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REVIEW

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Recent advances and challenges in metal-based antimicrobial materials: a review of strategies to combat antibiotic resistance

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Abstract

Despite the availability of a series of classical antibiotic drugs, bacterial infections continue to represent a significant and urgent threat to global human health. The emergence of drug-resistant bacteria and the slow pace of antibiotic development have rendered current treatment methods inadequate in meeting the clinical demands of bacterial infections. Consequently, there is an increasingly urgent and vital need for the development of safe, efficient, and alternative novel antimicrobial agents in the medical and healthcare field. Over the past five years, there has been a notable expansion in the field of nanomedicine with regard to the prevention and control of infectious diseases. The objective of this article is to provide a comprehensive review of the latest research developments in the field of metal nanomaterials for medical antimicrobial therapy. We begin by delineating the gravity of the bacterial infection crisis, subsequently undertaking a comprehensive examination of the potential mechanisms through which nanoparticles may combat bacterial infections and the specific applications of these nanomaterials in the treatment of diverse infectious diseases. In conclusion, we eagerly anticipate the future development directions of metal nanomaterials in the field of antimicrobial therapy. We believe that with continuous technological advancements and innovations, this field will make even more outstanding contributions to safeguarding human health and well-being.

Keywords Bacterial infections, Antibiotic resistance, Metallic nanoparticles

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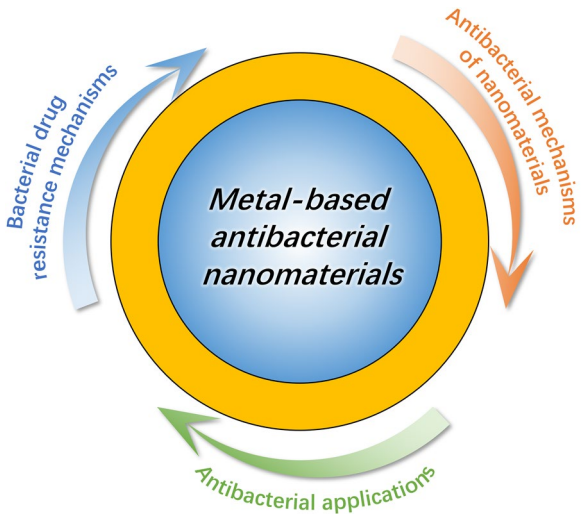
Graphical Abstract



Introduction

Over the past five years, bacterial infections have constituted a significant challenge for global public health [1, 2]. The 2019 Antibiotic Resistance Threats Report indicates that over 2.8 million cases of antimicrobial-resistant infections occur annually in the United States, resulting in the unfortunate loss of over 35,000 lives [3]. Of particular note are the three major infection syndromes of lower respiratory tract infection, bloodstream infection, and intra-abdominal infection, which account for an alarming proportion of antibiotic resistance-related deaths worldwide—78.8% [4]. This data not only highlights the dominance of these infection syndromes in antibiotic resistance deaths, but also further warns us that antibiotic resistance has risen to the top public health issue that needs to be addressed globally.

Bacteria gain access to the body's defensive barriers through a variety of routes, leading to the onset of a spectrum of illnesses. In the event of physical trauma, such as burns or lacerations, or chemical irritation, as may occur with adverse drug reactions, the equilibrium of flora is readily disrupted. The bacteria then exploit this vulnerability, significantly increasing the risk of infection, which could potentially evolve into a pandemic. Localized bacterial infections not only impede the natural healing process of wounds, causing suppuration, redness, swelling, and inflammation, but also pose a risk of systemic consequences, including, but not limited to, life-threatening conditions such as pneumonia, encephalitis, sepsis, and even malignancy [5–7]. Although antibiotics have been the primary treatment for such infections in the past, the increasing problem of resistance, coupled with the inherent limitation of their short half-lives, has significantly compromised their efficacy in combating specific types of bacterial infections [8]. Consequently, the development of novel therapeutic strategies and approaches to address multidrug-resistant (MDR) bacterial strains and the diseases they cause has become an urgent and critical issue requiring immediate attention.

The rapid advancements in nanomedicine technology have led to a significant expansion in the potential applications of metallic nanomaterials in bacterial therapy [9, 10]. A variety of metallic nanomaterials have been successfully developed by researchers, including gold nanoparticles, silver nanoparticles, and metal complex-based liposomes [11–13]. These materials have been widely applied in preclinical and clinical treatments for acute and chronic bacterial infections. These nanoparticles have been demonstrated to exhibit remarkable bactericidal efficacy while simultaneously exhibiting no adverse effects on surrounding tissues. Nanomedicine has significant advantages over traditional small molecule antibacterial agents in the application of antibacterial agents. Nanomedicine can make more drugs enter the body and play a role by changing the physical and chemical properties of drugs, such as particle size and surface charge. At present, nanocomposites that integrate antibacterial, anti-inflammatory, and wound healing functions have been developed [14, 15]. These multifunctional materials use highly effective antimicrobial strategies such as photodynamic therapy, photothermal therapy and sonodynamic therapy

to precisely kill pathogens, providing new therapeutic tools for complex infectious diseases [16, 17]. In addition, nanocarriers can protect antibacterial agents from being destroyed in the body and actively target them to specific cells or tissues. It is worth noting that nanocarriers can achieve sustained release of drugs, thereby maintaining long-term antibacterial effects. This is especially important for patients who need long-term treatment [18].

This review comprehensively summarizes the latest research results and development trends in the field of antibacterial nanomaterials. First, we conducted an in-depth analysis of the complex and ever-changing mechanisms of bacterial drug resistance. Next, the key antibacterial principles of metal nanomaterials are elaborated in detail, which reveal how they effectively inhibit the growth and reproduction of bacteria through specific mechanisms. The core part of the article focuses on the latest application examples of metal nanomaterials in the field of antibacterial therapy, highlighting their excellent application effects. Finally, we discuss the challenges faced by metal nanomaterials in antibacterial applications, and we also look forward to the potential of metal nanomaterials based on innovative design concepts in addressing the challenges of MDR bacteria.

Mechanisms of bacterial resistance

Currently, the number of bacterial infection cases caused by antibiotic resistance is soaring globally, with intricate mechanisms underlying this resistance [19]. Almost all existing antibiotics are facing the challenge of resistance, making the development of novel drugs that can effectively curb multidrug resistance an urgent task. Notably, some bacteria are inherently resistant to certain antibiotics, for instance, their complex cell wall structures can hinder the penetration of antibacterial drugs, thereby reducing the absorption efficiency of antibiotics [20]. Furthermore, the acquisition of bacterial resistance is closely linked to the expression regulation of resistance genes and chromosomal gene mutations. Through horizontal gene transfer mechanisms, bacteria can utilize mobile genetic elements (such as plasmids and transposons) to acquire foreign genetic information from other resistant strains, further enhancing their resistance [21]. As shown in Figure 1, Bacterial resistance mechanisms can be broadly classified into four categories: protecting of biofilm, reducing intracellular drug concentration, modifying or protecting drug targets, and directly modifying antibiotic molecules. Readers interested in delving deeper into the details of bacterial resistance mechanisms are advised to consult authoritative literature in related fields [22, 23].

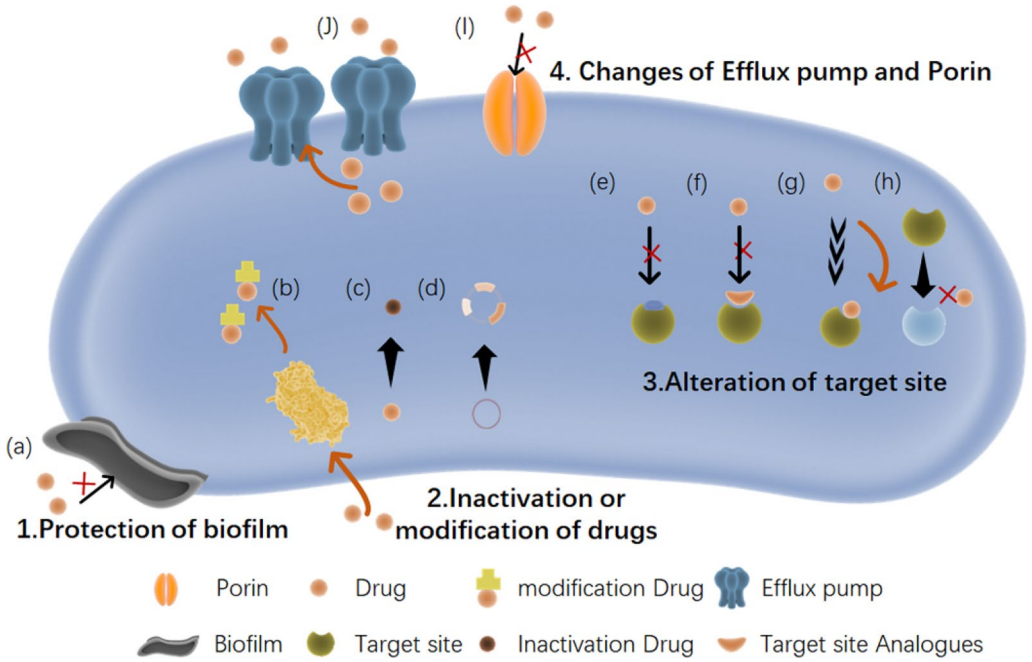


Fig. 1 Mechanisms of bacterial resistance. (**a**)The formation of bacterial biofilms; (**b**) Modification of drugs with acetylation, phosphorylation and adenosylation; (**c**) Drug degradation or hydrolysis; (**d**) Production of drug resistance genes; (**e**) Factor-associated protection, such as steric hindrance; (**f**) Overexpression of similar targets; (**g**) Formation of target bypass; (**h**) Target site mutation; (**j**) Overexpression of efflux pumps; (**i**) Porin mutation/loss/impaired function

