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## Strategies to overcome antibiotic resistance: silver nanoparticles and vancomycin in pathogen eradication

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The increasing prevalence of antibiotic resistance presents a significant challenge to public health, undermining the efficacy of conventional antibiotic treatments. Given the scarcity of new antibiotics and efficient preventive strategies, the exploration of alternative treatments has become imperative. For many years, vancomycin, a glycopeptide antibiotic, has been considered a last resort for treating severe Gram-positive bacterial infections. However, the emergence of vancomycin-resistant bacteria has raised significant concerns. The expanding use of nanomaterials in healthcare settings has shifted the spotlight towards innovative antibacterial nanomaterials, potentially offering solutions to the resistance crisis. One of the promising approaches to combat resistance involves employing metal nanoparticles to enhance antibiotic efficacy. Silver nanoparticles (AgNPs) have garnered particular interest due to their extensively documented broad-spectrum and robust antimicrobial properties, especially against bacterial biofilms, making them useful against multidrug-resistant pathogens. Recent evidence suggests synergistic antibacterial activity when AgNPs are combined with vancomycin. This innovative approach offers the potential to mitigate associated side effects and improve susceptibility to resistant strains. Consequently, the combination of vancomycin and AgNPs presents a compelling strategy for addressing bacterial infections. This review delves into the interactions between AgNPs and vancomycin, providing valuable insights into combating antibiotic resistance. Current research efforts continue to investigate and underscore the advancement of formulation strategies and their performance evaluation in a wide array of infection paradigms. This continuing work aims to enhance our understanding of drug delivery systems and their therapeutic potential across various infectious diseases.

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### 1. Introduction

Antimicrobial resistance refers to the ability of microorganisms to resist or endure the effects of antimicrobial drugs, including commonly used antibiotics. Bacteria can develop drug resistance through intrinsic traits or acquired mechanisms, rendering antibiotics less effective.<sup>1,2</sup> In the United States, it is estimated that annually, more than 2.8 million individuals acquire antimicrobial-resistant infections, leading to over 35 000 fatalities.<sup>3</sup> Future projections suggest that deaths due to antimicrobial resistance will increase over the next few decades, with a nearly 70% rise by 2050 compared to

2022, predominantly affecting the aging population.<sup>4</sup> The prevalence of multidrug-resistant (MDR) bacteria, which exhibit resistance to at least one agent in three or more antimicrobial classes, has become increasingly common, particularly in healthcare settings.<sup>5</sup> In July 2024, the Centers for Disease Control and Prevention (CDC) reported a 20% increase in six bacterial antimicrobial-resistant hospital-onset infections during the COVID-19 pandemic. These infections peaked in 2021 and remained above pre-pandemic levels in 2022.<sup>6</sup> Concerns have been raised about the 'post-antibiotic era', where common infections may become life-threatening due to ineffective treatments. Many experts, including those at the CDC, believe we are already experiencing this era.<sup>3</sup> In 2017, the World Health Organization (WHO) released its first-ever list of "priority pathogens" in light of increasing antibiotic resistance. It identified 12 families of bacteria associated with increased disease burden and treatment failures.<sup>7,8</sup> Bacteria can develop resistance through several mechanisms, including

