HJs nanomaterials improve CDT strategies when combined with PDT and PTT therapies, helping to eliminate bacterial infections and promote the healing of diabetic wounds. **B)** Schematic representation of the electron transfer process between CN and MoS_2 based on DFT calculations, illustrating the synergistic antibacterial mechanism of C-bio-HJs. **C-D)** Real-time photothermal images and cycling curves of nanomaterials under continuous laser irradiation. **E-F)** The ability of nanomaterials to generate ·OH and ·O_2^- under dual light irradiation. **G-H)** Schematic of the CpBT nanoreactor preparation process and its ability to trigger SDT and CDT cascade reactions under US activation to treat *S. aureus* infections. **I-K)** EPR spectra of ·OH generated by CpBT nanoreactors and a schematic of CpBT nanoreactors enhancing CDT strategies under US stimulation. A-F) Reproduced with permission [39]. Copyright 2022, Elsevier Ltd. G-K) Reproduced with permission [41]. Copyright 2024, Springer Nature.

cancer treatment, yielding excellent therapeutic outcomes [48–51]. Lately, the application of nano-enzyme catalyzed therapy in the treatment of bacterial infections has gained attention and is showing promising potential [52–54]. Different types of nanozymes possess distinct physicochemical properties and structures, resulting in varied antimicrobial efficacy.

Metal-based nanozymes, often incorporating noble metals like platinum, silver, and gold, demonstrate significant catalytic activity and are used in antimicrobial applications [55,56]. Hu and co-workers grew ultrasmall Au nanoparticles (UsAuNPs) by *in situ* reduction on ultrathin 2D MOFs, and prepared UsAuNPs/MOFs hybrids [57]. These hybrids leverage the benefits of both UsAuNPs and ultrathin 2D MOFs, showing excellent POD-like activity capable of decomposing H_2O_2 into toxic ·OH. The metal-based nanozyme material exhibits excellent antibacterial properties against both *E. coli* as well as *S. aureus in vitro* and *in vivo*, promotes wound healing, and is biocompatible. Yao *et al.* designed and synthesized dual-metal BiPt nanozymes coated with platelet-bacteria hybrid membrane (BiPt@HMVs) [58]. The synthesized dual-metal nanozymes exhibited dual enzyme-like activities, including peroxidase and oxidase mimic activities, and ultrasound stimulation greatly enhanced their catalytic efficiency. The platelet-bacteria hybrid membrane coating on the nanozymes endowed the material with excellent infection site targeting ability and showed outstanding therapeutic effects against infections caused by clinically relevant bacteria. To address the complex requirements of antibacterial therapy that cannot be met by nanozyme models with single enzyme activity, Shan *et al.* designed and developed nanozymes with multiple enzyme activities and synthesized a

novel metal enzyme (Ru-PC NPs) (Fig. 5A–B) [59]. Under acidic conditions, the synthesized Ru-PC NPs can consume GSH at the infection site and catalyze the production of ·OH through POD-like activity for antibacterial therapy. Under neutral conditions, Ru-PC NPs display CAT-like activity, breaking down H_2O_2 to produce O_2, which helps alleviate infection-related hypoxia. Additionally, its SOD-like activity eliminates excess ROS in neutral environments, preventing excessive inflammation. The quadruple enzyme activity of the synthesized Ru-PC NPs highlights its significant potential in antibacterial therapy and wound healing promotion.

Metal oxide/sulfide-based nanozymes have shown remarkable enzyme-like catalytic activity, and several studies have highlighted their use as nanozyme catalysts in antibacterial research [60–63]. Li *et al.* synthesized tannic acid-chelated Fe-modified MoS_2 nanosheets (MoS_2@TA/Fe NSs) and integrated them into a multifunctional hydrogel, imparting it with POD and CAT-like activities [64]. Under acidic conditions, MoS_2 in the nanozyme system catalyzes the production of toxic ·OH from H_2O_2 *via* POD-like activity, while under neutral conditions, TA/Fe in the nanozyme system catalyzes the generation of O_2 from H_2O_2 *via* CAT-like activity, relieving hypoxia at the infection site. Furthermore, MoS_2@TA/Fe NSs exhibit excellent antioxidant capabilities, capable of eliminating excessive ROS generated at the infected wound, thus accelerating the wound healing process. Liu *et al.* fabricated multi-enzyme-like nanozymes by decorating manganese oxide nanoclusters on graphdiyne nanosheets (MnOx/GDY) and embedded them in hyaluronic acid and polymethyl methacrylate-based microneedles (MGMN) [65]. The prepared multi-enzyme catalytic platform possesses
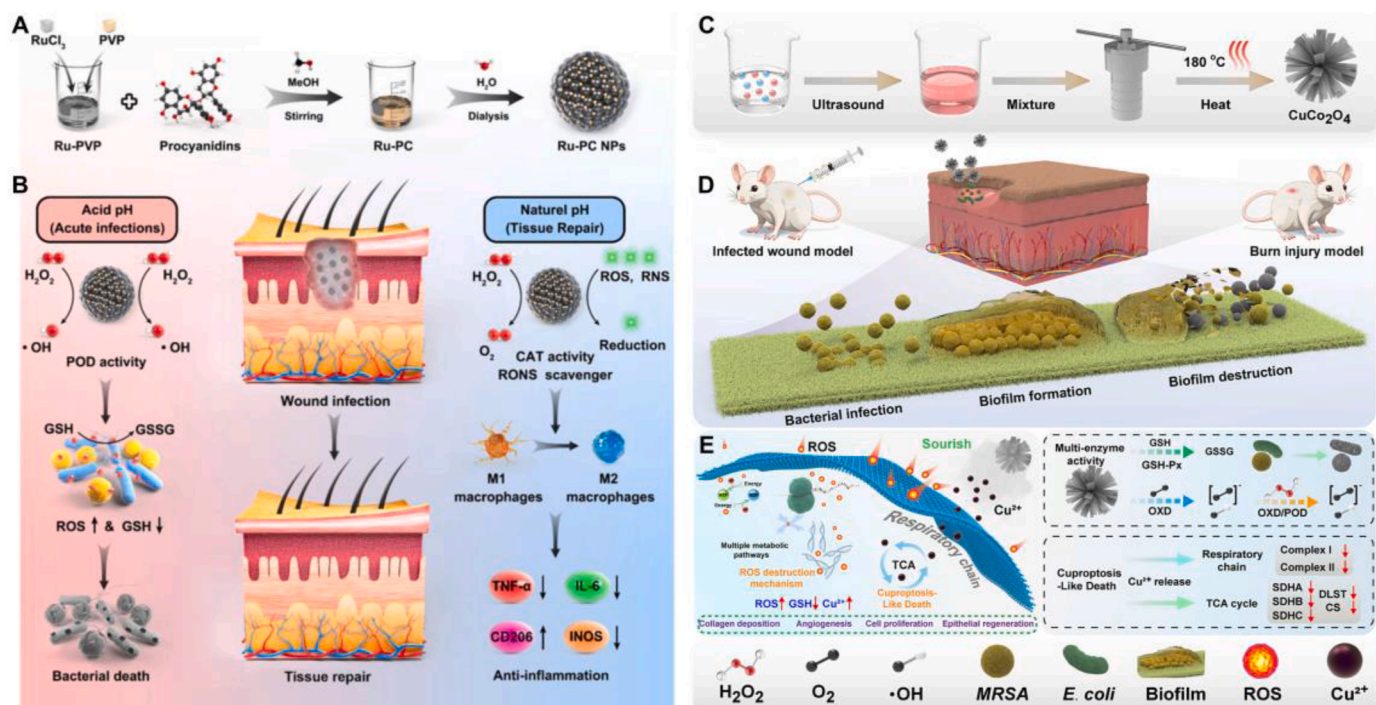
Fig. 5. Metal-based nanozymes and metal oxide/sulfide-based nanozymes are used for anti-infective therapy. **A)** Diagram of the synthesis process of nanozymes (Ru-PC NPs). **B)** The nanozyme (Ru-PC NPs) exhibits quadruple enzyme-like activities under acidic and neutral conditions. Under acidic conditions, it shows POD-like activity, consuming GSH and catalyzing the generation of ·OH from H_2O_2. Under neutral conditions, it exhibits CAT-like and SOD-like activities, catalyzing the decomposition of H_2O_2 to produce O_2 and clearing excess ROS. **C)** Diagram of the synthesis process of $CuCo_2O_4$ nanoflowers. **D)** Schematic illustration of $CuCo_2O_4$ nanoflowers eradicating pathogenic biofilms. **E)** Mechanism of $CuCo_2O_4$ nanoflowers generating abundant ROS through a multi-enzyme catalytic platform to combat bacterial infections. A-B) Reproduced with permission [59]. Copyright 2024, Elsevier Ltd. C-E) Reproduced with permission [66]. Copyright 2024, ACS Publications.

OXD, POD, CAT, and SOD-like activities, and also exhibits antibacterial and anti-inflammatory effects. They demonstrated that this multifunctional enzymatic nano-catalytic platform can eradicate pathogens, prevent biofilm formation, alleviate corneal inflammation, relieve ocular hypoxia, and accelerate the repair of corneal damage. Wang and co-workers synthesized $CuCo_2O_4$ nanoflowers, which possess dual enzyme activities of POD-like and OXD-like activities, capable of catalyzing the production of toxic ·OH and ·O_2^- from H_2O_2 (Fig. 5C–E) [66]. Additionally, $CuCo_2O_4$ nanoflowers exhibit glutathione peroxidase-like (GSH-Px-like) activity, which can degrade GSH at the infection site, further enhancing the ROS-mediated killing efficiency against infecting bacteria. They demonstrated that the $CuCo_2O_4$ nanoflowers, through its excellent enzymatic catalytic activities, can disrupt bacterial cell membrane structures, ultimately leading to copper-induced bacterial death, providing new insights and inspiration for treating bacterial biofilm infections.

MOFs are porous materials composed of metal ions or clusters coordinated with organic ligands. Their highly customizable structures and functional characteristics have attracted significant attention in biomedical applications [67]. The excellent physicochemical properties of MOF materials provide several advantages to MOF-based nanozyme catalytic platforms compared to traditional nanozymes [68–71]: (i) The porous structure and large surface area of MOFs allow substrates to fully reach the active sites, effectively increasing the catalytic reaction rate. (ii) The structure of MOFs is tunable, and their surfaces and pores can be functionalized to optimize catalytic performance. (iii) MOF-based nanozymes are capable of displaying multiple enzyme activities simultaneously (including oxidase, peroxidase, and catalase), allowing for multifunctional catalysis in complex biological environments. (iv) MOFs possess good chemical stability, maintaining their structure and function in various extreme environments. More importantly, MOF-based biomaterials generally exhibit good biocompatibility, which enables their

safe use *in vivo* without causing significant toxicity, demonstrating promising potential for antimicrobial applications [72,73]. Wang and colleagues introduced an acid-enhanced dual-mode antibacterial strategy using zeolitic imidazolate framework-8 (ZIF-8)-derived nanozymes, incorporating glucose oxidase (GOx) and gold nanoparticles (Au NPs) into ZIF-8. This approach enables ROS production through cascade catalytic reactions within the infection microenvironment [74]. This MOF-based nanocatalytic platform exhibited excellent bactericidal effects against bacteria at low doses (4–8 µg/mL), demonstrating the great potential of MOF-derived nanozymes for antibacterial applications. Wu *et al.* innovatively doped PCN-222 MOFs with bismuth nanoparticles (Bi NPs) to synthesize a biomimetic nanozyme catalyst, Bi-PCN-222 (Fig. 6A–E) [75]. When bacteria come into contact with Bi-PCN-222 in a physiological environment, its optimal redox potential triggers electron transfer *via* the bacterial membrane's electron transport pathways, ultimately penetrating the bacteria and disrupting their respiration and metabolism, resulting in the elimination of over 99.9 % of *S. aureus*. Furthermore, Liu *et al.* prepared hybrid nanozymes (Fe_3O_4@MOF@Au NPs, FMA NPs) by *in situ* growth of ultrasmall Au NPs on MOF- stabilised Fe_3O_4 NPs [76]. The FMA NPs demonstrated increased POD-like activity, efficiently catalyzing the generation of toxic ·OH in the presence of a low concentration of H_2O_2 (0.97 mM). They also demonstrated the strong bactericidal effects of FMA NPs against pathogens at the infection site while displaying excellent biocompatibility.