To keep the drug concentration at a low level in the cell

Two principal methods exist for reducing the concentration of drugs within cells: the overexpression of bacterial efflux pumps and alterations to the structure of porins [24, 25]. Bacterial efflux pumps are active antibiotic transport systems that are located on the bacterial cell membrane. When expressed at elevated levels, bacterial efflux pumps can enhance the active efflux of antibiotics out of the cell membrane, thus preventing drug-bacteria interactions. To date, bacterial drug efflux pumps have been classified into six families: the ATP-binding cassette (ABC) family, the multidrug and toxic compound extrusion (MATE) family, the major facilitator superfamily (MFS), the resistance-nodulation-division (RND) superfamily, the small multidrug resistance (SMR) family and the proteobacterial antimicrobial compound efflux (PACE) family [26, 27]. These efflux pump families are different in many ways, including the energy source, structural conformation, range of substrates they can pump out, and distribution of the efflux pump. In terms of energy source, the ABC family can directly use ATP as the source of energy, while other groups are all secondary active transporters that utilize proton exchange as the energy source. For example, Tet efflux pumps can cause tetracycline resistance and belong to the MFS [27]. *Staphylococcus aureus (S. aureus)* contains three chromosome-encoded efflux pump systems: NorA, NorB, and NorC. Their overexpression may result in resistance to fluoroquinolones [28]. The most common mechanism for the induction of efflux pump gene expression is the direct binding of molecules to transcription repressor proteins, which subsequently reduces the binding of repressor proteins to their target DNA. Hydrophilic antibiotics (such as β-lactams and tetracyclines) utilize water-filled diffusion channels (porins) to penetrate into the hydrophobic outer membrane of gram-negative bacteria [29]. Porins commonly associated with antibiotic resistance include OmpF, OmpC, PhoE and OprD. Such alterations to the porin are reflected in a number of different ways, including changes to the type of porin present, a reduction in the expression of the porin, and an impairment of the porin's function. In conclusion, these alterations of porins can result in antibiotic resistance, either independently or in conjunction with the overexpression of an efflux pump.

Modification or protection of the target

Modifying the target site of an antibiotic represents a common mechanism of drug resistance, whereby the affinity between the antibiotic and the target site is reduced [26, 30]. It has been reported that the modification of drug targets encompasses the following: The modification of drug targets may be achieved through three principal mechanisms: enzymatic target-site modification, bypass of the target site, and protection and mutation of the target site. To illustrate, the mechanism of resistance to β-lactams in gram-positive bacteria is partially attributable to modifications of the penicillin-binding proteins encoded by the MecA gene. The proteins produced following modification exhibit a reduced affinity for β-lactams, which is indicative of methicillin resistance in *S. aureus* [31]. Bacteria are capable of synthesizing related substances in order to compete with antibiotics for binding targets or to increase the production of the target in order to overcome the inhibition of antibiotics. This is known as 'target bypass'. To illustrate, the mechanism of sulfonamide resistance in *S. aureus* or Neisseria meningitidis is associated with the enhanced synthesis of 4-Aminobenzoic acid, which is a competitive molecule of antibiotics [30, 32]. Furthermore, the targets are protected by biofilms, which impede the efficacy of antibiotics by preventing them from reaching their binding sites. Biofilms are composed of surface-attached bacteria that are encased in a protective extracellular polymeric substance matrix [33–35]. The formation of biofilms represents a significant virulence factor for a range of microbial organisms, with the potential to contribute to antibiotic resistance and evasion of the host immune system [36]. The drug resistance mechanisms associated with biofilm formation are primarily attributable to metabolic dormancy and molecular persistence. To illustrate, the Staphylococcal Bap protein is capable of self-assembly into amyloid protein aggregates of bacteria in response to environmental signals, thereby promoting the formation of staphylococcal biofilms [37].

Modification of antibiotic

As mentioned above, bacteria can obtain foreign genes through the horizontal gene transfer process, and then they encode special enzymes to covalently modify antibacterial drugs by adding specific chemical moieties to the molecule or destroying the chemical structure of antibiotics [26, 27, 30]. In penicillin-resistant *S. aureus* isolates, the mechanism of resistance to penicillin encompasses the production of β-lactamases, which are capable of hydrolyzing the amide bond of the β-lactam ring, rendering the antimicrobial ineffective [38]. Furthermore, enzymatic modification of antibiotics can also result in their inactivation or alteration of the steric hindrance, which in turn affects their affinity for the target [30]. The classical drugs involved in enzymatic alteration are aminoglycoside agents [39]. Aminoglycoside agents are covalently modified with hydroxyl or amino groups among clinical isolates of *S. aureus* [40]. The most common biochemical reactions associated with enzymatic modification include acetylation, phosphorylation, and

adenylation [41–43]. To illustrate, chloramphenicol acetyltransferases are instrumental in the inactivation of chloramphenicol through acetylation at the C3 position [44] (Fig. 1).

Antibacterial mechanisms of metal-based nanomaterials

Given the complexity of bacterial resistance mechanisms, scientists are actively exploring and developing novel antibacterial strategies, with a focus on creating highly effective antibacterial nanoparticles. These nanoparticles possess exceptional antibacterial properties primarily due to their unique physical and chemical characteristics, including shape, size, charge state, dissociated ion species, functionalized surfaces, and core materials [45, 46]. Nanoparticles can carry a variety of antibacterial components such as antibiotics, photosensitizers, antimicrobial peptides, and phages [47, 48]. As illustrated in Figure 2, the multiple common mechanisms by which antibacterial nanoparticles exhibit their antibacterial efficacy encompass the generation of reactive oxygen species (ROS), the release of heavy metal ions, the simultaneous delivery of multiple drugs into bacterial cells, the modulation of bacterial membrane efflux and permeability, the excitation of photothermal effects, and the effective prevention of biofilm formation [49–52].

Destruction of cell wall and biofilm

The small size effect of nanomaterials enables them to penetrate through bacterial cell walls and membranes, leading to disruption of cellular structures [53]. This, in turn, causes leakage of cellular contents and ultimately bacterial death. Notably, positively charged nanomaterials, such as silver nanoparticles (Ag NPs), can interact with the negative charges on bacterial membranes, enhancing their penetration capability and damaging membrane structures. For example, Ding et al. designed an innovative bionic photothermal nanoscale platform that combines silver nanoparticles with poly-dopamine (Ag/PDA) [54]. When the Ag/PDA nanoscale platform is combined with near-infrared light irradiation (NIR), it can precisely destroy the complex spatial structure of the biofilm, and the synergistic effect with NIR laser effectively clears the resident bacteria, achieving deep clearance of bacteria within the biofilm.

