Antibacterial sonodynamic nanomedicine: mechanism, category, and applications

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Key Words:
antibacterial application; reactive oxygen species; sonodynamic therapy; sonosensitisers

From the Contents

ABSTRACT

Sonodynamic therapy (SDT) has emerged as a cutting-edge strategy for combating multidrug-resistant bacterial infections. Unlike conventional antibiotics, SDT leverages the generation of reactive oxygen species during the treatment process to inflict multifaceted damage on bacterial cells, thereby significantly reducing the likelihood of developing drug resistance. Compared to other physical sterilisation methods, such as ultraviolet irradiation, SDT offers enhanced tissue penetration, making it particularly suitable for addressing deep-seated infections, including osteomyelitis. Despite its significant advantages, the clinical translation of SDT for antibacterial applications faces several challenges. This review discusses the fundamental mechanisms of SDT, with a focus on phenomena such as cavitation-induced reactions and piezocatalytic generation of reactive oxygen species. Furthermore, it provides a comprehensive analysis of various sonosensitisers used in SDT, emphasising their potential to enhance therapeutic outcomes in areas such as infected wound healing, bone regeneration, and the mitigation of deep tissue inflammation. While SDT shows great promise in addressing multidrug-resistant bacterial infections, further research and development are essential to overcome existing limitations and unlock its full clinical potential.

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Introduction

Traditional antibacterial drugs have played a critical role in protecting patients from bacterial infections. However, the widespread overuse of antibiotics has been a primary driver of the emergence of multidrug-resistant (MDR) bacteria.[1] Treating infections caused by MDR bacteria often requires extended antibiotic regimens and, in severe cases, invasive procedures such as tissue debridement, leading to increased healthcare costs and compromised patient outcomes.[2, 3] Effectively addressing the MDR crisis is imperative to safeguarding public health against the growing threat of resistant bacterial infections. In addition to the widespread challenges posed by antibiotic resistance, the healthcare burden continues to grow. The World Health Organization reports that by 2050, antimicrobial resistance could cause an estimated 10 million deaths per year globally, surpassing cancer as the leading cause of death. Furthermore, treatment failures of MDR infections incur higher medical costs, longer hospital stays, and increased complications, further highlighting the urgent need for alternative therapies.[4]

Sonodynamic therapy (SDT), a non-invasive treatment using sonosensitisers and ultrasound (US), has emerged as a promising approach for both cancer therapy and antibacterial treatment. Unlike photodynamic therapy (PDT), SDT exploits the superior tissue penetration capabilities of US, enabling treatment of deeper-seated infections and malignancies.[5-7] Upon exposure to US, sonosensitisers generate reactive oxygen species (ROS), which effectively induce cell death in both cancer cells and bacteria.[8] Additionally, US-induced phenomena, such as cavitation-generated heat, further enhance

tissue ablation and improve drug delivery efficiency.[9, 10] The antibacterial efficacy of SDT is attributed to its production of ROS and other sonodynamic effects, which target microbial lipids, proteins, and DNAs through multi-faceted mechanisms, significantly reducing the risk of bacterial resistance.[11, 12] This versatility makes SDT particularly well-suited for addressing challenging conditions such as osteomyelitis,[12] bone infections,[13] and methicillin-resistant *Staphylococcus aureus* (MRSA) myositis, highlighting its potential for a wide range of antibacterial applications.[14, 15]

This review primarily focuses on elucidating the mechanisms of SDT, exploring various types of sonosensitisers, and examining their applications in biomedical antibacterial settings (**Figure 1**). Researchers have extensively studied numerous sonosensitisers for cancer therapy, but research on their application in antibacterial treatment is still emerging and developing rapidly. Nanomedicine, specifically tailored for antibacterial SDT, holds great promise, particularly in addressing MDR infections within deep tissues. Providing a comprehensive overview of antibacterial sonodynamic nanomedicine is crucial for cataloging the diverse range of sonosensitisers currently available to researchers. This, in turn, will facilitate the development of novel sonosensitisers and innovative approaches to expand the therapeutic potential of antibacterial SDT.[13]

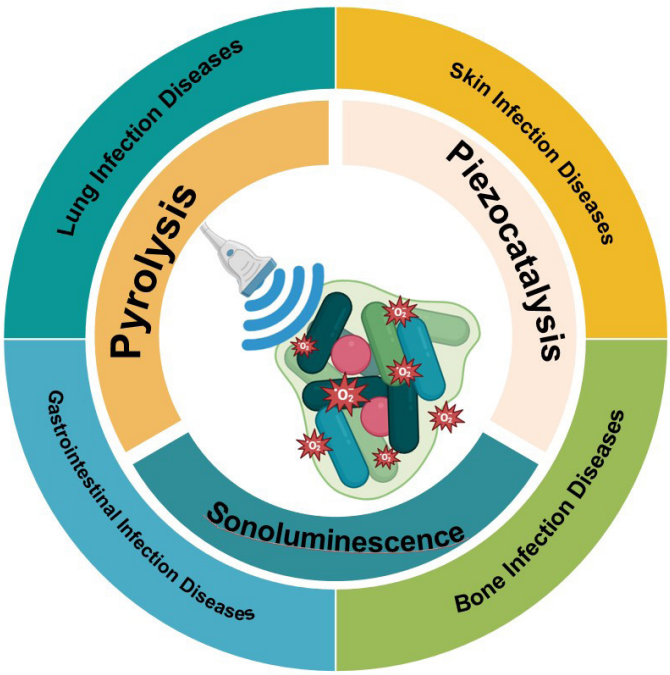

Figure 1. A schematic diagram of various mechanisms and applications of antibacterial sondynamic therapy. Created with BioRender.com.

Methods

Literature search strategy

To conduct a comprehensive literature review on the applications of SDT for antibacterial treatment, multiple databases were systematically searched. The primary databases used included Web of Science, PubMed, and Google Scholar. These databases were chosen for their extensive coverage of biomedical and scientific research articles.

Keywords and search terms

A set of carefully selected keywords and search terms were used to identify relevant studies. Search terms included combinations of the following keywords: "sonodynamic therapy", "antibacterial", "multidrug-resistant bacteria", "reactive oxygen species", "sonosensitizers", "infected wound healing", "bone repair", etc.

Inclusion and exclusion criteria

To ensure the selection of relevant and high quality studies, the following criteria were applied.

Inclusion criteria: (1) Studies published in high quality journals, (2) research articles focusing on the mechanisms of SDT, including cavitation effect and ROS production, (3) studies discussing the application of SDT in treating bacterial infections, particularly MDR bacteria, (4) articles examining the use and effectiveness of various sonosensitisers, and (5) articles from the past 5 years to ensure up-to-date information. Exclusion criteria: (1) Non-peer-reviewed articles, such as

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opinion pieces, editorials, and commentaries, and (2) articles not directly related to antibacterial applications of SDT.

Study selection

The initial search yielded a large number of articles, which were screened based on titles and abstracts. Studies that met the inclusion criteria were further assessed by reviewing the full text.

Data extraction and analysis

Relevant data were extracted from the selected studies, including study design, key findings, and conclusions related to SDT mechanisms and applications. This data was synthesised to provide a comprehensive overview of current research, identify gaps in knowledge, and suggest areas for future study. By following this systematic approach, the literature review aimed to provide an in-depth and reliable analysis of the potential and challenges of using SDT for antibacterial treatment.

Mechanisms of Sonodynamic Therapy for Antibacterial Effect

Despite several proposed principles to elucidate the mechanisms of SDT, its precise mode of action remains elusive due to the intricate nature of the process.[5] SDT is based on the principle of using US to activate sonosensitisers, which in turn generate ROS that induce therapeutic effects. These mechanisms of SDT can be broadly divided into two categories: chemical and physical effects.[14] These two types of effects interact synergistically to enhance therapeutic outcomes, especially in combating bacterial infections. The effectiveness of SDT is rooted in the synergistic interplay between the physical effects (US-induced mechanical forces) and the chemical effects (activation of sonosensitisers and ROS production). The physical effects encompass mechanical forces such as cavitation, microstreaming, and shear stress, which enhance the permeability of bacterial cell membranes. This increased permeability is crucial for facilitating the entry and accumulation of sonosensitisers within the cells. Once inside, the sonosensitisers remain inert until activated by US exposure, triggering the chemical effects of SDT, specifically the generation of ROS. These ROS are highly cytotoxic and can damage key cellular components, including DNA, lipids, and proteins, ultimately leading to cell death.[15, 16] Among these mechanisms, cavitation effect plays a crucial role in SDT and other US-based applications, influencing both physical and chemical processes. The cavitation effects not only lead to ROS generation but also produce mechanical forces such as microstreaming and shear stress. These forces disrupt bacterial cell membranes and facilitate better penetration of antimicrobial agents, further enhancing the therapeutic potential of SDT. Recent studies have shown that SDT-induced cavitation can enhance the effects of antibiotics like vancomycin and cephalosporins, making them more effective against resistant strains.[17] Furthermore, other phenomena, such as piezocatalytic activity, may also play an important role, especially with piezoelectric sonosensitisers. This dual contribution of chemical and physical mechanisms further emphasises the complexity of SDT and highlights the necessity for further research to better understand and optimise its therapeutic potential.