Single-atom nanozymes (SAzymes) are a novel class of artificial enzymes composed of individual metal atoms dispersed on a nanomaterial substrate. These single atoms are anchored at specific sites through strong interactions with the substrate material, forming nanostructures with unique catalytic activities [77,78]. Given the numerous advantages of SAzymes, including high catalytic activity, high selectivity, and high stability, making it an excellent alternative to natural enzymes and a research hotspot in nanozyme catalytic strategies [79–81]. Owing to the
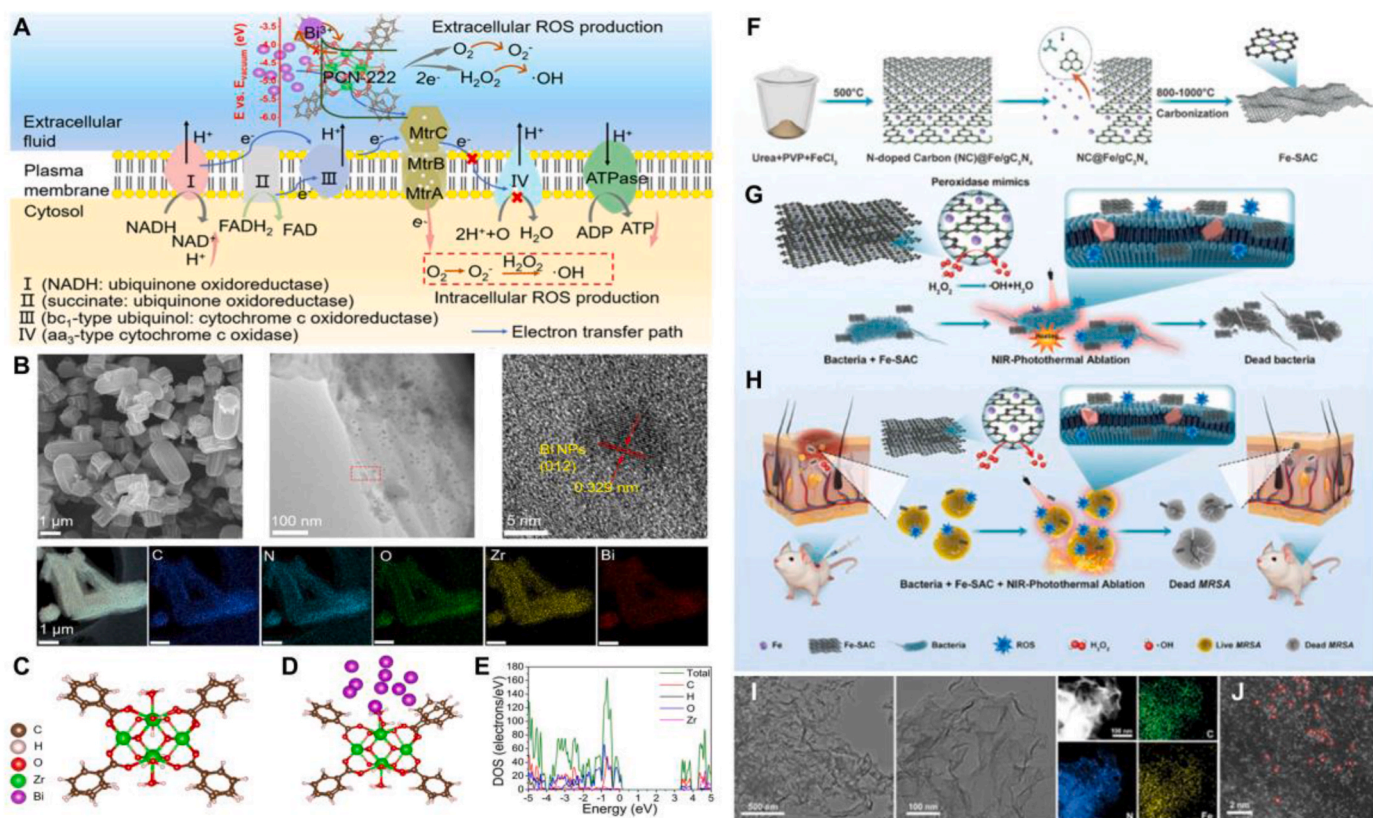
Fig. 6. MOF-based nanozymes and single-atom nanozymes for antibacterial therapy. **A)** Schematic representation of the antibacterial mechanism of the biomimetic nanozyme catalyst, Bi-PCN-222. **B)** HRTEM images and elemental mapping of Bi-PCN-222 nanozymes. **C-E)** DFT simulation results for Bi-PCN-222 nanozymes. **F)** Synthesis procedure of Fe-SAC. **G-H)** Schematic representation of Fe-SAC's antibacterial mechanism. **I)** TEM images and EDS elemental mapping of Fe-SAC. **J)** High-resolution HAADF-STEM image of Fe-SAC. A-E) Reproduced with permission [75]. Copyright 2023, ACS Publications. F-J) Reproduced with permission [78]. Copyright 2024, Wiley-VCH.

excellent catalytic activity of SAzymes, using SAzymes for antimicrobial therapy has gradually attracted the interest of researchers. Bai *et al.* presented a strategy involving a copper and silk fibroin (Cu-SF) composite for synthesizing copper SAzymes with atomically dispersed copper sites [82]. The synthesized Cu SAzymes exhibit three enzyme activities, including POD-like, CAT-like, and OXD-like activities, efficiently killing bacteria through cascade reactions that generate a large amount of toxic ROS. The data indicate that the synthesized Cu SAzymes effectively combat multidrug-resistant bacteria and eradicate biofilms, showing excellent therapeutic effects on IAIs. Gao *et al.* prepared Mn SAzymes-functionalized 3D-printed bioceramic scaffolds, which efficiently catalyze the local H_2O_2 through cascade reactions to produce sufficient $\cdot OH$ and $\cdot O_2^-$ for antibacterial therapy [83]. This study provides an effective approach for the treatment of clinical infectious bone defects. Li *et al.* synthesized a titanium carbide MXene (Ti_3C_2)-based hybrid incorporating Pt single atoms (Pt-Ti_3C_2) [84]. The Pt single atoms exhibited excellent POD-like activity, catalyzing the *in situ* conversion of H_2O_2 in the microenvironment into $\cdot OH$, effectively combating bacterial infections and eradicating biofilms. This work offers a novel approach for bio-catalytic antibacterial therapy. Most conventional nanozyme technologies encounter major challenges related to size, composition, and the limited availability of natural active sites. To address these issues, Liu and co-workers synthesized iron single-atom structures (Fe-SAC) through nitrogen-doped carbon (Fe-N) and demonstrated a high loading capacity (Fig. 6F–J) [78]. They proved that the synthesized Fe-SAC generates ROS through enzymatic catalytic activity, disrupting bacterial cell membrane structures, eradicating MRSA, and accelerating the wound healing process.

As an endogenous catalytic therapy, nanozyme catalytic therapy offers the advantage of not relying on external energy input, making it more broadly applicable in the field of anti-infection treatment. Compared to traditional antibiotic therapies, it provides higher bactericidal efficiency, lower rates of resistance development, and broad-spectrum antibacterial activity. However, nanozyme catalytic therapy also faces challenges, particularly regarding its distribution within the host, long-term biosafety and metabolism *in vivo*, which require further investigation. Future research should focus on improving the design of nanozyme catalysts to enhance their catalytic efficiency and biocompatibility, as well as exploring their combination with other therapies to achieve broader antibacterial efficacy.

3. External stimuli-responsive nanocatalytic medicine anti-infection

3.1. Photocatalytic therapy (PCT)

Photocatalytic reactions are essentially light-triggered redox reactions [85]. Under irradiation of specific wavelengths, photocatalytic materials can excite electron transitions to form electron-hole pairs. These electrons and holes react with water molecules and oxygen to generate various ROS and can damage bacterial cell membranes, DNA, and proteins, leading to bacterial death [86]. The reaction equations for the photocatalyst are as follows:

$$O_2 + H_2O \xrightarrow{PS/light} \cdot O_2^- + \cdot OH + H^+ \tag{3}$$

$$O_2 \xrightarrow{PS/light} {}^1O_2 \tag{4}$$

Equation (3) describes a Type I photocatalytic reaction, where light

of specific wavelengths activates the photocatalyst to generate electron-hole pairs. These electron-hole pairs can react with O_2 and H_2O to produce $\cdot O_2^-$ and $\cdot OH$, respectively. Equation (4) describes a Type II photocatalytic reaction, where in the presence of the photocatalyst and specific wavelengths of light, environmental O_2 can be converted into highly toxic $^1O_2$ through direct energy transfer [87]. Photocatalysts can be categorized into Type I and Type II materials based on the type of photocatalytic reactions. Type I photocatalytic materials are mainly semiconductors, including metal oxides, nitrides, carbides, and sulfides. Type II photocatalytic materials predominantly consist of phthalocyanines, porphyrins, black phosphorus, and MOFs [88]. Photocatalytic therapy can generate abundant toxic ROS, and it has been extensively explored and studied in both tumor treatment and antibacterial applications [89–92].

Type I photocatalytic materials generate $\cdot OH$ and $\cdot O_2^-$ through photocatalytic reactions when irradiated with light of energy, which has a strong bactericidal effect. Among type I photocatalytic materials, titanium oxide (TiO_2) and zinc oxide (ZnO) nanomaterials have become focal points of research in photocatalytic antibacterial materials. Yang *et al.* reported a TiO_2/TiO_{2-x} metasurface with strong NIR-responsive antibacterial activity on the surface of titanium implants through a novel alkali-acid bidirectional hydrothermal method (aaBH) based on topochemical conversion (Fig. 7A–G) [93]. After low-power NIR irradiation, the material exhibited powerful antibacterial capabilities and

excellent biocompatibility. *In vivo* data showed that the antibacterial efficiency reached 91.80 % after 10 min of NIR laser irradiation, demonstrating the potential of this TiO_2/TiO_{2-x} metasurface material for the treatment of IAIs. Kang and co-workers developed a new technique capable of inducing the phase separation of inorganic salts during the electrospinning process to synthesize nanofibers with a surface concentrated in Zn components, named I@ZnO/ACNFs (Fig. 7H–N) [94]. These nanofibers are densely coated with high-aspect-ratio ZnO nanospikes, capable of producing significant amounts of $\cdot OH$ and $\cdot O_2^-$ through photocatalytic reactions under sunlight. This shows significant antibacterial efficacy against airborne infectious pathogens, demonstrating the potential of photocatalytic materials for disinfection of airborne microorganisms and air purification.

Despite Type I photocatalytic materials can produce $\cdot OH$ and $\cdot O_2^-$ to combat bacterial infections, challenges remain in enhancing their photocatalytic performance. Type I antibacterial photocatalysts, like TiO_2, are wide bandgap semiconductors that can only absorb and utilize ultraviolet (UV) light, which makes up a small fraction of sunlight. Moreover, UV light poses risks to human health and has limited penetration ability [95]. Achieving satisfactory antibacterial effects requires higher light intensity or prolonged exposure, which can significantly raise the toxicity risk to the host [96,97]. Thus, it is essential to broaden the light absorption range, enhance visible light utilization, and boost photocatalytic activity. A practical approach is to modify impurity
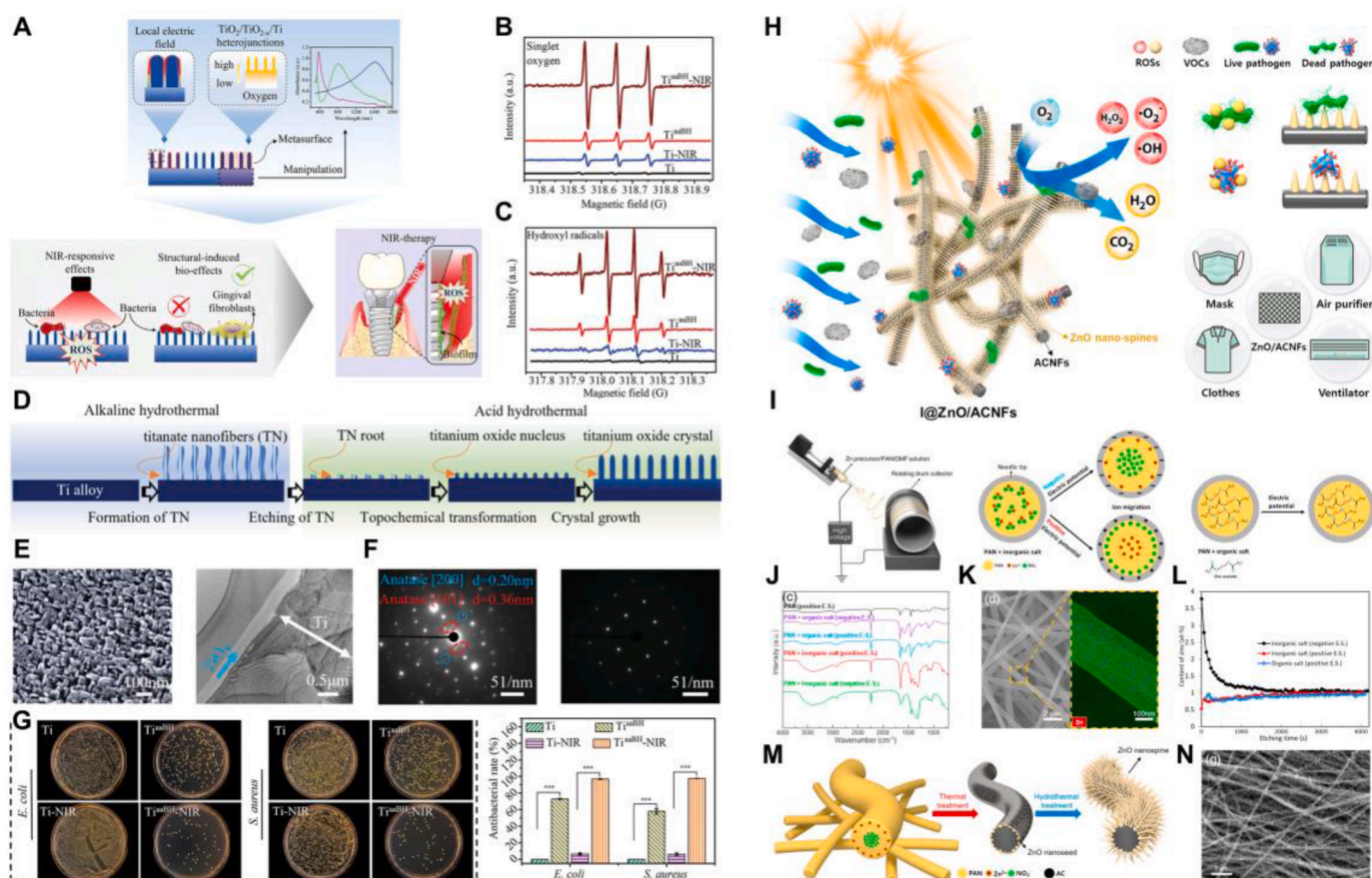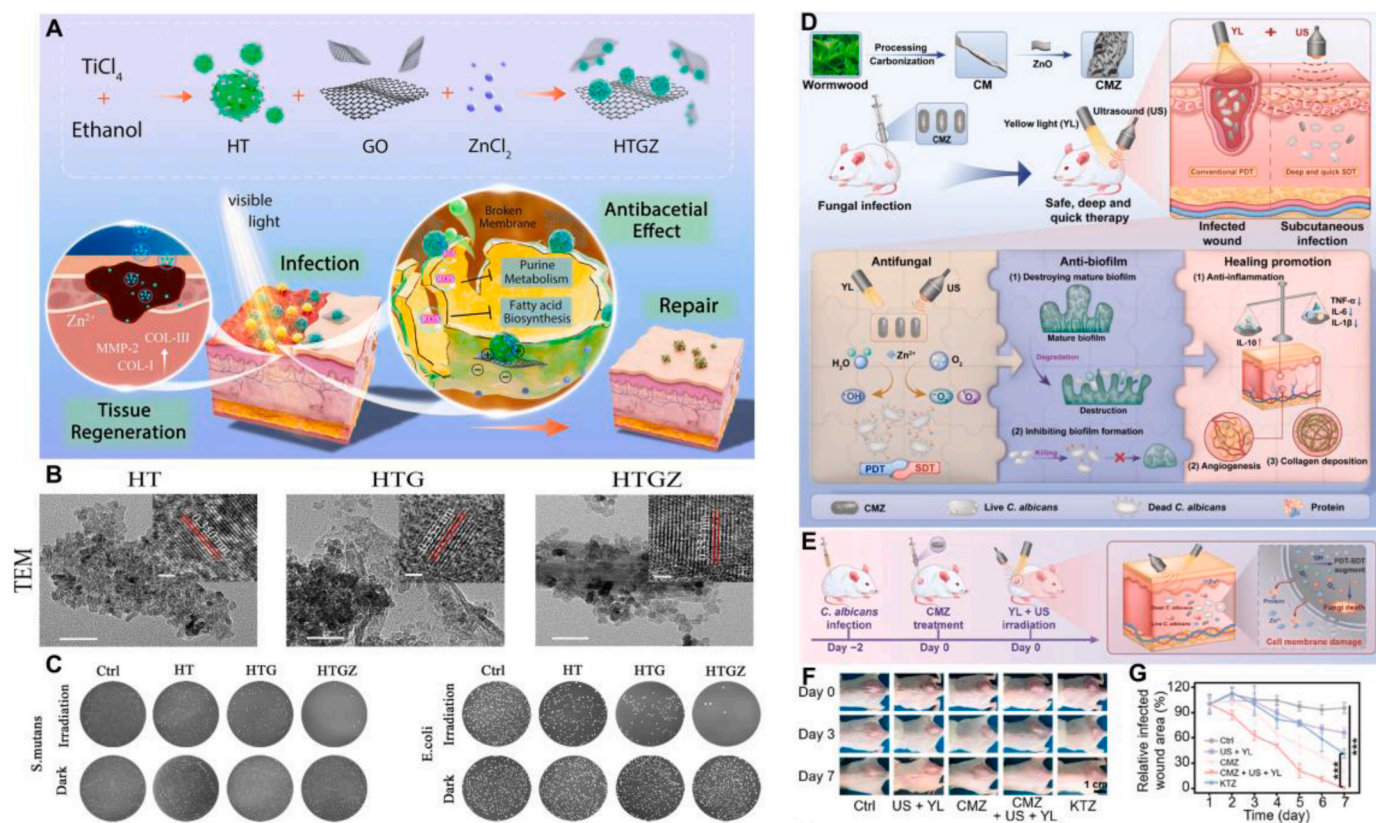