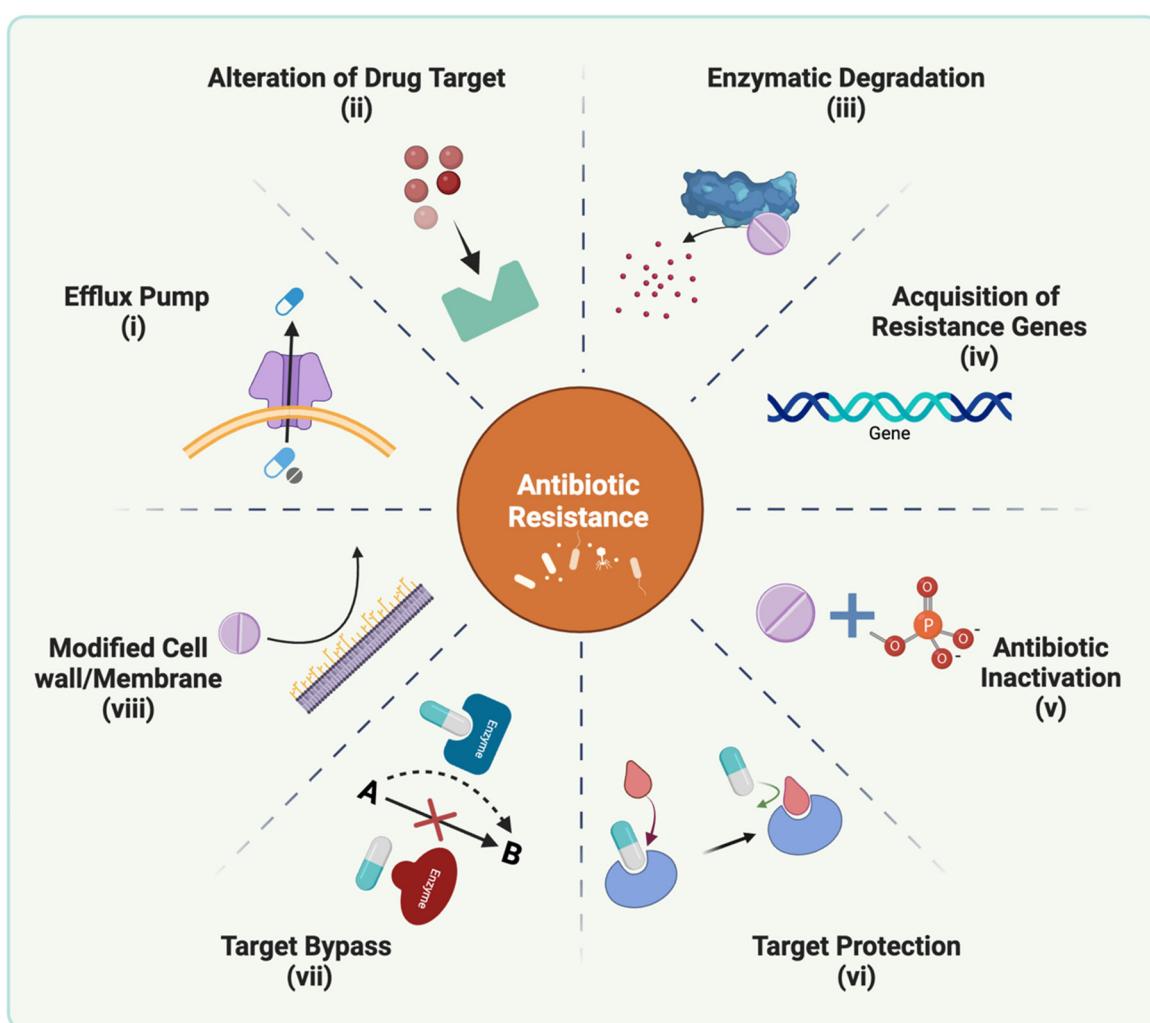
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the destruction or modification of antibiotics, prevention of access to the target, mutations in target genes or acquisition of genes encoding drug resistance, alteration of the antibiotic target site, and resistance due to global cellular adaptive processes, rendering antibiotics ineffective (Fig. 1).<sup>2</sup>

Many strategies have been devised to combat drug-resistant bacteria, including bacteriophage therapy, antimicrobial peptides, phytochemicals, metallo-antibiotics, and combination therapies.<sup>9</sup> Metal nanoparticles have emerged as a promising avenue for research, demonstrating significant antibacterial activity against resistant strains.<sup>10</sup> Among them, silver nanoparticles (AgNPs) offer the potential to address these chal-

lenges due to their broad-spectrum and robust antimicrobial properties, especially against bacterial biofilms.<sup>11,12</sup> While planktonic bacteria are susceptible, biofilms, which are far more resistant to antibiotics, account for nearly 80% of all microbial infections in the body.<sup>13</sup> Some reports suggest biofilm formation can prevent the penetration of drugs, increasing the effective doses up to 1000-fold compared to planktonic bacteria.<sup>14</sup> Therefore, combining conventional antibiotics with AgNPs offers an effective strategy for enhancing antibacterial efficacy.<sup>15</sup> AgNPs influence, induce, and modulate different inflammatory, metabolic, biochemical, and cellular processes, contributing to their multifaceted antimicrobial