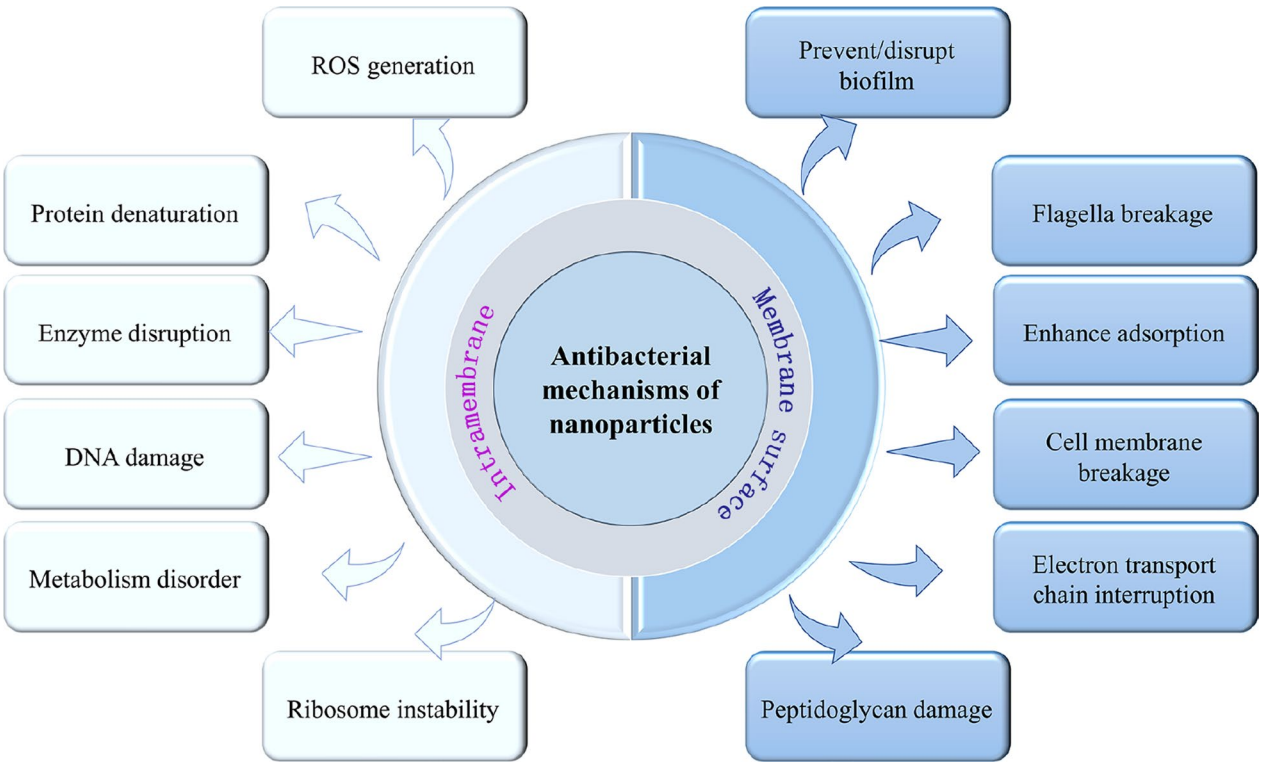


Fig. 2 Various antimicrobial mechanisms of metallic nanoparticles. In addressing the global crisis of antibiotic resistance, research into the antibacterial mechanisms of nanomaterials offers a novel perspective for the development of new antibacterial therapies. Nanomaterials, with their unique physicochemical properties such as high specific surface area, quantum size effect, and surface modifiability, exhibit tremendous antibacterial potential. These properties enable nanomaterials to interact with bacterial cell walls, membranes, or intracellular components in various ways, thereby achieving the goal of antibacterial activity

In addition, the sharp edges or high surface energy of nanomaterials can directly inflict physical damage on bacterial cell walls or membranes, compromising their integrity and rendering bacteria nonviable [55]. Noronha et al. proposed a strategy of combining cellulose nanocrystals (CNCs) with silver nanoparticles (CNC/Ag) to enhance their antibacterial properties and resistance to biofouling. CNCs, as a type of carbon nanotubular nanomaterial, possess the ability to physically puncture bacterial cell walls, thereby killing bacteria. This mechanism is mediated by membrane stress, similar to the phenomenon where CNCs, upon contact with lipid vesicles, cause the release of encapsulated dyes. Once bacteria are punctured by CNCs, silver ions can passively permeate into the bacterial interior, further disrupting the integrity of DNA and other cellular organelles.

ROS-induced disruption of bacterial membrane and intracellular contents

The ROS generated by metal nanomaterials mainly include the following types: hydroxyl radical (•OH), superoxide radical ($\bullet O_2^-$), singlet oxygen($^1O_2$), and hydrogen peroxide(H_2O_2) [56–58]. •OH is highly reactive ROS with strong oxidizing power, capable of damaging bacterial cell membranes and DNA, thereby inhibiting or killing bacteria [59]; $\bullet O_2^-$ is a single-electron reduction product of oxygen molecules, and their reactivity is relatively low, but they can generate other ROS through a series of reactions. Although the direct antibacterial effect may not be as good as that of hydroxyl radicals, it plays an important role in the ROS generation chain and can indirectly promote the production of other ROS, thereby enhancing the antibacterial effect [60]; $^1O_2$ is a high-energy state of oxygen molecules with a long lifetime and high reactivity. Singlet oxygen can destroy bacterial cell membranes and intracellular biomolecules, such as proteins and nucleic acids, thereby inhibiting or killing bacteria [61]. H_2O_2 is a relatively stable ROS that can be produced in or outside cells through various pathways. Hydrogen peroxide can penetrate into the interior of bacterial cells, destroy intracellular biomolecules, and also trigger bacterial death through oxidative stress mechanisms [62]. These ROS types have different characteristics in terms of antibacterial effect, but which one is the most effective is not absolute, because it depends on a variety of factors, including the type of nanomaterial, the mechanism of ROS generation, the type and physiological state of the bacteria, and so on. For example, Au nanoparticles are capable of generating •OH and $\bullet O_2^-$ under x-ray and UV irradiations [63, 64]; Manganese or iron-based nanoparticles catalyze the decomposition of H_2O_2 through a Fenton-like reaction and generate •OH with strong oxidizing properties [65, 66]. In some cases, one ROS type may play a dominant role, while in other cases, multiple ROS types may work together to achieve optimal antimicrobial effects.

Utilization of metal ions for inhibition of bacterial activity

In the field of antibacterial, the ions released from metal materials, especially Ag ions, exhibit excellent antibacterial properties, mainly due to their ability to damage the bacterial cell structure or interfere with the bacterial metabolic process. Under the action of acidic stimulation in the microenvironment or intracellular of the tissue, the metal nanomaterials will gradually decompose and release metal ions. These metal ions can bind to bacterial proteases(carbonic anhydrase, guanosine triphosphate hydrolyzing proteins and lytic transglycosylase), thereby inhibiting their activity and disrupting the metabolic processes of bacteria [67–69]. There are many proteases distributed on the surface of bacterial membrane, which play a crucial role in the development of antibacterial drugs. For example, LspA is involved in the post-translational processing of *Pseudomonas aeruginosa* lipoproteins and is crucial for the maturation of lipoproteins [70]. In addition, MraY is also an indispensable membrane enzyme that is crucial for the synthesis of bacterial cell walls, and is therefore considered a promising target in the development of antimicrobial drugs [71]. Similarly, bacterial respiratory chain dehydrogenases are also important drug targets. This is because bacteria rely on respiratory enzymes on their cell membrane to capture chemical energy to maintain their metabolic activity [72]. These respiratory enzymes capture energy by facilitating the transport of protons or sodium ions across the cell membrane, and convert it into a form that bacteria can use to drive their energy metabolism. It is noteworthy that silver ions can disrupt the electron transfer of the bacterial cell respiratory chain, leading to a decrease in the activity of respiratory chain dehydrogenases, ultimately resulting in bacterial death [73]. This antibacterial mechanism highlights the unique advantages and application potential of metal materials in the field of antibacterial. By screening specific metal ions that bind to key bacterial active targets, we can develop more effective and safer antibacterial metal nanoparticles to address the increasingly serious problem of bacterial infections.

Research of metal nanomaterials in the field of medical antibacterials

Metal nanomaterials have demonstrated immense application potential and broad research prospects in the field of medical antibacterials due to their unique physicochemical properties [74]. Research in this area not only focuses on the development of novel materials but also delves into optimizing their antibacterial performance,

ensuring biocompatibility and safety, and ultimately facilitating their widespread clinical applications (Table 1).

Development of metal nanomaterials

In recent years, significant advancements have been made in the preparation techniques of metal nanomaterials, providing a solid technological foundation for innovation in antibacterial materials. Researchers have successfully synthesized composites with complex nanostructures and multifunctionality by precisely controlling synthesis conditions. For instance, metallic nanoparticles such as gold, silver, and copper have garnered significant attention due to their superior antibacterial properties. By modulating the size, morphology (spherical, rod-shaped, and flake-like), and surface roughness of these nanoparticles, their antibacterial efficiency can be significantly enhanced [75]. Furthermore, integrating metal nanoparticles with other materials (e.g., polymers and bioactive molecules) not only strengthens the mechanical properties and stability of the materials but also endows them with novel biological functions, such as targeted delivery and sustained-release of antibacterial agents, thereby offering more possibilities for antibacterial therapy [76].