Fig. 7. **Photocatalytic antibacterial strategy based on Type I photocatalysts. A)** Preparation process of TiO_2/TiO_{2-x} super surfaces. **B-C)** ESR curves of $^1O_2$ and ●OH generated by Ti^{aaBH} samples under 808 nm laser irradiation. **D)** Design principle of constructing quasi-periodic titanium oxide super surfaces on titanium alloy implants. **E)** SEM and TEM images of Ti^{aaBH}. **F)** Diffraction patterns of Ti^{aaBH} and Ti. **G)** Plate images and corresponding bactericidal rates after different treatments. **H)** Schematic illustration of the synthesis of ZnO nanospikes grown on activated carbon nanofibers and its photocatalytic antibacterial mechanism. **I)** Schematic diagram of the electrospinning preparation process and the distribution of inorganic and organic phases under different potentials. **J)** Infrared spectra of different electrospun fibers. **K)** TEM and Zn elemental mapping images of electrospun fibers. **L)** The relationship between atomic content of Zn in the fibers and etching depth. **M)** Schematic representation of the I@ZnO/ACNFs synthesis process. **N)** FE-SEM images of I@ZnO/ACNFs. A-G) Reproduced with permission [93]. Copyright 2021, Wiley-VCH. H-N) Reproduced with permission [94]. Copyright 2021, Elsevier Ltd.

energy levels by metal and non-metal doping and introducing vacancies, thereby lowering the energy needed to excite photogenerated carriers, expanding the light absorption range, and improving light absorption capacity [98,99]. Lu *et al.* prepared novel carbon-modified TiO_2 nanoparticles (HT) and uniformly dispersed them on reduced graphene oxide (rGO), doping Zn during the preparation process to ultimately obtain the Zn-HT/rGO (HTGZ) nano-system (Fig. 8A–C) [100]. Zn ions were integrated into the TiO_2 nanoparticle lattice, generating additional defect energy levels. The photoexcited electrons could transition from the valence band to the defect levels or from the defect levels to the conduction band, reducing the required photon energy and broadening the optical response range. They proved that the formed HTGZ nano-system significantly increased ROS production under visible light irradiation, enhancing antibacterial performance. Similarly, the photodynamic antibacterial activity of conventional ZnO, with a wide bandgap ($\sim$3.37 eV), relies primarily on ultraviolet light. However, this not only poses risks to normal tissues but also suffers from limitations like low photocatalytic efficiency and poor penetration depth, restricting its use in photocatalytic therapy [101]. To address these challenges, Weng *et al.* introduced carbonized moxa to synthesize narrow bandgap ZnO (carbonized moxa@ZnO, CMZ) (Fig. 8D–G) [102]. This material exhibits excellent photocatalytic performance, high ROS production, and strong antibacterial efficiency under long-wavelength visible light (yellow light) irradiation. Type I photocatalytic materials like TiO_2 can be combined with other substances, such as MXenes, to enhance electron transfer. Due to their lower energy levels compared to the conduction band of semiconductors and their excellent conductivity, these materials can transfer photogenerated electrons, enabling the separation of electrons and holes, which boosts photocatalytic efficiency. Furthermore,

the formation of Schottky junctions prevents the electrons from returning to TiO_2 and recombining with holes. Based on this, Cheng and co-workers prepared $ZnTCPP/Ti_3C_2T_X$ nano-photocatalytic materials, which exhibited excellent antibacterial effects against *S. aureus* and *E. coli* under visible light irradiation [103]. After 10 min of visible light irradiation, this material exhibited antibacterial efficiencies of 99.86 % against *S. aureus* and 99.92 % against *E. coli*, demonstrating significant potential for enhancing the application of photocatalytic therapy in antibacterial treatments.

When Type II photocatalysts are excited by photons, they absorb energy from the ground state and transition to the excited state, transferring this energy to oxygen molecules. The triplet oxygen then absorbs the energy from the photosensitizer and converts into singlet oxygen ($^1O_2$). While the oxidizing power of $^1O_2$ is slightly weaker than ·OH, it still exhibits strong antibacterial effects. Therefore, there have been numerous studies on using Type II photocatalysts for antimicrobial treatments based on photocatalytic therapy [104,105]. Zhu *et al.* developed new AIE photocatalysts by modifying two cationic 4-vinyl-pyridine units on tetraphenylethylene (TPE) and isolated pure stereoisomers to obtain (*Z*)-TPE-EPy and (*E*)-TPE-EPy (Fig. 9A–C) [106]. The synthesized AIE photocatalysts exhibited extremely strong photocatalytic capabilities, producing large amounts of $^1O_2$ and ·O_2^- after 10 min of white light irradiation. This led to nearly 100 % killing efficiency against *Saccharomyces cerevisiae* and *Candida albicans*. In another study, Lochenie and co-workers reported the design of a novel benzothiadiazole photocatalyst with broad-spectrum antibacterial activity under non-toxic light irradiation [107]. They demonstrated that it has significant bactericidal effects against MDR bacteria and it showed excellent therapeutic effects in a pig keratitis model. Black phosphorus (BP) is also

Fig. 8. Photocatalytic enhancement strategy based on Type I photocatalytic materials. **A)** Schematic illustration of the HTGZ nanosystem enhancing photodynamic antibacterial efficacy and accelerating infected wound healing. **B)** HR-TEM images of HT, HTG, and HTGZ nanomaterials. **C)** Plate images of bacteria after intervention with nanomaterials. **D)** Schematic illustration of the CMZ antibacterial platform producing ROS through photocatalysis and sonocatalysis to eliminate fungi. **E)** workflow of the *in vivo* experiment of CMZ against Candida albicans. **F)** Images of Candida albicans infection sites. **G)** Area curve of Candida albicans infection sites. A-C) Reproduced with permission [100]. Copyright 2023, Springer Nature. D-G) Reproduced with permission [102]. Copyright 2024, ACS Publications.
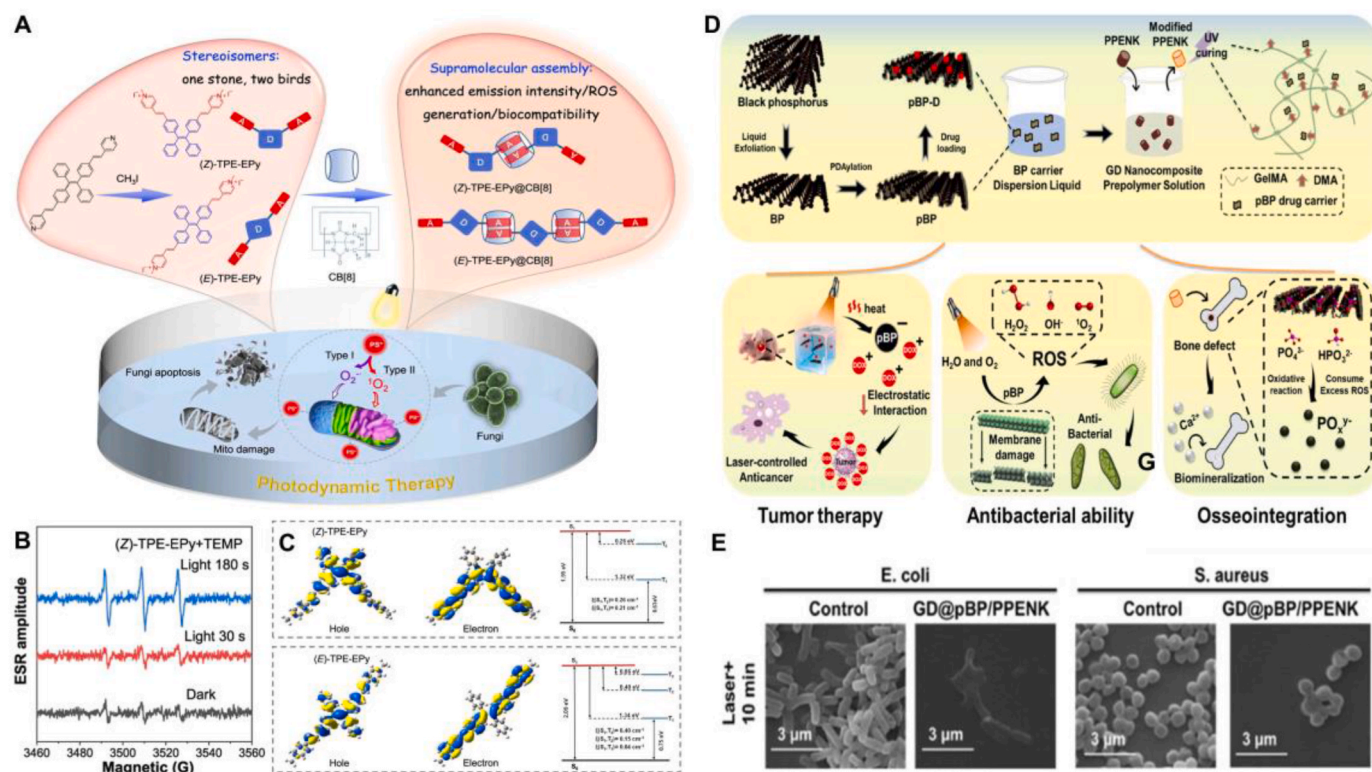
Fig. 9. Photocatalytic antibacterial strategy based on Type II photocatalysts. A) Schematic representation of the structures and antifungal mechanisms of AIE photocatalysts. **B)** ESR spectra of AIE photocatalysts showing the generation of $^1O_2$ and $\cdot O_2^-$. **C)** Energy level diagram depicting the singlet and triplet states of AIE photocatalysts. **D)** Schematic illustration of the preparation of GelMA/DMA nanocomposite photo-crosslinked hydrogel coating on PPENK implants. E) SEM images of bacteria after treatment with different materials under dark and laser conditions. A-C) Reproduced with permission [106]. Copyright 2022, Springer Nature. D-E) Reproduced with permission [109]. Copyright 2023, Elsevier Ltd.

an excellent Type II photocatalytic material that can generate a variety of ROS under laser irradiation, making it one of the promising nanomaterials for photocatalytic antibacterial therapy [108]. Based on this, Li *et al.* developed a mussel-inspired multifunctional photo crosslinked gelatin (GD) hydrogel coating on bioinert PPENK, which contains black phosphorus nanosheets wrapped in PDA (Fig. 9D–E) [109]. Under 808 nm laser irradiation, this coating material can generate and release toxic ROS to achieve antibacterial effects and exhibits good biocompatibility.