Cavitation effect

The cavitation effect, which has been widely recognised in numerous studies, is considered the primary mechanism of SDT, responsible for generating ROS, shear forces, and heat.[5-7, 10, 15, 18-22] Cavitation can be classified into two types: inertial cavitation and stable cavitation. Stable cavitation arises from the consistent oscillation of gas bubbles within the US field, whereas inertial cavitation involves the rapid expansion and subsequent collapse of gas bubbles under high US pressure.[9] During inertial cavitation, the collapse of gas bubbles generates extreme localised conditions, with temperatures exceeding 5000 K and pressures reaching approximately 250 MPa.[23] This elevated temperature can induce pyrolysis, facilitating the breakdown of sonosensitisers and the release of free radicals. These free radicals can further react with endogenous substrates to form ROS.[5,6] Molybdenum disulfide (MoS_2)-based sonosensitisers have demonstrated significant enhancement of the bactericidal effects of SDT through inertial cavitation mechanisms. Specifically, MoS_2 nanosheets, especially those in the 1T-phase (M-MoS_2), are used to generate ROS when activated by US and near-infrared (NIR) laser irradiation. The rapid collapse of gas bubbles during inertial cavitation within the presence of M-MoS_2 leads to the generation of high-energy free radicals, significantly augmenting ROS production and thereby improving the overall therapeutic efficacy of SDT. In this study, *Pseudomonas aeruginosa* (*P. aeruginosa*), a prominent MDR pathogen, was subjected to SDT in the presence of M-MoS_2, resulting in near-complete eradication of the bacteria. The findings highlight that the cavitation-induced effects, coupled with the photothermal properties of M-MoS_2, work synergistically to enhance SDT's ability to kill bacteria and disrupt biofilms, offering a promising approach to combating resistant bacterial infections.[24] Comparatively, stable cavitation occurs when microbubbles oscillate continuously without collapsing, generating microstreaming and shear forces, which will further enhance cell membrane permeability and facilitating drug/sonosensitiser uptake.[6] The use of iron oxide nanoparticles as sonosensitisers in treating bacterial biofilms, which are often difficult to eradicate with conventional therapies, revealed that stable cavitation facilitated ROS generation through the oscillation of nanoparticles within the US field. In this study, the mechanical forces induced by cavitation caused significant disruption of the biofilm matrix, leading to enhanced penetration of the therapeutic agents and greater bactericidal effects. The combination of stable cavitation and ROS generation resulted in the effective disruption of *Staphylococcus aureus* (*S. aureus*) biofilms, a common pathogen in chronic infections. Notably, iron oxide nanoparticles not only acted as sonosensitisers but also provided a photothermal effect when exposed to NIR light, further enhancing the overall SDT efficacy.[25] In addition to the mechanical and thermal effects generated by cavitation, sonoluminescence—the emission of light from gas bubbles during collapse—plays a crucial role in the generation

of ROS in SDT. The intense light emission produced by bubble collapse can initiate electron-hole separation in sonosensitisers, particularly those that also function as photosensitisers. This phenomenon allows the sonosensitiser to undergo a process similar to PDT, where the light activates the sonosensitiser to generate ROS.[6] This process significantly enhances the antibacterial efficacy of SDT by promoting ROS generation through multiple mechanisms, thus increasing the overall therapeutic efficacy of the treatment.

Piezocatalytic effect

The piezocatalytic effect is believed to occur when piezoelectric materials undergo deformation under external forces, such as US waves, leading to the generation of ROS. Upon exposure to US irradiation, the displacement between the centres of positive and negative charges within these materials changes,[26] resulting in polarisation along the direction of the applied stress. This polarisation induces the release of surface free charges, producing piezoelectricity.[27] Through the formation of piezoelectric potential, piezoelectric sonosensitisers are capable of converting mechanical energy into electrical energy.[28] Under mechanical wave stimulation, these piezoelectric sonosensitisers can separate electrons and holes, which act as negative and positive charges, respectively. The sustained separation of electron-hole pairs under the vibrational influence of US may generate an internal electric field, thereby enhancing the catalytic production of ROS.[29, 30] Furthermore, the collapse of cavitation bubbles can exert significant pressure on piezoelectric materials, further amplifying the piezocatalytic effect.[25]

Antibacterial effect

ROS have been extensively studied for their powerful oxidative properties, which enable them to cause damage to a variety of cellular components, including DNA, proteins, and lipid membranes.[26, 27] This oxidative capacity plays a central role in the efficacy of SDT as an antibacterial treatment. In the context of SDT, ROS are primarily generated when sonosensitisers, activated by US irradiation, undergo reactions that produce these highly reactive species. Once formed, ROS can inflict significant damage on bacterial cells, particularly targeting the cell wall and cytoplasmic membrane. The oxidative damage to the bacterial cell wall weakens the structural integrity of the pathogen, while the oxidation of the cytoplasmic membrane leads to its rupture, causing the leakage of essential intracellular components such as nucleic acids, proteins, and ions, ultimately resulting in cell death.[13, 28, 29] In addition to the oxidative effects, mechanical forces induced by cavitation play a critical role in enhancing the efficacy of SDT. Cavitation, the rapid formation and collapse of bubbles in the solution, generates intense shear forces and microstreaming, which can physically disrupt the bacterial cell membrane. These forces lead to the formation of transmembrane pores, which further compromise the integrity of the cytoplasmic membrane. The combination of oxidative and mechanical damage induced by SDT enhances the bactericidal effect, allowing for more effective targeting and destruction of a broad range of bacterial pathogens. As a result, SDT has become a promising approach to combating MDR bacteria by leveraging both chemical (ROS-induced) and physical (cavitation-induced) of damage mechanisms.[10, 30]

Different Sorts of Sonosensitisers

Sonosensitisers are specialised agents that enhance the generation of ROS under US irradiation, making them highly effective for antibacterial applications. These agents can be broadly classified into organic and inorganic categories.[31] Organic sonosensitisers, such as porphyrins, are well-established for their ROS generation capabilities, but they are often limited by stability and oxygen-deprived environments. Inorganic sonosensitisers, including nanoparticles, offer increased stability and tunable properties, making them more adaptable for clinical use. Recently, hybrid sonosensitisers—combinations of organic and inorganic materials—have emerged, leveraging the strengths of both types to overcome individual limitations. Furthermore, integrating SDT with other therapeutic approaches, such as PDT and photothermal therapy (PTT), has shown great promise in enhancing its antibacterial efficacy. These combination therapies enable a multi-faceted attack on bacterial cells, especially in cases involving MDR pathogens and biofilm-related infections. This section highlights the latest advancements in sonosensitiser development and their integration with other therapeutic modalities, highlighting their potential to revolutionise SDT for more effective antibacterial treatments.

Organic sonosensitisers

Organic sonosensitisers are typically small molecules or polymeric materials that are capable of generating ROS upon exposure to US. One of the most studied classes of organic sonosensitisers are porphyrins and their derivatives, which have shown significant potential in both cancer and antibacterial SDT.[32] Porphyrin-based sonosensitisers generate singlet oxygen ($^1O_2$), a highly reactive species that is particularly effective in targeting bacterial membranes. However, the efficacy of these compounds is often limited by the availability of oxygen in the treatment site, especially in infected tissues where oxygen supply can be limited.[21] Recent advances have led to the development of hybrid sonosensitisers that integrate organic and inorganic materials. These hybrid systems are designed to take advantage of both organic compounds' fine-tuned electronic properties and inorganic materials' robust physical stability and higher ROS generation capacity. One example is the combination of mesoporous silica nanoparticles with organic dyes, which not only enhance ROS production but also improve drug delivery and targeting in infected tissues. To address this, researchers have developed oxygen self-supplying systems that combine porphyrins with nanomaterials capable of releasing oxygen *in situ*. For example, Pt nanodots grown on Pd nanosheets fomated Pd@Pt nanoplates combined with meso-tetra(4-carboxyphenyl) porphine (T790) have been shown to enhance the generation of $^1O_2$ by increasing oxygen availability at infection sites.[29] These compounds are valued for their reproducibility, high capacity for ROS generation, significant biodegradability, and the ability to control molecular structure.[21] Organic sonosensitisers have thus emerged as pivotal agents in the realm of antibacterial therapy.

Porphyrin and its derivatives

Porphyrin and its derivatives, including haematoporphyrin monomethyl ether and protoporphyrin IX, are among the most extensively researched organic sonosensitisers.[33, 34] Despite the development of numerous porphyrin analogs, challenges persist, such as the limited availability of oxygen (O_2) in infected tissues. This limitation is critical because ROS generated by porphyrin-based sonosensitisers primarily consists of $^1O_2$, which relies heavily on the surrounding O_2 levels for its production. To address these challenges and optimise SDT efficacy, researchers are exploring modifications to existing porphyrin derivatives and investigating combinations with other therapeutic approaches.

To enhance O_2 levels at disease sites, Sun et al.[29] used Pd@Pt nanoplates as carriers for the sonosensitiser T790, creating a self-supplying O_2 sonosensitiser system (**Figure 2**). Pd@Pt nanoplates possess catalase-like activity, which was effectively shielded by T790 to prevent undesired O_2 generation in normal tissues. When exposed to US irradiation, the nanozyme activity of Pd@Pt was significantly restored, facilitating self-supply of O_2 (**Figure 2A**). This innovation notably enhanced the production of $^1O_2$ by T790 (**Figure 2B**, and **C**). Consequently, Pd@Pt-T790 effectively disrupted the morphology of MRSA (**Figure 2D**) and reduced MRSA viability to less than 10%, while other experimental groups still exhibited substantial MRSA survival (**Figure 2E**).