Antibacterial applications of gold nanomaterials

Gold nanoparticles (Au-NPs) exhibit extensive antibacterial activity due to their unique surface plasmon resonance properties, which are determined by their size, shape, and stability. Furthermore, Au-NPs can be prepared through both chemical and green synthesis methods, offering low toxicity, photothermal activity, and surface modification versatility for superior antibacterial effects.

Recent studies have shown that gold nanoparticles modified with 4,6-diamino-2-pyrimidinethiol, known as D-Au NPs, possess potent antibacterial capabilities against most Gram-negative MDR bacteria, including *MDR Pseudomonas aeruginosa*(*P. aeruginosa*) and *MDR Escherichia coli*(*E. coli*) [77]. Research on Au-NPs has also propelled the development of photothermal therapy, where Au-NPs inhibit or kill bacteria primarily through laser-induced hyperthermia. In one study, Au-NPs were utilized to disrupt biofilm integrity and increase intercellular spaces through vapor nanobubbles generated by high-intensity, short-pulse (< 10 ns) laser irradiation, thereby enhancing drug diffusion. Zhou et al. developed a core–shell nanoplatform (CeO_2@ZIF-8/Au) that combines the antibacterial function of ROS with ROS-scavenging anti-inflammatory activity, achieving self-regulation of ROS balance. The Au nanoparticles on the shell exhibit efficient peroxidase-like activity, generating ROS to kill bacteria. CeO_2 exerts superoxide dismutase and catalase-like activities. Subsequently, as the ZIF-8 structure decomposes in an acidic microenvironment, the CeO_2 core gradually releases, exerting its ROS-scavenging activity to eliminate excess ROS generated by the Au NPs [78] (Fig. 3).

Table 1 Antibacterial applications of metallic nanoparticles

Metallic element	Nanoparticles	Targeted pathogens	Antimicrobial mechanisms	Refs.
Zn	ZIF-8/Au-GOx	*E. coli; S. aureus*	ROS generation	[97]
	Zn-MOF	*E. coli*; *S. aureus*	ROS generation; membrane damage	[98]
Mg	Ag/MgO–NC	*E. Coli*	Photocatalytic; ROS generation	[99]
Co	Co SS	*S. aureus*	ROS generation	[100]
Fe	FeCo@G	*H. pylori*	Upregulate the cytoprotective HSP70 in gastric epithelial cells	[101]
	GDY-Fe@HA-DA	*E. coli*; *S. aureus; P. gingivalis*	ROS generation; PTT	[102]
Ni	Ni@Co-NC	MRSA	NIR laser irradiation; Heat ablation against bacteria	[103]
Ag	$AgNO_3$	*Mcr-positive bacteria*	Bind and disrupt the Function of MCR enzymes	[104]
	Chiral AgNCs	*P. aeruginosa*	Membrane damage	[105]
Pd	Pd(H)@ZIF-8@AP	*H. pylori*	Inhibit the activity of urease; Membrane damage	[106]
Cu	Cu-CDNEs	*E. coli; S. aureus*	ROS generation	[107]
Ru	Ruthenium metallacycle	*E. coli*; *S. aureus*	ROS generation	[108]

AP ascorbyl palmitate, AgNCs silver nanoclusters, *DA* dopamine, *E. coli Escherichia coli*, *S. aureus*, *Staphylococcus aureus*, *MgO* magnesium oxide, *Co SS* Co superstructures, *CmgO* chitosan-modified magnesium oxide, *Cu-CDNEs* copper-doped CDNEs, *GDY-Fe* graphdiyne-iron, *HA* hyaluronic acid, *K. pneumoniae, Klebsiella pneumoniae, S. dysenteriae Shigella dysenteriae, P. aeruginosa Pseudomonas aeruginosa, P. vulgaris Proteus vulgaris, P. aeruginosa Porphyromonas gingivalis, PTT* Photothermal therapy, *V. cholerae Vibrio cholera, S. epidermidis Staphylococcus epidermidis, MCR* mobile colistin resistance gene, *MRSA methicillin-resistant Staphylococcus aureus*

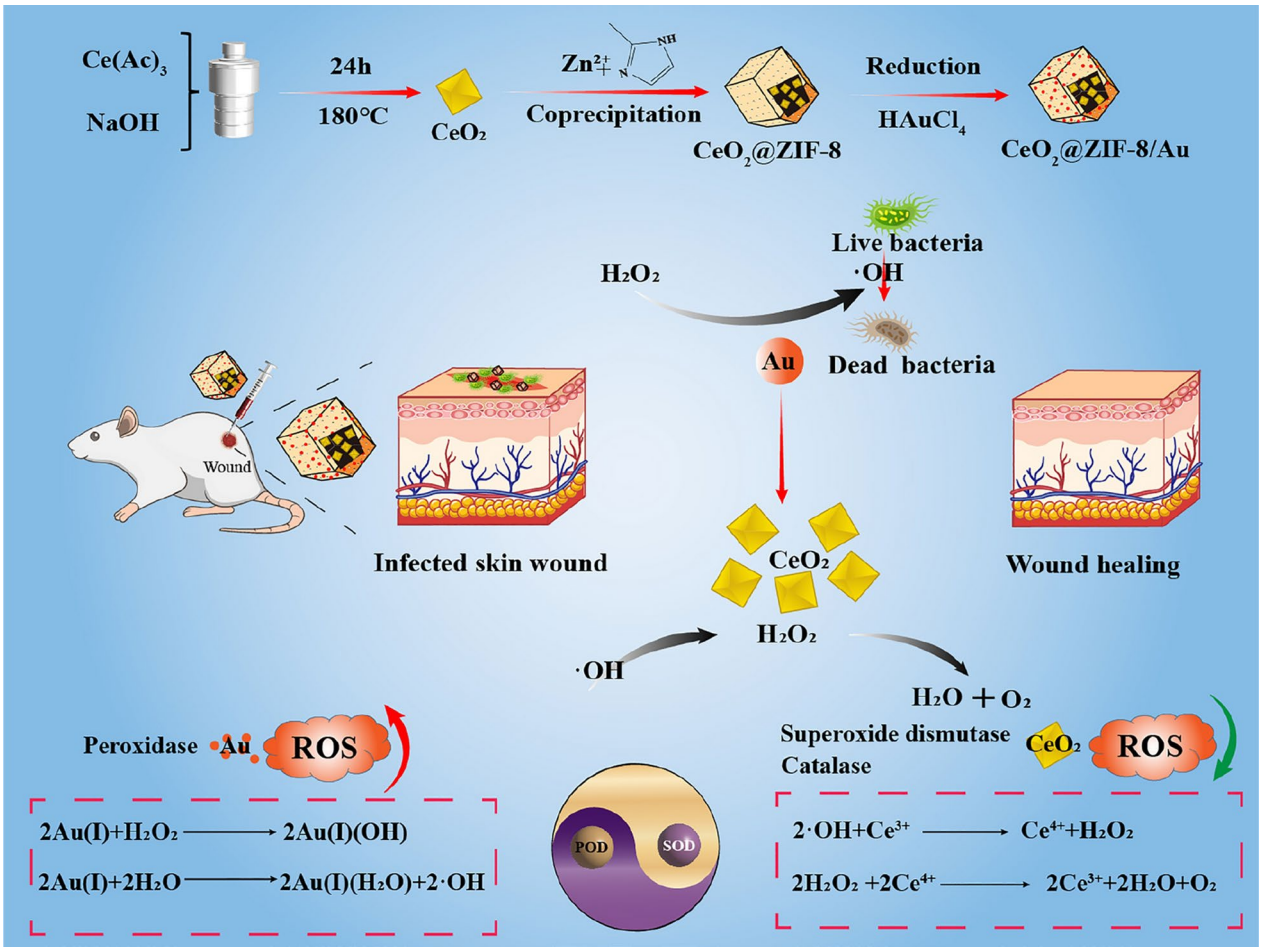


Fig. 3 The mechanism of action of CeO_2@ZIF-8/Au NPs in promoting healing of bacterial infected wounds in mice. It presents equations describing the production and clearance of ROS. Reproduced with permission [78]

Antibacterial applications of silver nanomaterials

Silver and its compounds possess broad-spectrum antibacterial activity with a long history of use [79]. The primary antibacterial mechanisms of silver nanoparticles (Ag NPs) rely on the release of silver ions, generation of ROS, effective inhibition of biofilms, and disruption of bacterial membranes, all of which can denature microbial proteins and interfere with DNA replication. Ag NPs have been reported to exhibit excellent antibacterial effects, inhibiting a wide range of bacteria, fungi, and viruses [80].

