



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

Received 27th May 2025,  
Accepted 13th September 2025

DOI: 10.1039/d5ma00552c

rsc.li/materials-advances

## Beyond antibiotics: novel solutions to address antibacterial resistance

Afsaneh Arshadi Edlo, <sup>a</sup> Kamran Akhbari \*<sup>a</sup> and David J. Henry <sup>b</sup>

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.

<sup>a</sup> School of Chemistry, College of Science, University of Tehran, P.O. Box 14155-6455, Tehran, Iran. E-mail: akhbari.k@ut.ac.ir; Fax: +98 21 66495291; Tel: +98 21 61113734

<sup>b</sup> School of Mathematics, Statistics, Chemistry and Physics, Murdoch University, Murdoch, Western Australia 6150, Australia. E-mail: d.henry@murdoch.edu.au; Tel: +61 8 9360 2681

### 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



Afsaneh Arshadi Edlo

Afsaneh Arshadi Edlo is an Inorganic Chemistry researcher specializing in metal–organic frameworks (MOFs) and metal nanoparticles (MNPs). Her research focuses on designing and functionalizing nanomaterials for biomedical applications, particularly in the areas of antibacterial activity, drug delivery, cancer treatment, and environmental catalysis. Afsaneh completed her Master's degree in Inorganic Chemistry at the University of

Tehran in 2022, following her Bachelor's degree in Applied Chemistry from Shahid Beheshti University. Her scientific contributions include publications in peer-reviewed journals and presentations at international conferences, where she highlights innovative strategies to combat antimicrobial resistance.



Kamran Akhbari

Kamran Akhbari joined University of Tehran, Department of Chemistry in 2013. He earned a Bachelor's Degree in Chemistry from Shahid Beheshti University in 2005, a Master of Science Degree in 2008 and PhD Degree in 2012 in Inorganic Chemistry from Tarbiat Modares University. He completed a post-doctoral fellowship under the supervision of Prof. Ali Morsali at Tarbiat Modares University. He has published more than 150 papers, and his current research focuses on the crystal engineering of coordination polymers and supramolecular compounds, metal–organic frameworks (MOFs) and their potential applications in energy storage materials, separation, drug delivery and catalysis. He also conducts research into the synthesis and characterization of nano-scale materials. In 2013, he won second place in the Khwarizmi Young Award for his work in the field of modulating methane storage in nanoporous anionic MOFs via post synthetic cation exchange.



settings.<sup>1</sup> Excessive antibiotic use and misuse have contributed to the emergence of superbugs – pathogens that can withstand even the most potent medications, exacerbating antibiotic resistance.<sup>2</sup> 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.<sup>3</sup> The World Health Organization (WHO) cautions that by 2050, antibiotic-resistant diseases may account for more deaths than cancer if nothing is done.<sup>4</sup> 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.<sup>5,6</sup> These materials facilitate controlled encapsulation and release of antimicrobial agents while providing direct bactericidal activity *via* sustained metal ion delivery (*e.g.*, Ag<sup>+</sup>, Zn<sup>2+</sup>, Cu<sup>2+</sup>).<sup>7–10</sup> Their structural versatility, achieved through tailored ligand design and synthesis strategies, permits precise modulation of pore geometry, functionality, and biocompatibility.<sup>11,12</sup> Enhanced

antimicrobial efficacy is realized through advanced mechanisms such as photocatalytic reactive oxygen species (ROS) generation and stimuli-responsive agent release.<sup>13</sup> Engineered defects in MOFs further optimize cargo loading capacity and enable targeted delivery under environmental triggers.<sup>14–16</sup> 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.<sup>17–21</sup>

Another highly successful method for combating antibacterial resistance is the use of metal nanoparticles (MNPs).<sup>22</sup> These materials have shown excellent results both independently and in combination with other approaches, playing a very significant role in this field.<sup>23</sup> 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.<sup>24–26</sup> 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.<sup>27,28</sup> MNPs also exhibit synergistic effects when combined with conventional antibiotics, reducing resistance and improving therapeutic outcomes by lowering dosage requirements and minimizing side effects.<sup>29</sup> Intermetallic nanoparticles, formed by combining different metals, have demonstrated superior antibacterial properties compared to monometallic forms, further broadening their biomedical applications.<sup>30,31</sup> 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.<sup>32</sup>

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.<sup>33–35</sup> 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.<sup>36–38</sup>

Beyond these metal-based strategies, a host of other innovations is emerging in the fight against resistant bacteria.<sup>39</sup> 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.<sup>40,41</sup> 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.<sup>42</sup> Their mechanism of action, based on membrane



**David J. Henry**

*Professor David J. Henry is a Professor in the Department of Chemistry and Physics at Murdoch University, Australia. He earned his PhD in Biological and Chemical Sciences from Deakin University in 1998. Following this, he undertook a Postdoctoral Fellowship at the Research School of Chemistry, Australian National University. He later joined Murdoch University in 2015, where he has since advanced to his current*

*role. Professor Henry's research is interdisciplinary, spanning inorganic and computational chemistry, nanomaterials, and environmental chemistry. His work employs advanced computational methods, including density functional theory (DFT), quantum chemical modeling, and molecular dynamics simulations, to investigate problems in soil water repellency, bio-inorganic systems, and the design of nanostructured materials. He has published nearly 100 peer-reviewed articles, with over 2500 citations, and continues to contribute actively to both fundamental and applied aspects of chemistry.*



destruction, minimizes the risk of inducing bacterial resistance, and they have been effectively demonstrated in both *in vitro* and *in vivo* models.<sup>43–45</sup> AMPs hold significant promise for applications in clinical antibacterial treatments, animal and plant disease resistance, and as food preservatives.<sup>46–49</sup> 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.<sup>50,51</sup>

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.<sup>52,53</sup> 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.<sup>54</sup> 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.<sup>55</sup>

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.<sup>56,57</sup> This process arises from the development of resistance genes through horizontal gene transfer and genetic alterations.<sup>58</sup> Overcoming bacterial resistance requires an understanding of the mechanisms by which resistance is achieved.<sup>59</sup> 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.<sup>60</sup> 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*.<sup>61</sup> 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).<sup>57,62</sup> 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.<sup>63</sup> Aminoglycoside-modifying enzymes, chemically alter antibiotics, diminishing their ability to bind to bacterial targets.<sup>64</sup> 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,<sup>65</sup> while mutations in DNA gyrase or topoisomerase IV confer resistance to fluoroquinolones.<sup>66</sup> 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. <i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i> )	Cephalosporins ( <sup>a</sup> ESBL-producers), fluoroquinolones, aminoglycosides	73
Enterococcus spp. (especially <i>E. faecium</i> )	Cephalosporins ( <sup>a</sup> ESBL-producers), fluoroquinolones, aminoglycosides, carbapenems	74
<i>Pseudomonas aeruginosa</i>	Ampicillin, aminoglycosides (high-level)	74
	Ampicillin, aminoglycosides (high-level), glycopeptides	
	Piperacillin/tazobactam, ceftazidime, ciprofloxacin, aminoglycosides	75
<i>Staphylococcus aureus</i> (healthcare-associated)	Piperacillin/tazobactam, ceftazidime, ciprofloxacin, aminoglycosides, carbapenems	75
	b-Lactam antibiotics (except new anti- <sup>b</sup> MRSA cephalosporins), macrolides, fluoroquinolones, aminoglycosides	76

<sup>a</sup> ESBL, extended-spectrum b-lactamase. <sup>b</sup> MRSA, methicillin-resistant *S. aureus*.





Fig. 1 Main antibiotic targets and associated mechanisms of resistance.<sup>77</sup> 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.<sup>67</sup> 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.<sup>68</sup> 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.<sup>69</sup> They reduce drug penetration and provide a protective environment for dormant bacterial cells, making them highly resistant to treatment.<sup>70</sup>

Understanding these diverse mechanisms is critical for addressing the resistance crisis and guiding the development of next-generation antimicrobial strategies.<sup>71</sup> 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.<sup>78–80</sup> 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.<sup>14,79,81–87</sup> 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.<sup>88–91</sup> 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*.<sup>92–94</sup> Compared to traditional antibiotics, MOFs offer several distinct benefits: (i) they can be constructed with bactericidal ions and antimicrobial ligands;<sup>95,96</sup> (ii) their chelation effect enhances lipophilicity and improves membrane penetration;<sup>97,98</sup> (iii) their high porosity allows for significant drug loading;<sup>99</sup> and (iv) their electronic tunability enables efficient photocatalytic ROS generation.<sup>100–102</sup>

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 <sup>2+</sup>	Trimesic acid	<i>E. coli</i> , <i>S. aureus</i> , <i>Pseudomonas</i> , <i>Klebsiella</i> , <i>Candida</i>	100 µg mL <sup>-1</sup> ; outperformed ampicillin/ciprofloxacin	Nutrient broth, 10 <sup>6</sup> CFU per mL, 24 h, 37 °C	24, 106
Zn-MOFs	Zn <sup>2+</sup>	Terephthalate	<i>S. aureus</i> , <i>E. coli</i>	Zn-MOF strongest via Zn <sup>2+</sup> release	Broth culture	104
Ni-MOFs	Ni <sup>2+</sup>	Organic linker	ESBL <i>E. coli</i> , <i>P. aeruginosa</i> , MRSA	IC50 = 15–25 µg mL <sup>-1</sup> ; biofilm inhibition	Standard broth	107
ZIF-4, ZIF-7, ZIF-8	Zn <sup>2+</sup>	Imidazolate	<i>S. aureus</i> , <i>E. coli</i>	ZIF-8 strongest; ZnO derived from ZIF-4 enhanced activity	Normal broth	91
Zr-TCPP (PCN-224, Cu <sup>2+</sup> -doped)	Zr <sup>4+</sup> (Cu <sup>2+</sup> -doped)	Porphyrin (TCPP)	<i>S. aureus</i>	99.71% inhibition	Light irradiation (660 nm, 20 min)	109
ZIF-8-PAA-MB@AgNPs@Van-PEG	Zn <sup>2+</sup>	Imidazolate	<i>E. coli</i> , <i>S. aureus</i> , MRSA	Synergistic killing under laser irradiation	Laser irradiation	120
UIO-66-NH2@PEG	Zr <sup>4+</sup>	Amino-terephthalate	VRSA	Superior antibacterial & anti-biofilm vs. free drugs	Standard broth	114
Zr-MOF-1/2 (CIP delivery)	Zr <sup>4+</sup>	Organic linker	<i>E. coli</i> (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.<sup>103–105</sup> 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<sup>-1</sup>. Experiments were conducted in nutrient broth with an initial inoculum of ~10<sup>6</sup> 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.<sup>106</sup> In 2021, Nakhai *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<sup>2+</sup> ion release, particularly in its activated form, which disrupts bacterial cell integrity through sustained metal ion release.<sup>104</sup> 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<sup>-1</sup> and 25.14 ± 0.75 µg mL<sup>-1</sup>, respectively. The antimicrobial effect was attributed to the positively charged Ni<sup>2+</sup> 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.<sup>107</sup> 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<sup>2+</sup> ion release. ZnO nanoparticles derived from ZIF-4 further enhanced antibacterial performance, attributed to their uniform nanostructure and controlled ion release.<sup>91</sup> 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 bio-applications, 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.<sup>108</sup> Han *et al.* introduced a Cu<sup>2+</sup>-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<sup>2+</sup> 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.<sup>109</sup> 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<sub>2</sub> and H<sub>2</sub>O. Li *et al.* compared five MOFs (MIL-100, NH<sub>2</sub>-MIL-125, NH<sub>2</sub>-UiO-66, ZIF-11, and ZIF-8) for photocatalytic inactivation of *E. coli*; ZIF-8 (Zn<sup>2+</sup>/Hmim) achieved >99.9999% reduction within 2 h in saline under simulated solar light (Xe lamp, AM 1.5, 100 mW cm<sup>-2</sup>). Blank controls (light only, ZIF-8 in dark) showed negligible killing, while ZnO and TiO<sub>2</sub> achieved only ~2–3 log reductions, confirming ZIF-8's superior photocatalytic activity.<sup>110</sup> 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.<sup>111</sup> 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.<sup>111</sup> (3) Drug and antibacterial delivery vehicles: MOFs serve as carriers for antibiotics or other antimicrobial agents, enhancing their solubility, stability, and targeted delivery.<sup>112</sup> 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.<sup>113</sup> Also, Rahmanian *et al.* developed a PEG-coated UIO-66-NH<sub>2</sub> 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<sub>2</sub>@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.<sup>114</sup>