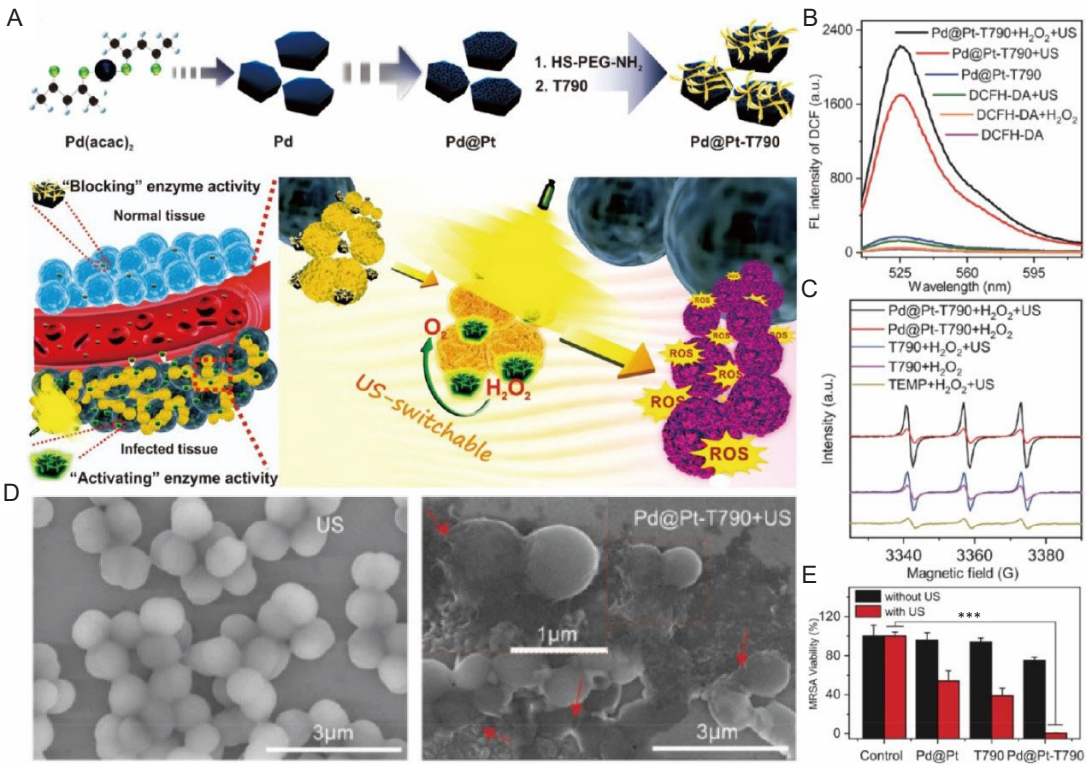

Figure 2. Mechanisms and applications of Pd@Pt-T790. (A) Schematic diagram of Pd@Pt-T790. (B) Fluorescence changes of DCFH-DA of each group under different treatments. (C) Electron spin resonance spectra of $^1O_2$ by TEMP. (D) SEM image of MRSA incubated with Pd@Pt-T790 with or without US. Scale bars indicated in figure. (E) Bacterial viability of MRSA under different treatment *in vitro*. Reprinted from Sun et al.[29] Copyright 2020, American Chemical Society. a.u.: absorbance unit; DCFH-DA: 2',7'-Dichlorodihydrofluorescein diacetate; FL: fluorescence; H_2O_2: hydrogen peroxide; HS-PEG-NH_2: thiol polyethylene glycol amine; MRSA: methicillin-resistant *Staphylococcus aureus*; O_2: oxygen; Pd: palladium; $Pd(acac)_2$: palladium acetylacetonate; Pd@Pt: platinum nanodots grown on Pd; Pd@Pt-T790: Pd@Pt nanoplates loaded meso-tetra (4-carboxyphenyl) porphine; ROS: reactive oxygen species; SEM: scanning electron microscope; TEMP: 2, 2, 6, 6-tetramethylpiperidine; US: ultrasound.

Alongside increasing the surrounding O_2 concentration, minimising electron-hole pair recombination stands out as another effective approach to boost the rate of ROS production. For instance, Yu et al.[35] developed HNTM-Pt@Au by integrating platinum (Pt) single atoms and gold nanorods (AuNRs) onto a zirconium-doped porphyrin metal-organic framework (HNTM). In this framework, excited electrons can transfer to Au or Pt, thereby hindering the recombination of electron-hole pairs. This mechanism enables HNTM-Pt@Au to generate more $^1O_2$, as depicted in **Figure 3A**. **Figure 3B** illustrates that the photocurrent of HNTM-Pt significantly exceeded that of HNTM, indicating the successful electron transfer. Subsequent antibacterial experiments confirmed that both HNTM-Pt + US and HNTM-Pt@Au + US groups exhibited markedly enhanced antibacterial effects under US irradiation. Upon US stimulation, the porphyrin component in HNTM transitions to an excited state, followed by conversion to the triplet state (**Figure 3C–E**), highlighting the efficacy of the electron-transfer strategy in enhancing the SDT effect of sonosensitisers.

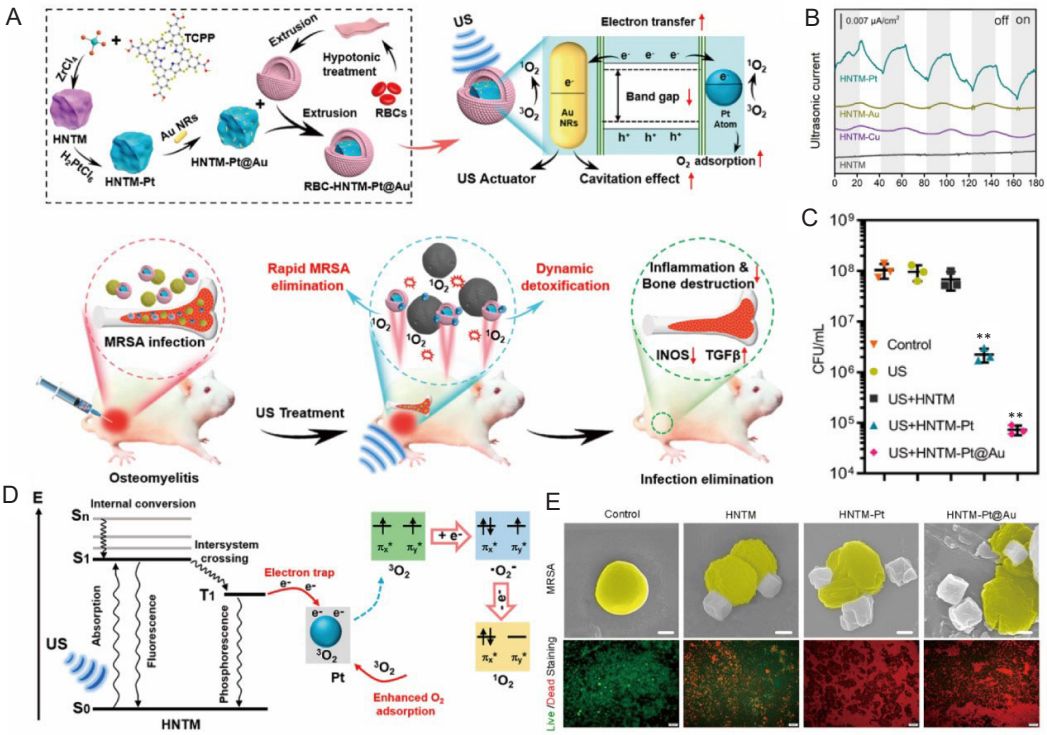

Figure 3. Synthesis, mechanisms and antibacterial efficacy of HNTM-Pt@Au. (A) Scheme of HNTM-Pt@Au in osteomyelitis therapy. (B) Ultrasonic current test of HNTM alone and combined with different metals. (C) Quantitative analysis of antibacterial effect. $^{**}P < 0.01$. (D) Mechanism of enhancement. (E) SEM and live/dead staining. Scale bar: 50 μm. Reprinted from Yu et al.[35] Copyright 2021, American Chemical Society. $^1O_2$: singlet oxygen; $^3O_2$: oxygen in the triplet state; Au NPs: gold nanorods; H_2PtCl_6: chloroplatinic acid; HNTM: zirconium-based porphyrin metal–organic framework; HNTM-Au: gold atoms loaded on the surface of HNTM; HNTM-Cu: copper atoms loaded on the surface of HNTM; HNTM-Pt: platinum atoms loaded on the surface of HNTM; HNTM-Pt@Au: Pt single-atoms and Au nanorods modified haematoporphyrin monomethyl ether; INOS: inducible nitric oxide synthase; MRSA: methicillin-resistant *Staphylococcus aureus*; Pt: platinum; RBC: red blood cell; TCPP: tris chloropropyl phosphate; TGFβ: transforming growth factor beta; US: ultrasound; $ZrCl_4$: zrconium tetrachloride.

Through systematic design, porphyrin-based sonosensitisers can be combined with other functional materials to achieve synergistically enhanced antibacterial therapy. For instance, a zeolitic imidazolate framework-8 (ZIF-8) loaded with haematoporphyrin monomethyl ether (HFH@ZIF-8) was developed by incorporating F127 and haemoglobin onto the ZIF-8 surface via electrostatic interactions.[36] This modification endowed HFH@ZIF-8 with improved water solubility, biocompatibility, and disease-targeting capabilities. Moreover, the SDT efficacy of this nanomedicine was augmented by the O_2 supplied by haemoglobin, leading to significant inhibition of MRSA in infected mouse legs. To further utilise SDT in conjunction with other ROS-generating strategies, an mesoporous silica-protoporphyrin IX-iron ion (M@P-Fe) platform was synthesised by integrating mesoporous silica nanoparticles, protoporphyrin IX, and iron ions. This Fenton-enhanced SDT demonstrated promising results in biofilm removal and bacterial eradication in root canals, highlighting the potential of collaborative Fenton reactions and SDT in antibacterial therapy.