**Fig. 1** Schematic representation depicting the mechanisms by which bacteria develop antibiotic resistance, shown with specific examples. The primary mechanisms of resistance include (i) active efflux pump, where transmembrane efflux pumps work to remove the antibiotic from the bacteria, decreasing antibiotic concentration to sub-toxic levels; (ii) alteration of the drug target such as a bacterial mutation that changes the structure of the target molecule to which the antibiotic usually binds, resulting in the loss of antibiotic ability to bind; (iii) enzymatic degradation, for example the production of beta-lactamase enzymes can render beta-lactam antibiotics such as penicillin, carbapenems, and cephalosporins ineffective by hydrolyzing their beta-lactam ring; (iv) gene acquisition, for example horizontal gene transfer (HGT) by transduction, conjugation and transformation of antibiotic resistance genes from one species to another; (v) antibiotic inactivation/modification, for example chloramphenicol acetyltransferases that acetylate chloramphenicol, preventing it from binding to the 50S ribosomal subunit; (vi) target protection, entails the physical association of a target protection protein with the antibiotic target; (vii) target bypass, involves overproduction of the target enzyme or developing a bypass for the target enzyme; (viii) modified cell envelope composition, such as alterations in peptidoglycan biosynthesis and membrane proteins like porins, changing the membrane permeability or lipo- and exopolysaccharides, rendering antibiotic resistance in bacteria. Created with BioRender.com.



action in addressing multidrug resistance in bacteria. Their direct antimicrobial activity is linked to adhesion to cell surfaces, penetration, intracellular damage, induction of oxidative stress by reactive oxygen species (ROS) generation, and modulation of signal transduction pathways.<sup>16</sup>

This review explores the potential of AgNPs in combination with vancomycin, the first discovered glycopeptide antibiotic. Despite its effectiveness against a wide range of Gram-positive bacteria, vancomycin has notable limitations. These include its poor stability, short half-life *in vivo*, substantial first-pass effect, slow bactericidal activity, poor tissue penetration (especially in the lungs), and the risk of severe side effects like nephrotoxicity and ototoxicity.<sup>17,18</sup> Its high molecular weight and hydrophilic nature result in poor gastrointestinal absorption, limiting its administration to intravenous routes, which are associated with patient compliance issues and systemic toxicity.<sup>19</sup> While nanocarrier systems, such as polymeric micelles and surface-modified liposomes, improve drug delivery, they face challenges in stability during storage, scalable production, and regulatory concerns over long-term safety and immunogenicity.<sup>20</sup> Furthermore, variability in patient responses, driven by immune status and comorbidities, further complicates treatment outcomes, highlighting the urgent need for novel and effective therapeutic strategies.

Investigating the combination of AgNPs and vancomycin presents a promising approach to tackle the growing challenge of vancomycin-resistant Gram-positive bacteria. The conjugation of vancomycin with AgNPs has demonstrated enhanced antibacterial activity against Gram-positive bacteria, including Vancomycin-resistant Enterococci (VRE) and methicillin-resistant

ant *Staphylococcus epidermidis* (MRSE).<sup>21</sup> This synergistic effect not only expands the range of treatable infections but also improves vancomycin's ability to penetrate biofilms, thereby enhancing its bactericidal action. Such combination therapy may offer a more effective solution for managing infections that are increasingly difficult to treat with traditional antibiotics alone.