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<sup>+</sup> ions, and reactive oxygen species (ROS) generation. However, excessive Ag<sup>+</sup> 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<sup>+</sup> or standalone Ag NPs.<sup>112,115</sup> 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.<sup>116</sup> 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<sup>2+</sup> ions and CHX, achieving lower MIC values compared to individual components.<sup>117</sup> 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<sub>2</sub>O<sub>2</sub>-responsive release (47.7% cumulative release in infected tissue conditions) and maintained potent antibacterial activity (MIC < 0.6 μg mL<sup>-1</sup>) comparable to free GEM, while enabling sustained, targeted delivery to reduce off-target effects.<sup>118</sup> Arenas-Vivo *et al.* proposed a photoactive composite coating, Ag-encapsulated MIL-125(Ti)-NH<sub>2</sub>, 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.<sup>119</sup> 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<sub>3</sub>, followed by the addition of Van-PEG to load antibacterial agents.<sup>120,121</sup> 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.<sup>121</sup>

Antibacterial performance depends strongly on MOF composition. Zn-based frameworks often show strong activity due to sustained Zn<sup>2+</sup> 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.<sup>122</sup> The precise mechanisms of their activity are not yet fully understood, although significant research efforts have been directed at elucidating these processes (Table 3).<sup>123</sup> 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.<sup>124</sup> 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.<sup>125</sup> Positively charged NPs show enhanced bactericidal activity due to electrostatic interactions with the negatively charged bacterial cell surface.<sup>126</sup> 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.<sup>127</sup> 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.<sup>128</sup> Similarly, Korshed *et al.* discovered an inverse relationship between the size of NPs and their bactericidal effects.<sup>129</sup> 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.<sup>130</sup>

In recent studies, surface functionalization and charge modulation have been shown to significantly affect NP biocompatibility and antimicrobial properties.<sup>131</sup> For example, positively charged NPs demonstrate higher affinity for bacterial cells, enhancing their bactericidal potential.<sup>132</sup> Conversely, bacterial cells can adapt by modifying their surface charges or employing efflux systems to reduce NP toxicity.<sup>133</sup> 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.<sup>134</sup>

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.<sup>135</sup> Certain metal NPs, such as silver, zinc oxide, and titanium dioxide, are particularly effective at ROS generation.<sup>136</sup> Additionally, nanocomposites like silver-copper NPs have demonstrated enhanced ROS-mediated antibacterial activity.<sup>137</sup> Wang *et al.* reported that the bactericidal effect of Ag/CeO<sub>2</sub> 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.<sup>138</sup> Similarly, Mujeeb *et al.* demonstrated that silver-copper nanocomposites (Ag-Cu NCs) synthesized using *Oxalis scandens* leaf extract exhibited superior antimicrobial activity compared to monometallic Ag NPs, primarily due to enhanced ROS production.<sup>139</sup>

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.<sup>140</sup> 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.<sup>141</sup> For instance,

**Table 3** The main mechanisms of bacterial resistance to NPs

Bacteria	Nanoparticles (size in nm)	Resistance mechanisms	Year Ref.
<i>B. subtilis</i> , <i>S. aureus</i> , <i>E. coli</i>	Nanoscale zero-valent iron (NS)	ROS response	2013 157
<i>E. coli</i>	ZnO nanorod (diameter ~ 45 and length ~ 250)	Changes in plasma membrane	2013 158
<i>E. coli</i>	Ag NP (10–30)	Production of extracellular substance	2014 159
<i>Mycobacterium smegmatis</i>	Ag NP (21.7)	Genetic changes	2014 160
<i>B. subtilis</i>	Ag NP (8.3)	ROS response, production of extracellular substances, quorum sensing, stress response	2015 161
<i>E. coli</i>	SiO <sub>2</sub> NP (15)	Production of extracellular substances	2016 162
<i>P. aeruginosa</i> PAO1	CuO NP (<50)	Genetic changes, regulation of porins, metal efflux transporters	2017 163
<i>E. coli</i>	ZnO NP (18)	Adaptive morphogenesis, regulation of porins	2018 164
<i>Pseudomonas</i>	CeO <sub>2</sub> NP (50)	Biofilm formation, stress response	2019 165
<i>S. aureus</i>	Ag NP (18)	ROS response, genetic changes	2020 166
<i>E. coli</i>	Ag NP (NS)	Changes in plasma membrane, genetic changes	2021 167
<i>E. faecalis</i>	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<sup>2+</sup> ions.<sup>142</sup> Similarly, Saliani *et al.* found that the antibacterial effect of ZnO NPs was stronger when the pH dropped from 7 to more acidic levels.<sup>143</sup> Peretyazhko *et al.* noted that when Ag NPs are released into aquatic environments, they undergo oxidative dissolution, which results in the release of Ag<sup>+</sup> ions and triggers antibacterial activity.<sup>144</sup>

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.<sup>145</sup> Structural features like corners, edges, and defects further enhance the interaction of NPs with bacterial cells, increasing their toxicity.<sup>146</sup> Huynh *et al.* found that gold nanostars could replace antibiotics in acne treatment due to their strong bactericidal effect against propionibacterium acne.<sup>135</sup> 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.<sup>147</sup> The same study also showed that silver nanocubes outperformed nanospheres in antimicrobial activity, as they provided larger contact areas and had more reactive facets.<sup>145</sup>

MNPs' ability to disrupt bacterial biofilms and prevent bacterial adhesion on surfaces has inspired the development of artificial antimicrobial surfaces.<sup>148</sup> By leveraging the natural bactericidal properties of nanostructures, researchers have created advanced materials with enhanced antimicrobial activity for medical and commercial applications.<sup>149</sup> 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.<sup>150</sup>

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.<sup>151</sup> Nanotechnology offers an innovative solution by enabling targeted delivery of antimicrobial agents to both extracellular and intracellular pathogens.<sup>152</sup> 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.<sup>148</sup> Fe<sub>3</sub>O<sub>4</sub> 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.<sup>153</sup> Remarkable efficacy has also been observed against biofilms. Research by Ali *et al.* demonstrated that  $\alpha$ -Fe<sub>2</sub>O<sub>3</sub> 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.<sup>154</sup>

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.<sup>155</sup> 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.<sup>156</sup> 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.<sup>169,170</sup> 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.<sup>171</sup> 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<sub>2</sub><sup>•-</sup>).<sup>172</sup> These radicals disrupt bacterial cell



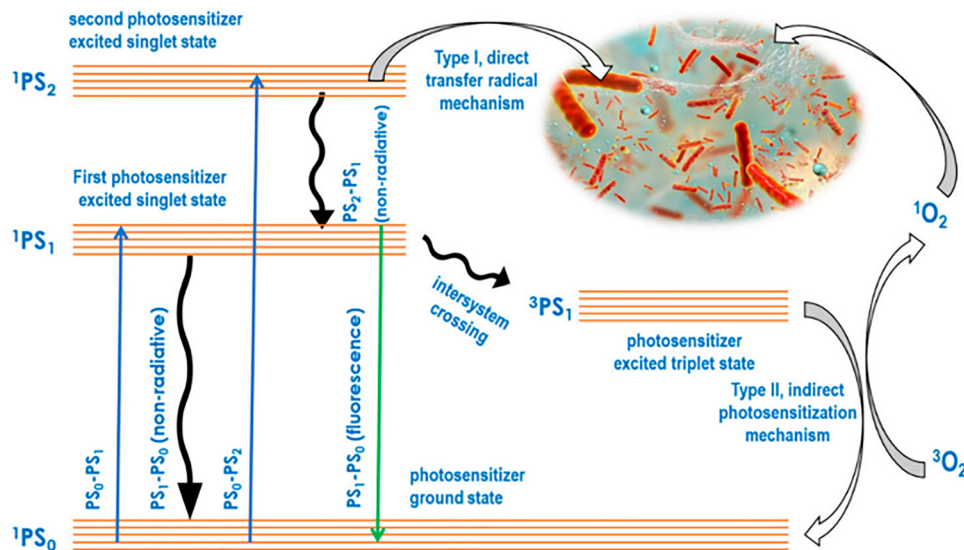


Fig. 2 Jablonski diagram to depict the type I and II mechanisms of APDT.<sup>177</sup> Reproduced under the terms of Creative Commons Attribution 4.0 International (CC BY 4.0) license. Copyright 2022, the Authors. Published in MDPI.

membranes by initiating lipid peroxidation, leading to structural damage and increased ion permeability.<sup>173</sup> The type II mechanism involves the transfer of energy from the triplet state PS molecules to oxygen, generating singlet oxygen (<sup>1</sup>O<sub>2</sub>), 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).<sup>172,174</sup>

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.<sup>175</sup> 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.<sup>176</sup> Additionally, ROS production within biofilms weakens the extracellular polymeric substance (EPS) matrix, reduces biofilm adhesion, and compromises pathogen metabolic activity, facilitating bacterial eradication.<sup>70</sup>

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.<sup>178</sup> 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.<sup>179–183</sup> 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.<sup>180,184,185</sup> 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*.<sup>186</sup> 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.<sup>187</sup> 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.<sup>188</sup> Non-nanomaterials also present certain limitations.<sup>189</sup> Due to their lack of adjustable properties, it is difficult to effectively control the interaction of their physical and chemical characteristics and targeting capabilities.<sup>190</sup> 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.<sup>17,191,192</sup> 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.<sup>193</sup> 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.<sup>194</sup> 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.<sup>183</sup>

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;<sup>196</sup> (2) broad-spectrum antibacterial properties due to nonspecific targeting, preferentially binding to bacteria at infection sites;<sup>197</sup> (3) minimal damage to host cells, ensuring treatment safety;<sup>198</sup> (4) reliability, convenience, and reusability; and (5) compatibility with other therapies like radiotherapy, chemotherapy, and photothermal therapy (PTT).<sup>199–201</sup> 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.<sup>182</sup> 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.<sup>202–204</sup> 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).<sup>205–207</sup> 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.<sup>208,209</sup> 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.<sup>210–213</sup>

AMPs employ two primary mechanisms to kill bacteria: membrane targeting and intracellular activity.<sup>220</sup> 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.<sup>221</sup> This mechanism is displayed by magainin 2, and human cathelicidin LL-37.<sup>222</sup> (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	$\alpha$ -Helix	Gram-negative bacteria	214
LL-37	LLGDFFRKSKEKIGKEFKRIVQRIKDFLRNLPRTES	Human (cathelicidin)	$\alpha$ -Helix	Broad-spectrum, including bacteria, fungi, and viruses	215
Nisin	ILLSKFLRNWAILAILKWRNA	Bacteria <i>Lactococcus lactis</i>	Polycyclic $\beta$ -sheet with loops	Gram-positive bacteria	216
Defensin (HNP-1)	ACYCRIPACIAGERRYGTCIYQGRWLWAFCC	Human (neutrophil)	$\beta$ -Sheet	Broad-spectrum, including bacteria, fungi, viruses (s HIV, influenza)	217
Gramicidin A	VGALAVVWLWLWLWG	Soil bacterium <i>Brevibacillus brevis</i>	Linear	Gram-positive bacteria	218
Melittin	GIGAVLKVLTTGLPALISWIKRKRQQ	Bee venom	$\alpha$ -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.<sup>223,224</sup> (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. aureus* 1.2, and cecropin.<sup>225</sup> AMPs also target bacterial cell walls, disrupting peptidoglycan synthesis in Gram-positive bacteria and lipopolysaccharide layers in Gram-negative bacteria.<sup>226</sup> 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).<sup>227–230</sup>

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*.<sup>231</sup> 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.<sup>232</sup> The human cathelicidin peptide LL-37 has demonstrated effectiveness against biofilms formed by *Staphylococcus aureus* in both methicillin-sensitive *Staphylococcus aureus* (MSSA) and methicillin resistant *Staphylococcus aureus* (MRSA) strains and can serve as an adjunct therapy for wound infections where biofilm development plays a significant role.<sup>233</sup> 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.<sup>234</sup>

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.<sup>235</sup> This approach aims to minimize adverse effects, increase compound selectivity, improve bacterial membrane permeability, and decrease the efflux of antibiotics, thereby inhibiting bacterial survival.<sup>236</sup> 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.<sup>237</sup> 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*.<sup>238</sup> 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.<sup>239</sup> 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.<sup>240</sup>

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.<sup>241</sup> 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.<sup>242,243</sup> 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<sup>-1</sup> 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.<sup>244</sup>

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.<sup>245</sup> 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.<sup>246,247</sup> 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.<sup>248</sup>

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.<sup>249</sup> 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.<sup>250</sup>

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.<sup>251</sup> 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 <i>in vitro</i> activity	Cytotoxicity, <i>in vivo</i> 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, nano-carrier 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.