Photocatalytic antibacterial materials based on Type II photocatalytic reactions require O_2 to produce $^1O_2$. However, similar to tumor sites, infection sites are often hypoxic environments with insufficient oxygen content, which significantly limits the *in vivo* antibacterial efficiency of Type II photocatalytic materials. To address this challenge, researchers have investigated several strategies to boost oxygen levels at infection sites, thereby improving the antibacterial effectiveness of photocatalysis. Given the excessive production of H_2O_2 at infection sites, Wang *et al.* utilized the catalase-like activity of MnO_2 to design and prepare PEG-modified MnO_2 nanoparticles loaded with the photosensitizer Ce6 (Ce6@MnO$_2$-PEG NPs) [110]. These nanoparticles can catalyze the endogenous H_2O_2 to generate O_2, thus enhancing the photocatalytic ability of the nanoparticles. They proved that the prepared nanoparticles could efficiently kill *S. aureus* under laser irradiation, significantly improving the condition of *S. aureus*-induced mice subcutaneous abscesses. Moreover, reducing the distance between the photosensitizer and the bacteria maximizes the bactericidal effect of photocatalytically produced ROS, making bacterial targeting strategies essential in the design of photocatalytic therapies. Our group designed and developed multifunctional photocatalytic nanoparticles (BMCV NPs) by conjugating vancomycin groups onto the surface of BSA-MnO$_2$ nanoclusters loaded with Ce6, thereby targeting *S. aureus* (Fig. 10A–E) [111]. The synthesized BMCV NPs can specifically adhere to the surface

of *S. aureus*, catalyze H_2O_2 to generate O_2, and produce ROS through photocatalysis around the bacteria, maximizing the bactericidal effect on *S. aureus* and disrupting the eDNA in biofilms. Similarly, Zhang *et al.* designed a nanoplatform (Arg-PCN@Gel) targeting *S. aureus* as a photocatalytic antibacterial system [112]. They demonstrated that Arg-PCN@Gel can target MRSA and can generate ROS to prevent and treat biofilms formed by *S. aureus*. Recently, Zhuang and co-workers reported that the combination of the natural substrate carvacrol (CA) and a classic Type II PS (such as Ce6) could enhance the generation of $\cdot O_2^-$ by promoting the electron transfer process, significantly mitigating the limitations of hypoxic infection environments on Type II photocatalytic efficiency (Fig. 10F–H) [113]. This study creatively converted a Type II PS into a Type I PS by enhancing the electron transfer process, enabling the Type II PS to better tolerate hypoxic microenvironments and offering new perspectives for improving photocatalytic therapy effectiveness in oxygen-deficient conditions.

Photocatalytic therapy is capable of efficiently generating ROS, which disrupt bacterial structures and exhibit significant inhibitory effects against a broad spectrum of bacteria, including antibiotic-resistant strains. Unlike traditional antibiotics, this therapeutic approach operates through mechanisms that do not rely on specific biochemical pathways, thereby reducing the risk of bacterial resistance development. However, the efficacy of photocatalytic therapy is dependent on the availability of specific wavelengths of light, limiting its application under certain conditions. Moreover, the recombination of photogenerated electrons and holes within the material can diminish the efficiency of ROS generation, thus constraining the antibacterial performance of the photocatalyst [114]. Additionally, the potential toxicity of photocatalysts and their long-term safety in biological systems require further investigation and evaluation. Through ongoing optimization of material design and process improvements, this therapy
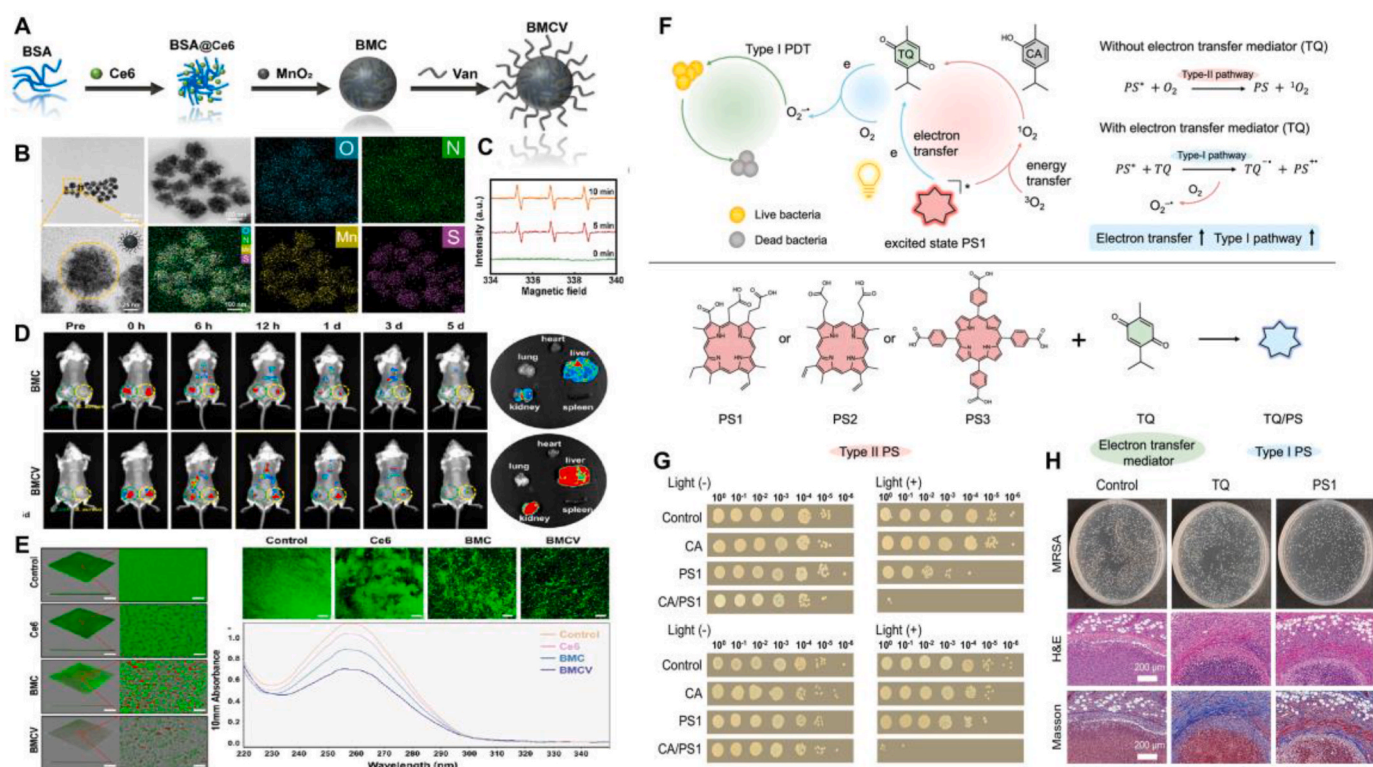
Fig. 10. Photocatalytic enhancement strategy based on Type II photocatalytic materials. **A)** Schematic depiction of BMCV nanoparticle synthesis. **B)** TEM images and elemental mapping images of BMCV. **C)** ESR spectra of $^1O_2$ generation by BMCV nanoparticles. **D)** Evaluation of the targeting ability of BMCV nanoparticles to the infection site. **E)** Impact of BMCV nanoparticles on *S. aureus* biofilms and eDNA. **F)** Schematic illustration of the promotion of $\cdot O_2^-$ generation through an electron transfer strategy. **G)** *In vitro* antibacterial assay of CA/PS1 complex against *S. aureus*. **H)** *In vivo* antibacterial evaluation of CA/PS1 complex. A-E) Reproduced with permission [111]. Copyright 2024, ACS Publications. F-H) Reproduced with permission [113]. Copyright 2024, Springer Nature.

holds promise as a significant tool in future antibacterial treatments.

3.2. Sonocatalytic therapy (SCT)

Ultrasound, a mechanical wave with long propagation distance, strong tissue penetration, and highly concentrated energy, has traditionally been used for disease imaging and diagnosis. Unlike external lasers, ultrasound offers deeper tissue penetration and causes minimal damage to tissues and organs, which has drawn growing attention in the biomedical field in recent years [115,116]. Sonocatalytic therapy (SCT) combines ultrasound with sonosensitizers to achieve therapeutic effects by generating ROS through ultrasound-activated catalysts [117–120]. The core mechanism involves the interaction between ultrasound waves (typically with frequencies ranging from 20 kHz to 1 MHz) and the catalyst, producing ROS, capable of destroying pathogens or cancer cells. Ultrasound can non-invasively penetrate tissues and reach deep-seated lesions, offering excellent therapeutic efficacy for deep-seated diseases, particularly in the treatment of deep solid tumors, which is currently being widely explored [121–125]. Host bacterial infections are not limited to superficial infections such as skin wound infections but also include deep tissue infections like subcutaneous abscesses and infections of bone and muscle tissues (osteomyelitis and implant-related infections), where sonocatalytic therapy holds significant therapeutic advantages and potential. The efficiency of sonocatalytic therapy critically depends on the selection and development of sonosensitizers. An increasing number of sonosensitizers are currently being synthesized and applied in the biomedical field, encompassing organic, inorganic, and organic-inorganic hybrid types. Different types of sonosensitizers exhibit varying sonocatalytic properties and therapeutic effects.