## 2. Silver nanoparticles

The bactericidal activity of silver has been documented since ancient times. It is effective against over 650 microorganisms and provides a means to control vector-borne infections.<sup>22,23</sup> In the early 17<sup>th</sup> century, Angelus Sola utilized systemic silver nitrate to treat epilepsy and cholera. Subsequently, during the 19th century, German obstetrician Carl Crede and Austrian surgeon Johann Nepomuk Rust used a diluted solution of silver nitrate to prevent microbial infections.<sup>24</sup> Given the increasing decline in antibiotic effectiveness, AgNPs have regained prominence, with the Food and Drug Administration (FDA) approving numerous silver-infused wound dressings and topical agents for marketing.<sup>25,26</sup> In wound management, for example, a clinical trial by Pathi *et al.* demonstrated that Kadermin, a silver nanoparticle-based cream, outperformed Mupirocin in promoting faster wound healing and bacterial clearance. This highlights the potential for AgNPs to serve as antibiotic-sparing agents in treating infections.<sup>27</sup> While AgNPs are capable of killing both Gram-positive and Gram-negative bacteria, they demonstrate higher efficacy against Gram-negative bacteria,<sup>16</sup> as shown in Table 1.

Table 1 Antibacterial activity of silver nanoparticles

Bacteria	Size (nm)	MIC ( $\mu\text{g mL}^{-1}$ )	Type of strain	Ref.
<i>Acinetobacter baumannii</i>	10–50	4–25	Gram-negative	28
<i>Burkholderia pseudomallei</i>	10–20	32–48	Gram-negative	29
<i>Campylobacter jejuni</i>	10–50	4.92–39.4	Gram-negative	30
<i>Escherichia coli</i>	5	10	Gram-negative	31
<i>Enterobacter hormaechei</i>	5–15	4	Gram-negative	32
<i>Helicobacter pylori</i>	10–40	5	Gram-negative	33
<i>Klebsiella pneumonia</i>	50–65	62.5–125	Gram-negative	34
<i>Neisseria gonorrhoeae</i>	120	12.5	Gram-negative	35
<i>Pseudomonas aeruginosa</i>	45–53	2	Gram-negative	36
<i>Proteus mirabilis</i>	54	10	Gram-negative	37
<i>Salmonella typhus</i>	5–45	16	Gram-negative	38
<i>Shigella flexneri</i>	40–170	20	Gram-negative	39
<i>Vibrio cholera</i>	20–30	10	Gram-negative	40
<i>Yersinia enterocolitica</i>	16.56	50	Gram-negative	41
<i>Bacillus subtilis</i>	5–55	0.8–6	Gram-positive	42
<i>Clostridium difficile</i>	25–35	—	Gram-positive	43
<i>Enterococcus faecalis</i>	—	5	Gram-positive	44
<i>Listeria monocytogenes</i>	2–35	8	Gram-positive	45
<i>Micrococcus luteus</i>	62.09	60	Gram-positive	46
<i>Mycobacterium tuberculosis</i>	3–20	12.5	Gram-positive	47
<i>Staphylococcus epidermidis</i>	10–100	1–6	Gram-positive	48
<i>Staphylococcus aureus</i>	11.02–17.92	4–64	Gram-positive	49
<i>Streptococcus mutans</i>	10–78	4–16	Gram-positive	50

Abbreviation: minimum inhibitory concentration (MIC).