## References

- W. H. Organization, Interagency Coordination Group on Antimicrobial Resistance, No time to wait: securing the future from drug-resistant infections, Report to the secretary-general of the united nations, 2019, vol. 1, p. 28.
- A. Catalano, D. Iacopetta, J. Ceramella, M. Pellegrino, F. Giuzio, M. Marra, C. Rosano, C. Saturnino, M. S. Sinicropi and S. Aquaro, Antibiotic-resistant ESKAPE pathogens and COVID-19: the pandemic beyond the pandemic, *Viruses*, 2023, **15**, 1843.
- J. Davies and D. Davies, Origins and evolution of antibiotic resistance, *Microbiol. Mol. Biol. Rev.*, 2010, **74**, 417–433.
- W. H. Organization, Thirteenth general programme of work, 2019–2023: promote health, keep the world safe, serve the vulnerable, World Health Organization, 2019.
- Y. Yang, X. Wu, C. He, J. Huang, S. Yin, M. Zhou, L. Ma, W. Zhao, L. Qiu and C. Cheng, Metal-organic framework/Ag-based hybrid nanoagents for rapid and synergistic bacterial eradication, *ACS Appl. Mater. Interfaces*, 2020, **12**, 13698–13708.
- R. Karimi Alavijeh and K. Akhbari, Biocompatible MIL-101 (Fe) as a smart carrier with high loading potential and sustained release of curcumin, *Inorg. Chem.*, 2020, **59**, 3570–3578.



- 7 T. Yao, X. Zeng, X. Tao and H. Xu, Recent progress of MOF-based antibacterial hydrogels, *Chem. Eng. J.*, 2024, **487**, 150641.
- 8 A. A. Edlo and K. Akhbari, Modulating the antibacterial activity of a CuO@ HKUST-1 nanocomposite by optimizing its synthesis procedure, *New J. Chem.*, 2023, **47**, 20770–20776.
- 9 M. Kalati and K. Akhbari, Optimizing the metal ion release and antibacterial activity of ZnO@ ZIF-8 by modulating its synthesis method, *New J. Chem.*, 2021, **45**, 22924–22931.
- 10 M. Kalati and K. Akhbari, Copper (II) nitrate and Copper (II) oxide loading on ZIF-8; synthesis, characterization and antibacterial activity, *J. Porous Mater.*, 2022, **29**, 1909–1917.
- 11 Z. Zhang, D. Xing, Q. Liang, D. Yong and X. Han, Size controllable synthesis and antimicrobial activity of poly-N,N'-[(4,5-dihydroxy-1,2-phenylene) bis (methylene)] bisacrylamide microspheres, *RSC Adv.*, 2014, **4**, 57891–57898.
- 12 R. K. Alavijeh, S. Beheshti, K. Akhbari and A. Morsali, Investigation of reasons for metal–organic framework's antibacterial activities, *Polyhedron*, 2018, **156**, 257–278.
- 13 Y. Yang, Y. Deng, J. Huang, X. Fan, C. Cheng, C. Nie, L. Ma, W. Zhao and C. Zhao, Size-transformable metal–organic framework–derived nanocarbons for localized chemophotothermal bacterial ablation and wound disinfection, *Adv. Funct. Mater.*, 2019, **29**, 1900143.
- 14 M. Parsaei and K. Akhbari, MOF-801 as a nanoporous water-based carrier system for in situ encapsulation and sustained release of 5-FU for effective cancer therapy, *Inorg. Chem.*, 2022, **61**, 5912–5925.
- 15 M. Parsaei and K. Akhbari, Smart multifunctional UiO-66 metal–organic framework nanoparticles with outstanding drug-loading/release potential for the targeted delivery of quercetin, *Inorg. Chem.*, 2022, **61**, 14528–14543.
- 16 M. Nakhaei, K. Akhbari and A. Davoodi, Biocompatible MOF-808 as an iodophor antimicrobial agent with controlled and sustained release of iodine, *CrystEngComm*, 2021, **23**, 8538–8545.
- 17 H. Wang, L. Song, R. Jiang, Y. Fan, J. Zhao and L. Ren, Super-repellent photodynamic bactericidal hybrid membrane, *J. Membr. Sci.*, 2020, **614**, 118482.
- 18 A. Terzopoulou, J. D. Nicholas, X.-Z. Chen, B. J. Nelson, S. Pane and J. Puigmarti-Luis, Metal–organic frameworks in motion, *Chem. Rev.*, 2020, **120**, 11175–11193.
- 19 D. Wang, D. Jana and Y. Zhao, Metal–organic framework derived nanozymes in biomedicine, *Acc. Chem. Res.*, 2020, **53**, 1389–1400.
- 20 A. Davoodi, K. Akhbari and M. Alirezvani, Prolonged release of silver and iodine from ZIF-7 carrier with great antibacterial activity, *CrystEngComm*, 2023, **25**, 3931–3942.
- 21 S. Soltani, K. Akhbari and A. Phuruangrat, Improved antibacterial activity by incorporation of silver sulfadiazine on Nanoporous Cu-BTC Metal-organic-framework, *Inorg. Chim. Acta*, 2022, **543**, 121182.
- 22 J. W. Lim, D. Ha, J. Lee, S. K. Lee and T. Kim, Review of micro/nanotechnologies for microbial biosensors, *Front. Bioeng. Biotechnol.*, 2015, **3**, 61.
- 23 T. Mocan, C. T. Matea, T. Pop, O. Mosteanu, A. D. Buzoianu, C. Puia, C. Iancu and L. Mocan, Development of nanoparticle-based optical sensors for pathogenic bacterial detection, *J. Nanobiotechnol.*, 2017, **15**, 1–14.
- 24 J. S. Möhler, W. Sim, M. A. Blaskovich, M. A. Cooper and Z. M. Ziora, Silver bullets: A new lustre on an old antimicrobial agent, *Biotechnol. Adv.*, 2018, **36**, 1391–1411.
- 25 C. Mutalik, G. Okoro, D. I. Krisnawati, A. Jazidie, E. Q. Rahmawati, D. Rahayu, W.-T. Hsu and T.-R. Kuo, Copper sulfide with morphology-dependent photodynamic and photothermal antibacterial activities, *J. Colloid Interface Sci.*, 2022, **607**, 1825–1835.
- 26 E. Sánchez-López, D. Gomes, G. Esteruelas, L. Bonilla, A. L. Lopez-Machado, R. Galindo, A. Cano, M. Espina, M. Etcheto and A. Camins, Metal-based nanoparticles as antimicrobial agents: an overview, *Nanomaterials*, 2020, **10**, 292.
- 27 T. Nguyen, R. Selvanayagam, K. Ho, R. Chen, S. Kutty, S. Rice, N. Kumar, N. Barraud, H. Duong and C. Boyer, Co-delivery of nitric oxide and antibiotic using polymeric nanoparticles, *Chem. Sci.*, 2016, **7**, 1016–1027.
- 28 L. Tian, W. Zhou, X. Wu, Z. Hu, L. Qiu, H. Zhang, X. Chen, S. Zhang and Z. Lu, CTLs: killers of intracellular bacteria, *Front. Cell. Infect. Microbiol.*, 2022, **12**, 967679.
- 29 P. A. Hernández-Venegas, R. E. Martínez-Martínez, E. A. Zaragoza-Contreras, R. A. Domínguez-Pérez, S. Y. Reyes-López, A. Donohue-Cornejo, J. C. Cuevas-González, N. Molina-Frechero and L. F. Espinosa-Cristóbal, Bactericidal activity of silver nanoparticles on oral biofilms related to patients with and without periodontal disease, *J. Funct. Biomater.*, 2023, **14**, 311.
- 30 M. F. Salas-Orozco, A. C. Lorenzo-Leal, I. de Alba Montero, N. P. Marín, M. A. C. Santana and H. Bach, Mechanism of escape from the antibacterial activity of metal-based nanoparticles in clinically relevant bacteria: A systematic review, *Nanomedicine*, 2024, **55**, 102715.
- 31 Y. Song, Q. Sun, J. Luo, Y. Kong, B. Pan, J. Zhao, Y. Wang and C. Yu, Cationic and anionic antimicrobial agents co-templated mesostructured silica nanocomposites with a spiky nanotopology and enhanced biofilm inhibition performance, *Nano-Micro Lett.*, 2022, **14**, 83.
- 32 B. Essghaier, H. Hannachi, R. Nouir, F. Mottola and L. Rocco, Green Synthesis and characterization of Novel Silver nanoparticles using *Achillea maritima* subsp. *maritima* Aqueous Extract: antioxidant and antidiabetic potential and effect on virulence mechanisms of bacterial and fungal pathogens, *Nanomaterials*, 2023, **13**, 1964.
- 33 J. H. M. Sin, L. J. Walsh, C. M. Figueredo and R. George, Evaluation of effectiveness of photosensitizers used in laser endodontics disinfection: A systematic review, *Transl. Biophotonics*, 2021, **3**, e202000007.
- 34 S. Bera, *Nanotechnology Based Strategies for Combating Antimicrobial Resistance*, Springer, 2024, pp. 351–391.
- 35 A. Kiang, S. Benson, C. Lochenie, S. Duncan, S. M. P. Mohanan, G. O. Williams, K. Dhaliwal, M. Vendrell and B. Mills, Novel dual antimicrobial-imaging photodynamic



