Materials Advances

ROYAL SOCIETY OF CHEMISTRY

REVIEW

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Cite this: *Mater. Adv.*, 2025, **6**, 7662

Beyond antibiotics: novel solutions to address antibacterial resistance

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Received 27th May 2025,
Accepted 13th September 2025

DOI: 10.1039/d5ma00552c

rsc.li/materials-advances

In recent years, there has been a significant increase in antibacterial resistance, leading to a decline in the effectiveness of antibiotic drugs. This situation underscores the urgent need to explore suitable alternatives to antibiotics. To address this global challenge, it is crucial to understand new approaches, including their mechanisms, advantages, and limitations, which can help in the design of effective substitutes for antibiotics. Extensive research in this field has yielded notable progress. This review article aims to summarize innovative strategies for combating antibacterial resistance, such as metal–organic frameworks (MOFs), metal nanoparticles, photodynamic therapy (PDT), and antibacterial peptides. Additionally, the article discusses examples of their effectiveness and applications. Further research has also focused on combining these methods to enhance their efficiency, with some relevant studies highlighted. It is hoped that in the future, these materials will serve as replacements for current drugs, ultimately resolving the issue of antibacterial resistance.

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1. Introduction

One of the biggest challenges to humanity today is antibacterial resistance, which has significantly grown globally in recent years and presents a serious medical problem in healthcare

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settings.[1] Excessive antibiotic use and misuse have contributed to the emergence of superbugs – pathogens that can withstand even the most potent medications, exacerbating antibiotic resistance.[2] This resistance is a natural phenomenon, driven by the prevalence of resistance genes and their interaction with complex ecosystems. Furthermore, the use of antibiotics in agriculture and animal husbandry, as well as their role as growth promoters, compounds the problem, while global factors like travel, trade, and immigration accelerate its spread. These combined issues put millions of lives at risk annually and threaten to undo decades of medical progress. Additionally, the unsupervised release of antibacterial chemicals into the environment increases selection pressure on microbes, further intensifying the crisis.[3] The World Health Organization (WHO) cautions that by 2050, antibiotic-resistant diseases may account for more deaths than cancer if nothing is done.[4] In order to address this rising global health concern, it is critical that techniques for fighting bacterial infections be reconsidered, with a focus on innovation beyond conventional antibiotics.

Metal–organic frameworks (MOFs) demonstrate significant promise in antibacterial applications owing to their tunable porosity, high surface area, and structural adaptability.[5,6] These materials facilitate controlled encapsulation and release of antimicrobial agents while providing direct bactericidal activity *via* sustained metal ion delivery (*e.g.*, Ag^{+}, Zn^{2+}, Cu^{2+}).[7–10] Their structural versatility, achieved through tailored ligand design and synthesis strategies, permits precise modulation of pore geometry, functionality, and biocompatibility.[11,12] Enhanced antimicrobial efficacy is realized through advanced mechanisms such as photocatalytic reactive oxygen species (ROS) generation and stimuli-responsive agent release.[13] Engineered defects in MOFs further optimize cargo loading capacity and enable targeted delivery under environmental triggers.[14–16] When integrated with nanotechnology, MOFs exhibit synergistic antibacterial effects, reduced off-target toxicity, and precision in infection control, positioning them as innovative solutions for combating resistant pathogens.[17–21]

Another highly successful method for combating antibacterial resistance is the use of metal nanoparticles (MNPs).[22] These materials have shown excellent results both independently and in combination with other approaches, playing a very significant role in this field.[23] These particles can physically disrupt bacterial membranes, produce reactive oxygen species (ROS) that damage cellular components, and inhibit critical processes like RNA and protein synthesis, biofilm formation, and membrane potential.[24–26] Advances in technology have enabled precise control over nanoparticle size, shape, surface charges, and functionalization, enhancing their efficacy and safety in combating multi-drug-resistant bacterial infections.[27,28] MNPs also exhibit synergistic effects when combined with conventional antibiotics, reducing resistance and improving therapeutic outcomes by lowering dosage requirements and minimizing side effects.[29] Intermetallic nanoparticles, formed by combining different metals, have demonstrated superior antibacterial properties compared to monometallic forms, further broadening their biomedical applications.[30,31] With their stability, cost-effectiveness, and ability to enhance drug solubility and efficacy, MNPs represent a promising alternative to traditional antibiotics, offering versatile and multi-faceted approaches to tackle antibiotic-resistant pathogens.[32]

In recent years, photodynamic therapy (PDT) has emerged as a promising and innovative approach to combat resistant bacteria by using light to activate photosensitizers (PS), which produce reactive oxygen species (ROS) to selectively destroy target cells without inducing bacterial resistance.[33–35] Widely utilized in fields such as dermatology, oncology, and infectious disease, PDT combines the localized or systemic application of PS compounds with light irradiation to achieve precise microbial inactivation. Advances in nanomedicine have significantly improved PDT's efficacy by enhancing biocompatibility, safety, and site-specific enrichment.[36–38]

Beyond these metal-based strategies, a host of other innovations is emerging in the fight against resistant bacteria.[39] Antimicrobial peptides (AMPs), for instance, inspired by natural immune defenses, offer a promising solution to combat bacterial resistance through their unique ability to selectively target bacterial membranes. These diverse small proteins, also known as cationic host defense peptides, are found in animals, plants, bacteria, and yeast, and can also be synthesized in laboratories.[40,41] AMPs exhibit broad-spectrum antimicrobial, antiviral, antifungal, and anti-mitogenic properties. Alongside their roles as immune modulators and anti-inflammatory agents, AMPs have potential as alternatives to conventional drugs.[42] Their mechanism of action, based on membrane

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destruction, minimizes the risk of inducing bacterial resistance, and they have been effectively demonstrated in both *in vitro* and *in vivo* models.[43–45] AMPs hold significant promise for applications in clinical antibacterial treatments, animal and plant disease resistance, and as food preservatives.[46–49] However, challenges such as high production costs, susceptibility to clearance, and potential adverse reactions currently limit their widespread use. Strategies like combining AMPs with metal ions, self-assembly to enhance stability, and developing responsive and synergized forms aim to overcome these hurdles and expand their therapeutic potential.[50,51]

Addressing antibacterial resistance requires a multifaceted approach that combines diverse strategies and leverages complementary mechanisms for more effective and sustainable outcomes. The focus of antimicrobial research has shifted from merely killing bacteria to combating antibiotic-resistant pathogens. Combination therapies are also emerging as a key solution.[52,53] Using multiple drugs together reduces individual drug dosages, minimizes side effects, lowers the risk of resistance development, and achieves synergistic effects with enhanced antibacterial efficacy.[54] Additionally, combination therapies offer wide-spectrum action and the ability to target multiple sites simultaneously, making them a powerful tool in the fight against resistant infections.[55]

This review critically examines four key non-antibiotic strategies: metal–organic frameworks (MOFs), metal nanoparticles (MNPs), photodynamic therapy (PDT), and antimicrobial peptides (AMPs). Rather than simply summarizing the existing literature, we provide a novel integrative analysis of these strategies. Our unique contribution lies in synthesizing these diverse fields by connecting fundamental molecular mechanisms to their potential applications and the challenges of translating these findings into practice. We emphasize how innovative synthesis methods, such as the modulated synthesis of MOF nanocomposites, significantly influence key parameters, including antibacterial efficacy, metal ion release kinetics, and biocompatibility. Additionally, this review critically evaluates the synergistic potential of combining these approaches, an important frontier for overcoming the limitations of single-mode therapies. By integrating perspectives from materials science, nanotechnology, photochemistry, and peptide engineering, we propose a comprehensive framework for developing the next generation of antimicrobials. We conclude with concrete and innovative integrated systems for future research, aiming to stimulate the interdisciplinary collaboration necessary to translate these promising materials from the laboratory to clinical practice.