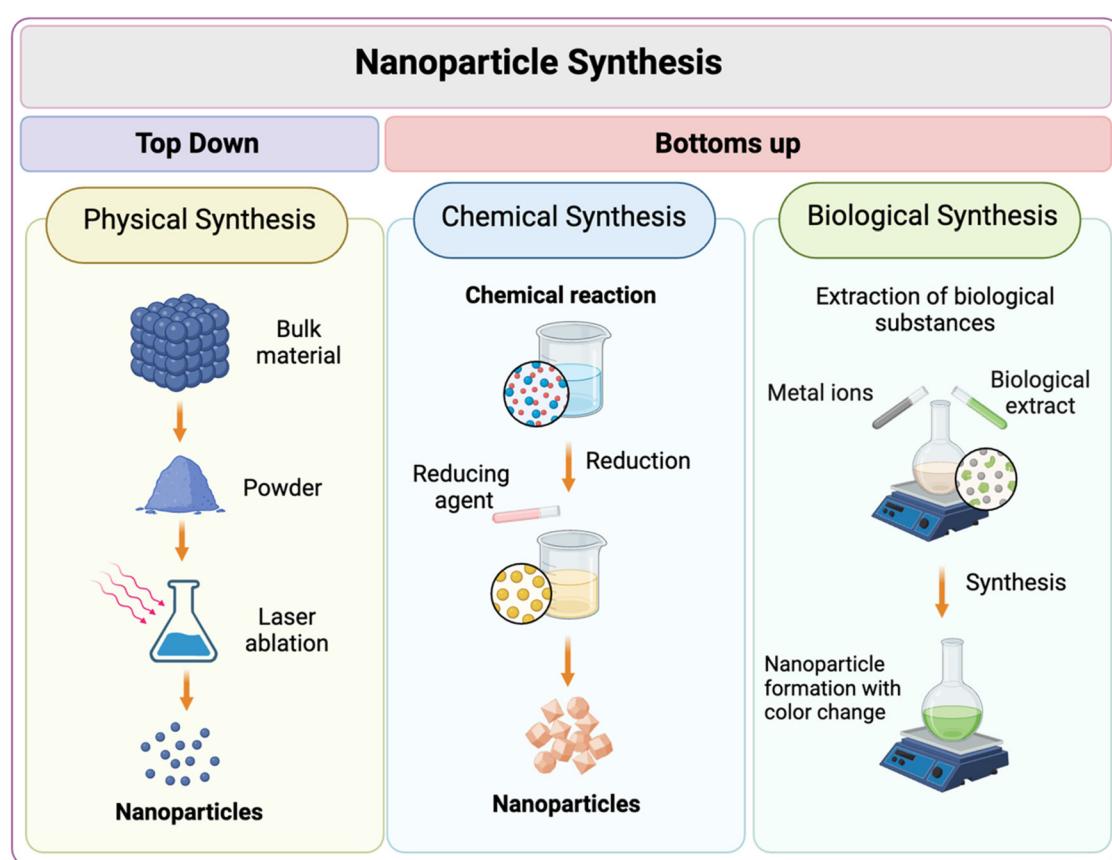
Recent studies have explored the application of AgNPs in dental materials such as adhesives, root canal fillers, implant surfaces, and denture resins due to their ability to inhibit bacterial growth and biofilm formation. Ongoing research is investigating their potential as nano-vectors for gene transfer and drug delivery, highlighting the expanding role of AgNPs in advancing oral health treatments.<sup>51</sup> Moreover, AgNPs are being investigated for therapeutic applications beyond antimicrobial uses. Rehman *et al.* demonstrated that AgNPs synthesized from plant extracts exhibit notable antidiabetic properties.<sup>52</sup> In another study, Khajeh *et al.* showed that AgNPs derived from the extracts of *Moringa oleifera* could upregulate the *MLH1* (Mult homolog1) gene, which plays a crucial role in promoting DNA repair and apoptosis in colorectal cancer cells.<sup>53</sup> AgNPs are also being explored for their antiviral activity against a wide range of viruses, including hepatitis B virus, human immunodeficiency virus, herpes simplex virus, and monkeypox virus, indicating their ability to inhibit viral attachment and entry into host cells.<sup>54</sup> This multifunctionality paves the way for AgNP applications beyond healthcare, making it a highly sought-after material across multiple industries. The antibacterial potential of AgNPs has led to their incorporation into a variety of consumer and medical products, including

textiles,<sup>55</sup> agriculture,<sup>56</sup> packaging,<sup>57</sup> optoelectronics,<sup>58</sup> and environmental remediation.<sup>59</sup>

Despite significant progress, the widespread clinical and industrial adoption of AgNPs remains restricted by challenges such as cytotoxicity, environmental concerns, scalability, manufacturing uniformity, and regulatory constraints.<sup>60,61</sup> Additionally, achieving precise control over nanoparticle size, morphology, and dispersion is a persistent hurdle.<sup>62</sup> Addressing these factors will be crucial in ensuring the safe and effective utilization of AgNPs in biomedical applications and expanding their commercial viability.