- therapy agent labels and kills AMR gram-positive bacteria, *SPIE*, 2024, **PC12822**, PC1282207.
- 36 Q. Yu, C. Wang, X. Zhang, H. Chen, M. X. Wu and M. Lu, Photochemical Strategies toward Precision Targeting against Multidrug-Resistant Bacterial Infections, *ACS Nano*, 2024, **18**, 14085–14122.
- 37 M. Lu, S. Li, Y. Liu, B. Xu, S. Liu, J. Zhang, D. Zhou and H. Liu, Advances in phototherapy for infectious diseases, *Nano Today*, 2024, **57**, 102327.
- 38 T. W. Rees, P. Y. Ho and J. Hess, Recent advances in metal complexes for antimicrobial photodynamic therapy, *ChemBioChem*, 2023, **24**, e202200796.
- 39 X. Wang, L. He, Z. Huang, Q. Zhao, J. Fan, Y. Tian and A. Huang, Isolation, identification and characterization of a novel antimicrobial peptide from *Moringa oleifera* seeds based on affinity adsorption, *Food Chem.*, 2023, **398**, 133923.
- 40 M. Mahlapuu, J. Håkansson, L. Ringstad and C. Björn, Antimicrobial peptides: an emerging category of therapeutic agents, *Front. Cell. Infect. Microbiol.*, 2016, **6**, 235805.
- 41 J. Mwangi, X. Hao, R. Lai and Z.-Y. Zhang, Antimicrobial peptides: new hope in the war against multidrug resistance, *Zool. Res.*, 2019, **40**, 488.
- 42 S. Ji, F. An, T. Zhang, M. Lou, J. Guo, K. Liu, Y. Zhu, J. Wu and R. Wu, Antimicrobial peptides: An alternative to traditional antibiotics, *Eur. J. Med. Chem.*, 2024, **265**, 116072.
- 43 M. Erdem Büyükkiraz and Z. Kesmen, Antimicrobial peptides (AMPs): A promising class of antimicrobial compounds, *J. Appl. Microbiol.*, 2022, **132**, 1573–1596.
- 44 T. Takahashi and K. Yamasaki, Psoriasis and antimicrobial peptides, *Int. J. Mol. Sci.*, 2020, **21**, 6791.
- 45 K.-T. Cheng, C.-L. Wu, B.-S. Yip, H.-Y. Yu, H.-T. Cheng, Y.-H. Chih and J.-W. Cheng, High level expression and purification of the clinically active antimicrobial peptide P-113 in *Escherichia coli*, *Molecules*, 2018, **23**, 800.
- 46 H. Chen, C. Liu, D. Chen, K. Madrid, S. Peng, X. Dong, M. Zhang and Y. Gu, Bacteria-targeting conjugates based on antimicrobial peptide for bacteria diagnosis and therapy, *Mol. Pharmaceutics*, 2015, **12**, 2505–2516.
- 47 E. Finkina, D. Melnikova, I. Bogdanov and T. Ovchinnikova, Peptides of the innate immune system of plants. Part I. Structure, biological activity, and mechanisms of action, *Russ. J. Bioorg. Chem.*, 2018, **44**, 573–585.
- 48 Y. Qin, Z. D. Qin, J. Chen, C. G. Cai, L. Li, L. Y. Feng, Z. Wang, G. J. Duns, N. Y. He and Z. S. Chen, From antimicrobial to anticancer peptides: the transformation of peptides, *Recent Pat. Anti-Cancer Drug Discovery*, 2019, **14**, 70–84.
- 49 T.-J. Sun, H.-L. Bu, X. Yan, Z.-H. Sun, M.-S. Zha and G.-F. Dong, LABAMPsGCN: A framework for identifying lactic acid bacteria antimicrobial peptides based on graph convolutional neural network, *Front. Genet.*, 2022, **13**, 1062576.
- 50 U. L. Urmi, A. K. Vijay, R. Kuppusamy, S. Islam and M. D. Willcox, A review of the antiviral activity of cationic antimicrobial peptides, *Peptides*, 2023, **166**, 171024.
- 51 H. Li, J. Niu, X. Wang, M. Niu and C. Liao, The Contribution of Antimicrobial Peptides to Immune Cell Function: A Review of Recent Advances, *Pharmaceutics*, 2023, **15**, 2278.
- 52 G. Cottarel and J. Wierzbowski, Combination drugs, an emerging option for antibacterial therapy, *Trends Biotechnol.*, 2007, **25**, 547–555.
- 53 A. R. Coates, Y. Hu, J. Holt and P. Yeh, Antibiotic combination therapy against resistant bacterial infections: synergy, rejuvenation and resistance reduction, *Expert Rev. Anti-Infect. Ther.*, 2020, **18**, 5–15.
- 54 N. Wang, J. Luo, F. Deng, Y. Huang and H. Zhou, Antibiotic combination therapy: a strategy to overcome bacterial resistance to aminoglycoside antibiotics, *Front. Pharmacol.*, 2022, **13**, 839808.
- 55 Z. Si, K. Pethe and M. B. Chan-Park, Chemical basis of combination therapy to combat antibiotic resistance, *JACS Au*, 2023, **3**, 276–292.
- 56 R. J. Fair and Y. Tor, Antibiotics and bacterial resistance in the 21st century, *Perspect. Med. Chem.*, 2014, **6**, PMC.S14459.
- 57 Z. Alexander, Interference plasmids and their use in combating bacterial resistance, *Microbiol. Independ. Res. J.*, 2019, **6**, 37–42.
- 58 W. Y. Belay, M. Getachew, B. A. Tegegne, Z. H. Teffera, A. Dagne, T. K. Zeleke, R. B. Abebe, A. A. Gedif, A. Fenta and G. Yirdaw, Mechanism of antibacterial resistance, strategies and next-generation antimicrobials to contain antimicrobial resistance: A review, *Front. Pharmacol.*, 2024, **15**, 1444781.
- 59 M. Alavi and M. Rai, Recent advances in antibacterial applications of metal nanoparticles (MNPs) and metal nanocomposites (MNCs) against multidrug-resistant (MDR) bacteria, *Expert Rev. Anti-Infect. Ther.*, 2019, **17**, 419–428.
- 60 C. K. Lai, R. W. Ng, S. S. Leung, M. Hui and M. Ip, Overcoming the rising incidence and evolving mechanisms of antibiotic resistance by novel drug delivery approaches—an overview, *Adv. Drug Delivery Rev.*, 2022, **181**, 114078.
- 61 A. Gupta, S. Mumtaz, C.-H. Li, I. Hussain and V. M. Rotello, Combatting antibiotic-resistant bacteria using nanomaterials, *Chem. Soc. Rev.*, 2019, **48**, 415–427.
- 62 H. C. Neu, The crisis in antibiotic resistance, *Science*, 1992, **257**, 1064–1073.
- 63 U. Theuretzbacher, Global antibacterial resistance: The never-ending story, *J. Global Antimicrob. Resist.*, 2013, **1**, 63–69.
- 64 S. Jana and J. Deb, Molecular understanding of aminoglycoside action and resistance, *Appl. Microbiol. Biotechnol.*, 2006, **70**, 140–150.
- 65 A. Zapun, C. Contreras-Martel and T. Vernet, Penicillin-binding proteins and  $\beta$ -lactam resistance, *FEMS Microbiol. Rev.*, 2008, **32**, 361–385.
- 66 R. Azargun, M. H. S. Barhaghi, H. S. Kafil, M. A. Oskouee, V. Sadeghi, M. Y. Memar and R. Ghotaslou, Frequency of DNA gyrase and topoisomerase IV mutations and plasmid-



- mediated quinolone resistance genes among *Escherichia coli* and *Klebsiella pneumoniae* isolated from urinary tract infections in Azerbaijan, Iran, *J. Global Antimicrob. Resist.*, 2019, **17**, 39–43.
- 67 R. Alenazy, Drug efflux pump inhibitors: a promising approach to counter multidrug resistance in Gram-negative pathogens by targeting AcrB protein from AcrAB-TolC multidrug efflux pump from *Escherichia coli*, *Biology*, 2022, **11**, 1328.
- 68 S. R. Partridge, S. M. Kwong, N. Firth and S. O. Jensen, Mobile genetic elements associated with antimicrobial resistance, *Clin. Microbiol. Rev.*, 2018, **31**, e00088-17.
- 69 L. K. Vestby, T. Grønseth, R. Simm and L. L. Nesse, Bacterial biofilm and its role in the pathogenesis of disease, *Antibiotics*, 2020, **9**, 59.
- 70 M. Jamal, W. Ahmad, S. Andleeb, F. Jalil, M. Imran, M. A. Nawaz, T. Hussain, M. Ali, M. Rafiq and M. A. Kamil, Bacterial biofilm and associated infections, *J. Chin. Med. Assoc.*, 2018, **81**, 7–11.
- 71 B. Ribeiro da Cunha, L. P. Fonseca and C. R. Calado, Antibiotic discovery: where have we come from, where do we go?, *Antibiotics*, 2019, **8**, 45.
- 72 I. Kyriakidis, E. Vasileiou, Z. D. Pana and A. Tragiannidis, *Acinetobacter baumannii* antibiotic resistance mechanisms, *Pathogens*, 2021, **10**, 373.
- 73 J. Iredell, J. Brown and K. Tagg, Antibiotic resistance in Enterobacteriaceae: mechanisms and clinical implications, *BMJ*, 2016, **352**, h6420.
- 74 J. R. Hayes, L. L. English, P. J. Carter, T. Proescholdt, K. Y. Lee, D. D. Wagner and D. G. White, Prevalence and antimicrobial resistance of Enterococcus species isolated from retail meats, *Appl. Environ. Microbiol.*, 2003, **69**, 7153–7160.
- 75 D. Subedi, A. K. Vijay and M. Willcox, Overview of mechanisms of antibiotic resistance in *Pseudomonas aeruginosa*: an ocular perspective, *Clin. Exp. Optom.*, 2018, **101**, 162–171.
- 76 L. M. Weiner-Lastinger, S. Abner, J. R. Edwards, A. J. Kallen, M. Karlsson, S. S. Magill, D. Pollock, I. See, M. M. Soe and M. S. Walters, Antimicrobial-resistant pathogens associated with adult healthcare-associated infections: summary of data reported to the National Healthcare Safety Network, 2015–2017, *Infect. Control Hosp. Epidemiol.*, 2020, **41**, 1–18.
- 77 G. D. Wright, Q&A: Antibiotic resistance: where does it come from and what can we do about it?, *BMC Biol.*, 2010, **8**, 1–6.
- 78 M. Parsaei, K. Akhbari, E. Tylianakis, G. E. Froudakis and J. M. White, Efficient Gas Adsorption in MUT-11: Insights from Theoretical Calculations and GCMC Simulations, *Cryst. Growth Des.*, 2024, **24**, 10299–10313.
- 79 M. Parsaei, K. Akhbari and S. Kawata, Computational Simulation of CO<sub>2</sub>/CH<sub>4</sub> Separation on a Three-Dimensional Cd-Based Metal–Organic Framework, *Cryst. Growth Des.*, 2023, **23**, 5705–5718.
- 80 M. Parsaei and K. Akhbari, Synthesis and application of MOF-808 decorated with folic acid-conjugated chitosan as a strong nanocarrier for the targeted drug delivery of quercetin, *Inorg. Chem.*, 2022, **61**, 19354–19368.
- 81 D. M. Amidi and K. Akhbari, Iodine-loaded ZIF-7-coated cotton substrates show sustained iodine release as effective antibacterial textiles, *New J. Chem.*, 2024, **48**, 2016–2027.
- 82 M. Parsaei, K. Akhbari, E. Tylianakis and G. E. Froudakis, Computational Simulation of a Three-Dimensional Mg-based Metal–Organic Framework as Nanoporous Anti-cancer Drug Carrier, *Cryst. Growth Des.*, 2023, **23**, 8396–8406.
- 83 R. K. Alavijeh, K. Akhbari and J. White, Solid–liquid conversion and carbon dioxide storage in a calcium-based metal–organic framework with micro- and nanoporous channels, *Cryst. Growth Des.*, 2019, **19**, 7290–7297.
- 84 S. Salimi, K. Akhbari, S. M. F. Farnia and J. M. White, Multiple Construction of a Hierarchical Nanoporous Manganese (II)-Based Metal–Organic Framework with Active Sites for Regulating N<sub>2</sub> and CO<sub>2</sub> Trapping, *Cryst. Growth Des.*, 2022, **22**, 1654–1664.
- 85 M. Parsaei, K. Akhbari and J. White, Modulating carbon dioxide storage by facile synthesis of nanoporous pillared-layered metal–organic framework with different synthetic routes, *Inorg. Chem.*, 2022, **61**, 3893–3902.
- 86 R. Ghasemzadeh, K. Akhbari and S. Kawata, Ag@ MUT-16 nanocomposite as a Fenton-like and plasmonic photocatalyst for degradation of Quinoline Yellow under visible light, *Dalton Trans.*, 2024, **53**, 11094–11111.
- 87 R. Ghasemzadeh, K. Akhbari and S. Kawata, rGO/MUT-15 nanocomposite as a Fenton-like photocatalyst for the degradation of Acid Yellow 73 under visible light, *Dalton Trans.*, 2024, **53**, 18268–18282.
- 88 P. K. Kermanshahi, K. Akhbari, M. T. HesarAmiri, R. Karimi, E. Zivari and M. Madadi, The effect of layering order of ZIF-8@ PCL/PLA composites in electrospinning and electrospinning process on antibacterial wound healing, *Mater. Chem. Phys.*, 2024, **328**, 129878.
- 89 M. Parsaei and K. Akhbari, Magnetic UiO-66-NH<sub>2</sub> Core–Shell Nanohybrid as a Promising Carrier for Quercetin Targeted Delivery toward Human Breast Cancer Cells, *ACS Omega*, 2023, **8**, 41321–41338.
- 90 R. K. Alavijeh and K. Akhbari, Cancer therapy by nano MIL-n series of metal-organic frameworks, *Coord. Chem. Rev.*, 2024, **503**, 215643.
- 91 P. K. Kermanshahi and K. Akhbari, The antibacterial activity of three zeolitic-imidazolate frameworks and zinc oxide nanoparticles derived from them, *RSC Adv.*, 2024, **14**, 5601–5608.
- 92 A. Arshadi Edlo and K. Akhbari, Modulated antibacterial activity in ZnO@ MIL-53 (Fe) and CuO@ MIL-53 (Fe) nanocomposites prepared by simple thermal treatment process, *Appl. Organomet. Chem.*, 2024, **38**, e7326.
- 93 R. Li, T. Chen and X. Pan, Metal–organic-framework-based materials for antimicrobial applications, *ACS Nano*, 2021, **15**, 3808–3848.
- 94 D. Mohammadi Amidi, K. Akhbari and S. Soltani, Loading of ZIF-67 on silk with sustained release of iodine as