Other organic sonosensitisers

Excluding porphyrin-based sonosensitisers, curcumin, rose bengal, and indocyanine green (ICG) have been used as both sonosensitisers and photosensitisers in antibacterial applications. There is ongoing research to combine SDT and PDT to enhance therapeutic outcomes, recognising that SDT alone may have limitations in antibacterial therapy.[37] To boost the production of ROS from curcumin under US and NIR light, copper(II) sulfide (CuS) was employed to bind curcumin by growing curcumin nanoparticles on CuS nanoplates.[38] When exposed to NIR light and US irradiation, both CuS and curcumin generate electron-hole pairs. Electrons from CuS's conduction band can combine with holes from curcumin's highest occupied molecular orbital, resembling a Z-scheme heterojunction. This synergistic mechanism leads to enhanced ROS production compared to either CuS or curcumin alone. The localised heating due to the photothermal effect of CuS further enhances the antibacterial efficacy of this nanomedicine, achieving 99.56% eradication of *S. aureus* and 99.48% of *Escherichia coli* (*E. coli*) under US and NIR light irradiation. In contrast, without the synergistic effects of NIR and US, less than 50% of these bacteria were eliminated.

ICG, an U.S. Food and Drug Administration-approved NIR imaging agent for clinical use, holds promise in *in vivo* SDT applications. In the antibacterial realm, an ICG-loaded liposome conjugated with monoclonal antibodies was engineered for targeting and killing *Helicobacter pylori*

(*H. pylori*).[39] This functionalised liposome not only enhances targeting but also protects ICG from degradation in the acidic gastric environment. Additionally, leveraging the photoacoustic signal of ICG, an *in situ* diagnostic method has been introduced as an alternative to radiolabelled imaging. Following oral administration, this nanomedicine exhibits peak signal intensity within 5 minutes and remains detectable for approximately 2 hours. This imaging-guided sonosensitiser has effectively eliminated *H. pylori* without causing significant organ damage or chronic inflammation.

Inorganic sonosensitisers

Inorganic sonosensitisers, primarily composed of semiconductors, are valued for their high stability and superior physicochemical properties.[40] The unique energy band structure of semiconductors facilitates the separation of electron-hole pairs when exposed to US, which leads to the generation of ROS by interacting with H_2O or O_2. To enhance the efficiency of these sonosensitisers, strategies such as incorporating noble metals and narrowing the band gap have been developed. These modifications help prolong electron-hole separation, thus improving ROS production and boosting the overall performance of SDT for antibacterial applications.

Metallic oxides and bimetallic oxides based sonosensitisers

Metal oxides and bimetallic oxide-based sonosensitisers, including titanium dioxide (TiO_2), zinc oxide (ZnO), barium titanate ($BaTiO_3$, BTO), manganese tungsten oxide (MnWOx), and cobalt tetraoxideferrate ($CoFe_2O_4$), have seen significant development in recent decades.[41-45] These materials are valued for their adjustable physicochemical properties, straightforward surface modification capabilities, exceptional stability in biological environments, and prolonged circulation in the bloodstream. These attributes make them highly suitable for applications in antibacterial SDT.

TiO_2 based sonosensitisers

Introduced initially for sonodynamic cancer therapy in 2011, TiO_2 has garnered considerable interest as a prototypical inorganic sonosensitiser.[46] However, due to the rapid recombination of electron-hole pairs (50 ± 30 ns) in TiO_2, the production yield of ROS has not been sufficient to achieve satisfactory antibacterial effects.[47]

Su et al.[48] improved a titanium bone screw by applying an S-doped, O_2-deficient TiO_2 layer (Ti–S–TiO_{2-x} implant) to replace conventional antibacterial coatings and prevent periprosthetic infections. The S-doped, O_2-deficient TiO_2 layer modification resulted in improved sonocatalytic and photothermal properties. Specifically, the introduction of sulfur increased O_2 deficiency in the TiO_2, narrowing its band gap and thereby boosting the rate of ROS generation. Additionally, O_2-deficient TiO_{2-x} exhibited high efficiency in converting NIR light into heat.[49] Consequently, the Ti–S–TiO_{2-x} implant demonstrated effective antibacterial capabilities by disrupting bacterial membranes under NIR laser and US irradiation (**Figure 4A–C**). *In vivo* studies showed that the implanted bone screws achieved approximately 99.26% antibacterial efficiency under NIR light and US irradiation, highlighting S–TiO_{2-x} as a promising antibacterial sonosensitiser (**Figure 4D**, and **E**).

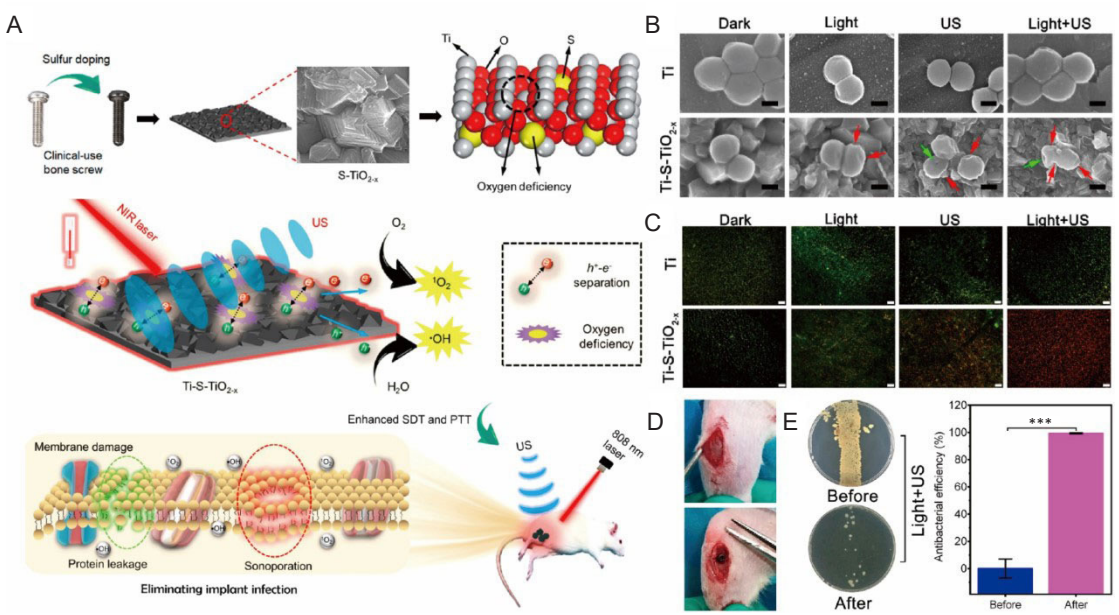

Figure 4. Antibacterial abilities and mechanisms of Ti implant coated by S-doped TiO_2. (A) Schematic illustration of Ti-S-TiO_{2-x} bone screw. (B) SEM images of *Staphylococcus aureus* after treatment. Red arrows indicate varying degrees of damage of *Staphylococcus aureus*, while green arrows indicate holes in *Staphylococcus aureus*. Scale bar: 200 nm. (C) Fluorescence images of *Staphylococcus aureus* while green/red fluorescence represent live/dead bacteria. (D) Implant site of Ti-S-TiO_{2-x} bone screws. (E) Antibacterial performance of Ti-S-TiO_{2-x} bone screws. Reprinted from Sun et al.[48] Copyright 2020, American Chemical Society. $^1O_2$: singlet oxygen; PTT: photothermal therapy; SDT: sonodynamic therapy; S-TiO_2: sulfur-titanium dioxide; Ti: titanium; Ti-S-TiO_{2-x}: titanium sulfur titanium oxide with oxygen vacancies; US: ultrasound.

Besides its conventional antibacterial applications, sonosensitisers also hold promise for treating lung infections. A sonosensitiser named ZTN was synthesised for this purpose by coating a carbonised TiO_2 layer on ZIF-8.[50] To treat lung infections in mice, ZTN was administered via aerosolised intratracheal inoculation (**Figure 5A**). Incorporating carbon-derived ZIF-8 narrowed the band gap of ZTN (2.68 eV), enhancing its ability to separate electron-hole pairs under US irradiation compared to TiO_2 (3.10 eV). This modification resulted in improved production of $^1O_2$ and •OH, as confirmed by electron paramagnetic resonance (ESR) spectra (**Figure 5B**, and **C**). Consequently, ZTN demonstrated effective antibacterial activity *in vivo* when exposed to US irradiation. Treatment with ZTN + US for 6 days notably reduced lung inflammation in mice (**Figure 5D–F**).