2. Mechanisms of antibacterial resistance

When bacteria learn to withstand exposure to antibiotics that would typically kill them or stop their growth, antibacterial resistance develops.[56,57] This process arises from the development of resistance genes through horizontal gene transfer and genetic alterations.[58] Overcoming bacterial resistance requires an understanding of the mechanisms by which resistance is achieved.[59] Bacteria can be broadly classified as either Gram-positive or Gram-negative, according to the structure of their cell walls. Gram-negative bacteria have a thinner peptidoglycan layer than Gram-positive bacteria because they have a different outer membrane.[60] Examples of common multidrug-resistant (MDR) pathogens include Gram-negative bacteria such as *Escherichia coli*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Klebsiella pneumoniae*, and *Serratia marcescens*, as well as Gram-positive bacteria such as *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Staphylococcus epidermidis*.[61] Table 1 includes some examples of commonly encountered multidrug-resistant pathogens associated with healthcare. The antibacterial activity of conventional antibiotics, such as penicillin, rifampicin, and tetracycline, stems from their ability to inhibit cell wall synthesis or interfere with DNA, RNA, or protein synthesis. However, bacteria have developed a range of resistance mechanisms (Fig. 1).[57,62] Many bacteria produce enzymes that deactivate antibiotics. For example, Enterobacteriaceae, such as *E. coli* and *K. pneumoniae*, produce extended-spectrum beta-lactamases (ESBLs) that hydrolyze beta-lactam antibiotics.[63] Aminoglycoside-modifying enzymes, chemically alter antibiotics, diminishing their ability to bind to bacterial targets.[64] In addition, mutations in bacterial proteins can also prevent antibiotics from binding effectively. For instance, modifications in penicillin-binding proteins (PBPs) reduce the efficacy of beta-lactam antibiotics,[65] while mutations in DNA gyrase or topoisomerase IV confer resistance to fluoroquinolones.[66] Efflux pumps actively expel antibiotics

Table 1 Monitoring list for healthcare-associated multidrug-resistant and extensively drug-resistant pathogens (key indicator organisms)

Bacteria	Common resistance to	Ref.
Acinetobacter	Ceftazidime, aminoglycosides, fluoroquinolones, carbapenems	72
Enterobacteriaceae (*e.g. Escherichia coli*, *Klebsiella pneumoniae*)	Cephalosporins ([a]ESBL-producers), fluoroquinolones, aminoglycosides Cephalosporins ([a]ESBL-producers), fluoroquinolones, aminoglycosides, carbapenems	73
Enterococcus spp. (especially *E. faecium*)	Ampicillin, aminoglycosides (high-level) Ampicillin, aminoglycosides (high-level), glycopeptides	74
Pseudomonas aeruginosa	Piperacillin/tazobactam, ceftazidime, ciprofloxacin, aminoglycosides Piperacillin/tazobactam, ceftazidime, ciprofloxacin, aminoglycosides, carbapenems	75
Staphylococcus aureus (healthcare-associated)	b-Lactam antibiotics (except new anti-[b]MRSA cephalosporins), macrolides, fluoroquinolones, aminoglycosides	76

[a] ESBL, extended-spectrum b-lactamase. [b] MRSA, meticillin-resistant *S. aureus*.

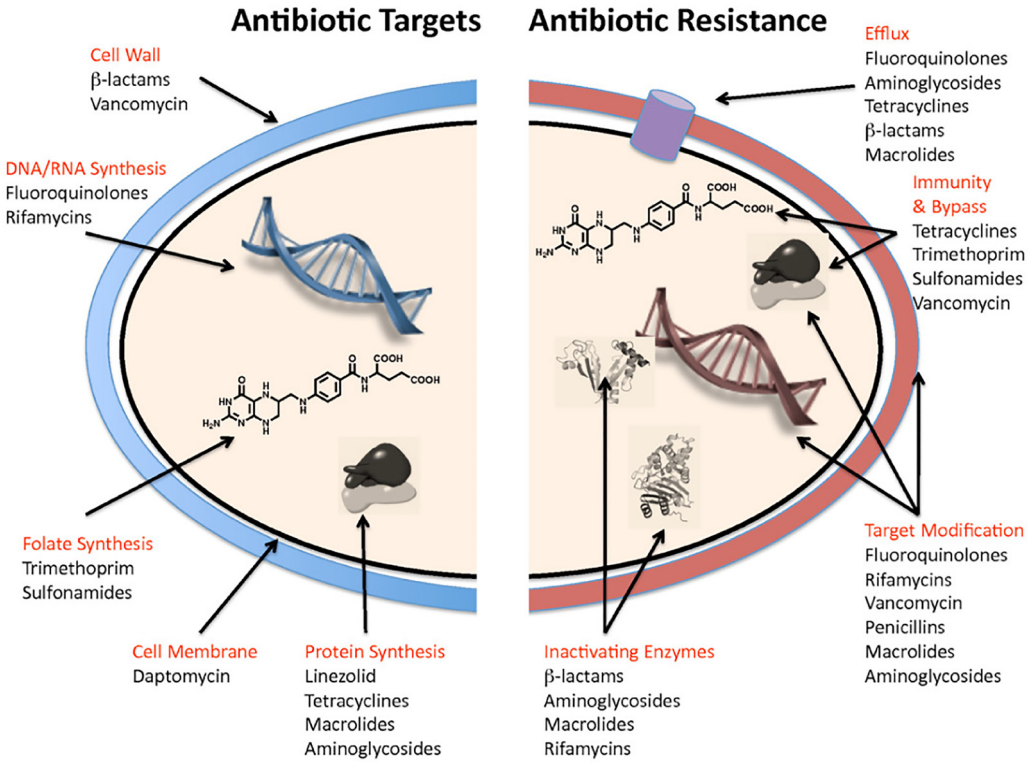

Fig. 1 Main antibiotic targets and associated mechanisms of resistance.[77] Reproduced under the terms of the Creative Commons Attribution 2.0 International Public License (CC BY 2.0). Copyright 2010, the Authors. Published by BioMed Central Ltd.

from bacterial cells, reducing intracellular concentrations. The AcrAB-TolC efflux system in Gram-negative bacteria is an example that confers resistance to multiple drug classes.[67] In another way, bacteria acquire resistance genes through conjugation, transformation, or transduction. Mobile genetic elements like plasmids and integrons facilitate the rapid spread of resistance within and across bacterial species.[68] Moreover, a lot of studies have indicated that bacteria in biofilms are embedded in a self-produced matrix that shields them from antibiotics. Biofilms contribute to 80% of bacterial infections and are a key factor in the persistence of infections.[69] They reduce drug penetration and provide a protective environment for dormant bacterial cells, making them highly resistant to treatment.[70]

Understanding these diverse mechanisms is critical for addressing the resistance crisis and guiding the development of next-generation antimicrobial strategies.[71] Effective solutions must consider not only the biological intricacies of resistance but also the environmental and societal factors that contribute to its rise.

3. Metal–organic frameworks (MOFs) as antibacterial agents

Metal–organic frameworks (MOFs) represent a groundbreaking class of low-density, crystalline porous materials constructed from metal nodes (metal ions or clusters) and organic linkers.[78–80] Their high surface area, adjustable porosity, and functional versatility make them promising candidates for a variety of applications, including catalysis, sensing, gas storage, and biomedical uses.[14,79,81–87] In the fight against antibacterial resistance, MOFs present unique advantages: they can release bactericidal ions in a controlled way, generate reactive oxygen species (ROS), or serve as carriers for antimicrobial drugs, providing multifunctional strategies to combat pathogens.[88–91] Table 2 provides a summary of various metal–organic frameworks (MOFs) assessed for antibacterial activity. It includes details about their metal ions or cores, ligands, target bacterial strains, and activity indicators, as well as the experimental conditions used. Commonly used metal nodes in MOFs include silver, zinc, copper, and cobalt, all of which exhibit intrinsic antibacterial properties against both Gram-positive and Gram-negative bacteria, such as *E. coli* and *S. aureus*.[92–94] Compared to traditional antibiotics, MOFs offer several distinct benefits: (i) they can be constructed with bactericidal ions and antimicrobial ligands;[95,96] (ii) their chelation effect enhances lipophilicity and improves membrane penetration;[97,98] (iii) their high porosity allows for significant drug loading;[99] and (iv) their electronic tunability enables efficient photocatalytic ROS generation.[100–102]