- biocompatible antibacterial fibers, *Appl. Organomet. Chem.*, 2023, **37**, e6913.
- 95 Z. Song, Y. Wu, Q. Cao, H. Wang, X. Wang and H. Han, pH-responsive, light-triggered on-demand antibiotic release from functional metal-organic framework for bacterial infection combination therapy, *Adv. Funct. Mater.*, 2018, **28**, 1800011.
- 96 G. Huang, Y. Li, Z. Qin, Q. Liang, C. Xu and B. Lin, Hybridization of carboxymethyl chitosan with MOFs to construct recyclable, long-acting and intelligent antibacterial agent carrier, *Carbohydr. Polym.*, 2020, **233**, 115848.
- 97 H. Ghasempour, K.-Y. Wang, J. A. Powell, F. ZareKarizi, X.-L. Lv, A. Morsali and H.-C. Zhou, Metal-organic frameworks based on multicarboxylate linkers, *Coord. Chem. Rev.*, 2021, **426**, 213542.
- 98 B. Sun, M. Bilal, S. Jia, Y. Jiang and J. Cui, Design and bio-applications of biological metal-organic frameworks, *Korean J. Chem. Eng.*, 2019, **36**, 1949–1964.
- 99 S. Soltani and K. Akhbari, Facile and single-step entrapment of chloramphenicol in ZIF-8 and evaluation of its performance in killing infectious bacteria with high loading content and controlled release of the drug, *CrystEngComm*, 2022, **24**, 1934–1941.
- 100 Y. Zhang, P. Sun, L. Zhang, Z. Wang, F. Wang, K. Dong, Z. Liu, J. Ren and X. Qu, Silver-infused porphyrinic metal-organic framework: Surface-adaptive, on-demand nanoplatform for synergistic bacteria killing and wound disinfection, *Adv. Funct. Mater.*, 2019, **29**, 1808594.
- 101 K. Wang, Y. Yin, C. Li, Z. Geng and Z. Wang, Facile synthesis of zinc (II)-carboxylate coordination polymer particles and their luminescent, biocompatible and antibacterial properties, *CrystEngComm*, 2011, **13**, 6231–6236.
- 102 A. Dastneshan, S. Rahiminezhad, M. N. Mezajin, H. N. Jevinani, I. Akbarzadeh, M. Abdihaji, R. Qahremani, M. Jahanbakhshi, Z. A. Lalami and H. Heydari, Cefazolin encapsulated UIO-66-NH<sub>2</sub> nanoparticles enhance the antibacterial activity and biofilm inhibition against drug-resistant *S. aureus*: In vitro and in vivo studies, *Chem. Eng. J.*, 2023, **455**, 140544.
- 103 H. Qiu, F. Pu, Z. Liu, Q. Deng, P. Sun, J. Ren and X. Qu, Depriving bacterial adhesion-related molecule to inhibit biofilm formation using CeO<sub>2</sub>-decorated metal-organic frameworks, *Small*, 2019, **15**, 1902522.
- 104 M. Nakhaei, K. Akhbari, M. Kalati and A. Phuruangrat, Antibacterial activity of three zinc-terephthalate MOFs and its relation to their structural features, *Inorg. Chim. Acta*, 2021, **522**, 120353.
- 105 M. Z. Isfahani, K. Akhbari, S. Soltani and A. Phuruangrat, Be safe against bacteria with nano CuBDC metal-organic framework loaded on silk fibers, *Mater. Chem. Phys.*, 2022, **290**, 126582.
- 106 S. M. Sheta, S. M. El-Sheikh and M. M. Abd-Elzaher, Simple synthesis of novel copper metal-organic framework nanoparticles: biosensing and biological applications, *Dalton Trans.*, 2018, **47**, 4847–4855.
- 107 P. Raju, T. Ramalingam, T. Nooruddin and S. Natarajan, In vitro assessment of antimicrobial, antibiofilm and larvicidal activities of bioactive nickel metal organic framework, *J. Drug Delivery Sci. Technol.*, 2020, **56**, 101560.
- 108 K. Zhang, X. Meng, Y. Cao, Z. Yang, H. Dong, Y. Zhang, H. Lu, Z. Shi and X. Zhang, Metal-organic framework nanoshuttle for synergistic photodynamic and low-temperature photothermal therapy, *Adv. Funct. Mater.*, 2018, **28**, 1804634.
- 109 D. Han, Y. Han, J. Li, X. Liu, K. W. K. Yeung, Y. Zheng, Z. Cui, X. Yang, Y. Liang and Z. Li, Enhanced photocatalytic activity and photothermal effects of Cu-doped metal-organic frameworks for rapid treatment of bacteria-infected wounds, *Appl. Catal., B*, 2020, **261**, 118248.
- 110 P. Li, J. Li, X. Feng, J. Li, Y. Hao, J. Zhang, H. Wang, A. Yin, J. Zhou and X. Ma, Metal-organic frameworks with photocatalytic bactericidal activity for integrated air cleaning, *Nat. Commun.*, 2019, **10**, 2177.
- 111 D. Ma, P. Li, X. Duan, J. Li, P. Shao, Z. Lang, L. Bao, Y. Zhang, Z. Lin and B. Wang, A hydrolytically stable Vanadium (IV) metal-organic framework with photocatalytic bacteriostatic activity for autonomous indoor humidity control, *Angew. Chem.*, 2020, **132**, 3933–3937.
- 112 Y.-F. Guo, W.-J. Fang, J.-R. Fu, Y. Wu, J. Zheng, G.-Q. Gao, C. Chen, R.-W. Yan, S.-G. Huang and C.-C. Wang, Facile synthesis of Ag@ ZIF-8 core-shell heterostructure nanowires for improved antibacterial activities, *Appl. Surf. Sci.*, 2018, **435**, 149–155.
- 113 M. Ishfaq, D. Lateef, Z. Ashraf, M. Sajjad, M. Owais, W. Shoukat, M. Mohsin, M. Ibrahim, F. Verpoort and A. H. Chughtai, Zirconium-based MOFs as pH-responsive drug delivery systems: encapsulation and release profiles of ciprofloxacin, *RSC Adv.*, 2025, **15**, 26647–26659.
- 114 N. Rahmanian, P. Moulavi, F. Ashrafi, A. Sharifi and S. Asadi, Surface-functionalized UIO-66-NH<sub>2</sub> for dual-drug delivery of vancomycin and amikacin against vancomycin-resistant *Staphylococcus aureus*, *BMC Microbiol.*, 2024, **24**, 462.
- 115 G. Ximing, G. Bin, W. Yuanlin and G. Shuanghong, Preparation of spherical metal-organic frameworks encapsulating Ag nanoparticles and study on its antibacterial activity, *Mater. Sci. Eng., C*, 2017, **80**, 698–707.
- 116 H. Abd El Salam, H. N. Nassar, A. S. Khidr and T. Zaki, Antimicrobial activities of green synthesized Ag nanoparticles@ Ni-MOF nanosheets, *J. Inorg. Organomet. Polym. Mater.*, 2018, **28**, 2791–2798.
- 117 S. Soltani and K. Akhbari, Cu-BTC metal-organic framework as a biocompatible nanoporous carrier for chlorhexidine antibacterial agent, *JBIC, J. Biol. Inorg. Chem.*, 2022, 1–7.
- 118 S. Soltani and K. Akhbari, Embedding an extraordinary amount of gemifloxacin antibiotic in ZIF-8 framework with one-step synthesis and measurement of its H<sub>2</sub>O<sub>2</sub>-sensitive release and potency against infectious bacteria, *New J. Chem.*, 2022, **46**, 19432–19441.
- 119 A. Arenas-Vivo, G. Amariei, S. Aguado, R. Rosal and P. Horcajada, An Ag-loaded photoactive nano-metal