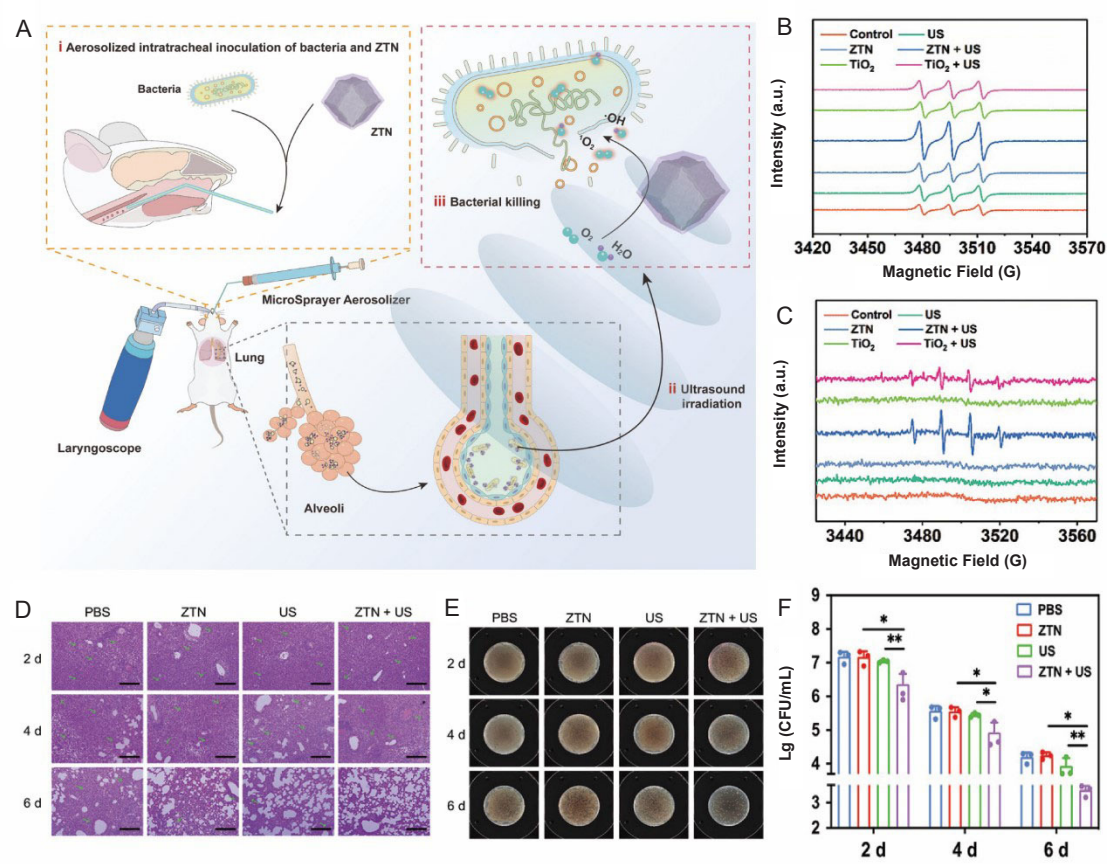

Figure 5. Functions for producing ROS and eliminating bacteria in lung infection of ZTN. (A) Schematic illustration of ZTN for antibacterial SDT in lung infections. (B, C) ESR measurements of $^1O_2$ (B) and •OH (C) generation of ZTN or TiO_2 with or without US. (D) H&E stained images of infected lungs after different treatments. Scale bars: 100 μm. (E) Photos of bacterial colonies recovered from treated lung. (F) Statistics of bacterial loads in the differently treated lungs of infected mice. $^*P < 0.05$, $^{**}P < 0.01$. Reprinted from Pan et al.[50] Copyright 2022, Wiley-VCH GmbH. •OH: hydroxyl radical; $^1O_2$: singlet oxygen; a.u.: absorbance unit; CFU: colony-forming unit; ESR: electron paramagnetic resonance; H&E: haematoxylin-eosin staining; PBS: phosphate buffer solution; ROS: reactive oxygen species; SDT: sonodynamic therapy; TiO_2: titanium dioxide; US: ultrasound; ZIF-8: zeolitic imidazolate framework-8; ZTN: carbonised TiO_2 coated ZIF-8.

$BaTiO_3$ based sonosensitisers

$BaTiO_3$, known for its piezoelectric properties, has been shown to combat breast cancer in mice through a piezocatalytic effect.[43] Furthermore, combining $BaTiO_3$ with Au enhances its antibacterial capabilities.[13] By forming a Schottky barrier between the piezoelectric material and the metal, the recombination of charge carriers in Au@$BaTiO_3$ (Au@BTO) is suppressed, thereby boosting its piezocatalytic activity. Beyond bacterial eradication, the ROS generated by the piezocatalytic effect accelerate wound healing by promoting fibroblast migration in mice (**Figure 6A**). Colony-forming unit counting reveals significant antibacterial efficacy under Au@BTO + US treatment, with *E. coli* survival reduced to 17.37% and *S. aureus* eliminated by 99.23% (**Figure 6B**, and **C**). *In vivo* studies on infected wounds demonstrate that the Au@BTO + US group exhibits faster wound healing compared to other treatments (**Figure 6D**). H&E staining shows regenerated follicles and integrated epidermal layers in dermal tissues treated with Au@BTO + US, while Masson's trichrome staining indicates orderly collagen deposition (**Figure 6E**), highlighting the wound healing potential of sonosensitisers.

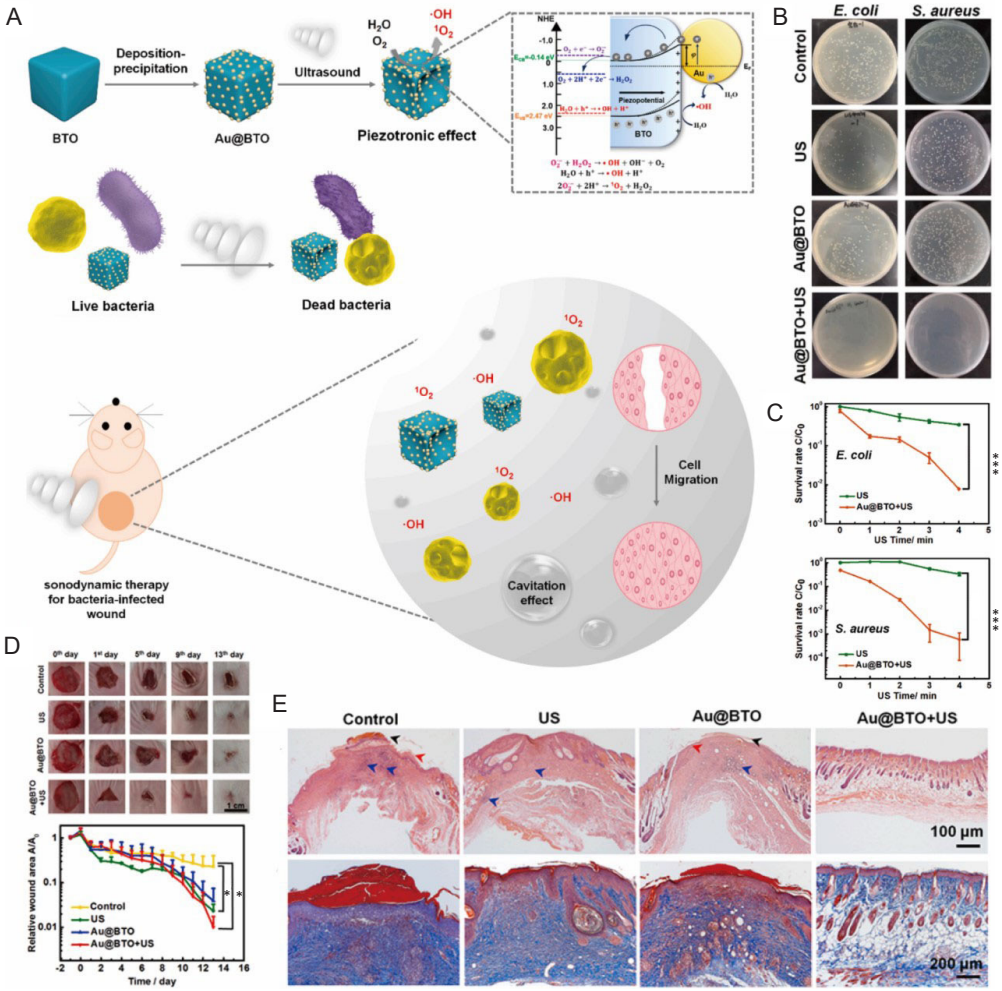

Figure 6. Mechanism and application of Au-BTO in bacterial killing and wound healing. (A) Schematic diagram of Au@BTO for sonodynamic antibacterial therapy. (b) CFU comparison of different groups of treated bacteria. (C) Statistical analysis of bacterial survival rate of Au@BTO + US treated groups. ***$P < 0.001$. (D) Representative photographs and relative wound area of treated mice during therapy. *$P < 0.05$. (E) H&E and Masson's trichrome staining of the tissue around wounded regions; Black arrows indicate obvious scabs, and red arrows indicate accumulation of fluid in dermis, while blue arrows indicate infiltration of inflammatory cells. Scale bars indicated in figure. Reprinted from Wu et al.[13] Copyright 2021, Elsevier Ltd. •OH: hydroxyl radical; $^1O_2$: singlet oxygen; Au-BTO: Au@$BaTiO_3$; BTO: barium titanate; CFU: colony-forming unit; *E. coli*: *Escherichia coli*; H&E: haematoxylin-eosin staining; O_2: oxygen; *S. aureus*: *Staphylococcus aureus*; US: ultrasound.