Wound dressings represent another significant research area for silver nanomaterials. In hydrogel-based wound dressings, cationic polymers and Ag NPs are widely incorporated into hydrogels through physical embedding (including hydrogen bonding, chain entanglement, and coordination), chemical crosslinking (such as Michael addition, click chemistry, Schiff base formation, enzyme-mediated, and photochemical crosslinking reactions), or in situ synthesis. Cationic dendrimers and Ag NPs were encapsulated into hydrogels via Schiff base linkages, which are acid-sensitive. The linkages within the gel respond to the acidic environment generated by bacterial growth, breaking down and releasing antibacterial components, including silver ions. The presence of dendrimers may disrupt the peptidoglycan layer, facilitating the penetration of silver ions into bacterial interiors. Significant obstacles in the process of skin wound healing mainly include bacterial infection, exacerbation of inflammatory response, and excessive oxidative stress. To effectively address these challenges, Yan et al. developed a multifunctional wound dressing [81]. This dressing cleverly combines the natural antibacterial properties of silver nanoparticles NPs with near-infrared NIR light-induced antibacterial therapy, aiming to accelerate the healing process of infected skin wounds. Among them, L-ascorbic acid, as a highly efficient reducing agent, combined with Polyvinyl pyrrolidone (PVP) as a stable dispersion medium, successfully embedded silver nanoparticles

into the reduced graphene oxide (rGO) matrix to form the Ag@rGO composite material. This process not only ensures the uniform distribution of silver nanoparticles, but also significantly improves their antibacterial performance. Zhang et al. developed an innovative Ag nanocomposite hydrogel by incorporating Ag NPs into a matrix formed by the conjugation of catechol-modified hyaluronic acid (HA-CA) with 4-arm PEG-SH. The Ag NPs serve dual functions: they act as reservoirs for the release of Ag/Ag + at wound sites to combat bacterial infections, and they also function as crosslinkers to ensure sustained release of basic fibroblast growth factor [82] (Fig. 4).

Antibacterial application of metal complex-based liposomes

Liposomes are self-assembled lipid vesicles composed of a phospholipid bilayer membrane with an inner aqueous compartment, which can encapsulate hydrophilic drugs in the core and contain hydrophobic drugs within the bilayer. The components of liposomes resemble cell membranes, which allows sufficient ability to fuse directly with the bacteria and control the release of antibacterial drugs. The diameter of liposomes ranges from 25 to 400 nm, and most liposomal formulations are 50–300 nm, which have undergone clinical trial investigation [83]. Small liposomes have the advantage of accumulating around the site of infection through the

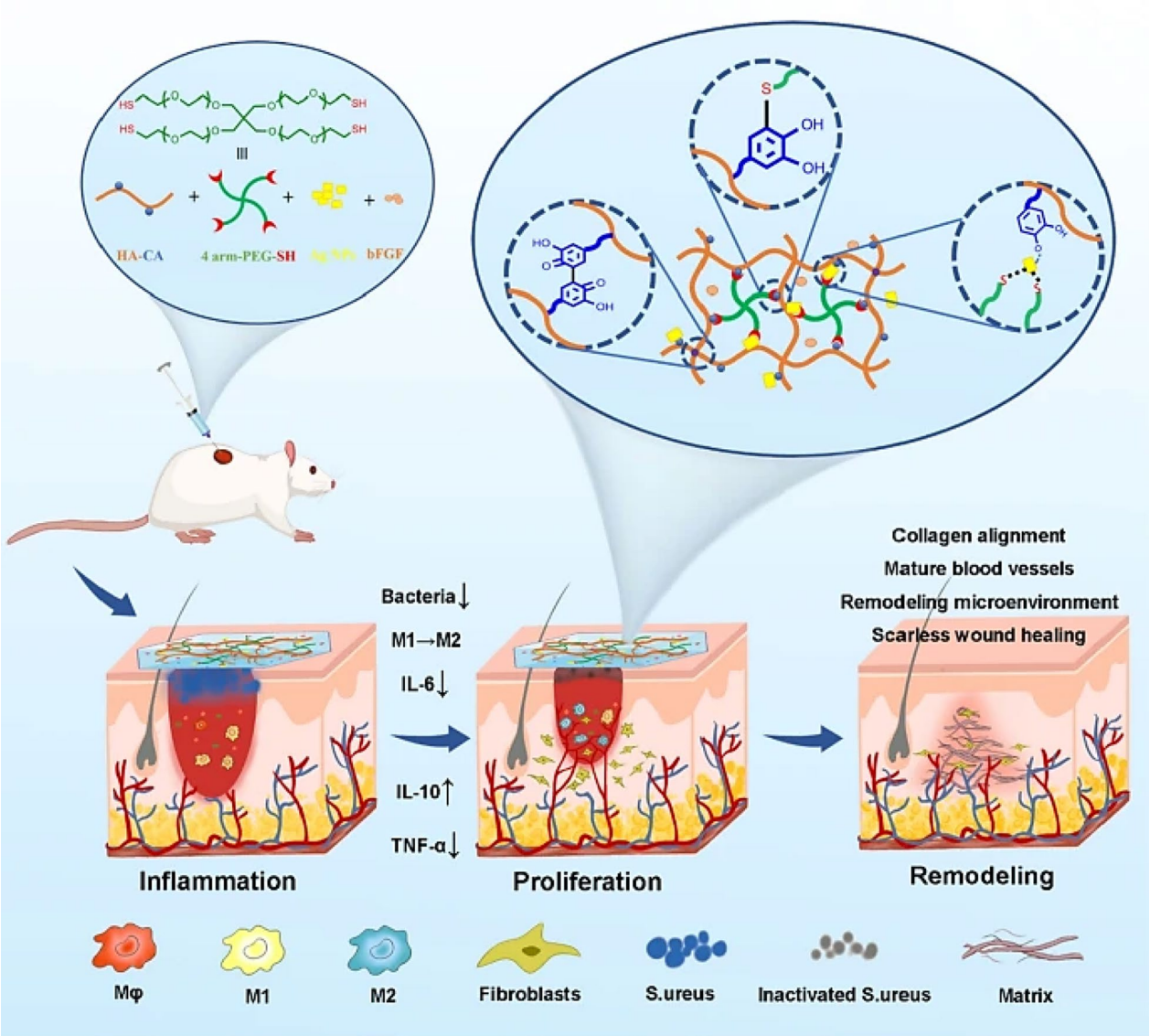


Fig. 4 Immune- and regenerative microenvironment-modulating Ag nanocomposite hydrogels for promoting scarless healing of infected wounds. Reproduced with permission [82]

Table 2 Application of other antibacterial drugs

Classification	Fomulations	Drugs	Nanocarriers	Target pathogens	Mechanisms	Refs.
Antimicrobial peptides	Macolacin	–	–	*K. Pneumoniae; A. baumannii*	Disruption of bacterial membranes	[109]
	AMP–urease motors	LL-37; K7-Pol	Mesoporous silica	Gram-negative and gram-positive bacterial	Disruption of bacterial membranes	[110]
	MLPGa	PDA; Ga	Mesoporous silica	*C. albicans*	Disruption of cell wall and biofilm	[111]
Lysozyme	CHG@PTL	CHG	PTL	*E. faecalis; S. mutans; A. viscous*	Inhibit the formation of biofilm	[112]
	UCMB-LYZ-HP	Lysozyme; MB	UCNP	MRSA	ROS generation; PDT	[92]
Perovskite	SiO_2-coated HPNCs	–	SiO_2	*E. coli*	ROS generation	[113]
Ionic Liquid	Ionic liquid derivatives	Diketopyrrolopyrrole	–	*E. coli*	Membrane thinning; membrane disorder	[114]
	Dual-gradient poly(ionic liquid)	ADHex-Br; HVIm-TFSI	Nanofiber Membranes	*E. coli; S. aureus*	Membrane damage	[115]

viscous, Actinomyces viscous; ADHex-Br, *N*-(2-(acryloyloxy)ethyl)-*N*,*N*-dimethylhexan-1-aminium bromide; *C. albicans*, *Candida albicans*; Chlorhexidine gluconate(CHG); *E. faecalis, Enterococcus faecalis*; HPNCs, Halide perovskite nanocrystals; HVIm-TFSI, 1-hexyl-3-vinylimidazole bis(trifluoromethylsulfonyl) imide; MB, methylene blue; *MRSA, methicillin-resistant Staphylococcus aureus*; MLPGa, lyticase and gallium ions cointegrated polydopamine-modified mesoporous silicon nanosystem; PLA NPs, perovskite lanthanum aluminate nanoparticles; PTL, phase-transited lysozyme; *S. mutans*, *Streptococcus mutans;* UCNP, lanthanide-doped upconversion nanoparticles.

enhanced permeability and retention effect. Moreover, liposome surfaces can be easily modified to ensure more specific drug delivery, such as ligands, PEG, and aptamers. PEGylated liposomes more easily escape the elimination of the body's immune cells. In turn, the easily engulfed nature of liposomes makes them suitable for the treatment of special sites. Liposomes were reportedly applied to the infection of ocular, orthopedic and lung disease and skin wounds. To take advantage of their easy-to-cluster properties in macrophages and other cells, liposomes have the potential ability to treat intracellular infections, including *Mycobacterium avium* Complex, *S. aureus* and *Salmonella* [84, 85].