- organic framework as a promising biofilm treatment, *Acta Biomater.*, 2019, **97**, 490–500.
- 120 H. Chen, J. Yang, L. Sun, H. Zhang, Y. Guo, J. Qu, W. Jiang, W. Chen, J. Ji and Y. W. Yang, Synergistic chemotherapy and photodynamic therapy of endophthalmitis mediated by zeolitic imidazolate framework-based drug delivery systems, *Small*, 2019, **15**, 1903880.
- 121 S. Lin, X. Liu, L. Tan, Z. Cui, X. Yang, K. W. Yeung, H. Pan and S. Wu, Porous iron-carboxylate metal-organic framework: a novel bioplatfrom with sustained antibacterial efficacy and nontoxicity, *ACS Appl. Mater. Interfaces*, 2017, **9**, 19248–19257.
- 122 A. Frei, A. D. Verderosa, A. G. Elliott, J. Zuegg and M. A. Blaskovich, Metals to combat antimicrobial resistance, *Nat. Rev. Chem.*, 2023, **7**, 202–224.
- 123 A. Girma, Alternative mechanisms of action of metallic nanoparticles to mitigate the global spread of antibiotic-resistant bacteria, *Cell Surf.*, 2023, **10**, 100112.
- 124 S. T. Khan, J. Musarrat and A. A. Al-Khedhairi, Countering drug resistance, infectious diseases, and sepsis using metal and metal oxides nanoparticles: current status, *Colloids Surf., B*, 2016, **146**, 70–83.
- 125 M. Rai, K. Kon, A. Gade, A. Ingle, D. Nagaonkar, P. Paralikar and S. da Silva, *Antibiotic resistance: can nanoparticles tackle the problem*, 2016, ch. 6, pp. 121–143.
- 126 F. Amaro, Á. Morón, S. Díaz, A. Martín-González and J. C. Gutiérrez, Metallic nanoparticles—friends or foes in the battle against antibiotic-resistant bacteria?, *Microorganisms*, 2021, **9**, 364.
- 127 A. Panáček, L. Kvítek, M. Smékalová, R. Večřová, M. Kolář, M. Röderová, F. Dyčka, M. Šebela, R. Prucek and O. Tomanec, Bacterial resistance to silver nanoparticles and how to overcome it, *Nat. Nanotechnol.*, 2018, **13**, 65–71.
- 128 M. Zare, K. Namratha, K. Byrappa, D. Surendra, S. Yallappa and B. Hungund, Surfactant assisted solvothermal synthesis of ZnO nanoparticles and study of their antimicrobial and antioxidant properties, *J. Mater. Sci. Technol.*, 2018, **34**, 1035–1043.
- 129 P. Korshed, L. Li, Z. Liu, A. Mironov and T. Wang, Size-dependent antibacterial activity for laser-generated silver nanoparticles, *J. Interdiscip. Nanomed.*, 2019, **4**, 24–33.
- 130 L. Cui, P. Chen, S. Chen, Z. Yuan, C. Yu, B. Ren and K. Zhang, In situ study of the antibacterial activity and mechanism of action of silver nanoparticles by surface-enhanced Raman spectroscopy, *Anal. Chem.*, 2013, **85**, 5436–5443.
- 131 A. Abbaszadegan, Y. Ghahramani, A. Gholami, B. Hemmateenejad, S. Dorostkar, M. Nabavizadeh and H. Sharghi, The effect of charge at the surface of silver nanoparticles on antimicrobial activity against Gram-positive and Gram-negative bacteria: a preliminary study, *J. Nanomater.*, 2015, **2015**, 720654.
- 132 Z. Li, J. Ma, J. Ruan and X. Zhuang, Using positively charged magnetic nanoparticles to capture bacteria at ultralow concentration, *Nanoscale Res. Lett.*, 2019, **14**, 1–8.
- 133 N. Mammari, E. Lamouroux, A. Boudier and R. E. Duval, Current knowledge on the oxidative-stress-mediated antimicrobial properties of metal-based nanoparticles, *Microorganisms*, 2022, **10**, 437.
- 134 A. El Badawy, *Assessment of the fate and transport of silver nanoparticles in porous media*, University of Cincinnati, 2011.
- 135 P. T. Huynh, G. D. Nguyen, K. T. L. Tran, T. M. Ho, B. T. Duong, V. Q. Lam and T. V. K. Ngo, One-Pot, Surfactant-Free Synthesis of Gold Nanostars and Evaluation of Their Antibacterial Effects against *Propionibacterium acnes*, *J. Nanomater.*, 2021, **2021**, 6650661.
- 136 S. Ranjan and C. Ramalingam, Titanium dioxide nanoparticles induce bacterial membrane rupture by reactive oxygen species generation, *Environ. Chem. Lett.*, 2016, **14**, 487–494.
- 137 H. Xu, F. Qu, H. Xu, W. Lai, Y. Andrew Wang, Z. P. Aguilar and H. Wei, Role of reactive oxygen species in the antibacterial mechanism of silver nanoparticles on *Escherichia coli* O157: H7, *Biometals*, 2012, **25**, 45–53.
- 138 L. Wang, H. He, Y. Yu, L. Sun, S. Liu, C. Zhang and L. He, Morphology-dependent bactericidal activities of Ag/CeO<sub>2</sub> catalysts against *Escherichia coli*, *J. Inorg. Biochem.*, 2014, **135**, 45–53.
- 139 A. A. Mujeeb, N. A. Khan, F. Jamal, K. F. Badre Alam, H. Saeed, S. Kazmi, A. W. F. Alshameri, M. Kashif, I. Ghazi and M. Owais, Olax scandens mediated biogenic synthesis of Ag-Cu nanocomposites: Potential against inhibition of drug-resistant microbes, *Front. Chem.*, 2020, **8**, 103.
- 140 S. Mohapatra, T. A. Nguyen and P. Nguyen-Tri, *Noble metal-metal oxide hybrid nanoparticles: Fundamentals and applications*, Elsevier, 2018.
- 141 N. Watanabe, K. Kryukov, S. Nakagawa, J. S. Takeuchi, M. Takeshita, Y. Kirimura, S. Mitsuhashi, T. Ishihara, H. Aoki and S. Inokuchi, Detection of pathogenic bacteria in the blood from sepsis patients using 16S rRNA gene amplicon sequencing analysis, *PLoS One*, 2018, **13**, e0202049.
- 142 J. W. Moreau, P. K. Weber, M. C. Martin, B. Gilbert, I. D. Hutcheon and J. F. Banfield, Extracellular proteins limit the dispersal of biogenic nanoparticles, *Science*, 2007, **316**, 1600–1603.
- 143 M. Saliari, R. Jalal and E. K. Goharshadi, Effects of pH and temperature on antibacterial activity of zinc oxide nanofluid against *Escherichia coli* O157: H7 and *Staphylococcus aureus*, *Jundishapur J. Microbiol.*, 2015, **8**, e17115.
- 144 T. S. Peretyazhko, Q. Zhang and V. L. Colvin, Size-controlled dissolution of silver nanoparticles at neutral and acidic pH conditions: kinetics and size changes, *Environ. Sci. Technol.*, 2014, **48**, 11954–11961.
- 145 D. Franco, G. Calabrese, S. Petralia, G. Neri, C. Corsaro, L. Forte, S. Squarzone, S. Guglielmino, F. Traina and E. Fazio, Antimicrobial effect and cytotoxic evaluation of Mg-doped hydroxyapatite functionalized with Au-nano rods, *Molecules*, 2021, **26**, 1099.
- 146 X. Li, K. Z. Ahmad, J. He, H. Li, X. Wang, Z. Feng, X. Wang, G. Shen and X. Ding, Silver nanoflowers coupled with low



- dose antibiotics enable the highly effective eradication of drug-resistant bacteria, *J. Mater. Chem. B*, 2021, **9**, 9839–9851.
- 147 X. Hong, J. Wen, X. Xiong and Y. Hu, Shape effect on the antibacterial activity of silver nanoparticles synthesized via a microwave-assisted method, *Environ. Sci. Pollut. Res.*, 2016, **23**, 4489–4497.
- 148 E. Altun, M. O. Aydogdu, E. Chung, G. Ren, S. Homer-Vanniasinkam and M. Edirisinghe, Metal-based nanoparticles for combating antibiotic resistance, *Appl. Phys. Rev.*, 2021, **8**, e041303.
- 149 P. Makvandi, M. Ashrafzadeh, M. Ghomi, M. Najafi, H. H. S. Hossein, A. Zarrabi, V. Mattoli and R. S. Varma, Injectable hyaluronic acid-based antibacterial hydrogel adorned with biogenically synthesized AgNPs-decorated multi-walled carbon nanotubes, *Prog. Biomater.*, 2021, **10**, 77–89.
- 150 T. Russo, A. Gloria, R. De Santis, U. D'amora, G. Balato, A. Vollaro, O. Oliviero, G. Improta, M. Triassi and L. Ambrosio, Preliminary focus on the mechanical and antibacterial activity of a PMMA-based bone cement loaded with gold nanoparticles, *Bioact. Mater.*, 2017, **2**, 156–161.
- 151 A. Barui, R. Kotcherlakota and C. Patra, Inorganic Frameworks as Smart Nanomedicines, *William Publ*, 2018, **1**, 239–278.
- 152 S. Hussain, J. Joo, J. Kang, B. Kim, G. B. Braun, Z.-G. She, D. Kim, A. P. Mann, T. Mölder and T. Teesalu, Antibiotic-loaded nanoparticles targeted to the site of infection enhance antibacterial efficacy, *Nat. Biomed. Eng.*, 2018, **2**, 95–103.
- 153 U. A. Hasanova, M. A. Ramazanov, A. M. Maharramov, Q. M. Eyvazova, Z. A. Agamaliyev, Y. V. Parfyonova, S. F. Hajiyeva, F. V. Hajiyeva and S. B. Veliyeva, Nano-Coupling of Cephalosporin Antibiotics with Fe<sub>3</sub>O<sub>4</sub> Nanoparticles: Trojan Horse Approach in Antimicrobial Chemotherapy of Infections Caused by *Klebsiella* spp, *J. Biomater. Nanobiotechnol.*, 2015, **6**, 225–235.
- 154 K. Ali, B. Ahmed, M. S. Khan and J. Musarrat, Differential surface contact killing of pristine and low EPS *Pseudomonas aeruginosa* with Aloe vera capped hematite ( $\alpha$ -Fe<sub>2</sub>O<sub>3</sub>) nanoparticles, *J. Photochem. Photobiol., B*, 2018, **188**, 146–158.
- 155 S. J. Amina and B. Guo, A review on the synthesis and functionalization of gold nanoparticles as a drug delivery vehicle, *Int. J. Nanomed.*, 2020, 9823–9857.
- 156 T. A. Hagbani, H. Yadav, A. Moin, A. S. A. Lila, K. Mehmood, F. Alshammari, S. Khan, E.-S. Khafagy, T. Hussain and S. M. D. Rizvi, Enhancement of vancomycin potential against pathogenic bacterial strains via gold nano-formulations: a nano-antibiotic approach, *Materials*, 2022, **15**, 1108.
- 157 Q. Chen, J. Li, Y. Wu, F. Shen and M. Yao, Biological responses of Gram-positive and Gram-negative bacteria to nZVI (Fe<sup>0</sup>), Fe<sup>2+</sup> and Fe<sup>3+</sup>, *RSC Adv.*, 2013, **3**, 13835–13842.
- 158 A. Jain, R. Bhargava and P. Poddar, Probing interaction of Gram-positive and Gram-negative bacterial cells with ZnO nanorods, *Mater. Sci. Eng., C*, 2013, **33**, 1247–1253.
- 159 F. Kang, P. J. Alvarez and D. Zhu, Microbial extracellular polymeric substances reduce Ag<sup>+</sup> to silver nanoparticles and antagonize bactericidal activity, *Environ. Sci. Technol.*, 2014, **48**, 316–322.
- 160 C. Larimer, M. S. Islam, A. Ojha and I. Nettleship, Mutation of environmental mycobacteria to resist silver nanoparticles also confers resistance to a common antibiotic, *Biometals*, 2014, **27**, 695–702.
- 161 M. Gambino, V. Marzano, F. Villa, A. Vitali, C. Vannini, P. Landini and F. Cappitelli, Effects of sublethal doses of silver nanoparticles on *Bacillus subtilis* planktonic and sessile cells, *J. Appl. Microbiol.*, 2015, **118**, 1103–1115.
- 162 Q. Wang, F. Kang, Y. Gao, X. Mao and X. Hu, Sequestration of nanoparticles by an EPS matrix reduces the particle-specific bactericidal activity, *Sci. Rep.*, 2016, **6**, 21379.
- 163 J. Guo, S.-H. Gao, J. Lu, P. L. Bond, W. Verstraete and Z. Yuan, Copper oxide nanoparticles induce lysogenic bacteriophage and metal-resistance genes in *Pseudomonas aeruginosa* PAO1, *ACS Appl. Mater. Interfaces*, 2017, **9**, 22298–22307.
- 164 R. Zhang, F. Carlsson, M. Edman, M. Hummelgård, B. G. Jonsson, D. Bylund and H. Olin, *Escherichia coli* bacteria develop adaptive resistance to antibacterial ZnO nanoparticles, *Adv. Biosyst.*, 2018, **2**, 1800019.
- 165 Y. Xu, C. Wang, J. Hou, P. Wang, G. You and L. Miao, Effects of cerium oxide nanoparticles on bacterial growth and behaviors: induction of biofilm formation and stress response, *Environ. Sci. Pollut. Res.*, 2019, **26**, 9293–9304.
- 166 A. Kędziora, M. Wernecki, K. Korzekwa, M. Speruda, Y. Gerasymchuk, A. Łukowiak and G. Bugla-Płoskońska, Consequences of long-term bacteria's exposure to silver nanoformulations with different physicochemical properties, *Int. J. Nanomed.*, 2020, 199–213.
- 167 A. Kędziora, M. Speruda, M. Wernecki, B. Dudek, K. Kapczynska, E. Krzyżewska, J. Rybka and G. Bugla-Płoskońska, How bacteria change after exposure to silver nanoformulations: analysis of the genome and outer membrane proteome, *Pathogens*, 2021, **10**, 817.
- 168 M. F. Salas-Orozco, N. Niño-Martínez, G. A. Martínez-Castañón, F. T. Méndez, G. M. M. Morán, A. E. Bendaña-Piñeiro, F. Ruiz and H. Bach, Proteomic analysis of an *Enterococcus faecalis* mutant generated against the exposure to silver nanoparticles, *J. Appl. Microbiol.*, 2022, **132**, 244–255.
- 169 D. Muehler, C. M. Rupp, S. Keceli, C. Brochhausen, H. Siegmund, T. Maisch, K.-A. Hiller, W. Buchalla and F. Cieplik, Insights into mechanisms of antimicrobial photodynamic action toward biofilms using phenalen-1-one derivatives as photosensitizers, *Front. Microbiol.*, 2020, **11**, 589364.
- 170 L. Sharab, R. E. Baier, S. Ciancio and T. Mang, Influence of photodynamic therapy on bacterial attachment to titanium surface, *J. Oral Implantol.*, 2021, **47**, 427–435.