MOFs exhibit their antibacterial properties through multiple mechanisms:

(1) Release of metal ions: many MOFs are designed to release bioactive metal ions, such as zinc, copper, or silver, which can interfere with bacterial cell walls, membranes, and

Table 2 Summarizes representative MOFs evaluated for antibacterial activity

MOF/composite	Metal ion	Ligand	Target bacteria	Activity indicators	Experimental conditions	Ref.
Cu-MOF NPs	Cu^{2+}	Trimesic acid	*E. coli*, *S. aureus*, *Pseudomonas*, *Klebsiella*, *Candida*	100 μg mL^{-1}; outperformed ampicillin/ciprofloxacin	Nutrient broth, 10^6 CFU per mL, 24 h, 37 °C	106
Zn-MOFs	Zn^{2+}	Terephthalate	*S. aureus*, *E. coli*	Zn-MOF strongest *via* Zn^{2+} release	Broth culture	104
Ni-MOFs	Ni^{2+}	Organic linker	ESBL *E. coli*, *P. aeruginosa*, MRSA	IC50 = 15–25 μg mL^{-1}; biofilm inhibition	Standard broth	107
ZIF-4, ZIF-7, ZIF-8	Zn^{2+}	Imidazolate	*S. aureus*, *E. coli*	ZIF-8 strongest; ZnO derived from ZIF-4 enhanced activity	Normal broth	91
Zr-TCPP (PCN-224, Cu^{2+}-doped)	Zr^{4+} (Cu^{2+}-doped)	Porphyrin (TCPP)	*S. aureus*	99.71% inhibition	Light irradiation (660 nm, 20 min)	109
ZIF-8-PAA-MB@AgNPs@Van-PEG	Zn^{2+}	Imidazolate	*E. coli*, *S. aureus*, MRSA	Synergistic killing under laser irradiation	Laser irradiation	120
UIO-66-NH2@PEG	Zr^{4+}	Amino-terephthalate	VRSA	Superior antibacterial & anti-biofilm *vs.* free drugs	Standard broth	114
Zr-MOF-1/2 (CIP delivery)	Zr^{4+}	Organic linker	*E. coli* (CIP delivery)	Sustained release over 7 days, pH-responsive	pH 9.2 > neutral/acid; 7-day release study	113

intracellular components. These ions can disrupt enzymatic processes and promote the production of reactive oxygen species (ROS), which cause oxidative damage to bacterial cells.[103–105] In 2018, Sheta *et al.* prepared Cu-MOF nanoparticles (Cu-MOF-NPs) and tested them against *E. coli*, *S. aureus*, *Pseudomonas*, *Klebsiella*, and *Candida* spp. at 100 μg mL^{-1}. Experiments were conducted in nutrient broth with an initial inoculum of $\sim 10^6$ CFU per mL, incubated for 24 h at 37 °C, and compared to standard antimicrobial agents (ampicillin, ciprofloxacin, amphotericin B). Under these conditions, Cu-MOF-NPs matched or outperformed the reference drugs.[106] In 2021, Nakhaei *et al.* demonstrated that three zinc-terephthalate MOFs (MOF-5, Zn-MOF, TMU-3) exhibited antibacterial activity against *S. aureus* and *E. coli*, with Zn-MOF showing the highest efficacy due to its enhanced Zn^{2+} ion release, particularly in its activated form, which disrupts bacterial cell integrity through sustained metal ion release.[104] Prabhu *et al.* later developed Ni-MOFs, proving their potent antimicrobial effectiveness against extended-spectrum beta-lactamase (ESBL) strains such as ESBL-1 and *P. aeruginosa*. These materials also inhibited biofilm formation by the MRSA strain ATCC 33591 and clinical strain N7, with IC50 values of 15.19 ± 1.41 μg mL^{-1} and 25.14 ± 0.75 μg mL^{-1}, respectively. The antimicrobial effect was attributed to the positively charged Ni^{2+} ions interacting with the negatively charged bacterial cell walls, generating ROS to kill the bacteria, combined with a synergistic effect from the organic linker in the Ni-MOF.[107] In 2024, Khatami *et al.* demonstrated that three zinc-based zeolitic-imidazolate frameworks (ZIF-4, ZIF-7, ZIF-8) exhibited antibacterial activity against *S. aureus* and *E. coli*, with ZIF-8 showing the strongest effect due to its high Zn^{2+} ion release. ZnO nanoparticles derived from ZIF-4 further enhanced antibacterial performance, attributed to their uniform nanostructure and controlled ion release.[91] Despite their significant antibacterial potential, many MOFs face limitations due to the inherent toxicity and the low biocompatibility of certain metal ions and organic ligands. To expand their bioapplications, it is crucial to develop strategies for controlled release and efficient removal of excess metal ions and ligands, as well as to explore the use of biologically derived ligands to enhance their safety.

(2) ROS generation: MOFs can catalyze the production of ROS under specific conditions, such as light activation. These ROS can damage bacterial DNA, proteins, and lipids, leading to cell death.[108] Han *et al.* introduced a Cu^{2+}-doped Zr-based porphyrinic MOF (Zr-TCPP, PCN-224; TCPP = 5,10,15,20-tetrakis(4-carboxyphenyl) porphyrin) with remarkable bacteriostatic efficiency, achieving 99.71% inhibition of *S. aureus* within 20 minutes under 660 nm light irradiation. The doped Cu^{2+} ions played a key role by trapping electrons, enhancing carrier transfer, reducing electron–hole recombination, and converting absorbed light energy into heat. This process amplified ROS generation and photothermal effects, contributing to its strong antimicrobial activity.[109] In recent years, MOFs have increasingly been employed as photocatalysts for *in vitro* photocatalytic disinfection. This method relies on *in situ* ROS

generation to degrade bacteria into CO_2 and H_2O. Li *et al.* compared five MOFs (MIL-100, NH_2-MIL-125, NH_2-UiO-66, ZIF-11, and ZIF-8) for photocatalytic inactivation of *E. coli*; ZIF-8 (Zn^{2+}/Hmim) achieved >99.9999% reduction within 2 h in saline under simulated solar light (Xe lamp, AM 1.5, 100 mW cm^{-2}). Blank controls (light only, ZIF-8 in dark) showed negligible killing, while ZnO and TiO_2 achieved only ~2–3 log reductions, confirming ZIF-8's superior photocatalytic activity.[110] Importantly, ROS generation is not limited to light-activated mechanisms. Hamarawf *et al.* demonstrated that Zn- and Co-MOFs could exert potent antibacterial and antibiofilm effects through metal-ion-mediated ROS generation without the need for external light activation. The study proposed that the electrostatic attachment of the MOFs to bacterial cells initiates a process of lipid peroxidation, ultimately leading to lethal ROS production within the bacteria. This mechanism highlights an intrinsic reactive property of certain MOFs that can be harnessed for antimicrobial purposes, independent of photocatalysis.[111] Inspired by these results, ZIF-8 was used to create a MOF-based filter mask for integrated pollution control. Experimental findings demonstrated that the antibacterial performance of this MOF-based mask surpassed that of commercial masks, offering innovative prospects for using porous materials in public health protection.[111] (3) Drug and antibacterial delivery vehicles: MOFs serve as carriers for antibiotics or other antimicrobial agents, enhancing their solubility, stability, and targeted delivery.[112] This approach not only increases the effectiveness of the drugs but also reduces the required dosage and potential side effects. Ishfaq *et al.* investigated zirconium-based MOFs, Zr-MOF-1 and Zr-MOF-2, as pH-responsive carriers for the antibiotic ciprofloxacin (CIP). They found that CIP was released more quickly in a basic medium (pH = 9.2) compared to neutral or acidic conditions. Zr-MOF-2 exhibited sustained release over seven days, suggesting its potential for long-acting formulations in alkaline infections.[113] Also, Rahmanian *et al.* developed a PEG-coated UIO-66-NH_2 nanoparticle for the co-delivery of vancomycin and amikacin against vancomycin-resistant *Staphylococcus aureus* (VRSA). The dual-drug-loaded nanosystem (VAN/AMK-UIO-66-NH_2@PEG) exhibited superior antibacterial and anti-biofilm activity compared to the free drugs. Crucially, it also significantly downregulated the expression of key resistance (vanA, mecA) and biofilm-forming (icaA, icaD) genes in VRSA isolates. This study highlights the potential of engineered MOFs to overcome resistant pathogens by simultaneously delivering multiple antibiotics and suppressing resistance mechanisms at a genetic level.[114]