Chemical reactions are often used to develop new strategies. Yang Wu et al. developed liposome-based nanoreactors, including calcium peroxide (CaO_2) and rifampicin. After stimulation by a bacterial toxin in vivo, the surface of the nanoreactors will be penetrated to form pores. Then, water will react with CaO_2 to produce hydrogen peroxide, which can decompose into O_2 and drive antibiotic release. The body's immune response could be activated after attaching bacterial toxins, enhancing the therapeutic effect of bacterial infections [86]. As a classic drug delivery vehicle, liposomes have been reported to encapsulate and deliver antibiotics to the site of infection without increasing the risk of intoxication, which is expected to decrease the dosage of antibiotics. Although liposome is a form of drug preparation for a long time, with the discovery of novel drug research and development strategies, liposome is gaining unprecedented new life. For example, liposome particles with excellent safety greatly improve the stability and delivery efficiency of COVID-19 vaccine. In addition, combining liposomes and phage therapy is considered a promising therapeutic approach for combating MDR bacterial infections. The encapsulation method of bacteriophage in liposomes usually adopts a thin-film hydration method. Recently, researchers have harnessed liposomes to make progress in the development of phage formulations and delivery methods for topical applications. The encapsulation of phages in liposomes can shield them from exposure to physical and chemical stresses and accelerate their entry into macrophages [87]. Also, there are some formulations from Food and Drug Administration-approved liposomes for fungal infections, such as Amphotec® and Ambisome® in 1996 and 1997. In short, metal complex-based liposomes have a broad application prospect, and more use and exploration are still needed in the future (Fig. 5).

Optimization of antibacterial properties

To further enhance the antibacterial performance of metallic nanomaterials, researchers have focused on strategies such as altering the physical and chemical properties of the materials and implementing surface modifications. On one hand, by adjusting the specific surface area, charge state, and surface energy of nanomaterials, their interaction with bacterial cell membranes can be intensified, accelerating bacterial death. On the other hand, surface modification techniques like chemical modifications and biomolecular coatings not only improve the biocompatibility of the materials but also endow them with specific recognition capabilities, enabling precise targeting of specific pathogens.

As illustrated in Figure 6, harnessing external stimuli like light and heat to trigger the antibacterial activity of metallic nanomaterials is a current research hotspot, with these smart antibacterial materials holding immense potential for future antibacterial therapies.

Gold nanoparticles (Au NPs) functionalized with surface modifications exhibit robust antibacterial capabilities. A diverse range of materials, including albumin, cellulose, and keratin, can be used to modify Au NPs. Researchers have discovered that D-Au NPs can be further modified with bacterial cellulose (BC) for use as dressings in wound healing. BC-D-Au nanocomposites possess exceptional physical properties such as water absorption capacity and mechanical strength, facilitating full-thickness wound healing in rats infected with Gram-negative MDR bacteria. Similarly, Zhao et al. attempted to modify Au NPs with indole derivatives to develop wound dressings for treating MDR infections. They combined indole derivative-capped Au NPs (Au_IDs) with Au_AI fibers prepared via electrospinning to accelerate wound healing and kill MDR bacteria like polymyxin-resistant Klebsiella pneumoniae.

Moreover, an important application of Ag NPs involves their integration with other materials, including graphene oxide composites, lignin, lactoferrin, mesoporous silica nanoparticles (MSN), and more, to devise novel strategies for treating drug-resistant infections. Among these, MSN are ideal carriers for drug delivery systems due to their high specific surface area, tunable pore size, and ease of surface modification. Encapsulating Ag NPs within MSN or adsorbing them onto their surface can create an intelligent antibacterial nanoplatform that responds to external stimuli (pH, temperature and light) to release Ag NPs, enabling precise antibacterial therapy. Simultaneously, MSN can also serve as carriers for other antibacterial drugs, facilitating multidrug combinations and enhancing the efficacy of treating drug-resistant infections. The combination of metal nanoparticles with bioactive molecules or inorganic non-metallic materials has emerged as a highly promising strategy to significantly enhance the

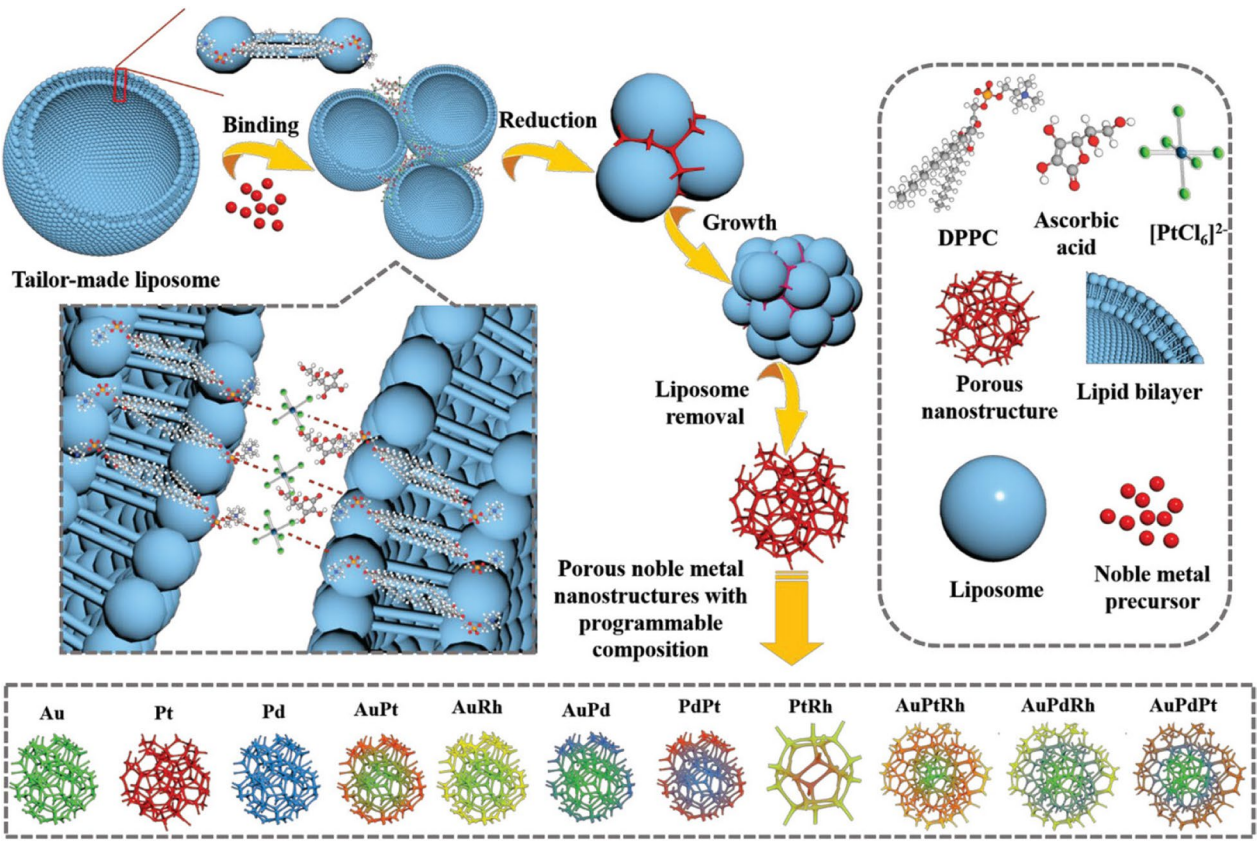


Fig. 5 The schematic illustration depicts the liposome-templated universal and green synthesis of mesoporous metal nanostructures. Reproduced with permission [88]