Organic sonosensitizers are types of organic molecules or compounds used in sonocatalytic therapy to enhance the catalytic effect of ultrasound, which primarily include porphyrins and their derivatives, phthalocyanines, 5-aminolevulinic acid, indocyanine green, xanthene dyes, and natural products [126–128]. Organic sonosensitizers have the advantages of high ROS generation efficiency, the ability to undergo structural modification to optimize therapeutic efficacy, and high biocompatibility. Additionally, organic sonosensitizers can be used not only for sonodynamic therapy but also for photodynamic therapy, enabling multimodal treatment. Organic sonosensitizers have the advantages of high ROS generation efficiency, structural modifiability for optimizing therapeutic efficacy, and high biocompatibility [129]. Additionally, organic sonosensitizers can be used not only for sonocatalytic therapy but also for photocatalytic therapy, enabling multimodal treatment [130]. To address the challenges of ineffective accumulation of sonosensitizers at infection sites, hypoxic microenvironments, and rapid oxygen consumption during SDT, Sun *et al.* proposed a sonication-activated switchable nanozyme system, which can controllably generate O_2 and sonosensitizer-mediated ROS during ultrasound activation [131]. By combining Pd@Pt nanoplates with the organic sonosensitizer *meso*-tetra(4-carboxyphenyl)porphine (T790), they developed a sonocatalytic nano-platform (Pd@Pt-T790). Under ultrasound activation, the catalase-like activity of Pd@Pt is activated, catalyzing the decomposition of H_2O_2 at the infection site to produce sufficient O_2, enhancing the sonocatalytic efficiency, and generating a large amount of toxic ROS. This system demonstrated excellent therapeutic effects on MRSA-induced muscle infections and provided a promising approach for enhancing sonocatalytic therapy for deep bacterial infections. To endow the nano-antibacterial materials with long-term resistance against bacterial infections, Xu and co-workers proposed a synergistic therapeutic strategy combining sonodynamic therapy with adaptive immune modulation (Fig. 11A–C) [132]. They
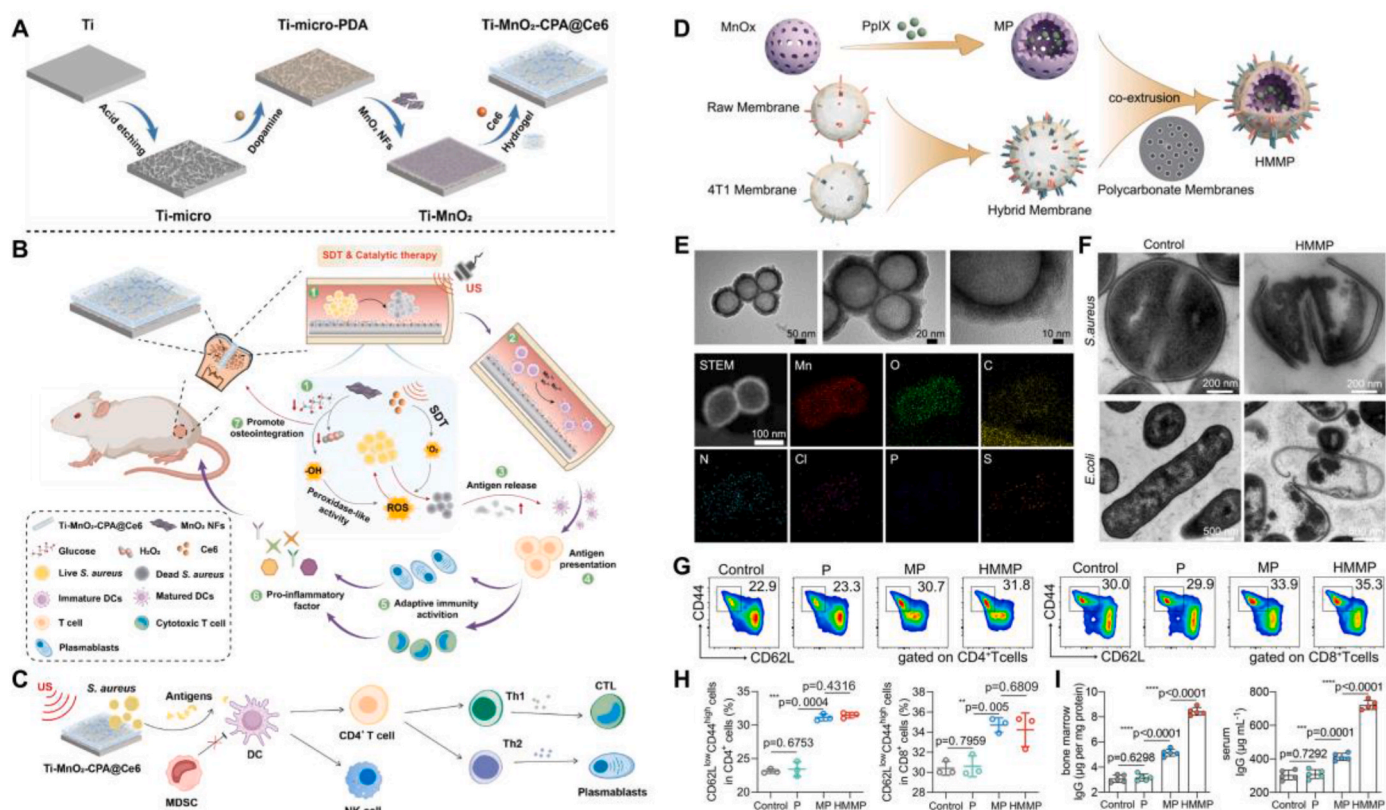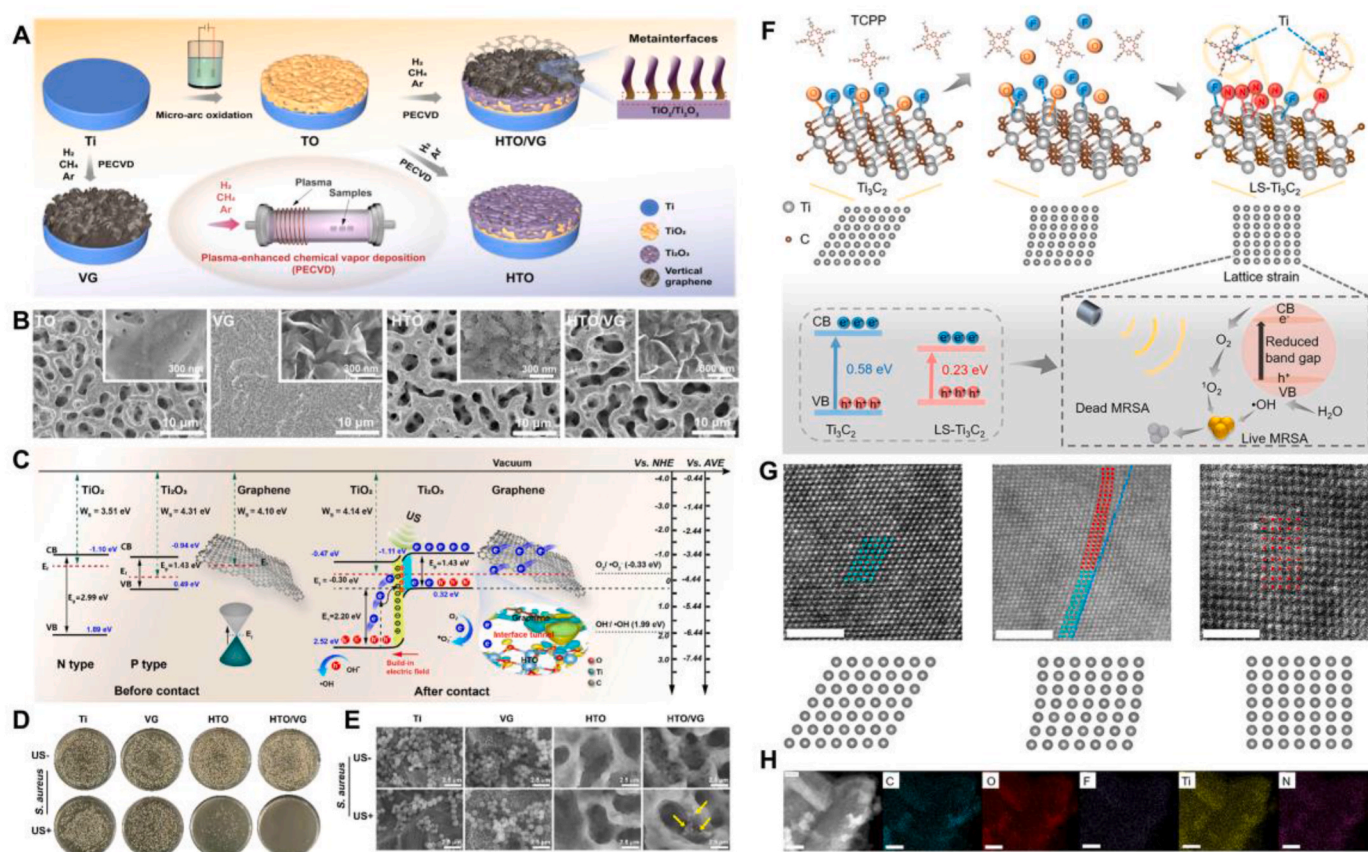
Fig. 11. Sonocatalytic therapy for bacterial infections based on organic sonosensitizers. **A)** Synthesis and preparation process of Ti–MnO$_2$-CPA@Ce6 substrate. **B)** The Ti–MnO$_2$-CPA@Ce6 substrate disrupts and kills *S. aureus* through sonocatalytic therapy and continuously combats infection by activating adaptive immunity through antigen release and manganese ions. **C)** Schematic illustration of the mechanism by which the Ti–MnO$_2$-CPA@Ce6 substrate activates adaptive immunity. **D)** Schematic depiction of HMMP nanoparticle synthesis. **E)** TEM images and elemental mapping images of HMMP nanoparticles. **F)** TEM images of bacteria after treatment with HMMP nanoparticles. **G-H)** Representative flow cytometry plots and corresponding quantitative data of CD4 and CD8 T memory cells in the spleen after secondary infection with *S. aureus*. **I)** IgG levels in serum and bone marrow after secondary infection with *S. aureus*. A-C) Reproduced with permission [132]. Copyright 2024, Elsevier Ltd. D-I) Reproduced with permission [133]. Copyright 2022, ACS Publications.

synthesized a responsive, degradable hydrogel containing an organic sonosensitizer (Ce6) on the surface of titanium implants. This multifunctional coating can kill bacteria *via* sonodynamic therapy and release bacterial antigens, while the manganese ions in the material can promote the maturation of dendritic cells (DCs), further activating both cellular and humoral adaptive immunity. This combined treatment strategy based on sonocatalytic therapy effectively clears diabetes-related IAIs and provides the host with long-term immune memory and antibacterial protection. Similarly, our group reported an *in situ* vaccination strategy for bacterial infection immunotherapy using an osteomyelitis model. We loaded the organic sonosensitizer PpIX into hollow MnOx nanoparticles and coated them with a hybrid membrane derived from macrophages and tumor cells, naming it HMMP (Fig. 11D–I) [133]. The synthesized HMMP nanoparticles are able to generate ROS *via* sonocatalysis of PpIX, release bacterial antigens as an *in situ* vaccine, initiate the antigen presentation process, and activate cellular and humoral adaptive immunity against bacterial infection. This *in situ* vaccine strategy, based on sonocatalytic therapy, equips the host with long-lasting bacteria-specific immune memory responses, helping to prevent infection recurrence.

Inorganic sonosensitizers exhibit multiple advantages in sonodynamic therapy, making them highly prominent in the field of antibacterial treatment [134,135]. Inorganic sonosensitizers possess excellent chemical stability, enabling sustained activity in complex biological environments, and they have a high capacity for generating ROS, which significantly enhances their antibacterial efficacy. Moreover, these materials typically exhibit good biocompatibility, ensuring their safe application within biological systems. The continuous development and

optimization of inorganic sonosensitizers have significantly broadened the application scope and therapeutic efficacy of sonocatalytic therapy [136]. Currently, inorganic sonosensitizers mainly include noble metal-based sonosensitizers, transition metal-based sonosensitizers, carbon-based nanomaterials, and silicon-based nanomaterials. Through an oxygen vacancy engineering strategy, Qian *et al.* synthesized TiO$_{2-x}$ microspheres with an abundance of Ti^{3+} using a simple reductant co-assembly method and deposited graphene quantum dot (GQD) nano-antibiotics on the TiO$_{2-x}$ microspheres to obtain GQD/TiO$_{2-x}$ [137]. This sonocatalytic nano-platform significantly enhances the antibacterial efficiency of SDT against bacteria through accelerated electron-hole pair separation, the POD-like enzyme activity of Ti^{3+}, and the depletion of GSH by Ti^{4+}. Constructing multifunctional sonocatalytic coating nanomaterials on titanium-based implants can be applied to combat IAIs. Zheng *et al.* integrated a dual-functional coating of two-dimensional (2D) photoacoustic-sensitive black phosphorus nanosheets (BPNSs) and polydopamine (PDA) on the surface of titanium implants with superior biocompatibility [138]. Under ultrasound and laser stimulation, the coating disrupts the cell membrane and antioxidant system of *S. aureus* through ROS generation and hyperthermia, exhibiting excellent bactericidal efficiency. Guan *et al.* developed a TiO$_2$/Ti$_2$O$_3$/vertical graphene metainterface heterostructure film on titanium implants, which exhibited remarkable sonodynamic and sonothermal conversion effects under low-intensity ultrasound (Fig. 12A–E) [139]. Antibacterial experiments demonstrated that this metainterface heterostructure enhanced sonocatalytic efficiency, killing over 99.99 % of *S. aureus* and 99.54 % of *E. coli*, providing a promising approach for applying sonocatalytic therapy to implant-related biofilm infections. To
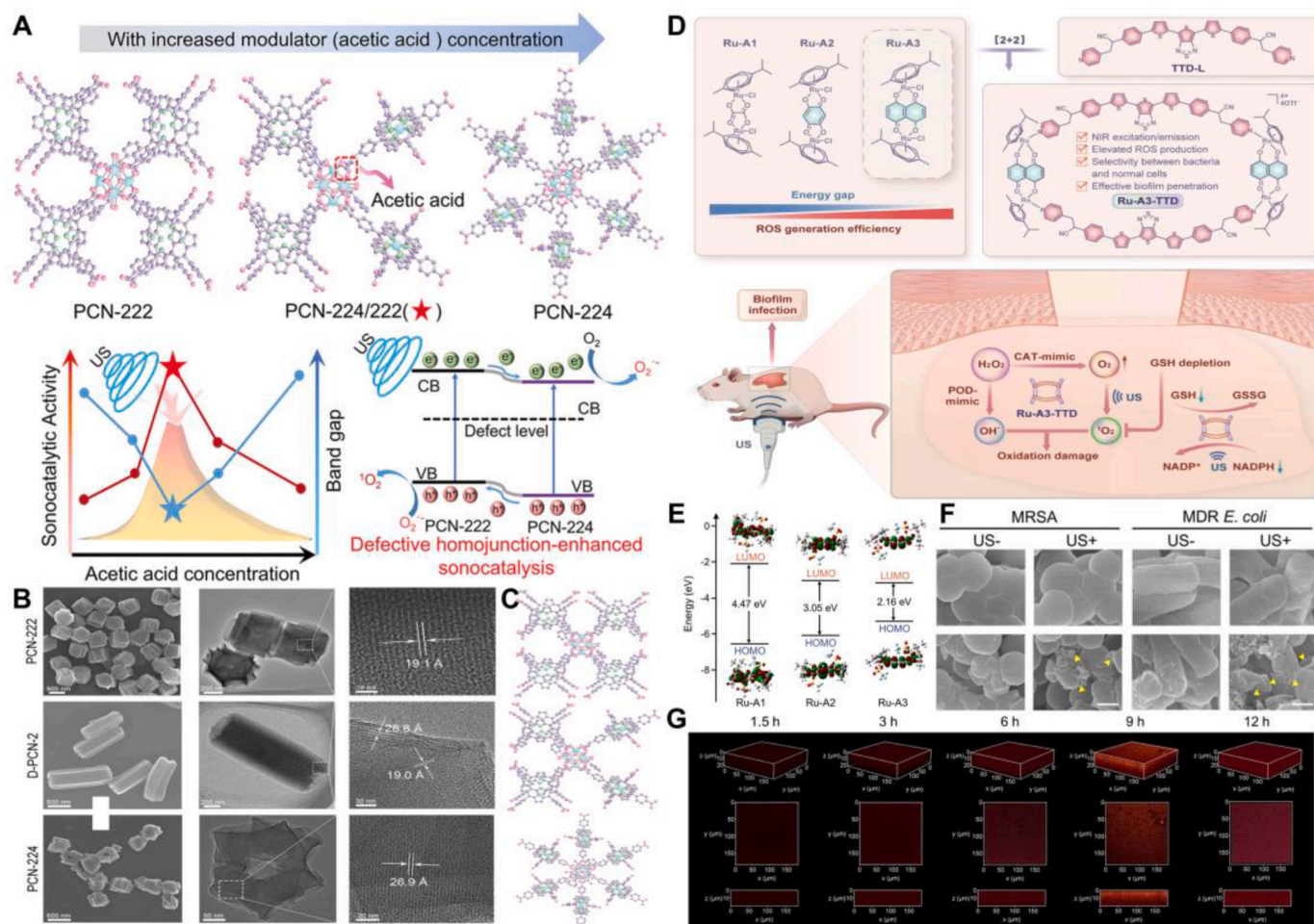
Fig. 12. Sonocatalytic therapy for bacterial infections based on inorganic sonosensitizers. A) Schematic illustration of the HTO/VG heterostructure preparation process. **B)** TEM images of HTO/VG heterostructure. **C)** Schematic depiction of the ROS generation mechanism *via* sonocatalysis in the HTO/VG heterostructure. **D)** CFU plate images of bacteria after treatment with HTO/VG heterostructure and US stimulation. **E)** SEM images of bacteria after treatment with HTO/VG heterostructure and US stimulation. **F)** Synthesis and preparation process of LS-Ti$_3$C$_2$ and its schematic illustration of the mechanism for killing MRSA based on sonocatalytic therapy. **G)** HAADF-STEM image of LS-Ti$_3$C$_2$. **H)** Elemental mapping images of LS-Ti$_3$C$_2$. A-E) Reproduced with permission [139]. Copyright 2024, ACS Publications. F-H) Reproduced with permission [140]. Copyright 2023, ACS Publications.

design more efficient inorganic sonosensitizers, Ku and co-workers synthesized lattice-strain-rich Ti$_3$C$_2$ (LS-Ti$_3$C$_2$) *via* a one-step solvothermal method using Ti$_3$C$_2$ and Tetrakis (4-carboxyphenyl) porphyrin (TCPP) (Fig. 12F–H) [140]. The introduction of TCPP led to the breakdown of all Ti-O chemical bonds and most Ti-F chemical bonds in the surface layer of Ti$_3$C$_2$. Subsequently, the amino groups of TCPP reacted with the exposed Ti atoms, disrupting their arrangement and causing atomic displacement, which ultimately resulted in lattice distortion in Ti$_3$C$_2$. This intrinsic lattice strain narrowed the band gap of Ti$_3$C$_2$, promoting the separation of electron-hole pairs and facilitating electron transfer under ultrasonic irradiation, thereby enhancing ROS generation efficiency and improving antibacterial activity.