Silver (Ag) nanoparticles (Ag NPs) have garnered significant attention for their broad-spectrum antimicrobial properties against bacteria, viruses, and fungi. Their effectiveness arises from direct interaction with microorganisms, the release of Ag^+ ions, and reactive oxygen species (ROS) generation. However, excessive Ag^+ release can harm normal tissues, making controlled release a crucial strategy for their use as antimicrobial agents. For instance, Guo *et al.* developed Ag-CuTCPP by synthesizing CuTCPP and encapsulating Ag NPs. This MOF material demonstrated superior antibacterial performance compared to penicillin against *S. aureus*, *B. subtilis*, and *E. coli*, with lower cytotoxicity than Ag^+ or standalone Ag NPs.[112,115] Similarly, Salam *et al.* synthesized Ag NPs@Ni-MOF, a Ni-MOF nanosheet loaded with Ag NPs. This composite showed enhanced antimicrobial effects compared to Ni-MOF alone, achieving inhibition rates of 93.85%, 92.15%, 87.43%, and 84.07% against *B. subtilis*, *E. coli*, *P. aeruginosa*, and *C. albicans*, respectively, due to the additional release of Ag NPs.[116] Soltani *et al.* developed a Cu-BTC MOF loaded with chlorhexidine (CHX@Cu-BTC), which exhibited enhanced antibacterial activity against *S. aureus* and *E. coli* through synergistic effects from controlled release of Cu^{2+} ions and CHX, achieving lower MIC values compared to individual components.[117] In another work, they embedded gemifloxacin (GEM) into ZIF-8 *via* a one-step aqueous synthesis, achieving remarkable drug loading (DLC = 69.82%, DLE = 89.03%). The GEM@ZIF-8 system exhibited H_2O_2-responsive release (47.7% cumulative release in infected tissue conditions) and maintained potent antibacterial activity (MIC < 0.6 μg mL^{-1}) comparable to free GEM, while enabling sustained, targeted delivery to reduce off-target effects.[118] Arenas-Vivo *et al.* proposed a photoactive composite coating, Ag-encapsulated MIL-125(Ti)–NH_2, which achieved an impressive 99.9999% inhibition rate against *S. aureus* biofilms. This efficacy was attributed to the combined antibacterial effects of the MOF, Ag NPs, and photoactivity under UVA light. In recent years, MOFs have gained interest for their ability to dynamically target antibacterial agents to specific microenvironments.[119] These systems respond to endogenous stimuli such as light, acidity, or oxidative stress associated with bacterial infections. For example, Chen *et al.* developed a composite nanomaterial, ZIF-8-PAA-MB@AgNPs@Van-PEG. The encapsulation of methylene blue (MB) into ZIF-8-PAA imparted light and pH responsiveness. Ag NPs were then formed on the ZIF-8-PAA-MB *via in situ* reduction of $AgNO_3$, followed by the addition of Van-PEG to load antibacterial agents.[120,121] This composite exhibited potent antibacterial activity against *E. coli*, *S. aureus*, and MRSA due to the synergistic effects of vancomycin and ROS generation under laser irradiation.[121]

Antibacterial performance depends strongly on MOF composition. Zn-based frameworks often show strong activity due to sustained Zn^{2+} release; Cu-based frameworks are effective *via* both ion release and photothermal contributions; Ni-based MOFs excel in biofilm inhibition due to strong electrostatic interactions; and Ag-based MOFs provide broad-spectrum efficacy but raise cytotoxicity concerns. Understanding these relationships provides guidance for designing safer, more effective MOFs. Despite their significant promise, challenges in stability, cytotoxicity, and scalable production must be addressed for the successful clinical translation of metal–organic frameworks (MOFs). To overcome these hurdles, future efforts could focus on integrating biologically derived ligands (*e.g.*, amino acid- or peptide-based linkers) to reduce toxicity, and combining experimental microbiology with computational modeling to predict ion release and reactive oxygen species (ROS) efficiency. By

leveraging their inherent biodegradability, diverse functionality, and molecular adaptability, MOFs can be rationally designed to become a cornerstone of next-generation antimicrobial strategies, offering sustainable solutions to the growing crisis of antibacterial resistance.

4. Metal nanoparticles and their antibacterial mechanisms

The antibacterial mechanisms of metal nanoparticles (MNPs) are multifaceted and complex, involving physical interactions, chemical properties, and reactive processes that contribute to their bactericidal activity.[122] The precise mechanisms of their activity are not yet fully understood, although significant research efforts have been directed at elucidating these processes (Table 3).[123] MNPs exhibit antibacterial effects through various pathways, including physical damage to the bacterial cell wall and membrane, ion leaching, and reactive oxygen species (ROS) production.[124] Physical interactions involve the adsorption and penetration of NPs into bacterial cell walls, which disrupts membrane integrity, depolarizes the cell wall, and leads to leakage of intracellular components.[125] Positively charged NPs show enhanced bactericidal activity due to electrostatic interactions with the negatively charged bacterial cell surface.[126] Additionally, the size and shape of NPs are critical factors; smaller NPs with higher surface-area-to-volume ratios penetrate cells more effectively and produce more ROS, which induces oxidative stress and damages essential biomolecules like lipids, proteins, and DNA.[127] Zare *et al.* synthesized ZnO NPs in various sizes and shapes, and their antibacterial and antioxidant activities were found to be dependent on both size and morphology.[128] Similarly, Korshed *et al.* discovered an inverse relationship between the size of NPs and their bactericidal effects.[129] They also found that smaller Ag NPs generated more reactive oxygen species (ROS) than larger ones. In another study, it was shown that 18 nm Ag NPs were more toxic than 80 nm Ag NPs in water, though their toxicity became similar when tested in PBS buffer.[130]

In recent studies, surface functionalization and charge modulation have been shown to significantly affect NP biocompatibility and antimicrobial properties.[131] For example, positively charged NPs demonstrate higher affinity for bacterial cells, enhancing their bactericidal potential.[132] Conversely, bacterial cells can adapt by modifying their surface charges or employing efflux systems to reduce NP toxicity.[133] El Badawy *et al.* investigated the toxicity of four types of Ag NPs with various surface charges, from highly negative to highly positive, and concluded that the toxicity of Ag NPs was dependent on the surface charge when tested against different bacterial species.[134]

ROS production remains a central mechanism in NP-induced antibacterial activity. These reactive species disrupt bacterial membranes, degrade proteins and nucleic acids, and inhibit metabolic functions, leading to cell death.[135] Certain metal NPs, such as silver, zinc oxide, and titanium dioxide, are particularly effective at ROS generation.[136] Additionally, nanocomposites like silver-copper NPs have demonstrated enhanced ROS-mediated antibacterial activity.[137] Wang *et al.* reported that the bactericidal effect of Ag/CeO_2 nanoparticles on *E. coli* was predominantly attributed to intracellular ROS generation and the disruption of the cell wall and membrane, rather than the release of silver ions.[138] Similarly, Mujeeb *et al.* demonstrated that silver–copper nanocomposites (Ag–Cu NCs) synthesized using Olax scandens leaf extract exhibited superior antimicrobial activity compared to monometallic Ag NPs, primarily due to enhanced ROS production.[139]

The chemical properties of NPs also play a vital role in their antibacterial activity. Metal ions released from NPs interact with bacterial phospholipid layers and interfere with intracellular biomacromolecules such as DNA and enzymes.[140] Transition metals (*e.g.*, Ag, Zn, Cu) and metalloids (*e.g.*, Se, Te) are particularly effective due to their ability to release ions that disrupt cellular processes. The dissolution of NPs in acidic conditions can enhance ion release and bactericidal activity, while ROS production—induced by NPs under various conditions—leads to cell wall damage, membrane permeability interference, and metabolic pathway disruption.[141] For instance,