- 171 N. Iluz, Y. Maor, N. Keller and Z. Malik, The synergistic effect of PDT and oxacillin on clinical isolates of *Staphylococcus aureus*, *Lasers Surg. Med.*, 2018, **50**, 535–551.
- 172 F. Vatansever, W. C. de Melo, P. Avci, D. Vecchio, M. Sadasivam, A. Gupta, R. Chandran, M. Karimi, N. A. Parizotto and R. Yin, Antimicrobial strategies centered around reactive oxygen species–bactericidal antibiotics, photodynamic therapy, and beyond, *FEMS Microbiol. Rev.*, 2013, **37**, 955–989.
- 173 F. Heinemann, J. Karges and G. Gasser, Critical overview of the use of Ru (II) polypyridyl complexes as photosensitizers in one-photon and two-photon photodynamic therapy, *Acc. Chem. Res.*, 2017, **50**, 2727–2736.
- 174 A. F. Silva, A. Borges, E. Giaouris, J. M. Graton Mikcha and M. Simões, Photodynamic inactivation as an emergent strategy against foodborne pathogenic bacteria in planktonic and sessile states, *Crit. Rev. Microbiol.*, 2018, **44**, 667–684.
- 175 N. R. Luke-Marshall, L. A. Hansen, G. Shafirstein and A. A. Campagnari, Antimicrobial photodynamic therapy with chlorin e6 is bactericidal against biofilms of the primary human otopathogens, *mSphere*, 2020, **5**, e00492-20.
- 176 Y. A. Anane, T. Apalata, S. Vasaikar, G. E. Okuthe and S. P. Songca, In vitro antimicrobial photodynamic inactivation of multidrug-resistant *Acinetobacter baumannii* biofilm using Protoporphyrin IX and Methylene blue, *Photodyn. Ther.*, 2020, **30**, 101752.
- 177 S. P. Songca and Y. Adjei, Applications of antimicrobial photodynamic therapy against bacterial biofilms, *Int. J. Mol. Sci.*, 2022, **23**, 3209.
- 178 R. Youf, M. Müller, A. Balasini, F. Thétiot, M. Müller, A. Hascoët, U. Jonas, H. Schönherr, G. Lemercier and T. Montier, Antimicrobial photodynamic therapy: Latest developments with a focus on combinatory strategies, *Pharmaceutics*, 2021, **13**, 1995.
- 179 A. Fraix and S. Sortino, Combination of PDT photosensitizers with NO photodonors, *Photochem. Photobiol. Sci.*, 2018, **17**, 1709–1727.
- 180 V. Pérez-Laguna, I. García-Luque, S. Ballesta, A. Rezusta and Y. Gilaberte, Photodynamic therapy combined with antibiotics or antifungals against microorganisms that cause skin and soft tissue infections: A planktonic and biofilm approach to overcome resistances, *Pharmaceutics*, 2021, **14**, 603.
- 181 L. Beytollahi, M. Pourhajibagher, N. Chiniforush, R. Ghorbanzadeh, R. Raoofian, B. Pourakbari and A. Bahador, The efficacy of photodynamic and photothermal therapy on biofilm formation of *Streptococcus mutans*: An in vitro study, *Photodiagn. Photodyn. Ther.*, 2017, **17**, 56–60.
- 182 Q. Gao, D. Huang, Y. Deng, W. Yu, Q. Jin, J. Ji and G. Fu, Chlorin e6 (Ce6)-loaded supramolecular polypeptide micelles with enhanced photodynamic therapy effect against *Pseudomonas aeruginosa*, *Chem. Eng. J.*, 2021, **417**, 129334.
- 183 X. Cai, J. Tian, J. Zhu, J. Chen, L. Li, C. Yang, J. Chen and D. Chen, Photodynamic and photothermal co-driven CO-enhanced multi-mode synergistic antibacterial nanoplateform to effectively fight against biofilm infections, *Chem. Eng. J.*, 2021, **426**, 131919.
- 184 L. Mei, Z. Xu, Z. Miao, M. Yun, Y. Luan, D. Yang and L. Xia, Polymyxin B-functionalized phthalocyanine for chemophotodynamic antibacterial therapy in enhanced wound healing, *New J. Chem.*, 2021, **45**, 6450–6457.
- 185 A. Woźniak, B. Kruszewska, M. K. Pierański, M. Rychłowski and M. Grinholc, Antimicrobial photodynamic inactivation affects the antibiotic susceptibility of *Enterococcus* spp. clinical isolates in biofilm and planktonic cultures, *Biomolecules*, 2021, **11**, 693.
- 186 M.-H. Shih and F.-C. Huang, Effects of photodynamic therapy on rapidly growing nontuberculous mycobacteria keratitis, *Invest. Ophthalmol. Visual Sci.*, 2011, **52**, 223–229.
- 187 J. Almeida, J. P. Tomé, M. G. Neves, A. C. Tomé, J. A. Cavaleiro, Â. Cunha, L. Costa, M. A. Faustino and A. Almeida, Photodynamic inactivation of multidrug-resistant bacteria in hospital wastewaters: influence of residual antibiotics, *Photochem. Photobiol. Sci.*, 2014, **13**, 626–633.
- 188 X. Hou, L. Yang, J. Liu, Y. Zhang, L. Chu, C. Ren, F. Huang and J. Liu, Silver-decorated, light-activatable polymeric antimicrobials for combined chemo-photodynamic therapy of drug-resistant bacterial infection, *Biomater. Sci.*, 2020, **8**, 6350–6361.
- 189 J. Dolansky, P. Henke, P. Kubat, A. Fraix, S. Sortino and J. Mosinger, Polystyrene nanofiber materials for visible-light-driven dual antibacterial action via simultaneous photogeneration of NO and O<sub>2</sub> (1Δg), *ACS Appl. Mater. Interfaces*, 2015, **7**, 22980–22989.
- 190 M. Pourhajibagher, G. Plotino, N. Chiniforush and A. Bahador, Dual wavelength irradiation antimicrobial photodynamic therapy using indocyanine green and metformin doped with nano-curcumin as an efficient adjunctive endodontic treatment modality, *Photodiagn. Photodyn. Ther.*, 2020, **29**, 101628.
- 191 A. A. Al-Kheraif, A. A. Khan, N. A. AlMufareh, D. D. Divakar, H. Dewan, S. Al-Jadani, J. Alrahimi, S. Hassoubah and K. S. Allemailem, Photodynamic antimicrobial chemotherapy through photosensitizers loaded poly-L-glycolic acid on *Candida albicans* in denture lining material: Release, biological and hardness study, *Photodiagn. Photodyn. Ther.*, 2021, **33**, 102134.
- 192 Q. Yu, X. Huang, T. Zhang, W. Wang, D. Yang, J. Shao and X. Dong, Near-infrared Aza-BODIPY dyes through molecular surgery for enhanced photothermal and photodynamic antibacterial therapy, *Chem. Res. Chin. Univ.*, 2021, **37**, 951–959.
- 193 D. Bagchi, V. S. Rathnam, P. Lemmens, I. Banerjee and S. K. Pal, NIR-light-active ZnO-based nanohybrids for bacterial biofilm treatment, *ACS Omega*, 2018, **3**, 10877–10885.
- 194 W. Teng, Z. Zhang, Y. Wang, Y. Ye, E. Yinwang, A. Liu, X. Zhou, J. Xu, C. Zhou and H. Sun, Iodine Immobilized



- Metal–Organic Framework for NIR-Triggered Antibacterial Therapy on Orthopedic Implants, *Small*, 2021, **17**, 2102315.
- 195 H. Lv, Y. Zhang, P. Chen, J. Xue, X. Jia and J. Chen, Enhanced synergistic antibacterial activity through a smart platform based on UiO-66 combined with photodynamic therapy and chemotherapy, *Langmuir*, 2020, **36**, 4025–4032.
- 196 Y.-Y. Xie, Y.-W. Zhang, X.-Z. Liu, X.-F. Ma, X.-T. Qin, S.-R. Jia and C. Zhong, Aggregation-induced emission-active amino acid/berberine hydrogels with enhanced photodynamic antibacterial and anti-biofilm activity, *Chem. Eng. J.*, 2021, **413**, 127542.
- 197 J. Sun, Y. Fan, W. Ye, L. Tian, S. Niu, W. Ming, J. Zhao and L. Ren, Near-infrared light triggered photodynamic and nitric oxide synergistic antibacterial nanocomposite membrane, *Chem. Eng. J.*, 2021, **417**, 128049.
- 198 Q. Yao, Z. Ye, L. Sun, Y. Jin, Q. Xu, M. Yang, Y. Wang, Y. Zhou, J. Ji and H. Chen, Bacterial infection microenvironment-responsive enzymatically degradable multilayer films for multifunctional antibacterial properties, *J. Mater. Chem. B*, 2017, **5**, 8532–8541.
- 199 Y. Wang, Y. Jin, W. Chen, J. Wang, H. Chen, L. Sun, X. Li, J. Ji, Q. Yu and L. Shen, Construction of nanomaterials with targeting phototherapy properties to inhibit resistant bacteria and biofilm infections, *Chem. Eng. J.*, 2019, **358**, 74–90.
- 200 M. A. Castriciano, R. Zagami, M. P. Casaletto, B. Martel, M. Trapani, A. Romeo, V. Villari, M. T. Sciortino, L. Grasso and S. Guglielmino, Poly (carboxylic acid)-cyclodextrin/anionic porphyrin finished fabrics as photosensitizer releasers for antimicrobial photodynamic therapy, *Biomacromolecules*, 2017, **18**, 1134–1144.
- 201 F. Nederberg, Y. Zhang, J. P. Tan, K. Xu, H. Wang, C. Yang, S. Gao, X. D. Guo, K. Fukushima and L. Li, Biodegradable nanostructures with selective lysis of microbial membranes, *Nat. Chem.*, 2011, **3**, 409–414.
- 202 Y. Zhao, M. Hu, Y. Zhang, J. Liu, C. Liu, S. K. Choi, Z. Zhang and L. Song, Multifunctional therapeutic strategy of Ag-synergized dual-modality upconversion nanoparticles to achieve the rapid and sustained cidal activity of methicillin-resistant *Staphylococcus aureus*, *Chem. Eng. J.*, 2020, **385**, 123980.
- 203 J. Dolanský, P. Henke, Z. Malá, L. Žárská, P. Kubát and J. Mosinger, Antibacterial nitric oxide-and singlet oxygen-releasing polystyrene nanoparticles responsive to light and temperature triggers, *Nanoscale*, 2018, **10**, 2639–2648.
- 204 E. J. Son, J. H. Kim, K. Kim and C. B. Park, Quinone and its derivatives for energy harvesting and storage materials, *J. Mater. Chem. A*, 2016, **4**, 11179–11202.
- 205 J. K. Boparai and P. K. Sharma, Mini review on antimicrobial peptides, sources, mechanism and recent applications, *Protein Pept. Lett.*, 2020, **27**, 4–16.
- 206 A. de Breij, M. Riool, R. A. Cordfunke, N. Malanovic, L. de Boer, R. I. Koning, E. Ravensbergen, M. Franken, T. van der Heijde and B. K. Boekema, The antimicrobial peptide SAAP-148 combats drug-resistant bacteria and biofilms, *Sci. Transl. Med.*, 2018, **10**, eaan4044.
- 207 N. G. Oliveira Júnior, C. M. Souza, D. F. Buccini, M. H. Cardoso and O. L. Franco, Antimicrobial peptides: structure, functions and translational applications, *Nat. Rev. Microbiol.*, 2025, 1–14.
- 208 G. Buda De Cesare, S. A. Cristy, D. A. Garsin and M. C. Lorenz, Antimicrobial peptides: a new frontier in antifungal therapy, *mBio*, 2020, **11**, e02123-20.
- 209 Q.-Y. Zhang, Z.-B. Yan, Y.-M. Meng, X.-Y. Hong, G. Shao, J.-J. Ma, X.-R. Cheng, J. Liu, J. Kang and C.-Y. Fu, Antimicrobial peptides: mechanism of action, activity and clinical potential, *Mil. Med. Res.*, 2021, **8**, 1–25.
- 210 H.-Q. Zhang, C. Sun, N. Xu and W. Liu, The current landscape of the antimicrobial peptide melittin and its therapeutic potential, *Front. Immunol.*, 2024, **15**, 1326033.
- 211 I. Nagaoka, H. Tamura and J. Reich, Therapeutic potential of cathelicidin peptide LL-37, an antimicrobial agent, in a murine sepsis model, *Int. J. Mol. Sci.*, 2020, **21**, 5973.
- 212 S. Zhang, M. Ma, Z. Shao, J. Zhang, L. Fu, X. Li, W. Fang and L. Gao, Structure and formation mechanism of antimicrobial peptides temporin b-and l-induced tubular membrane protrusion, *Int. J. Mol. Sci.*, 2021, **22**, 11015.
- 213 C. A. Roque-Borda, L. M. D. G. Primo, K. P. Medina-Alarcón, I. C. Campos, C. D. F. Nascimento, M. M. Saraiva, A. Berchieri Junior, A. M. Fusco-Almeida, M. J. S. Mendes-Giannini and J. Perdigão, Antimicrobial peptides: a promising alternative to conventional antimicrobials for combating polymicrobial biofilms, *Adv. Sci.*, 2025, **12**, 2410893.
- 214 U. Silphaduang and E. J. Noga, Peptide antibiotics in mast cells of fish, *Nature*, 2001, **414**, 268–269.
- 215 K. A. Henzler Wildman, D.-K. Lee and A. Ramamoorthy, Mechanism of lipid bilayer disruption by the human antimicrobial peptide, LL-37, *Biochemistry*, 2003, **42**, 6545–6558.
- 216 K. Scherer, I. Wiedemann, C. Ciobanasi, H.-G. Sahl and U. Kubitscheck, Aggregates of nisin with various bactoprenol-containing cell wall precursors differ in size and membrane permeation capacity, *Biochim. Biophys. Acta, Biomembr.*, 2013, **1828**, 2628–2636.
- 217 K. R. Parducho, B. Beadell, T. K. Ybarra, M. Bush, E. Escalera, A. T. Trejos, A. Chieng, M. Mendez, C. Anderson and H. Park, The antimicrobial peptide human beta-defensin 2 inhibits biofilm production of *Pseudomonas aeruginosa* without compromising metabolic activity, *Front. Immunol.*, 2020, **11**, 805.
- 218 Y. Takada, H. Itoh, A. Paudel, S. Panthee, H. Hamamoto, K. Sekimizu and M. Inoue, Discovery of gramicidin A analogues with altered activities by multidimensional screening of a one-bead-one-compound library, *Nat. Commun.*, 2020, **11**, 4935.
- 219 X. Yu, S. Jia, S. Yu, Y. Chen, C. Zhang, H. Chen and Y. Dai, Recent advances in melittin-based nanoparticles for anti-tumor treatment: from mechanisms to targeted delivery strategies, *J. Nanobiotechnol.*, 2023, **21**, 454.
- 220 E. V. Ledger, A. Sabnis and A. M. Edwards, Polymyxin and lipopeptide antibiotics: membrane-targeting drugs of last resort, *Microbiology*, 2022, **168**, 001136.