Sulfur-doped $BaTiO_3$ (SDBTO) has demonstrated significant potential in the treatment of bone infections, offering enhanced antibacterial properties and improved therapeutic efficacy. Recently, SDBTO has been developed, offering enhanced antibacterial properties while simultaneously promoting bone regeneration.[51] S-doping creates O_2 vacancies, narrowing the band gap of SDBTO and inhibiting electron-hole pair recombination. Additionally, the piezoelectric coefficient (d^*_{33}) increases significantly to 13.95 pm/V after S-doping, nearly three times its original value (4.78 pm/V). Leveraging these advancements, SDBTO + US exhibits anti-inflammatory effects comparable to vancomycin. Moreover, SDBTO + US treatment induces osteogenic differentiation by upregulating the transforming growth factor-beta/bone morphogenetic protein/small mother against decapentaplegic proteins (TGF-β/BMP/Smad) signaling pathway, underscoring the potential of $BaTiO_3$-based sonosensitisers in repairing infected bones.

Au@Cu_2O

Copper(I) oxide (Cu_2O) has traditionally been used as a p-type semiconductor in applications such as the degradation of organic pollutants and water splitting as a photosensitiser. Recently, Au@Cu_2O has emerged as a promising candidate for use as a sonosensitiser, demonstrating significant potential in SDT.[52, 53] By forming a Schottky barrier, which prevents the backflow of electrons excited by US, Au@Cu_2O extends the separation time of electron-hole pairs. Encapsulated within red blood cell (RBC) membranes, Au@Cu_2O demonstrates remarkable effectiveness in eliminating over 90% of *S. aureus* under US stimulation, a capability not observed with Cu_2O alone. This research provides initial evidence of Cu_2O's antibacterial potential, opening doors for its application as a sonosensitiser in antibacterial research.

Other inorganic sonosensitisers

MoS_2, distinguished from conventional metal oxides, stands out among inorganic sonosensitisers due to its unique piezoelectric properties, which have been widely applied in pollutant catalysis.[52] In recent research, MoS_2 nanosheets with tailored metallic phases have been synthesised to further enhance the PTT and SDT efficacy against bacterial infections. The metallic 1T/1T′-phase MoS_2 (referred to as M-MoS_2) offers a distinct advantage over the more stable 2H-phase by introducing defects that increase ROS generation when exposed to US stimulation. These enhanced properties significantly improve the sonodynamic efficacy of MoS_2 in targeting and eradicating bacterial pathogens. In addition to its enhanced ROS production, MoS_2's ability to absorb NIR light enhances its PTT capabilities, providing a synergistic effect that boosts SDT performance. When irradiated with US and NIR laser, M-MoS_2 not only generates ROS but also generates heat, which adds a thermal component to the antibacterial treatment, increasing its overall efficiency. In *in vitro* studies, M-MoS_2 has demonstrated nearly complete eradication of *P. aeruginosa* and *S. aureus*, two commonly resistant pathogens. Furthermore, the effectiveness of MoS_2 as a sonosensitiser extends beyond bacterial killing. In an *in vivo* mouse model, wounds treated with M-MoS_2 combined with US and NIR laser showed significant wound healing over a 10-day period, further emphasising its potential as a versatile sonosensitiser. These promising results demonstrate MoS_2's dual function as both an antibacterial agent and a wound healing promoter, paving the way for its application in SDT for managing infections and enhancing tissue regeneration.

Organic-inorganic combined sonosensitisers

Organic sonosensitisers are known for their biodegradability and well-defined molecular structures, yet they face limitations *in vivo* due to hydrophobicity, rapid metabolism, and phototoxicity. In contrast, inorganic sonosensitisers offer advantages such as *in vivo* stability, extended circulation time, and customisable surface properties, although their biodegradability is less favourable. Combining both organic and inorganic types could exploit enhanced electron transfer, and is a promising approach.

One such innovation is the creation of RBC-HNTM-MoS_2, an organic-inorganic hybrid sonosensitiser assembled from a porphyrin-based HNTM, MoS_2 nanosheets, and a RBC membrane.[54] Both HNTM and MoS_2 act as sonosensitisers, influencing each other's electron transfer under US excitation. Specifically, electrons from the highest occupied molecular orbital of HNTM can interact with positive charges on MoS_2 edges, while holes from the unoccupied molecular orbital could be trapped by negative charges. RBC-HNTM-MoS_2 demonstrates efficacy in bone regeneration and bacterial elimination (**Figure 7A**). The combined HNTM-MoS_2 complex exhibits significantly enhanced $^1O_2$ production compared to HNTM and MoS_2 alone, as measured by relative fluorescence intensity of 9,10-dimethylanthracene (**Figure 7B**). *In vitro* antibacterial studies also show increased ROS generation with HNTM-MoS_2, enhancing its antibacterial efficacy (**Figure 7C**). Moreover, in treating bone defects, RBC-HNTM-MoS_2 outperforms even vancomycin groups, highlighting its dual capability in antibacterial action and bone repair (**Figure 7D**, and **E**).

Applications of Sonodynamic Therapy in Bacterial Infectious Diseases

SDT has emerged as a highly promising approach for the treatment of various infectious diseases, particularly those caused by antibiotic-resistant microorganisms. SDT uses sonosensitising agents that, when exposed to low-intensity US, generate cytotoxic ROS. These ROS are capable of inducing microbial cell death by damaging cellular components such as proteins, lipids, and DNAs. The versatility of SDT has been demonstrated across multiple infection models, including bacterial biofilms, which are known to pose significant treatment challenges due to their protective matrix, and systemic infections caused by both Gram-positive and Gram-negative pathogens. Research efforts have increasingly focused on evaluating the efficacy of sonosensitisers in these diverse infection models, with studies exploring their potential to overcome the limitations of conventional antimicrobial therapies.[55] This section provides a comprehensive overview of the ongoing research and critically assesses the application of SDT in addressing a broad spectrum of bacterial infections, emphasising its ability to target and disrupt biofilms, as well as its effectiveness against a range of pathogens resistant to traditional treatments (**Table 1**).[29, 35, 38, 39, 48, 50, 55-57]

Bone infection diseases

Bone infections, such as osteomyelitis, osteoporosis, osteoarthritis, and nonunion defects, pose significant public health challenges due to the progressive aging of bone SDT, leveraging the deep tissue penetration capabilities and non-invasiveness of US during treatment, shows potential to replace antibiotic therapies and circumvent multiple surgical debridements for bone infections.[29, 58] Pd@Pt-T790 was developed to enhance SDT for treating MRSA-infected myositis, demonstrating complete eradication of bacterial infection both *in vitro* and *in vivo* under US irradiation. It also serves as a versatile imaging agent for guiding treatment and real-time monitoring.[29] Recently, single-atom catalysts have emerged as pivotal innovations in SDT, offering advantages such as enhanced catalytic activity, superior selectivity, and significant reduction in catalytic metal dosage. RBC-HNTM-Pt@Au, noted for its superior sonocatalytic activity, was evaluated for its antibacterial performance against MRSA under US irradiation (1.5 W/cm², 50% duty cycle, 1 MHz, 15 minutes). As shown in **Figure 8A**, compared to the control group (phosphate buffer solution), the US group exhibited no significant antibacterial effect, while HNTM, HNTM-Pt, and HNTM-Pt@Au displayed antibacterial efficiencies of 34.14%, 97.86%, and 99.93%, respectively, based on colony forming unit reduction of MRSA. The single-atom catalysts in this platform significantly enhance electron transfer and O_2 adsorption, thereby augmenting the sonosensitiser's antibacterial effectiveness and neutralising MRSA toxins, showing promise for rapid osteomyelitis treatment and advancing sonosensitiser development.[35]