Table 3 The main mechanisms of bacterial resistance to NPs

Bacteria	Nanoparticles (size in nm)	Resistance mechanisms	Year	Ref.
B. subtilis, *S. aureus*, *E. coli*	Nanoscale zero-valent iron (NS)	ROS response	2013	157
E. coli	ZnO nanorod (diameter ~ 45 and length ~ 250)	Changes in plasma membrane	2013	158
E. coli	Ag NP (10–30)	Production of extracellular substance	2014	159
Mycobacterium smegmatis	Ag NP (21.7)	Genetic changes	2014	160
B. subtilis	Ag NP (8.3)	ROS response, production of extracellular substances, quorum sensing, stress response	2015	161
E. coli	SiO_2 NP (15)	Production of extracellular substances	2016	162
P. aeruginosa PAO1	CuO NP (<50)	Genetic changes, regulation of porins, metal efflux transporters	2017	163
E. coli	ZnO NP (18)	Adaptive morphogenesis, regulation of porins	2018	164
Pseudomonas	CeO_2 NP (50)	Biofilm formation, stress response	2019	165
S. aureus	Ag NP (18)	ROS response, genetic changes	2020	166
E. coli	Ag NP (NS)	Changes in plasma membrane, genetic changes	2021	167
E. faecalis	Ag NP (10)	Production of extracellular substances, ROS response,	2022	168

NS = not specified.

Moreau *et al.* observed that ZnO NPs dissolved more readily under acidic conditions, leading to an increased release of Zn^{2+} ions.[142] Similarly, Saliani *et al.* found that the antibacterial effect of ZnO NPs was stronger when the pH dropped from 7 to more acidic levels.[143] Peretyazhko *et al.* noted that when Ag NPs are released into aquatic environments, they undergo oxidative dissolution, which results in the release of Ag^{+} ions and triggers antibacterial activity.[144]

The shape of NPs influences their antibacterial activity as well. Spherical, rod-shaped, and cubic NPs each exhibit different levels of effectiveness, with nanocubes and nanorods often showing higher bactericidal properties due to their exposed crystal planes and oxidation capabilities.[145] Structural features like corners, edges, and defects further enhance the interaction of NPs with bacterial cells, increasing their toxicity.[146] Huynh *et al.* found that gold nanostars could replace antibiotics in acne treatment due to their strong bactericidal effect against propionibacterium acne.[135] Additionally, Hong *et al.* discovered that Ag nanowires had lower antibacterial effectiveness compared to Ag nanocubes and nanospheres, likely due to reduced interaction with bacterial cells.[147] The same study also showed that silver nanocubes outperformed nanospheres in antimicrobial activity, as they provided larger contact areas and had more reactive facets.[145]

MNPs' ability to disrupt bacterial biofilms and prevent bacterial adhesion on surfaces has inspired the development of artificial antimicrobial surfaces.[148] By leveraging the natural bactericidal properties of nanostructures, researchers have created advanced materials with enhanced antimicrobial activity for medical and commercial applications.[149] Incorporating gold nanoparticles (Au NPs) into PMMA-based bone cement enhances the polymer matrix's mechanical properties and reduces *Staphylococcus aureus* biofilm formation. Reducing Au NPs to nanoclusters (NCs) within the 1–2 nm range significantly improves antimicrobial activity against Gram-positive and Gram-negative bacteria by increasing ROS levels while maintaining low cytotoxicity and genotoxicity in host cells.[150]

Pathogenic bacteria have evolved mechanisms to evade the immune system, making intracellular infections difficult to treat with conventional antibiotics due to limitations such as poor cellular permeability, low retention, and instability in mammalian cells.[151] Nanotechnology offers an innovative solution by enabling targeted delivery of antimicrobial agents to both extracellular and intracellular pathogens.[152] Metallic nanoparticles (MNPs) can act as carriers for antibiotics, improving pharmacokinetics, targeting infection sites, and enabling controlled drug release. Studies highlight the synergistic antibacterial effects of MNP–antibiotic composites.[148] Fe_3O_4 nanoparticles (NPs) can enter Gram-negative bacteria *via* siderophore channels located in their outer membrane. These nanoparticles can act as ''Trojan horses,'' facilitating the delivery of antibiotics attached to them, which are typically obstructed by the bacterial outer membrane.[153] Remarkable efficacy has also been observed against biofilms. Research by Ali *et al.* demonstrated that α-Fe_2O_3 nanoparticles interact with the extracellular polymeric substances (EPS) of biofilms and penetrate bacterial cells, inhibiting their growth by generating reactive oxygen species (ROS) within the cells.[154]

Nanoparticles can be functionalized in various ways to design advanced drug delivery systems. Drugs can be loaded *via* noncovalent binding, allowing efficient release without specific bond cleavage. Alternatively, covalent binding can link therapeutic, targeting, and functionalization agents to nanoparticles, functioning like prodrugs that release their payload upon specific stimuli. The use of metallic nanoparticles as drug carriers have been shown to significantly enhance the antibacterial activity of antibiotics, providing a promising approach to combat resistant pathogens and improve therapeutic outcomes.[155] Turki Al Hagbani and his team incorporated vancomycin into gold nanoparticles (AuNPs) using a simple one-pot method to create V-GNPs. *In vitro* antibacterial tests revealed that V-GNPs exhibited significantly stronger antibacterial activity compared to vancomycin alone against various bacterial strains.[156] Specifically, the inhibitory effectiveness of V-GNPs was 1.4 times greater against *Escherichia coli*, 1.6 times higher against *Klebsiella oxytoca*, 1.8 times more effective against *Pseudomonas aeruginosa*, and 1.6 times more potent against *Staphylococcus aureus*.

Despite their potential, the long-term stability and resistance mechanisms of bacteria against NPs pose challenges. Environmental factors, such as pH and medium composition, influence NP dissolution and ion release. Moreover, bacterial resistance strategies, including efflux systems and surface modifications, can diminish NP effectiveness over time. Further research is required to optimize their use and address potential resistance and cytotoxicity concerns.

Future advances should focus on developing biodegradable or self-degrading MNPs to minimize long-term environmental accumulation. Combining nanomaterial science with microbiology and toxicology can provide a clearer understanding of how MNPs interact with microbial membranes *versus* human cells, enabling selective antibacterial action while ensuring biosafety.

5. Photodynamic therapy-based synergistic antibacterial approach

Antimicrobial photodynamic therapy (APDT) represents an innovative approach for combating bacterial infections, particularly multidrug-resistant (MDR) strains.[169,170] The mechanism of APDT relies on the interaction of light, photosensitizer (PS) molecules, and molecular oxygen, producing reactive oxygen species (ROS) or reactive molecular species (RMS) that exert a bactericidal or bacteriostatic effect through two primary pathways: type I and type II mechanisms.[171] In the type I mechanism, light-activated PS molecules transition from a ground state to an excited singlet state and subsequently to a triplet state. From the triplet state, they transfer electrons or hydrogen atoms directly to surrounding substrates, forming free radicals such as hydroxyl radicals ($^{\bullet}OH$) and superoxide anions ($O_2^{\bullet-}$).[172] These radicals disrupt bacterial cell