Organic-inorganic hybrid sonosensitizers combine the benefits of both organic and inorganic materials. These hybrid sonosensitizers are created by integrating organic molecules or polymers with inorganic nanomaterials, resulting in composite materials with unique physicochemical properties. They mainly include MOFs, COFs, and other functional hybrid nanoparticles [141]. MOF nanomaterials, with its high sonosensitizer loading capacity and fast ROS diffusion, have huge potential in sonocatalytic therapy. Meng *et al.* reported a MIL@Ag heterostructure composed of a titanium-based MOF (MIL) with *in situ* assembled silver nanoparticles (Ag NPs), featuring high electron-hole pair separation efficiency and enhanced ROS catalytic generation capability [142]. Under ultrasound stimulation, Ag NPs in the MIL@Ag heterostructure can capture activated electrons from MIL, reducing surrounding O$_2$ and producing ·O$_2^-$, while the activated holes enable oxidizing H$_2$O to generate ·OH. This MOF-based sonocatalytic

enhancement strategy can effectively kill *S. aureus*, providing a new idea to improving the therapeutic efficacy of sonocatalytic therapy. Zeng *et al.* synthesized a porphyrin-based MOF with significantly enhanced sonocatalytic capacity through defect homojunctions and found that with increasing amounts of acetic acid, the crystal structure of the MOF transformed from PCN-222 to PCN-224 (Fig. 13A–C) [143]. The higher defect content in PCN-224 improves the separation of sonication-triggered electron-hole pairs, significantly enhancing the efficiency of ROS generation through sonocatalysis. They demonstrated that this defect-induced homojunction MOF exhibited excellent therapeutic efficacy in treating *S. aureus*-induced osteomyelitis in mice, significantly reducing the bacterial load in the mice. Based on the complex BME to design and fabricate sonosensitizers can more specifically and effectively enhance the sonocatalytic antibacterial efficacy. Xu and co-workers innovatively designed and developed a Ru(II)-based metallacycle sonosensitizer (Ru-A3-TTD) that significantly improves antibacterial efficiency by increasing O$_2$ in the BME, disrupting the antioxidant system within the BME, and enhancing the penetration of the sonosensitizer into biofilms (Fig. 13D–G) [144]. Additionally, Ru-A3-TTD demonstrated excellent biofilm eradication efficacy against MDR *E. coli*, providing a promising idea for addressing biofilm infections based on sonocatalytic strategies. Efficient sonodynamic therapy can disrupt bacterial structures and promote the release of bacterial-associated double-stranded DNA (dsDNA), thereby activating a robust adaptive immune response. Based on this, Xu *et al.* designed and fabricated an iron-based COF doped with curcumin and platinum (CFCP) for treating persistent IAIs. They demonstrated that

Fig. 13. Sonocatalytic therapy for bacterial infections based on organic-inorganic hybrid sonosensitizers. **A)** Transformation process of the MOF crystal structure with increasing acetic acid concentration and the corresponding defect-enhanced sonocatalytic mechanism. **B)** SEM and TEM images of various MOF nanomaterials. **C)** Schematic diagrams of the molecular frameworks of different MOF nanomaterials. **D)** Schematic illustration of the design of Ru-A3-TTD nano-sonosensitizers and the mechanism for treating biofilm infections. **E)** LUMO-HOMO distribution based on DFT calculations. **F)** SEM images of MRSA and MDR *E. coli* biofilms following treatment with Ru-A3-TTD. **G)** 3D reconstruction images of MDR *E. coli* biofilms after Ru-A3-TTD treatment at different time points. A-C) Reproduced with permission [143]. Copyright 2022, Wiley-VCH. D-G) Reproduced with permission [144]. Copyright 2024, Wiley-VCH.

sonocatalytic therapy could kill *S. aureus*, promote DCs maturation, and enhance neutrophil immune stimulation. Additionally, this treatment strategy can activate humoral immunity by stimulating B cells and T cells, producing antibodies to combat secondary IAIs and providing the host with long-term immune protection.

Sonocatalytic therapy, as an emerging antibacterial strategy, offers significant advantages in treating deep-seated infections such as osteomyelitis and implant-associated infections. However, the clinical application of SCT faces challenges, including limitations in ultrasound penetration depth and concerns regarding the biodistribution and potential toxicity of sonosensitizers. Future research should focus on optimizing the design of sonosensitizers to enhance their selectivity and safety, as well as exploring the combination of SCT with other therapeutic modalities to achieve broader clinical applicability and improved therapeutic outcomes.

3.3. Electrocatalytic therapy (ECT)

Electrocatalytic Therapy (ECT) is an emerging treatment method that utilizes electrocatalysis to generate ROS and other active intermediates to treat various diseases. Due to its high efficiency, precision, and minimally invasive nature, ECT has shown great potential in Biomedical field. The mechanism of action involves using electrocatalysts under an applied electric field to perform redox reactions, generating highly active ROS that can disrupt cellular components such as cell membranes, DNA, and proteins, thereby killing bacteria or cancer cells. Unlike chemodynamic therapy, which is affected by the microenvironment of infection, and photocatalytic or sonocatalytic therapies, which can cause harm to human cells due to high power density of light or US, ECT possesses advantages of being non-invasive, having high tissue penetration, and high selectivity. ECT was first proposed by Liu and colleagues, also known as electrodynamic therapy (EDT), and was applied in cancer treatment [145]. Subsequently, cancer treatment strategies based on ECT have gradually emerged [146,147]. Similarly, ECT has evident advantages in combating bacterial infections and clinical translation. The most commonly used nano-electrosensitizers in ECT are noble metal Pt nanoparticles [146]. Based on this, Qiao *et al.* developed a novel biomimetic nano-platform by using ginger-derived extracellular vesicles (EVs) to encapsulate Pd-Pt nanosheets (Fig. 14A–B) [148]. Experimental data and computational simulations demonstrated that Pd-Pt nanosheets exhibit higher electrocatalytic activity compared to Pt nanoparticles. Additionally, the encapsulation with cell membrane vesicles ensures the accumulation of the nano-platform at the infection site, significantly improving the treatment of *S. aureus*-induced subcutaneous abscesses in mice. To further enhance the efficiency of electrocatalytic
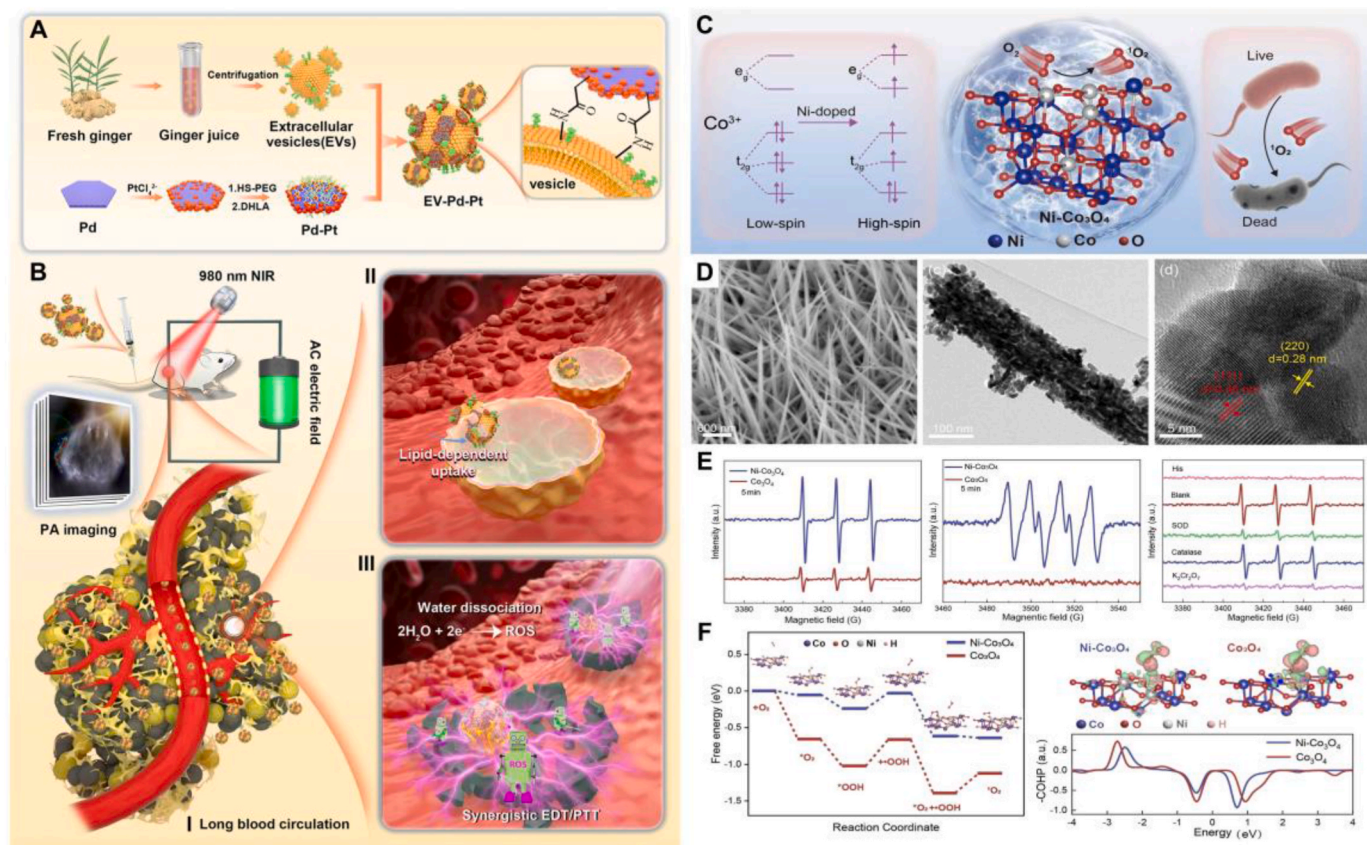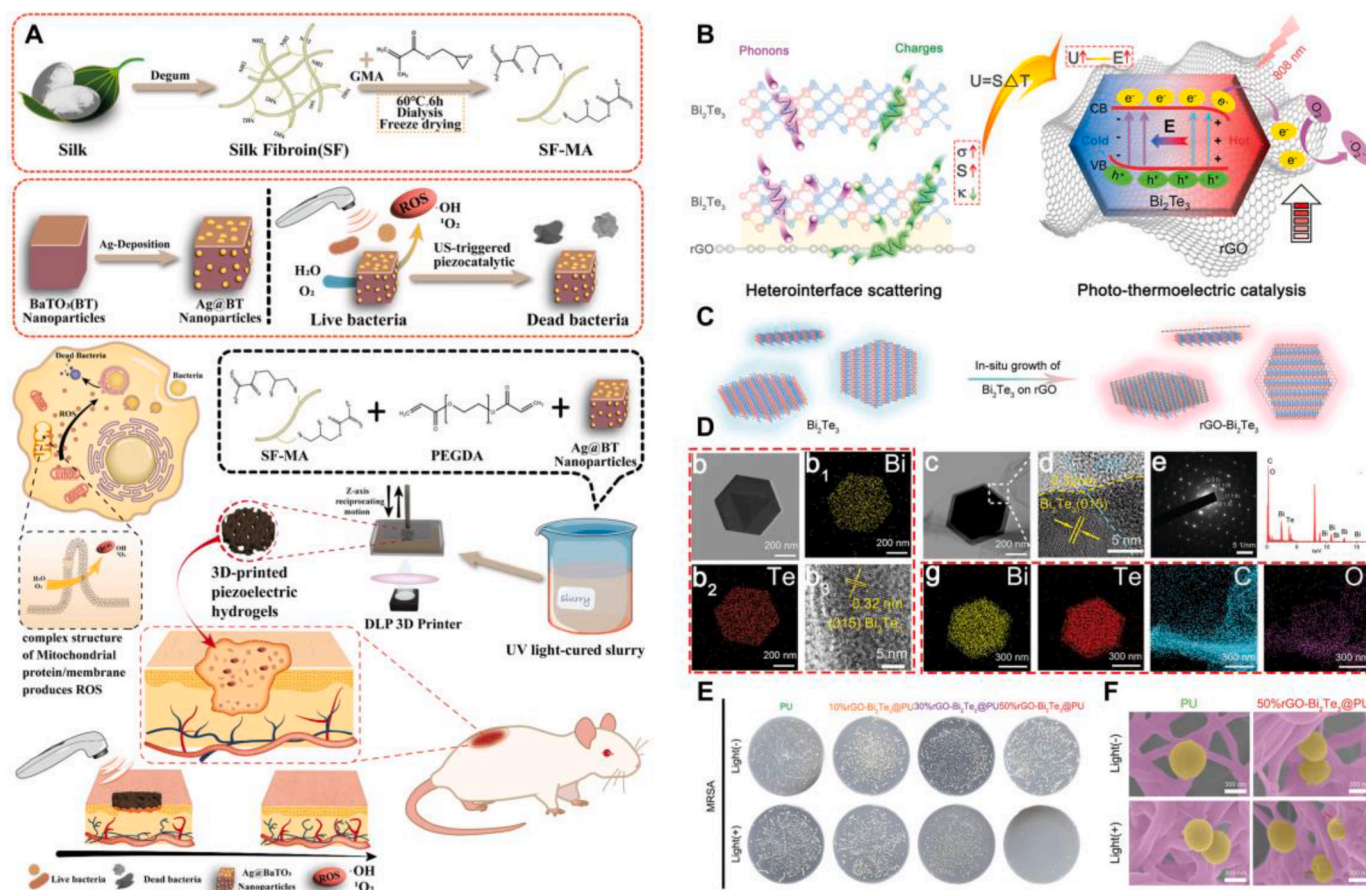
Fig. 14. Antibacterial strategy based on electrocatalytic therapy. **A)** Schematic depiction of EV-Pd-Pt nanoparticle synthesis by attaching carboxyl-functionalized Pd-Pt nanoparticles to amino group-rich ginger-derived EVs. **B)** *In vivo* synergistic ECT/PTT strategy to eliminate infection. **C)** Schematic depiction of the bactericidal mechanism of the Ni−Co3O4 system. **D)** Schematic representation of the antibacterial mechanism of the Ni−Co_3O_4 system. **E)** EPR spectra of Ni−Co_3O_4 producing $^1O_2$ and ·OOH/O_2^-. **F)** Free energy diagram of molecular oxygen activation processes for Ni−Co_3O_4 and Co_3O_4. A-B) Reproduced with permission [148]. Copyright 2022, Springer Nature. C-F) Reproduced with permission [149]. Copyright 2024, Wiley-VCH.