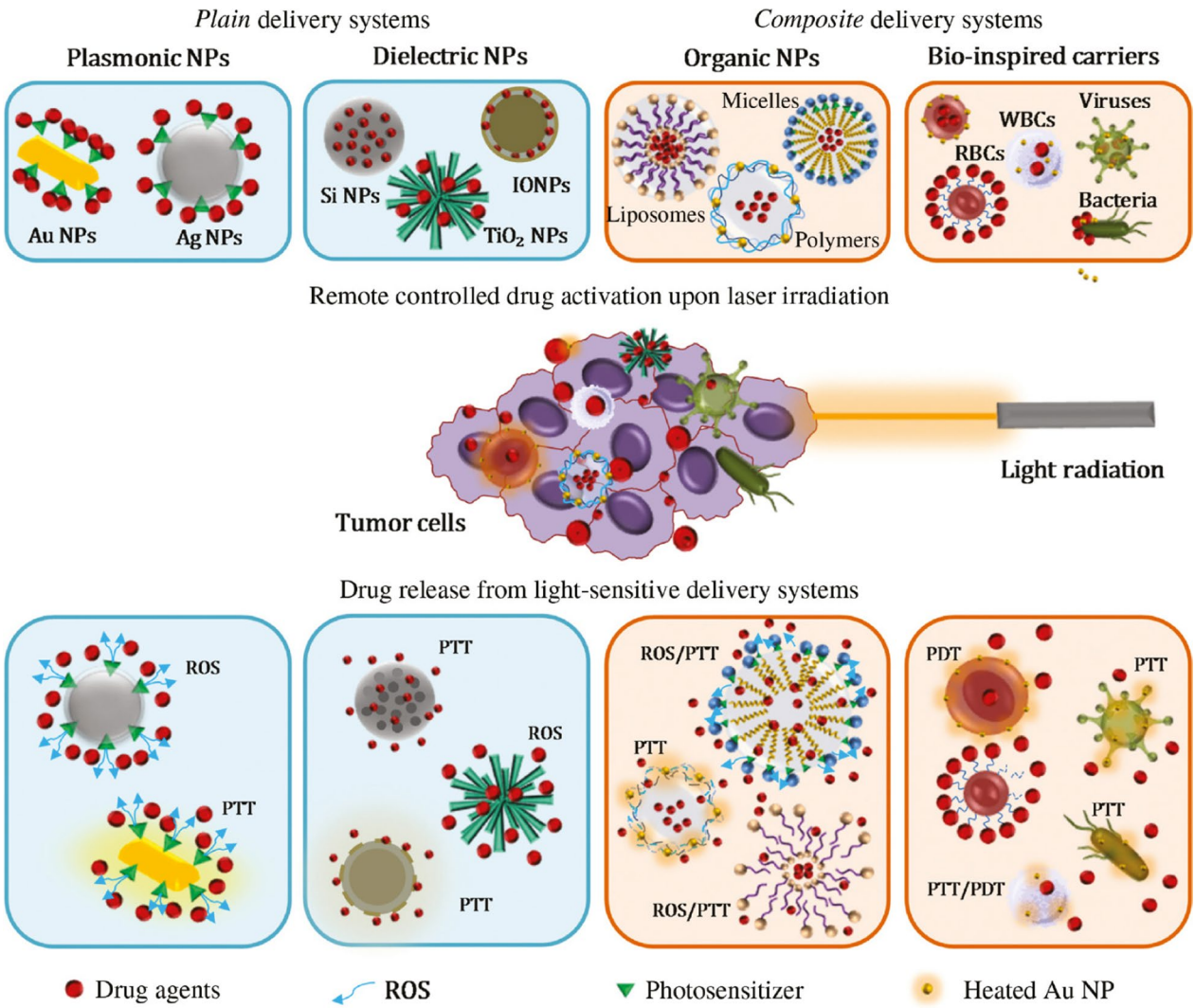


Fig. 6 Optically responsive delivery platforms: from the design considerations to biomedical applications. Reproduced with permission [89]

performance of materials in antibacterial applications. This innovative approach not only markedly strengthens the mechanical properties and stability of the materials but also successfully introduces a range of advanced biological functions, such as targeted delivery and sustained-release capabilities, thereby greatly expanding the therapeutic potential of antibacterial systems. Moreover, in recent years, the rapid progress in the field of non-metallic antimicrobial agents (summarized in Table 2) has further enriched our arsenal against resistant pathogens, offering more options for the development of novel antibacterial materials and therapeutic solutions.

Research on biocompatibility and safety

The widespread application of metallic nanomaterials in the medical field necessitates a solid foundation of biocompatibility and safety. For intestinal bacterial infections, conventional intravenous antibiotics like levofloxacin can disrupt the balance of gut microbiota. In a study, D-Au NPs, by disrupting the cell membranes of *E. coli* under anaerobic conditions, proved more effective than levofloxacin in inhibiting dysbiosis and eradicating *E. coli*. After 28 days of oral administration, D-Au NPs increased the relative abundance of typical probiotics without affecting the α-diversity of gut microbiota, including *Bacteroidetes*, *Akkermansia*, *and Bifidobacterium*. Furthermore, D-Au NPs demonstrated no toxicity to the small intestine, liver, or kidneys of mice. In short, D-Au NPs hold promise as oral antibiotic alternatives that do not compromise gut microbiota. Thus, thorough investigation into the material's behavior in vivo, its interactions with biological tissues, and potential toxic reactions is crucial for advancing their clinical translation. Researchers strive to minimize the potential toxicity of

metallic nanomaterials and ensure their safety in medical applications by optimizing material design, refining manufacturing processes, and conducting rigorous biosafety evaluations. For instance, utilizing biodegradable materials as carriers or designing nanostructures with self-elimination mechanisms can reduce long-term retention and potential hazards in the body.

Research on clinical applications

As research progresses, metal nanomaterials have achieved positive advancements in clinical applications within the medical antibacterial field. Due to their unique properties, metal nanoparticles have been formulated into various antibacterial medical devices, implants, and wound dressings. From initial in vitro experiments to validation in animal models, and gradually entering clinical trial stages, these materials have demonstrated promising therapeutic effects in treating skin infections, wound healing, implant infections, and more. For instance, beyond utilizing photothermal activity to combat bacterial infections, AuNPs are also widely applied in biomedical imaging, such as photoacoustic imaging and dual-energy CT imaging. As shown in Figure 7, gold nanorods (AuNRs), with their tunable optical properties and strong near-infrared (NIR) light absorption, are not only utilized as contrast agents for photoacoustic imaging but have also been engineered into a novel dual-modal nanoprobe (FFA)[90]. This probe integrates bioluminescence (firefly luciferase, Fluc) and photoacoustic imaging functions for early tumor-targeted diagnosis [91]. Zhang et al. further developed core-shell structured gold@copper selenide (Au@$Cu_{2-x}Se$) nanoparticles, combining photothermal therapy (PTT) and chemodynamic therapy (CDT) to significantly suppress tumor progression, offering a novel strategy for multimodal theranostics [92]

Furthermore, leveraging AuNPs' excellent biocompatibility and superior conductivity, various electrochemical immunosensors have been designed to detect proteins from clinical human serum samples, including alpha-fetoprotein and cardiac troponin I. However, it is important to note that while metal nanomaterials exhibit outstanding antibacterial performance, the long-term effects and safety of their clinical applications require further observation and evaluation. Additionally, balancing the materials' antibacterial efficacy with biocompatibility, as well as reducing production costs and enhancing material accessibility, are crucial directions for future research.

Conclusion and perspectives

At the intersection of medicine and technology, antibacterial nanomedicines are gradually emerging as brilliant stars in the treatment of infectious diseases, complementing antibiotics. This review not only elaborates on various antibacterial mechanisms of nanoparticles, but also delves into the latest breakthroughs of various novel nanomedicines in the antibacterial field. These achievements not only enrich the arsenal of antibacterial strategies but also point the way forward for future drug development.

However, the path to widespread application of antibacterial nanomedicines is not without obstacles. Despite fruitful basic research, translating these achievements into clinical treatment protocols faces numerous hurdles. Current research often focuses on the antibacterial efficacy of nanomedicines while relatively neglecting crucial issues such as biocompatibility, in vivo distribution, and long-term toxicity. Moreover, strategies to prevent emerging and refractory bacterial infections, particularly preventive measures like vaccine development, require intensified research efforts. Given that nanomedicines may penetrate biological barriers and affect multiple organ systems, their safety assessment must be more comprehensive and rigorous to ensure that while eradicating drug-resistant bacteria, they do not disrupt the normal microbial balance or harm human health.