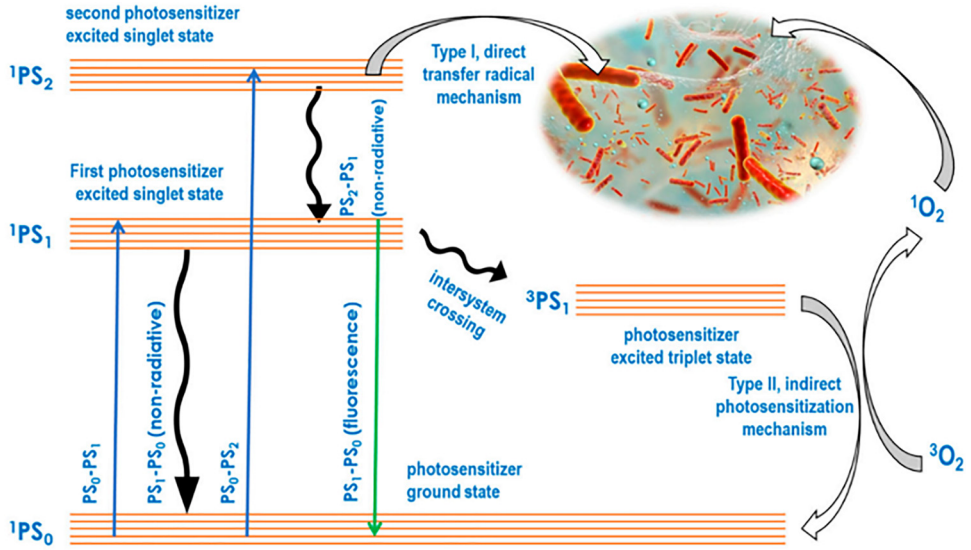

Fig. 2 Jablonski diagram to depict the type I and II mechanisms of APDT.[177] Reproduced under the terms of Creative Commons Attribution 4.0 International (CC BY 4.0) license. Copyright 2022, the Authors. Published in MDPI.

membranes by initiating lipid peroxidation, leading to structural damage and increased ion permeability.[173] The type II mechanism involves the transfer of energy from the triplet state PS molecules to oxygen, generating singlet oxygen ($^1O_2$), a highly reactive form of oxygen. This singlet oxygen oxidatively damages key bacterial biomolecules, including unsaturated lipids, proteins, and enzymes, effectively killing bacteria and weakening the structural integrity of biofilms (Fig. 2).[172,174]

The multitargeted nature of ROS generated by APDT enables the therapy to attack various cellular structures, including cell membranes, cell walls, and internal biomolecules such as DNA and proteins.[175] This broad-spectrum activity ensures effectiveness against bacteria regardless of antibiotic resistance mechanisms, with a lower risk of inducing further resistance compared to conventional antibiotics.[176] Additionally, ROS production within biofilms weakens the extracellular polymeric substance (EPS) matrix, reduces biofilm adhesion, and compromises pathogen metabolic activity, facilitating bacterial eradication.[70]

Photodynamic therapy (PDT) has been combined with various non-invasive treatment methods, demonstrating additive and synergistic effects that enhance outcomes in numerous *in vitro* studies, as well as in preclinical and clinical applications.[178] The approaches that photodynamic antibacterial therapy can integrate with can be categorized into six types: antibiotics, antibacterial agents, chemotherapy, photothermal therapy (PTT), nitric oxide (NO), and enhanced photosensitizers (PS). Table 4 provides a summary of the advantages and disadvantages of these methods.[179–183] These represent non-nanomaterial-based APDT synergistic antibacterial strategies. Among these, photodynamic antibiotic therapy (PACT) has emerged as a promising synergistic approach for bacterial inactivation.[180,184,185] In a study investigating the synergistic antibacterial effects of methylene blue (MB)-mediated photodynamic therapy (PDT) combined with antibiotics, Shih *et al.* assessed its efficacy against *Mycobacterium avium* keratitis. Using the micro-broth dilution method, they evaluated the bactericidal impact of combining MB-mediated PDT with antibiotics such as ciprofloxacin, moxifloxacin, and amikacin. The findings revealed that phototoxicity initially targets the cytoplasm during sterilization, followed by cell wall lysis, ultimately leading to the destruction of *M. avium*.[186] Almeida *et al.* assessed the antimicrobial effectiveness of APDT combined with antibiotics (ampicillin and chloramphenicol) and the surfactant SDS, utilizing cationic porphyrins as photosensitizers (PSs). The study was conducted in synergy with either phosphate buffer or filtered hospital wastewater containing multidrug-resistant bacteria. The results showed that at both subinhibitory and inhibitory concentrations, the combination of APDT and antibiotics led to a faster reduction in bacterial

Table 4 Comparison of combined PDT strategies

Strategy	Advantages	Disadvantages	Ref.
PDT + antibiotics	Lowers antibiotic dose; synergistic killing	Phototoxicity, limited penetration	180
PDT + antibacterial agents	Broadens antibacterial spectrum; multiple modes of action	Possible drug interactions, risk of toxicity	178
PDT + NO donors	Enhances ROS & NO synergy	Limited NO delivery efficiency	179
PDT + PTT (photothermal therapy)	Dual-mode killing; strong biofilm disruption	Heat damage to normal tissue	182
PDT + chemotherapy	Dual antibacterial–anticancer effect; versatile in infected tumors	Systemic side effects; limited selectivity	195
PDT + advanced PS nanocarriers	Targeted delivery, lower dark toxicity	Complexity of nanomaterial design	179

survival.[187] Hou *et al.* developed a polymeric antimicrobial agent designed to synergize chemotherapeutic and photodynamic therapy for combating drug-resistant bacterial infections. In this approach, amphiphilic polyaspartic acid-*block*-polycaprolactone polymeric micelles were used as carriers, with the photosensitizer protoporphyrin IX (PPIX) encapsulated in the micelle core. The micelle shell was then decorated with silver *via in situ* reduction. This polymeric antimicrobial agent demonstrated chemophotodynamic activity, effectively combining therapeutic strategies to eradicate drug-resistant bacterial infections.[188] Non-nanomaterials also present certain limitations.[189] Due to their lack of adjustable properties, it is difficult to effectively control the interaction of their physical and chemical characteristics and targeting capabilities.[190] As a result, non-nanomaterial-based photodynamic antibacterial strategies need to be optimized by adopting features of nanomaterials.

On the other hand, subcategories of the nanomaterials-based APDT synergistic antibacterial strategy include nanoparticles (NPs)-mediated approaches, nanomaterials-based PDT/PTT, and composite nanofiber membrane-based methods.[17,191,192] Bagchi *et al.* utilized squaraine (SQ) dye as a photosensitizer, covalently adsorbing it onto the surface of ZnO nanoparticles (ZnO NPs) to create ZnO-SQ nanohybrids. The photo-induced interfacial electron transfer (ET) process from the excited state of SQ to the ZnO conduction band enhanced the nanohybrids' reactive oxygen species (ROS) production, leading to a significant antibacterial effect against *S. aureus*. This synergistic mechanism, involving cell membrane disruption, nanoparticle internalization, and subsequent photo-induced intracellular ROS generation, enabled the nanohybrids to achieve 95% bacterial killing efficiency.[193] Teng *et al.* incorporated iodine into ZIF-8 and immobilized it on micro-arc titanium oxide. The combination of NIR light-induced iodine release and ZIF-8-mediated ROS oxidative stress significantly boosted the antimicrobial effectiveness of this approach both *in vitro* and *in vivo*. Furthermore, this composite coating promotes the osteogenic differentiation of bone marrow stromal cells without compromising the osteogenic potential of the implant, alongside the enhanced antimicrobial effect. The immobilization of iodine on orthopedic implants using MOFs provides a synergistic antimicrobial effect against bacterial infections.[194] Cai *et al.* developed a composite membrane of PCL/Cur@ZIF-8 with enhanced antimicrobial properties. The membrane incorporates the natural photosensitizer curcumin into the highly porous nanocrystals of ZIF-8 to improve curcumin's water solubility and stability. Upon release of zinc ions and curcumin, and under blue light irradiation, curcumin molecules generate singlet-state oxygen. The synergistic effect of zinc ions and singlet-state oxygen resulted in 99.9% inhibition of *E. coli* and *S. aureus*, as well as a 99.9% reduction in adherent flora when the Cur@ZIF-8 loading exceeded 15%. This composite membrane shows significant potential as an antimicrobial packaging material to extend the shelf life of fruits, meat, and other products.[183]

Antimicrobial photodynamic therapy is a promising strategy for combating infectious diseases caused by drug-resistant bacteria. Its key advantages include: (1) modifiability of light-controlled photosensitizers (PS), with high phototoxicity and low dark toxicity to reduce side effects;[196] (2) broad-spectrum antibacterial properties due to nonspecific targeting, preferentially binding to bacteria at infection sites;[197] (3) minimal damage to host cells, ensuring treatment safety;[198] (4) reliability, convenience, and reusability; and (5) compatibility with other therapies like radiotherapy, chemotherapy, and photothermal therapy (PTT).[199–201] However, PDT faces challenges in deep tissue application due to limited light penetration, which is affected by tissue thickness. Longer wavelengths have better tissue penetration but may not effectively promote ROS production due to low energy.[182] Additionally, the short lifespan and limited reach of reactive oxygen species (ROS) limit PDT's effectiveness, while some PSs suffer from dark toxicity, poor stability, and low bacterial targeting.[202–204] To improve PDT's practical application, strategies are needed to enhance its efficacy and address these limitations. The integration of PDT with immunotherapy and nanocarrier engineering represents a promising future direction. By combining light-activated antibacterial activity with immune stimulation and targeted delivery systems, interdisciplinary approaches may overcome the current limitations of tissue penetration and off-target phototoxicity.