antibacterial therapy, Duan and co-workers proposed a strategy to reverse the spin state of Ni−Co_3O_4, which can improve the production efficiency of $^1O_2$ through asymmetric orbital hybridization, thereby exhibiting strong bactericidal effects (Fig. 14C–F) [149]. The mechanism involves the transition of Co^{3+} from a low-spin to a high-spin state by introducing Ni, which enhances Co 3d-O 2p orbital hybridization between cobalt ions and adsorbed oxygen, thus increasing the oxygen catalytic activity of Ni−Co_3O_4. This study highlights the significant potential and value of spin engineering strategies in optimizing the efficiency of $^1O_2$ production by electrocatalysts and addressing microbial infections. Zhou and co-workers combined electrocatalytic therapy and photocatalytic therapy to develop a novel anti-sandwich structure of SeV^{2+}-PT loaded photo-electronic wound dressing (SeV^{2+}-PT PEWD) [150]. This dressing, under dual stimulation of visible light and electricity, efficiently generates ROS, enabling rapid bacterial eradication and reducing the wound healing time of bacterial infections to seven days.

Piezoelectric catalysis refers to the phenomenon where piezoelectric materials with non-centrosymmetric structures generate charges under external mechanical stress activation [151]. The generated charges further react with surrounding water or oxygen molecules to produce ROS. Therefore, piezoelectric catalytic materials can also be used to treat cancer and microbial infections [152–154]. Ultrasound generates mechanical strain that polarizes piezoelectric materials, creating an internal electric field that effectively separates electron-hole pairs. The resulting piezoelectric potential drives redox reactions. When the conduction band (CB) edge is more negative than the $O_2/·O_2^-$ redox potential (-0.33 V), ·O_2^- is produced. Similarly, when holes transfer to H_2O and the valence band (VB) edge is more positive than the $H_2O/·OH$ redox

potential (2.01 V), ·OH is generated. This mechanism is distinct from that of sonocatalytic therapy. Among various piezoelectric materials, functionalized barium titanate nanoparticles (BTO, $BaTiO_3$) have become classic piezoelectric catalytic materials due to its high piezoelectric performance, environmental friendliness, and simple structure. Lei *et al.* reported a novel piezoelectric catalytic nanomaterial consisting of barium titanate nanoparticles and selenium nanoparticles, which enhances electron-hole separation and promotes internal free carrier transfer. This results in stronger piezoelectric catalytic performance, effectively combating bacterial infections [155]. Similarly, Chen *et al.* also modified and optimized barium titanate ($BaTiO_3$) by depositing Ag NPs on the surface of $BaTiO_3$ to form a heterostructure (Fig. 15A) [156]. This configuration enabled the piezoelectric material to generate a strong piezoelectric catalytic reaction under low concentrations and short ultrasound stimulation. Additionally, they incorporated the synthesized high-efficiency piezoelectric nanoparticles into biodegradable silk fibroin (SF), resulting in a piezoelectric catalytic composite hydrogel. This hydrogel exhibited excellent piezoelectric catalytic performance, degradability, biocompatibility, and remarkable antibacterial activity, significantly accelerating the healing of infected wounds. The basic principle of thermoelectrocatalysis involves utilizing the potential difference generated by thermoelectric materials under a temperature gradient to drive electrocatalytic reactions. This technology combines the advantages of thermoelectric effects and electrocatalytic reactions, enabling efficient utilization of thermal energy while achieving high-selectivity chemical transformations. Bismuth telluride (Bi_2Te_3) is one of the most common and excellent thermoelectric materials near room temperature. Wang and co-workers developed an efficient thermoelectrocatalytic material (rGO-Bi_2Te_3) by *in situ* growing Bi_2Te_3

Fig. 15. Antibacterial strategy based on piezocatalytic therapy. A) Synthesis process of Ag@BT NPs and schematic illustration of the application and antibacterial mechanism of SF-MA/PEGDA hydrogels for treating infected wounds. **B)** Schematic illustration of the heterointerface scattering and photothermal electrocatalytic mechanism. **C)** Synthesis process of rGO-Bi$_2$Te$_3$ nanosheets. **D)** TEM images and EDS elemental mapping images of rGO-Bi$_2$Te$_3$ nanosheets. **E-F)** Plate images and SEM images of *S. aureus* after treated with different materials. A) Reproduced with permission [156]. Copyright 2024, Elsevier Ltd. B-F) Reproduced with permission [157]. Copyright 2022, Wiley-VCH.

nanosheets on reduced graphene oxide (rGO). In photothermal-driven thermoelectrocatalysis, the rGO-Bi$_2$Te$_3$ nanosheets can accelerate the separation and transfer of photogenerated charges, further promoting the effective generation of ROS, resulting in excellent therapeutic effects on MRSA-induced infected wounds (Fig. 15B–F) [157].

Electrocatalytic Therapy, as an emerging antibacterial strategy, holds significant potential for further development and research in the antibacterial field. It should be noted that the stability of piezoelectric materials' performance and their mechanical energy conversion efficiency in various biological environments still require further validation. Moreover, the biocompatibility and potential toxicity of piezoelectric materials need to be thoroughly investigated, particularly concerning the cumulative effects that may arise from long-term *in vivo* applications. In the future, ECT is expected to play a crucial role in combating antibiotic-resistant bacteria and complex infections, positioning itself as a valuable tool in the field of antibacterial treatment.

4. Catalysis-assisted immunotherapy (CAIT)

During the infection process, the interaction between pathogens and the host immune system creates a complex infection microenvironment, which not only directly affects the growth and spread of pathogens but also has profound impacts on the host immune response. In some cases, the infection microenvironment can lead to immunosuppression, rendering the host immune system unable to effectively clear the pathogens. This phenomenon of immunosuppression is particularly evident in chronic and refractory infections. Specifically, in biofilm-

associated infections, biofilms induce hypoxia, nutrient deficiency, and an acidic microenvironment, polarizing host immune cells towards an anti-inflammatory phenotype, thus reducing the ability of macrophages and other cells to clear bacteria and secrete pro-inflammatory factors [158]. Moreover, the adaptive immune system also plays a crucial role in combating infections, particularly by generating specific memory cells and antibodies, which are vital for preventing recurrent infections. Catalysis-assisted immunotherapy (CAIT) is a novel therapeutic strategy that combines catalytic reactions and immune modulation, aiming to activate and enhance the immune response through the action of catalysts to achieve disease treatment. This strategy leverages the ROS generated by catalysts, which can not only directly kill pathogens or cancer cells but also modulate the immune system to enhance the disease resistance of the host. In cancer treatment, catalytic therapy is often combined with immunotherapy, which on one hand can enhance anti-tumor efficacy and inhibit tumor recurrence and metastasis, and on the other hand, reduce side effects on the host [159–161]. Catalytic-assisted immunotherapy also holds significant potential and value in the field of infections and has started to attract increasing interest in recent years.

Innate immunity is the first line of defense in the host immune system, rapidly recognizing and responding to pathogens. Among the key players in this process are macrophages and neutrophils, which play crucial roles in antibacterial action. In the biofilm infection microenvironment, macrophage activity is often suppressed, leading to compromised macrophages. Based on this, Mei *et al.* proposed an intelligent Cu-doped Mo (VI)-based polyoxometalate nanocluster (Cu-POM)
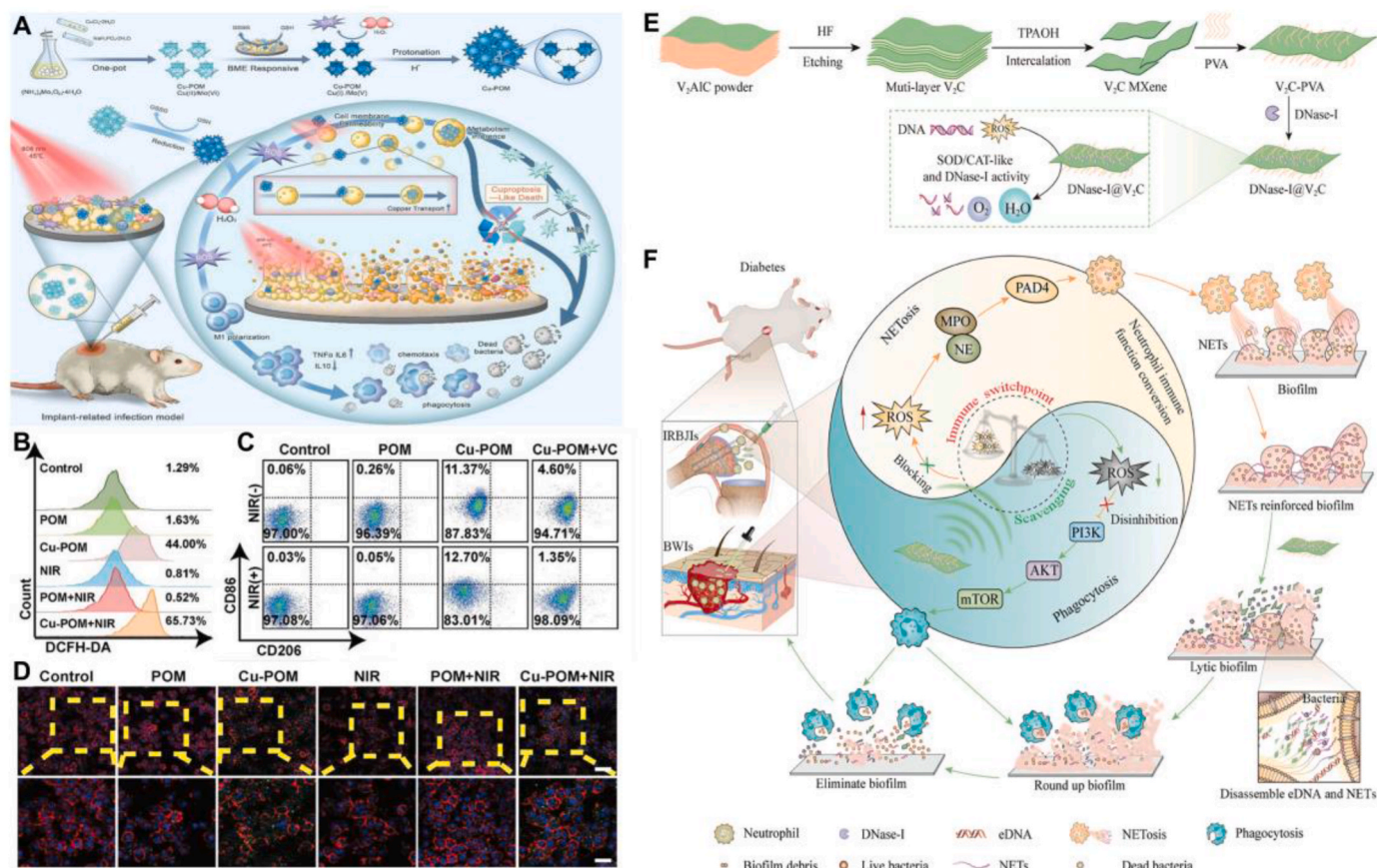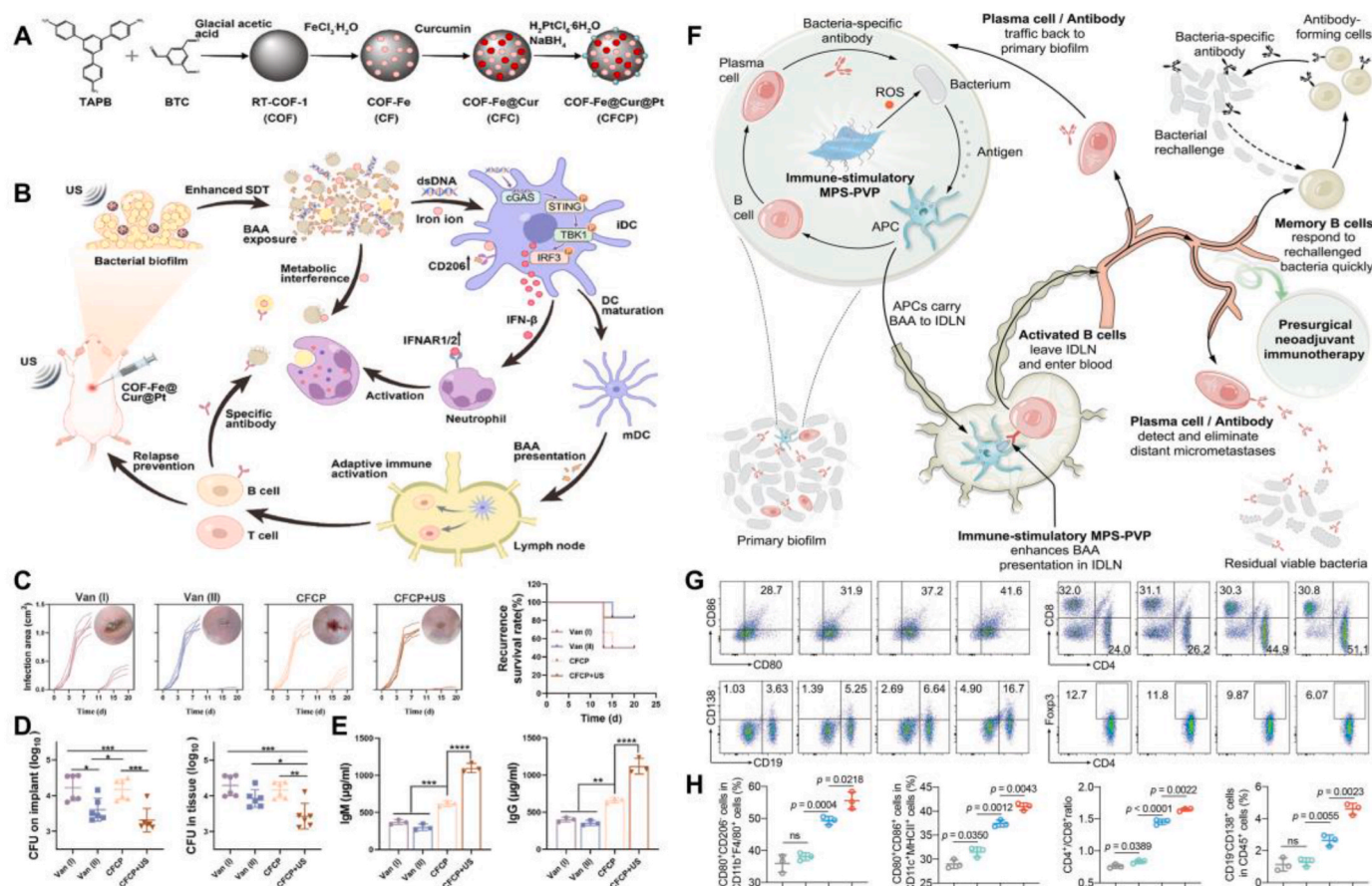
Fig. 16. Catalysis-assisted antibacterial strategies for activating innate immunity. **A)** Synthesis process of BME-responsive self-assembled nano-reactors and the mechanism of promoting macrophage reactivation in the biofilm infection microenvironment to eliminate IAIs. **B-C)** Flow cytometry images of intracellular ROS and surface markers CD80 and CD206 in macrophages after Cu-POM nanocatalytic platform intervention. **D)** Fluorescence images of phagocytosis of *S. aureus* by reactivated macrophages after Cu-POM nanocatalytic platform reactivation. **E)** Design and synthesis process of DNase-I@V$_2$C. **F)** Mechanism diagram of DNase-I@V$_2$C nanoplatform for treating diabetes-related IAIs through neutrophil function conversion. A-D) Reproduced with permission [162]. Copyright 2023, Wiley-VCH. E-F) Reproduced with permission [167]. Copyright 2023, Wiley-VCH.