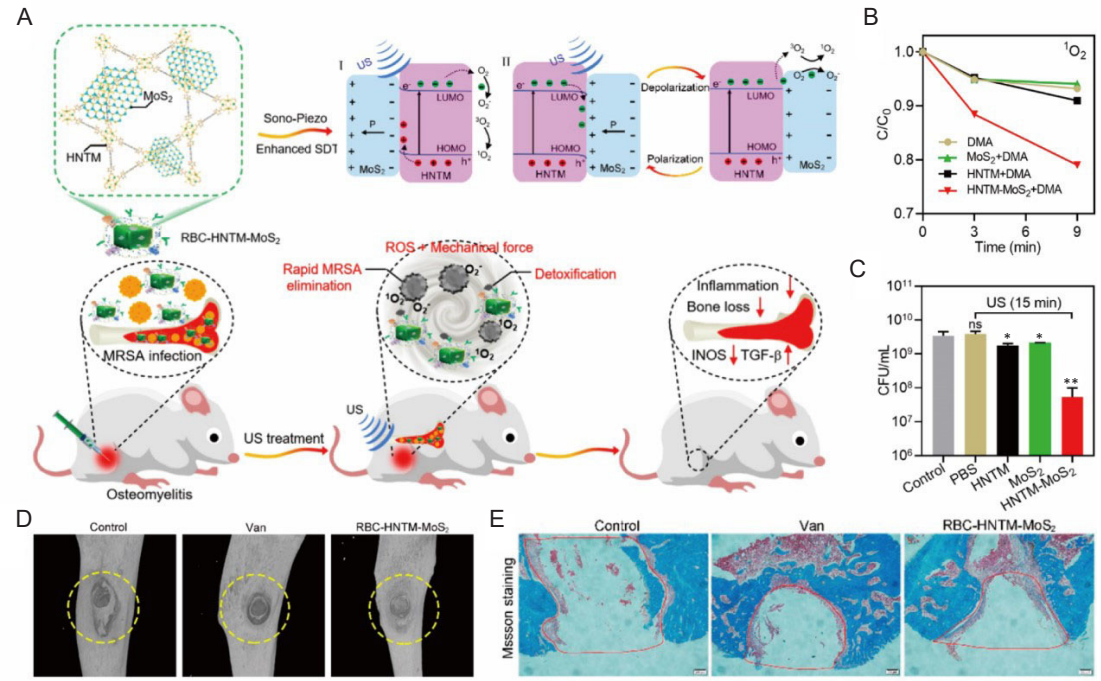

Figure 7. Construction of a porphyrin-based HNTM, MoS_2 nanosheets, and a RBC membrane, RBC-HNTM-MoS_2 was applied for treating bone infection via sonodynamic ability. (A) Mechanism and application of RBC-HNTM-MoS_2. (B) Relative fluorescence intensity of DMA, applied for detecting $^1O_2$ treated by HNTM-MoS_2. (C) Residual CFU of MRSA from differently treated samples. (D) Micro-CT of infected legs under different treatments. Yellow dash lines indicate bone destruction areas. (E) Masson staining of defects of the treated bones. Red dash lines indicate defect areas. Scale bars: 50 μm. Reprinted from Feng et al.[54] Copyright 2022, American Chemical Society. $^1O_2$: singlet oxygen; CFU: colony-forming unit; CT: computed tomography; DMA: 9, 10-dimethylanthracene; HNTM: hollow metal-organic framework; HOMO: highest occupied molecular orbital; INOS: inducible nitric oxide synthase; LUMO: lowest unoccupied molecular orbital; MoS_2: molybdenum disulfide; MRSA: methicillin-resistant *Staphylococcus aureus*; RBC: red blood cell; ROS: reactive oxygen species; SDT: sonodynamic therapy; TGF-β: transforming growth factor-beta; US: ultrasound; Van: vancomycin.

Table 1. The application of sonodynamic therapy in different infectious diseases

Disease	Material	Bacterial type	Antibacteria efficiency
Bone infection disease	Pd@Pt-T790[29]	*Staphylococcus aureus*	Nearly 100%
	HNTM-Pt@Au[35]	*Staphylococcus aureus*	99.93%
	Ti–S–TiO_{2-x}[48]	*Staphylococcus aureus*	99.995%
Gastrointestinal infection diseases	HpAb-LiP-ICG[39]	*Helicobacter pylori*	97.49%
	Fe-HMME@DHA@MPN[55]	*Helicobacter pylori*	> 99.99%
Skin infection disease	CuS/Cur[38]	*Staphylococcus aureus* *Escherichia coli*	99.56% 99.48%
	BTO-400[56]	*Staphylococcus aureus* *Escherichia coli*	99% 100%
Lung infection disease	ZTN[50]	*Klebsiella pneumoniae*	91.8%
	TMOS@ZIF-8[57]	*Pseudomonas aeruginosa*	86.5%

Note: CuS/Cur: copper(II) sulfide/curcumin; Fe-HMME@DHA@MPN: iron-hematoporphyrin monomethyl ester@dihydroartemisinin@manganese phosphate nanoparticles; HNTM-Pt@Au: Pt single-atoms and Au nanorods modified haematoporphyrin monomethyl ether; HpAb-LiP-ICG: haematoporphyrin antibody - liposome - indocyanine green; Pd@Pt-T790: Pd@Pt nanoplates loaded meso-tetra (4-carboxyphenyl) porphine; Ti–S–TiO_{2-x}: titanium sulfur titanium oxide with oxygen vacancies; TMOS@ZIF-8: tetraethyl orthosilicate mesoporous organosilica@zeolitic imidazolate framework-8; ZTN: zeolitic imidazolate framework-8 derived carbon@TiO_2 nanoparticles.

Gastrointestinal diseases

H. pylori, classified as a class I carcinogen by the World Health Organization, contributes to a range of gastrointestinal diseases including chronic active gastritis, gastroduodenal ulcer, and gastric cancer.[59] Given its widespread prevalence affecting over half of the global population, effective treatment strategies are imperative. SDT, utilising US for noninvasive localised therapy, is increasingly explored as an alternative to PDT, leveraging its ability to penetrate tissues beyond 10 cm. Recent research has focused on sonosensitisers such as ICG, valued for its safety and ROS generation capabilities under US irradiation, crucial for SDT. However, challenges such

as chemical instability and poor targeting efficiency limit the efficacy of free ICG. To address this, researchers developed a novel approach enhancing ICG's SDT activity by combining it with the robust stability of liposome (LiP) and the high binding affinity of monoclonal antibodies haematoporphyrin antibody (HpAb). This formulation significantly bolstered the therapeutic efficacy of HpAb-LiP-ICG against *H. pylori* infections. *In vitro* studies under US irradiation demonstrated that HpAb-LiP-ICG efficiently produced $^1O_2$, leading to substantial damage to *H. pylori*'s outer membrane and achieving a bactericidal efficiency of 99.9% at 200 μg/mL (ICG-equivalent concentration). Additionally, photoacoustic imaging highlighted rapid accumulation of HpAb-LiP-ICG on *H. pylori* surfaces, maintaining stability *in vivo* for up to 2 hours. In *H. pylori*-infected mice, HpAb-LiP-ICG exhibited notable antibacterial efficacy during SDT without adverse effects on normal tissues. This innovative approach contrasts with traditional antibiotic therapies, addressing concerns of drug resistance through its unique antibacterial mechanism (**Figure 8B**). Moreover, this formulation stabilises ICG in acidic gastric conditions and enhances ROS production upon US exposure, effectively targeting and neutralising *H. pylori* infections in animal models without cytotoxic effects.[39] This innovative theranostic strategy shows promise for advancing antimicrobial SDT, offering a potential breakthrough in treating *H. pylori*-related diseases.

Skin infection diseases

Skin wounds are highly susceptible to bacterial infections, which can induce inflammatory responses and impede the natural healing process.[60] SDT has emerged as an effective strategy for combating bacterial infections in wounds, offering significant antibacterial effects without the risk of antibiotic resistance. These therapies utilise light or US to activate photosensitising agents, generating ROS that selectively destroy bacterial cells. By avoiding antibiotic resistance, SDT represents an innovative approach to promoting wound healing by effectively controlling microbial populations. The rapid development of inorganic nanomaterials has highlighted the potential of piezoelectric materials with non-centrosymmetric characteristics, such as $BaTiO_3$, which demonstrate excellent ROS generation ability under US irradiation and find wide application in antibacterial treatments. $BaTiO_3$ with varying vacancy concentrations significantly enhances its ROS generation capacity crucial for antibacterial activity under US irradiation. Among these materials, BTO-400 exhibited the highest ROS generation efficacy, attributed to optimal vacancy levels that effectively disrupt bacterial cell membranes. The inhibitory rates of BTO-400 combined with US were calculated to be 100% for *E. coli* and 99% for *S. aureus*, respectively.[56] Recently, interfacial engineering strategies have endowed some specific materials with excellent photodynamic, sonodynamic, and wavedynamic effects excited by exogenous energy. A novel organic–inorganic hybrid, integrating CuS and Cur through photo–sono interfacial engineering, demonstrated exceptional bactericidal efficacy, achieving 99.56% elimination of *S. aureus* and 99.48% of *E. coli*. This hybrid effectively treated bacterial infections *in vivo* using both US and 808 nm NIR light irradiation. The interface between CuS and Cur created an internal electric field, facilitating electron transfer and enhancing separation of electron–hole pairs. This process promoted rapid generation of superoxideanion ($\bullet O_2^-$) and •OH on Cur under 808 nm irradiation, while synergistically utilising electrons from CuS and holes from Cur under US irradiation enhanced their redox capabilities (**Figure 8C**).[38] The treatment strategy with SDT can enhance the therapeutic efficacy of herbal nanomedicine against pathogenic bacterial infection in a short time.

Lung infection diseases

In the treatment of MDR bacterial pneumonia, challenges such as inadequate penetration of antibacterial drugs due to acidic infection environments and complex biofilm compositions hinder therapeutic efficacy. Recent advances highlight the potential of US-induced vacuoles and microjets to enhance drug diffusion, emphasising the feasibility of combining pulmonary inhalation drug delivery with SDT. Traditionally, TiO_2 serves as a standard inorganic sonosensitiser, but its effectiveness is often limited by a wide bandgap, leading to suboptimal sonodynamic effects. To address this issue, researchers have developed ZTNs, characterised by a narrower bandgap and enhanced US sensitivity. Administered via aerosolised intratracheal inoculation in mouse models, ZTNs under US irradiation demonstrated superior production of ROS, notably $^1O_2$ and •OH, compared to TiO_2. This capability facilitated effective eradication of Gram-negative MDR bacteria such as *Klebsiella pneumoniae* (*K. pneumoniae*), *Acinetobacter baumannii*, *P. aeruginosa*, and Enterobacter species. In experimental lung infection models involving immunocompetent (BALB/c), mildly immunodeficient (SCID), and severely immunodeficient (NOD/SCID) mice, ZTNs exhibited robust efficacy against MDR *K. pneumoniae*, achieving a 100% survival rate in lethally infected mice. Importantly, ZTNs demonstrated no discernible toxicity at both cellular and animal levels, positioning MOF-derived nanoparticles as promising candidates for safe and effective inhalable sonosensitisers in SDT-based treatments for bacterial pneumonia (**Figure 8D**).[50]

Limitations

Emerging application of sonodynamic therapy research

SDT for antibacterial treatment is an emerging field, and many studies are still in the preclinical stage. Clinical data is limited, and much of the evidence is based on *in vitro* and animal studies. This limitation restricts the ability to extrapolate findings to human clinical applications and underscores the need for more extensive clinical trials to validate the efficacy and safety of SDT in treating MDR bacterial infections.