6. Antimicrobial peptide-based multifunctional antibacterial strategies

Antimicrobial peptides (AMPs) are a diverse group of molecules characterized by their variation in chemical structures and amino acid compositions (Table 5).[205–207] Typically, AMPs are concise, with lengths ranging from 12 to 50 amino acids. Around 50% of these amino acids are hydrophobic, contributing to interactions with microbial membranes. Another key feature of AMPs is their amphiphilic nature and a net positive charge, generally ranging from +2 to +11, although some naturally occurring AMPs are negatively charged, such as dermcidin and histatin. AMPs are classified based on their source, structure, activity, and amino acid composition.[208,209] They possess advantages like low molecular weight, high solubility, thermal stability, low cytotoxicity, and environmental degradability, making them promising candidates for antimicrobial therapies. Unlike traditional antibiotics, AMPs degrade easily, reducing environmental pollution and resistance issues while serving as immune mediators.[210–213]

AMPs employ two primary mechanisms to kill bacteria: membrane targeting and intracellular activity.[220] Membrane-targeting mechanisms include: (1) toroidal pore model: AMPs interact with lipids and water to form transient pores, maintaining the lipid bilayer's integrity while allowing ion and molecule passage, ultimately leading to cell death.[221] This mechanism is displayed by magainin 2, and human cathelicidin LL-37.[222] (2) Barrel-Stave model: AMPs assemble into

Table 5 A list of some antimicrobial peptides based on various classification criteria

AMP	Sequence	Origin	Structure	Activity	Ref.
Piscidin	FFHHIFRGIVHVGKTIHRLVTG	Fish morone chrysops	α-Helix	Gram-negative bacteria	214
LL-37	LLGDFFRKSKEKIGKEFKRIVQRIKDFLRNLVPRTES	Human (cathelicidin)	α-Helix	Broad-spectrum, including bacteria, fungi, and viruses	215
Nisin	ILLSKFLRNWAILAILKWRNA	Bacteria *Lactococcus lactis*	Polycyclic β-sheet with loops	Gram-positive bacteria	216
Defensin (HNP-1)	ACYCRIPACIAGERRYGTCIYQGRLWAFCC	Human (neutrophil)	β-Sheet	Broad-spectrum, including bacteria, fungi, viruses (s HIV, influenza)	217
Gramicidin A	VGALAVVVWLWLWLWG	Soil bacterium *Brevibacillus brevis*	Linear	Gram-positive bacteria	218
Melittin	GIGAVLKVLTTGLPALISWIKRKRQQ	Bee venom	α-Helix	Broad-spectrum, including bacteria, fungi, cancer	219

oligomeric structures, forming transmembrane channels that disrupt the membrane's barrier function. Alamethicin, and ceratotoxins are examples of peptides acting by this mechanism.[223,224] (3) Carpet model where AMPs cover the membrane surface like a detergent, disrupting lipid packing and causing membrane destabilization and lysis. Examples of peptides that likely operate in a detergent-like manner include dermaseptin *S. aurein* 1.2, and cecropin.[225] AMPs also target bacterial cell walls, disrupting peptidoglycan synthesis in Gram-positive bacteria and lipopolysaccharide layers in Gram-negative bacteria.[226] For instance, nisin binds lipid II to inhibit cell wall synthesis. In addition to membrane-targeting, AMPs exhibit intracellular activity by entering bacterial cells and interfering with vital processes. They damage nucleic acids (*e.g.*, indolicidin unwinds bacterial DNA), inhibit protein synthesis (*e.g.*, PrAMPs block elongation or termination during translation), and affect organelles (*e.g.*, periplanetasin-4 disrupts mitochondria).[227–230]

Brevinin-1, a peptide obtained from frog skin secretions, was modified to improve its therapeutic efficacy by altering its net charge, structural conformation, and hydrophobicity. Both the peptide and its derivatives effectively inhibited biofilm formation by methicillin-resistant *S. aureus* and *Enterococcus faecalis*.[231] Another example is the synthetic antimicrobial peptide P5, which has demonstrated activity against carbapenem-resistant *Pseudomonas aeruginosa* (CRPA). Its mode of action involves disrupting bacterial cell membranes, with experimental findings highlighting its significant role in biofilm eradication, making it a promising candidate for treating multi-resistant infections.[232] The human cathelicidin peptide LL-37 has demonstrated effectiveness against biofilms formed by *Staphylococcus aureus* in both meticillin-sensitive *Staphylococcus aureus* (MSSA) and meticillin resistant *Staphylococcus aureus* (MRSA) strains and can serve as an adjunct therapy for wound infections where biofilm development plays a significant role.[233] Cbf-K16, a cathelicidin-like antimicrobial peptide, shows strong antimicrobial effects against both Gram-positive and Gram-negative bacteria, along with notable anti-biofilm properties. It has demonstrated a promising synergistic interaction with ceftazidime or ampicillin against MRSA.[234]

Beyond conventional AMPs, novel approaches and strategies are emerging for the treatment of drug-resistant bacterial infections. The combination of antibiotics and AMPs is emerging as a potential therapeutic strategy to combat antibiotic resistance, enhance bacterial killing, and reduce toxicity and side effects.[235] This approach aims to minimize adverse effects, increase compound selectivity, improve bacterial membrane permeability, and decrease the efflux of antibiotics, thereby inhibiting bacterial survival.[236] Peng *et al.* developed antibiotic-conjugated antimicrobial lipopeptides from paenipeptin C′ and ciprofloxacin. This design operates through a dual mechanism: the AMP disrupts the bacterial membrane, allowing the antibiotic to enter and inhibit targets like DNA gyrase.[237] Similarly, combining conventional antibiotics with new synthetic peptides inspired by human cationic peptides such as LL-37 and thrombocidin-1 (TC-1) has shown synergistic antibacterial and anti-biofilm activity against *S. aureus*.[238] Li *et al.* demonstrated that the combination of the tetracycline antibiotic demeclocycline hydrochloride (DMCT) and the AMP SAAP-148 exhibited synergistic antimicrobial activity against multidrug-resistant *Pseudomonas aeruginosa* strains PAO1 and ATCC27853.[239] Additionally, Tarvirdipour *et al.* developed a powerful surface-coating technology based on rifampicin-loaded peptide multi-compartment micelles (RIF-MCMs). Immobilized on a surface, these micelles provide a dual-function antimicrobial defense: they enable sustained, temperature-responsive release of antibiotics while simultaneously altering surface topography to passively inhibit bacterial adhesion and biofilm formation.[240]

The use of nanoparticle (NP)-conjugated systems for delivering AMPs has recently attracted attention. NPs offer a large surface area for AMP adsorption and help prevent AMP self-aggregation.[241] Nanostructures are emerging as potential drug delivery carriers. As effective carriers, they must possess two key properties: non-cytotoxicity and non-immunogenicity. These nanostructures can be internalized into the cytoplasm without the need for transfectants, utilizing endocytosis and exocytosis pathways that are independent of multidrug efflux pumps. Nanotechnology-based approaches can enhance the stability and efficacy of AMPs while reducing toxicity to host tissue cells. Encapsulating AMPs in nanomaterials holds significant potential due to their small size, high surface area, and strong targeting capabilities.[242,243] For instance, the proline-rich AMP dimer A3-APO and its single-chain metabolite (APO monomer) were tested in mice with burn wounds infected with MDR