(Fig. 16A–D) [162]. Cu-POM can catalytically generate ROS within the biofilm microenvironment, possessing direct antibacterial properties while reactivating compromised macrophages to enhance their chemotactic ability, phagocytic activity, and pro-inflammatory cytokine release capability, effectively clearing planktonic *S. aureus*. Additionally, their group reported a novel "interference-regulation strategy" using bovine serum albumin-iridium oxide nanoparticles (BIONPs) as biofilm homeostasis disruptors and immune modulators [163]. The synthesized BIONPs exhibit catalase-like activity, catalyzing H$_2$O$_2$ to produce O$_2$, thereby enhancing the efficacy of PDT by generating abundant ^{1}O$_2$ to effectively eradicate biofilms. More importantly, BIO-NPs successfully repolarized macrophages *in vivo* to the pro-inflammatory M1 phenotype, facilitating the phagocytosis of residual biofilm and preventing biofilm reformation. In the diabetic-related biofilm infection microenvironment (DRBI), neutrophils are prone to shift from phagocytosis to NETosis under high ROS stimulation, producing abundant net-like structures (NETs) and forming "NETs barriers" on the surface and inside the biofilm, thereby enhancing the EPS barrier around biofilms [164–166]. The reinforced biofilm structure and inhibited neutrophil phagocytosis perpetuate biofilm infections in DRBIs, leading to persistent and chronic infections. To address the DRBIs microenvironment, Guo and co-workers proposed a neutrophil immune function conversion (NIFC) strategy by designing DNase-I-loaded V$_2$C MXene (DNase-I@V$_2$C) to combat biofilm infections in diabetes (Fig. 16E–F) [167]. DNase-I-V$_2$C, through SOD and CAT-like enzymatic activities, scavenges ROS, reverses neutrophil function, disrupts the biofilm "EPS and NETs barriers" and enhances neutrophil

clearance of bacteria and biofilm debris.

Despite the significant progress in catalytic therapy for anti-infective immune modulation in recent years, strategies primarily focusing on innate immunity still lack the ability to provide long-term immunity, failing to effectively prevent infection recurrence. Therefore, future directions in catalytic-assisted immunotherapy may lie in simultaneously enhancing innate immune responses and activating adaptive immunity to achieve effective infection clearance and induce long-term immune memory. Based on this, Xu *et al.* proposed an iron-based covalent organic framework nanoadjuvant doped with curcumin and platinum (CFCP) to achieve effective treatment of IRIs by inducing a systemic immune response (Fig. 17A–D) [168]. The ROS generated through sonocatalysis can disrupt bacterial structures, induce the release of bacteria-related double-stranded DNA (dsDNA), and activate adaptive immunity through the cGAS-STING pathway to prevent infection recurrence. Similarly, our group have synthesized PVP-modified two-dimensional manganese phosphotelluride (MnPSe$_3$) nanosheets (MPS-PVP), which can trigger strong antibacterial humoral immunity in a mouse model of implant infection by modulating antigen presentation and co-stimulatory molecule expression in the BME (Fig. 17F–H) [169]. We demonstrated that using preoperative neoadjuvant immunotherapy with MPS-PVP successfully reduced the severity of primary and secondary infections in mice with implant infections, providing an antibiotic-free alternative for the treatment of IAIs.

Catalysis-assisted immunotherapy enhances the antibacterial effect by activating host anti-infection immunity, which has gradually become one of the research hotspots. However, this therapeutic approach still

Fig. 17. Catalysis-related antibacterial strategies for activating humoral and adaptive immunity. **A)** Schematic illustration of the synthesis of CFCP nanoparticles. **B)** CFCP nanoparticles promote the release of *S. aureus* antigens through sonocatalytic therapy and activate mouse adaptive immunity *via* the cGAS-STING pathway, treating IAIs and preventing infection recurrence. **C-D)** Graphs showing the area of infection regions on the back and CFU count results in different groups of mice after recurrent infection following CFCP nanoparticle treatment. **E)** Levels of IgM and IgG antibodies in different groups of mice after CFCP nanoparticle treatment. **F)** Immune-stimulating MPS-PVP nanosheets induce "*in situ*" amplification of bacteria-specific antibodies in biofilms by generating ROS, activating immune memory in mice, and thereby eliminating IAIs. **G-H)** Flow cytometry plots and corresponding data showing the activation of adaptive immunity in IAIs mice after treatment with MPS-PVP nanosheets. A-E) Reproduced with permission [168]. Copyright 2024, Elsevier Ltd. F-H) Reproduced with permission [169]. Copyright 2022, Springer Nature.

faces several challenges that require further investigation and resolution in the future, particularly in adjusting the host immune homeostasis to avoid excessive inflammatory responses. Additionally, more research is needed to focus on activating adaptive immunity and strengthening the host immune protection. In the future, CAIT will be a significant direction in the field of nanocatalytic antibacterial therapy, with promising potential for clinical translation.

5. Conclusion and perspective

Bacterial infections have posed a long-standing challenge for clinicians, especially in the post-antibiotic era with the prevalence of drug-resistant bacteria. Research on nano-biomaterials for antibacterial applications has been ongoing for many years, among which metal ions (such as Ag^+, Cu^{2+}, and Zn^{2+}) and their corresponding metal-based nano-biomaterials have made significant advances in recent years. Due to their unique bioactivity and diverse antibacterial mechanisms, metal ions have been widely applied in antibacterial treatments, medical device coatings, and packaging materials, helping to mitigate the issue of antibiotic-resistant infections caused by the overuse of antibiotics. However, the potential biotoxicity, metabolism, and accumulation of metal ions in the human body remain major challenges that limit their broader application. Photothermal antibacterial therapy is another area of extensive research in recent years, focusing on the use of

nanomaterials with photothermal conversion capabilities. Upon exposure to light at specific wavelengths, these materials absorb light energy and convert it into heat, leading to a localized temperature increase that directly damages bacterial cell membranes, proteins, and nucleic acids, ultimately causing bacterial death. Despite its numerous advantages, photothermal therapy also has notable drawbacks, including damage to surrounding healthy tissues and the limited penetration depth of near-infrared (NIR) light. Therefore, the development of multifunctional photothermal antibacterial materials based on mild photothermal therapy and NIR-II region light-excited photothermal materials is a promising direction for the future of photothermal antibacterial therapy.

Nanocatalytic medicine demonstrates distinct advantages over traditional nanomaterial-based treatments for bacterial infections, including lower dosage requirements, higher bactericidal efficiency, and selective catalytic effects in the infection microenvironment. Despite significant progress in recent years, the further development and clinical translation of nanocatalytic medicine still face numerous challenges. Due to the limited understanding of the complex physiological and pathophysiological mechanisms within the infection microenvironment, the catalytic activity of currently reported nanocatalytic biomaterials remains below clinical expectations. Furthermore, the potential biotoxicity and metabolic accumulation of nanocatalytic drugs in the human body are critical issues that must be addressed for future clinical application. The core mechanism of nanocatalytic medicine lies in the

production of ROS; however, excessive ROS generation can lead to inflammatory storms and pathological damage to the host. Balancing the efficiency of ROS production and its bactericidal effect is a crucial challenge worthy of attention.

The future direction of nanocatalytic medicine should focus on designing more efficient, intelligent, precise, and safe nanocatalytic materials. It is essential to improve the catalytic efficiency of nanocatalysts and enhance their antibacterial efficacy, particularly for biofilm-associated infections, where greater attention should be paid to biofilm infiltration and structural disruption. The combination of various catalytic therapies represents a key trend, whether exogenous catalysis (such as CDT and NCT) or endogenous catalysis (such as PCT, SCT, ECT), alongside immunotherapy and photothermal therapy. The synergistic treatment with multimodal nanobiomaterials can greatly improve material performance and reduce the occurrence of bacterial resistance.

Intelligence is a critical development direction for nanocatalytic medicine, aiming to precisely control and regulate catalytic performance, thereby improving therapeutic selectivity and efficacy while minimizing side effects. Notably, the treatment of bacterial infections requires a multifaceted approach, including bacterial clearance during acute and subacute phases, as well as tissue repair during chronic stages. Smart nanocatalytic materials should respond to multiple stimuli within the complex infection microenvironment, adjusting their activity according to changes in the pathological environment. Precision is essential, requiring the nanocatalysts to achieve targeted localization within the body to minimize impact on healthy tissues. This can be achieved by modifying the surface of nanomaterials with specific ligands, such as antibodies, peptides, or small molecules, that selectively bind to receptors in diseased tissues. Another promising approach is using external magnetic fields to guide magnetic nanoparticles to the infection site for efficient targeted delivery and catalytic reactions. Concerns about biosafety are widespread in nanomaterials, as they may be phagocytosed by different types of cells, leading to excessive ROS production or exacerbated inflammation, which could cause cytotoxicity and hinder the recovery of infected tissues. Reducing the toxicity of catalytic materials and minimizing their long-term accumulation within the host are critical considerations in future material design. Furthermore, most current biosafety studies of catalytic nanodrugs are conducted in cultured cells or mouse models, highlighting the need to establish biosafety testing systems that more closely mimic the human physiological environment.

In recent years, the rapid development of AI technology has significantly accelerated the design, optimization, and application of materials, increasing research efficiency and reducing costs. The combination of theoretical simulations and machine learning could expedite the structural optimization of nanocatalysts and the prediction of their catalytic activity. The future of catalytic nanomedicine will integrate chemistry, materials science, computer science, and medicine. This convergence not only advances material science but also provides new approaches to addressing major challenges such as global antimicrobial resistance.

Availability of data and materials

Not applicable.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

Consent for publication

Not applicable.

CRediT authorship contribution statement

Min Ge: Writing – review & editing, Writing – original draft, Conceptualization. **Feng Jiang:** Writing – original draft, Conceptualization. **Han Lin:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare no conflict of interest.

Data availability

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

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