Focus on specific mechanisms and applications

The review specifically discusses the cavitation effect, ROS production, and the antibacterial applications of various sonosensitisers. While these are critical aspects of SDT, other relevant factors and mechanisms, such as ultrasonic parameters, might not thoroughly explored. The review focus on these particular areas may result in an incomplete understanding of the broader potential and limitations of SDT.

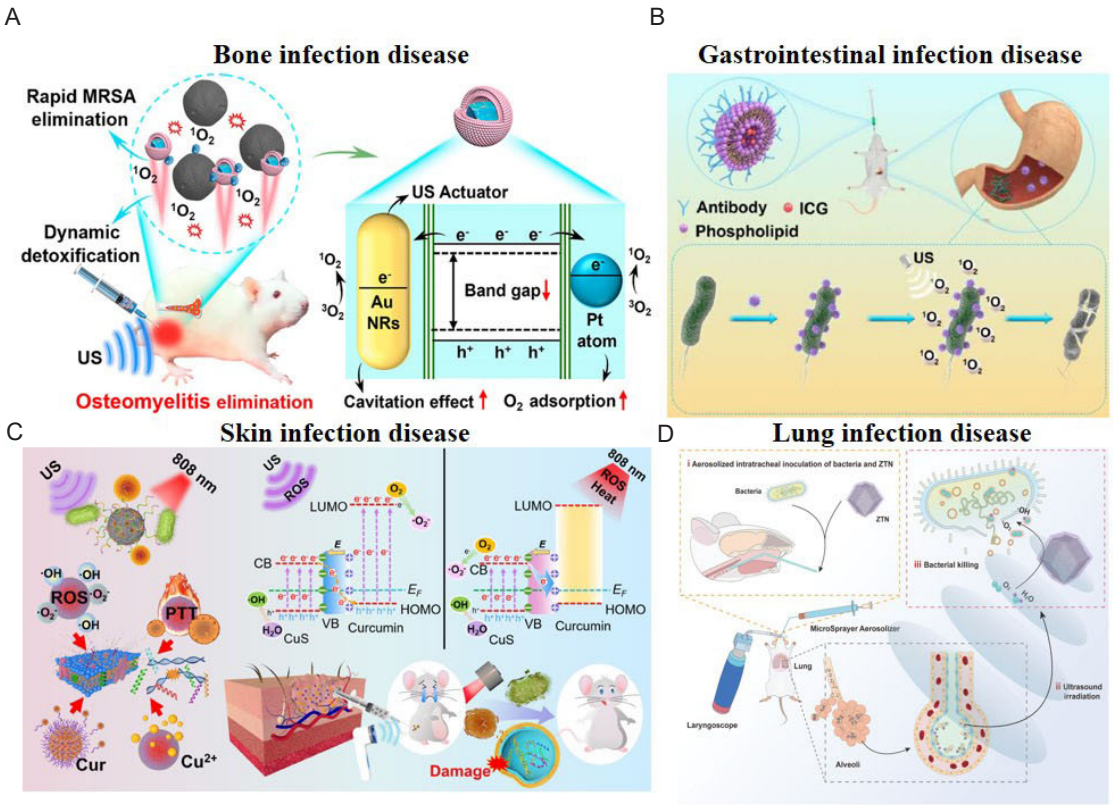

Figure 8. Schematic diagram of the application of SDT in bacterial infection disease. (A) Schematic illustration of RBC-HNTM-Pt@Au working mechanism and the treatment of osteomyelitis through efficient SDT. Reprinted from Yu et al.[35] Copyright 2021, American Chemical Society. (B) Schematic illustration of HpAb-LiP-ICG-mediated SDT for eradicating *Helicobacter pylori* under US. Reprinted from Wang et al.[39] Copyright 2022, Published by Elsevier Ltd on behalf of Acta Materialia Inc. (C) Antibacterial mechanism of CuS/Cur in *Staphylococcus aureus* infected wound model. Reprinted from Liu et al.[38] Copyright 2021, American Chemical Society. (D) Schematic illustration of ZTNs for SDT of bacterial lung infections. Reprinted from Pan et al.[50] $^1O_2$: singlet oxygen; $^3O_2$: oxygen in the triplet state; Au NPs: gold nanorods; CB: conduction band; Cur: curcumin; CuS: copper(II) sulfide; CuS/Cur: copper(II) sulfide/curcumin; HOMO: highest occupied molecular orbital; HpAb-LiP-ICG: haematoporphyrin antibody - liposome - indocyanine green; ICG: indocyanine green; LUMO: lowest unoccupied molecular orbital; MRSA: methicillin-resistant *Staphylococcus aureus*; Pt: platinum; PTT: photothermal therapy; RBC-HNTM-Pt@Au: red blood cell membrane - haematoporphyrin nanomaterial - platinum@gold nanoparticles; ROS: reactive oxygen species; SDT: photothermal therapy; US: ultrasound; ZIF-8: zeolitic imidazolate framework-8; ZTN: carbonised TiO_2 coated ZIF-8.

Summary and Further Perspectives

As we have mentioned above, ROS, heat, and shear forces are generated during the SDT process, which can damage bacteria without inducing bacterial resistance. The US required for antibacterial SDT offers advantages such as deep tissue penetration, non-invasiveness, and spatiotemporal controllability, making it widely used in clinical settings. These advantages render sonosensitisers effective antibacterial agents for patients suffering from MDR bacterial infections.[61] The non-resistance-inducing nature of SDT, in particular, presents it as a potential alternative to traditional antibiotic therapies, which are often hampered by the development of resistance over time. However, there are still barriers that need to be addressed before antibacterial SDT can be clinically applied. The path to clinical translation of SDT is not without its challenges. Regulatory bodies, such as the U.S. Food and Drug Administration, require robust evidence from preclinical studies, including large animal models and clinical trials. There is also a pressing need to standardise the sonosensitiser dosages, US parameters, and treatment protocols to ensure consistent results across different clinical settings. Furthermore, while SDT holds great promise, its long-term safety must be thoroughly assessed, particularly in regard to the potential for off-target effects and accumulation of sonosensitisers in vital organs.[62]

The development of efficient sonosensitisers is crucial to maximising the therapeutic potential of SDT. To achieve this, considerable focus must be placed on optimising the chemical structure of sonosensitisers to enhance their ability to generate ROS while maintaining stability under physiological conditions. This is particularly important for ensuring that sonosensitisers remain effective during *in vivo* applications without breaking down prematurely. In parallel, the biocompatibility of sonosensitisers needs to be prioritised to minimise any potential adverse immune responses or toxicity. Ensuring that sonosensitisers are non-toxic to healthy tissues

and capable of safely circulating in the body is paramount for the successful clinical implementation of SDT. In this regard, efforts to design targeted delivery systems, such as targeting ligands or antibodies, could help improve the selective accumulation of sonosensitisers in bacterial cells while sparing surrounding healthy tissues. By enhancing selectivity, the therapeutic index of SDT could be significantly improved, reducing the likelihood of off-target effects. Another critical avenue to improve SDT efficacy is to explore the potential for synergistic effects. Combining sonosensitisers with traditional antibiotics, PDT, or PTT could provide a multi-faceted approach to combat bacterial infections, particularly those involving complex biofilms or resistant strains. By exploiting the unique mechanisms of each therapy, such as ROS generation and heat production, it is possible to create more potent, combinatory treatment strategies that overcome bacterial defenses and enhance bacterial eradication. Considering the future perspective of clinical applications of SDT, the suggestions for improving antibacterial sonodynamic nanomedicine are as follows:

(1) Enhancing the efficacy of sonosensitisers is crucial. While integrating SDT with other therapeutic strategies shows significant potential, it may also complicate treatment protocols. Therefore, a deep understanding of the underlying sonodynamic mechanisms is essential to guide the rational chemical design of sonosensitisers. Developing high-efficiency sonosensitisers through simple and effective preparation methods is crucial for advancing their practical applications.

(2) Further investigation is required to assess the stability and potential toxicity of sonosensitisers. Organic sonosensitisers often face challenges in maintaining dispersion and stability within physiological environments, whereas inorganic sonosensitisers may leave residual deposits in organs such as the kidneys, posing potential toxic side effects due to their poor biodegradability. From the perspective of safety and *in vivo* stability, the rational design of efficient sonosensitisers, coupled with systematic studies on their long-term toxicity *in vivo*, is crucial for advancing the clinical translation of sonosensitisers for antibacterial applications.

(3) The scope of applications of antibacterial SDT could be expanded. Given the deep tissue penetration of US, antibacterial sonodynamic nanomedicine may demonstrate efficacy in treating infections in other organs, such as bladder infections. Exploring and expanding the applications of SDT will help address the threat of MDR bacteria in various clinical scenarios.

Considering the threat of MDR, the potential applications of antibacterial sonodynamic nanomedicine deserve more attention. It is hoped that antibacterial SDT will garner increased interest from researchers and clinicians alike. Future research should focus on advancing sonosensitiser development, improving their selectivity for bacterial cells, and overcoming the limitations of current US equipment. Collaborations between nanotechnologists, microbiologists, and clinicians will be essential to advancing SDT from laboratory-based experiments to real-world applications in combating MDR infections.

Author contributions

SY and GY conducted the primary literature search, selected relevant studies and wrote the first draft; LY and YC conceived the original idea, edited and improved the manuscript. All authors reviewed and approved the manuscript for publication.

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Conflicts of interest statement

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

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