Acinetobacter baumannii, a strain isolated from an injured soldier. A dose of 5 mg kg^{-1} A3-APO significantly improved survival and reduced bacterial counts in the blood and wounds compared to other antibiotic treatments, including colistin and imipenem. This approach not only enhances the industrial utility and commercial viability of the product but also offers added value in smart biomedical applications.[244]

Despite the high potential of antimicrobial peptides (AMPs), only a few have been FDA-approved for clinical use. The development of AMPs involves a lengthy and complex process, including discovery, optimization, and clinical trials. However, several challenges hinder AMP advancement. These include unclear mechanisms of action, instability, and weak antibacterial activity.[245] AMPs are vulnerable to degradation by proteases, sensitivity to pH, salt, and serum components, which can alter their structure and function. For example, salt ions can affect the antimicrobial activity by altering peptide conformation. Additionally, extreme pH conditions and serum proteins can impact AMP stability and efficacy.[246,247] To address these challenges, various strategies, such as modifying peptide sequences, encapsulating AMPs in nanoparticles, or using dimerization, are being explored to enhance their stability, bioavailability, and therapeutic potential.[248]

AMPs are generally low in cytotoxicity, but their potential toxicity can vary depending on factors like peptide sequence, concentration, and the route of administration. Some AMPs, such as pore-forming peptides, can be toxic to human cells, especially at high concentrations, which can lead to secondary diseases.[249] Hydrophobicity also plays a crucial role in antimicrobial activity, but excessive hydrophobicity may result in mammalian cell toxicity. Using drug carriers such as nanoparticles can reduce toxicity by targeting infected sites specifically. The administration route also impacts toxicity; systemic delivery may lead to more toxicity than topical applications.[250]

Lastly, the cost of producing AMPs is high due to the complex synthesis and purification processes required for peptides with long sequences. These peptides are more effective against a broader range of pathogens but come with challenges in terms of cost and scalability.[251] The application of artificial intelligence and synthetic biology offers new opportunities to design next-generation AMPs with enhanced stability, reduced cytotoxicity, and lower production costs. By bridging computational peptide design with industrial biotechnology, more clinically viable and scalable AMP-based therapies can be achieved.

7. Conclusion

The increasing global threat of antibiotic resistance underscores the urgent need for alternatives to traditional antibiotics. Emerging technologies, particularly metal–organic frameworks (MOFs), metal nanoparticles (MNPs), photodynamic therapy (PDT), and antimicrobial peptides (AMPs), show significant promise as complementary strategies (Fig. 3). When used together, these approaches could potentially overcome the

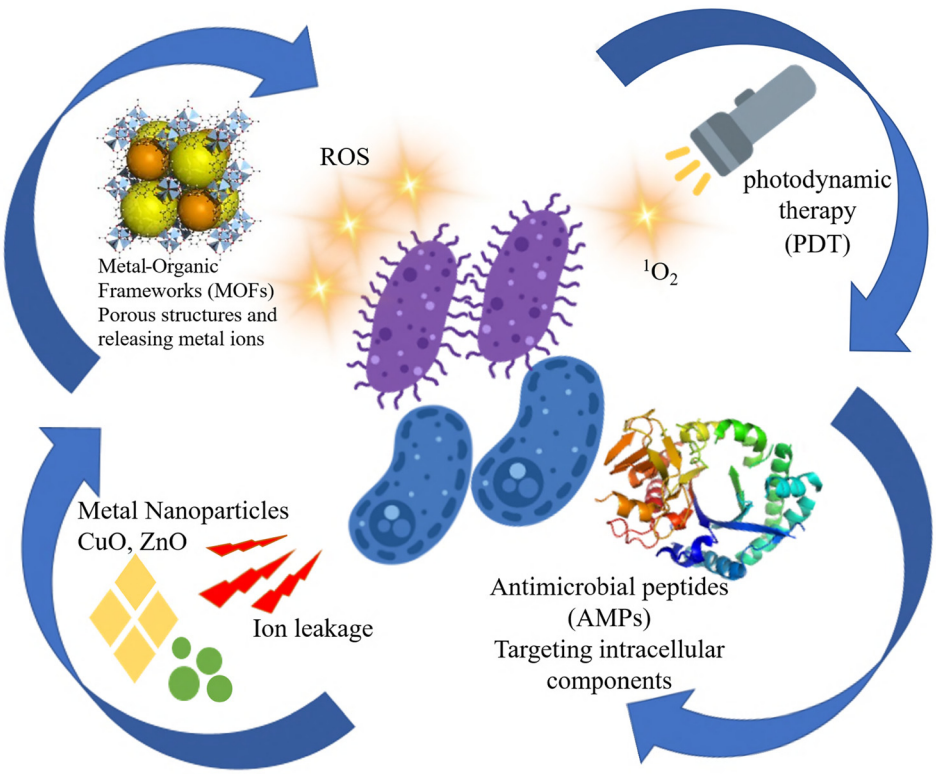

Fig. 3 Overview of Four Strategies to Combat Antimicrobial Resistanc.

Table 6 Comparison of the four methods: an overview

Strategy	Main mechanism	Strengths	Weaknesses
MOFs	Controlled metal ion release + ROS + drug delivery	Tunable, multifunctional, strong *in vitro* activity	Cytotoxicity, *in vivo* stability
MNPs	Membrane disruption, ion release, ROS	Broad-spectrum, synergize with antibiotics	Environmental accumulation, bacterial adaptation
PDT	Light-activated ROS	Resistance-free, precise, broad-spectrum	Poor penetration, phototoxicity
AMPs	Membrane targeting + intracellular action	Low resistance potential, multifunctional	High cost, instability, potential cytotoxicity

limitations of any single method, creating new pathways for sustainable antibacterial treatment.

Each strategy has distinct advantages but also faces critical challenges that hinder clinical application (Table 6). MOFs are tunable and multifunctional, yet concerns about *in vivo* degradation and potential immunotoxicity persist. MNPs offer broad-spectrum activity and strong synergy with antibiotics but raise issues regarding long-term environmental accumulation. PDT provides non-invasive, resistance-free bacterial inactivation; however, limited light penetration and phototoxicity restrict its use. AMPs uniquely disrupt bacterial membranes and evade conventional resistance mechanisms, but their high production costs and limited scalability pose challenges for industrial applications. Overcoming these hurdles requires an interdisciplinary approach integrating chemistry, biology, toxicology, and engineering.

Social and environmental considerations are essential for future strategies. As the use of nanotechnology in antimicrobial research grows, so do public concerns over the safety and environmental impact of nanomaterials. Future research should prioritize the design of nanomaterials that emphasize biocompatibility, biodegradability, and safe degradation pathways to minimize risks to human health and ecosystems while maximizing therapeutic potential.

Future research directions should focus on the following: (1) designing hybrid systems that integrate MOFs with AMPs or photosensitizers to enable multifunctional activity while reducing toxicity. (2) Developing biodegradable or self-degrading MNPs to mitigate long-term environmental accumulation. (3) Enhancing PDT through advanced light delivery systems, nanocarrier engineering, and combinations with immunotherapies. (4) Utilizing computational modeling, peptide engineering, and synthetic biology to create cost-effective and stable AMPs suitable for clinical use. By embracing these interdisciplinary and sustainability-focused directions, the antibacterial field can progress towards the safe and effective integration of innovative technologies. These combined strategies not only hold promise for reducing reliance on conventional antibiotics but also for responsibly addressing the growing crisis of antibiotic resistance.

Author contributions

Afsaneh Arshadi Edlo: conceptualization, resources, investigation, writing – original draft and visualization. Kamran Akhbari: validation, data curation, writing – review & editing, supervision, project administration. David J. Henry: review & editing.

Conflicts of interest

The authors declare no competing financial interests for this article.

Data availability

All data and materials supporting this review article are publicly available in the references listed. No original datasets were generated for this study.

Acknowledgements

The authors would like to acknowledge the support from the University of Tehran.

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