- 221 O. V. Kondrashov, M. V. Volovik, Z. G. Denieva, P. K. Gifer, T. R. Galimzyanov, P. I. Kuzmin, O. V. Batishchev and S. A. Akimov, Dialectics of antimicrobial peptides II: Theoretical models of pore formation and membrane protection, *Langmuir*, 2025, **41**, 19003–19022.
- 222 D. W. Juhl, E. Glattard, C. Aisenbrey and B. Bechinger, Antimicrobial peptides: mechanism of action and lipid-mediated synergistic interactions within membranes, *Faraday Discuss.*, 2021, **232**, 419–434.
- 223 G. Satchanska, S. Davidova and A. Gergova, Diversity and mechanisms of action of plant, animal, and human antimicrobial peptides, *Antibiotics*, 2024, **13**, 202.
- 224 D. Balleza, The Role of Flexibility in the Bioactivity of Short  $\alpha$ -Helical Antimicrobial Peptides, *Antibiotics*, 2025, **14**, 422.
- 225 H. Haddad, R. Mejri and A. Zaïri, Evaluation of the Antibacterial Activity of New Dermaseptin Derivatives against *Acinetobacter baumannii*, *Pharmaceuticals*, 2024, **17**, 171.
- 226 A. J. Clarke, Another brick in the wall, *Nat. Chem. Biol.*, 2017, **13**, 695–696.
- 227 K. N. Allen and B. Imperiali, Structural and mechanistic themes in glycoconjugate biosynthesis at membrane interfaces, *Curr. Opin. Struct. Biol.*, 2019, **59**, 81–90.
- 228 M. Graf and D. N. Wilson, Intracellular antimicrobial peptides targeting the protein synthesis machinery, *Antimicrobial Peptides: Basics for Clinical Application*, 2019, pp. 73–89.
- 229 Y. Zhang, S. Liu, S. Li, Y. Cheng, L. Nie, G. Wang, C. Lv, W. Wei, C. Cheng and F. Hou, Novel short antimicrobial peptide isolated from *Xenopus laevis* skin, *J. Pept. Sci.*, 2017, **23**, 403–409.
- 230 H. Lee, J. S. Hwang and D. G. Lee, Periplanetasin-4, a novel antimicrobial peptide from the cockroach, inhibits communications between mitochondria and vacuoles, *Biochem. J.*, 2019, **476**, 1267–1284.
- 231 Y. Luo and Y. Song, Mechanism of antimicrobial peptides: antimicrobial, anti-inflammatory and antibiofilm activities, *Int. J. Mol. Sci.*, 2021, **22**, 11401.
- 232 M. Martinez, S. Gonçalves, M. R. Felício, P. Maturana, N. C. Santos, L. Semorile, A. Hollmann and P. C. Maffia, Synergistic and antibiofilm activity of the antimicrobial peptide P5 against carbapenem-resistant *Pseudomonas aeruginosa*, *Biochim. Biophys. Acta, Biomembr.*, 2019, **1861**, 1329–1337.
- 233 M. Demirci, A. Yigin and C. Demir, Efficacy of antimicrobial peptide LL-37 against biofilm forming *Staphylococcus aureus* strains obtained from chronic wound infections, *Microb. Pathog.*, 2022, **162**, 105368.
- 234 B. Li, W. Kang, H. Liu, Y. Wang, C. Yu, X. Zhu, J. Dou, H. Cai and C. Zhou, The antimicrobial activity of Cbf-K 16 against MRSA was enhanced by  $\beta$ -lactam antibiotics through cell wall non-integrity, *Arch. Pharmacol Res.*, 2016, **39**, 978–988.
- 235 Z. Si, H. W. Lim, M. Y. Tay, Y. Du, L. Ruan, H. Qiu, R. Zamudio-Vazquez, S. Reghu, Y. Chen and W. S. Tiong, A glycosylated cationic block poly ( $\beta$ -peptide) reverses intrinsic antibiotic resistance in all ESKAPE Gram-negative bacteria, *Angew. Chem., Int. Ed.*, 2020, **59**, 6819–6826.
- 236 H. Mathur, D. Field, M. C. Rea, P. D. Cotter, C. Hill and R. P. Ross, Bacteriocin-antimicrobial synergy: a medical and food perspective, *Front. Microbiol.*, 2017, **8**, 1205.
- 237 X. Peng, Y. Luo, T. Xu, Z. Chen, P. Chen, C. Hu and S. Liu, Antibiotic-conjugated antimicrobial peptides for enhanced bacterial inhibition, *RSC Adv.*, 2025, **15**, 19751–19761.
- 238 B. C. Koppen, P. P. Mulder, L. de Boer, M. Riool, J. W. Drijfhout and S. A. Zaat, Synergistic microbicidal effect of cationic antimicrobial peptides and teicoplanin against planktonic and biofilm-encased *Staphylococcus aureus*, *Int. J. Antimicrob. Agents*, 2019, **53**, 143–151.
- 239 S. Li, P. She, L. Zhou, X. Zeng, L. Xu, Y. Liu, L. Chen and Y. Wu, High-throughput identification of antibacterials against *Pseudomonas aeruginosa*, *Front. Microbiol.*, 2020, **11**, 591426.
- 240 S. Tarvirdipour, S. N. Abdollahi, J. Köser, M. Bina, C.-A. Schoenenberger and C. G. Palivan, Enhanced antimicrobial protection through surface immobilization of antibiotic-loaded peptide multicompartiment micelles, *J. Mater. Chem. B*, 2025, **13**, 5365–5379.
- 241 H. Sun, Y. Hong, Y. Xi, Y. Zou, J. Gao and J. Du, Synthesis, self-assembly, and biomedical applications of antimicrobial peptide-polymer conjugates, *Biomacromolecules*, 2018, **19**, 1701–1720.
- 242 E. Lepeltier, P. Rijo, F. Rizzolio, R. Popovtzer, V. Petrikaite, Y. G. Assaraf and C. Passirani, Nanomedicine to target multidrug resistant tumors, *Drug Resist. Updates*, 2020, **52**, 100704.
- 243 A. O. Fadaka, N. R. S. Sibuyi, A. M. Madiehe and M. Meyer, Nanotechnology-based delivery systems for antimicrobial peptides, *Pharmaceutics*, 2021, **13**, 1795.
- 244 S. Gera, E. Kankuri and K. Kogermann, Antimicrobial peptides—unleashing their therapeutic potential using nanotechnology, *Pharmacol. Ther.*, 2022, **232**, 107990.
- 245 X. Luo, H. Chen, Y. Song, Z. Qin, L. Xu, N. He, Y. Tan and W. Dessie, Advancements, challenges and future perspectives on peptide-based drugs: Focus on antimicrobial peptides, *Eur. J. Pharm. Sci.*, 2023, **181**, 106363.
- 246 B. Lin, A. Hung, W. Singleton, K. K. Darmawan, R. Moses, B. Yao, H. Wu, A. Barlow, M. A. Sani and A. J. Sloan, The effect of tailing lipidation on the bioactivity of antimicrobial peptides and their aggregation tendency: Special issue: Emerging investigators, *Aggregate*, 2023, **4**, e329.
- 247 E. Malik, S. R. Dennison, F. Harris and D. A. Phoenix, pH dependent antimicrobial peptides and proteins, their mechanisms of action and potential as therapeutic agents, *Pharmaceuticals*, 2016, **9**, 67.
- 248 N. Chen and C. Jiang, Antimicrobial peptides: Structure, mechanism, and modification, *Eur. J. Med. Chem.*, 2023, **255**, 115377.
- 249 C. H. Chen and T. K. Lu, Development and challenges of antimicrobial peptides for therapeutic applications, *Antibiotics*, 2020, **9**, 24.



- 250 A. Mazurkiewicz-Pisarek, J. Baran and T. Ciach, Antimicrobial peptides: challenging journey to the pharmaceutical, biomedical, and cosmeceutical use, *Int. J. Mol. Sci.*, 2023, **24**, 9031.
- 251 J. Sun, Y. Xia, D. Li, Q. Du and D. Liang, Relationship between peptide structure and antimicrobial activity as studied by de novo designed peptides, *Biochim. Biophys. Acta, Biomembr.*, 2014, **1838**, 2985–2993.