In the field of antibacterial nanomedicine research, improving the selectivity of nanomaterials for gram-negative bacteria is a complex but crucial task [93, 94]. Given the unique cell wall structure of Gram-negative bacteria, including components such as the outer membrane, peptidoglycan layer, and lipoprotein, we can adopt the following strategies to develop specific nanometer-sized antibacterial agents: (1) For the outer membrane of Gram-negative bacteria, we should focus on developing antibacterial nanomaterials that can effectively destroy its integrity. This type of material can penetrate or weaken the barrier function of the outer membrane, making it easier for subsequent antimicrobial drugs to enter the bacteria and exert their bactericidal effect. In addition, we can also design and select photosensitizers or photothermal conversion materials that selectively target Gram-negative bacteria, activate these materials through light exposure, and generate ROS or thermal energy to efficiently kill bacteria [95, 96]; (2) Lipoproteins serve a crucial function in bridging the outer membrane with polysaccharides in the cell walls of Gram-negative bacteria, and they are also pivotal in bacterial physiology, virulence, and resistance to antibiotics [70]. Therefore, the design of new nanomedicines should focus on disrupting the structure and function of lipoproteins, aiming to ultimately achieve the goal of inhibiting bacterial growth; (3) To enhance the selective inhibitory effect of nanomaterials on gram-negative bacteria, we can screen for phospholipid molecules or polymer materials that can specifically bind to the peptidoglycan layer and use

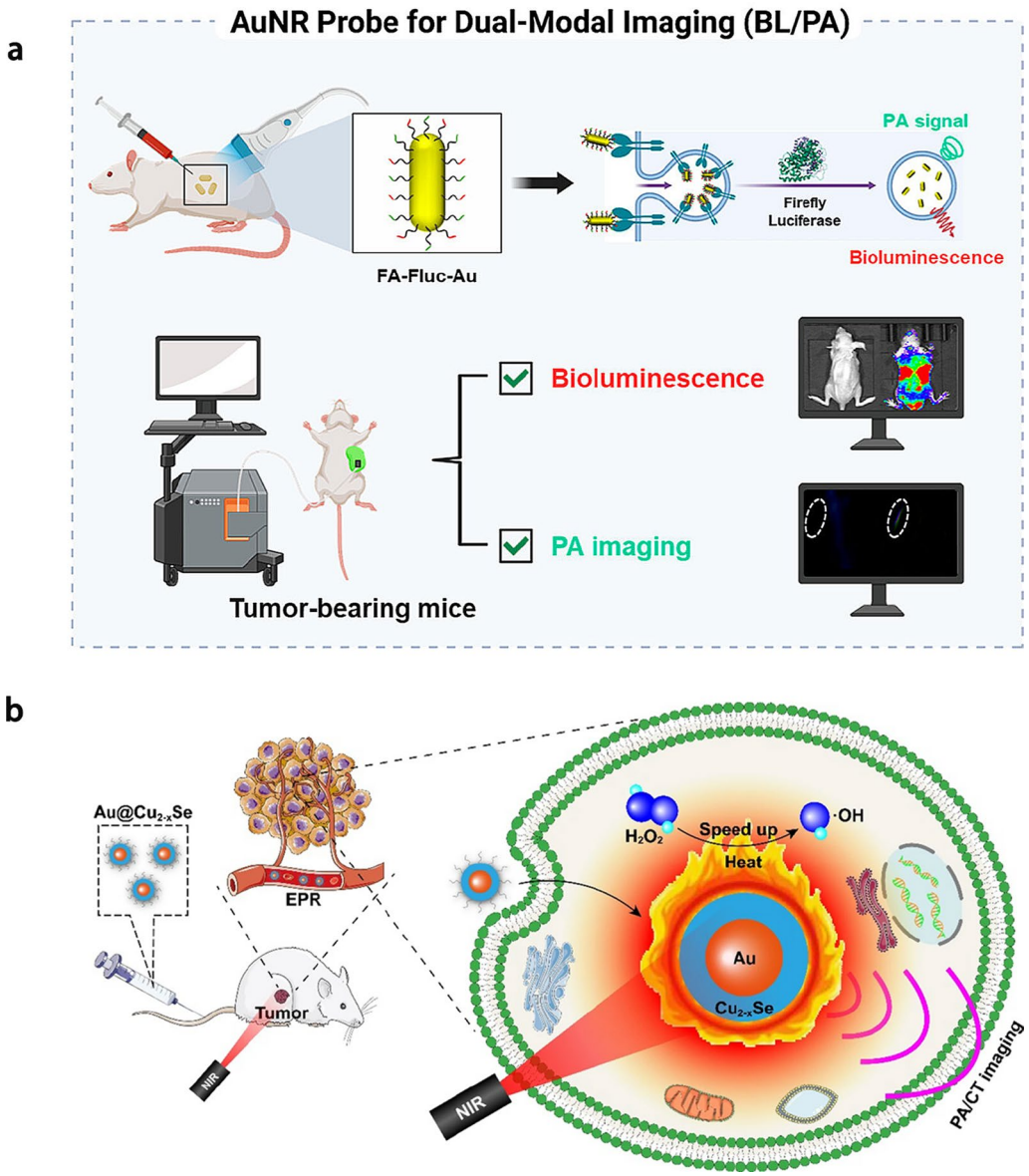


Fig. 7 Clinical application research of metal nanomaterials. **a** The schematic illustration depicts a dual-modal probe, FA-Fluc-Au (FFA), which has been developed for use in tumor-targeted bioluminescence and PA imaging. Reproduced with permission [91]. **b** A core–shell Au@Cu_2-xSe heterogeneous metal nanocomposite is proposed as a potential platform for dual-imaging-guided photothermal boosted chemo-dynamic therapy. Reproduced with permission [92]

them as modified ligands for nanocarriers to optimize the delivery system. This strategy can ensure that the antimicrobial agent maintains high activity when reaching the target bacteria and reduce damage to non-target cells such as gram-positive bacteria or mammalian cells. Through continuous research and innovation, we are expected to develop more nano-antibacterial materials with high selectivity and low toxicity, providing new solutions for clinical anti-infection treatment.

In addition, innovative technologies such as structure-based drug discovery and Artificial Intelligence-assisted drug design have emerged, providing new avenues for the development of selective antimicrobial strategies. By accurately identifying essential bacterial protein targets and developing effective, low-toxicity nanomedicines, these innovations have demonstrated promising antibacterial outcomes. Furthermore, the incorporation of sophisticated techniques such as molecular dynamics simulations and virtual screening expedites the

identification and optimization of innovative antimicrobials, encompassing antimicrobial peptides, metallic materials, and two-dimensional nanomaterials. In the future, research on antibacterial nanomedicines will place greater emphasis on interdisciplinary integration and technological innovation. This will enable a deeper understanding of the biological mechanisms of bacteria and the development of more precise, safe and effective antibacterial strategies. It is our firm belief that with continued research, novel antibacterial nanomedicines will be developed that can effectively target drug-resistant bacteria while maintaining microbial homeostasis. This will have a significant impact on reducing the burden of infectious diseases and safeguarding human health.

Abbreviations

ABC	ATP-binding cassette
ADHex-Br	*N*-(2-(Acryloyloxy)ethyl)-*N*,*N*-dimethylhexan-1-aminium bromide
Ag	Silver
$AgNO_3$	Silver nitrate
AMP	Antimicrobial peptides
AP	Ascorbyl palmitate
A. viscous	*Actinomyces viscous*
Au	Gold
BC	Bacterial cellulose
C. albicans	*Candida albicans*
CaO_2	Calcium peroxide
CmgO	Chitosan-modified magnesium oxide
CNCs	Cellulose nanocrystals
Co SS	Co superstructures
E. coli	*Escherichia coli*
GOx	Glucose oxidase
H_2O_2	Hydrogen peroxide
HA-CA	Catechol-modified hyaluronic acid
HVIm-TFSI	1-Hexyl-3-vinylimidazole bis(trifluoromethylsulfonyl) imide
K. pneumoniae	*Klebsiella pneumoniae*
LYZ	Lysozyme
MB	Methylene blue
MCR	Mobile colistin resistance gene
MDR	Multi-drug-resistant
MFS	Major facilitator superfamily
MgO	Magnesium oxide
MLPGa	Lyticase and gallium ions cointegrated polydopamine-modified mesoporous silicon nanosystem
MOF	Metal organic framework
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSN	Mesoporous silica nanoparticles
NCs	Nanocomplex
NIR	Near-infrared light irradiation
NPs	Nanoparticles
$\cdot O_2^-$	Superoxide radical
•OH	Hydroxyl radical
$^1O_2$	Singlet oxygen
P. aeruginosa	*Pseudomonas aeruginosa*
P. vulgaris	*Proteus vulgaris*
PDA	Poly-dopamine
PEG	Polyethylene glycol
PLA NPs	Perovskite lanthanum aluminate nanoparticles
PVP	Polyvinyl pyrrolidone
rGO	Reduced graphene oxide
ROS	Reactive oxygen species
S. aureus	*Staphylococcus aureus*
S. dysenteriae	*Shigella dysenteriae*
S. epidermidis	*Staphylococcus epidermidis*
S. mutans	*Streptococcus mutans*
STO	Strontium titanate
UCNP	Lanthanide-doped upconversion nanoparticles
V. cholerae	*Vibrio cholera*

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Availability of data and materials
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Declarations

Ethics approval and consent to participate
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Consent for publication
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Competing interests
The authors declare no competing interests.

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