## 2.1. Synthesis of AgNPs

AgNPs can be synthesized through a variety of methods, which include both modern biochemical techniques and traditional approaches. These methods provide the flexibility to control the size and structural properties of the nanoparticles. Researchers employ diverse techniques, broadly categorized into top-down and bottom-up approaches, as illustrated in Fig. 2, to produce AgNPs that meet specific requirements.<sup>63</sup> The top-down approach involves breaking down bulk material into nanoparticles, utilizing techniques such as laser ablation, evaporation-condensation, and mechanical milling. This



**Fig. 2** Schematic representation of various nanoparticle synthesis methods, categorized into top-down and bottom-up approaches. The top-down approach starts with bulk materials and breaks them down into nanoparticles, primarily using physical methods. The bottom-up approach builds nanoparticles from atoms or molecules, employing chemical and biological methods. Created with BioRender.com.



approach offers the advantage of producing pure and uncontaminated AgNPs without relying on hazardous chemicals, ensuring the production of high-quality nanoparticles. However, it is energy-intensive and requires advanced machinery, significant space, and long processing times, often resulting in relatively low yields. Conversely, bottom-up approaches are cost-effective, simple, and produce high yields with controllable particle sizes. However, they often involve the use of toxic reducing agents and stabilizers, leading to harmful waste, residual contaminants, and potential aggregation of nanoparticles.<sup>64,65</sup> This approach involves building nanoparticles from individual atoms or molecules in solution, encompassing methods like sol-gel processes and chemical reduction. The latter typically requires a silver salt precursor, reducing agents, and stabilizing chemicals.<sup>66-68</sup> Notably, the use of stabilizing or capping agents is crucial in this process. These agents are often employed to enhance stability and prevent coagulation.<sup>69</sup> This is particularly important because nanoparticles, due to their significantly reduced size compared to bulk materials, possess higher surface energy, which can lead to instability.<sup>70</sup> These agents work through various mechanisms, commonly categorized into five types: steric stabilization, electrostatic stabilization, depletion stabilization, stabilization by hydration forces, and stabilization by Van der Waals forces.<sup>54</sup>

Biological synthesis methods, a subset of bottom-up approaches, present a more eco-friendly and cost-effective alternative, utilizing plant extracts or microorganisms as reducing agents. This method leverages the reducing and stabilizing power of natural compounds, including flavonoids, alkaloids, and enzymes from plants or microorganisms, to control nanoparticle formation and enhance stability without introducing harsh chemicals.<sup>71</sup> Recent studies have demonstrated their effectiveness against various pathogens, including *Candida albicans*, *E. coli*, and *S. aureus*, often surpassing traditional antibiotics in efficacy. For instance, AgNPs synthesized using *Bacillus methylotrophicus* exhibited superior inhibition of microbial growth compared to conventional antibiotics.<sup>72</sup> Another study utilized *Aspergillus sydowii* to produce AgNPs with a spherical shape and sizes varying between 1 to 24 nm. These nanoparticles demonstrated significant antiproliferative and antifungal activities against clinical fungal pathogens, suggesting their potential use in biomedical applications.<sup>73</sup> Additionally, plant-based synthesis methods, such as those using *Prunus yedoensis*, have shown promise in producing AgNPs with enhanced effectiveness against skin bacteria compared to commercial alternatives.<sup>74</sup> Palanisamy *et al.* reviewed marine biomolecule-assisted synthesis using compounds such as polysaccharides, enzymes, vitamins, and proteins derived from a wide range of marine organisms, including but not limited to seaweed, seagrass, and microalgae.<sup>75</sup> This growing interest in biological synthesis is driven not only by its reduced environmental impact but also by its cost-effectiveness and reliability, positioning it as an attractive method for producing AgNPs to combat antibiotic resistance.<sup>66</sup> However, challenges remain, such as ensuring reproducibility, optimizing large-scale production, and understanding the long-term effects of AgNPs *in vivo*.

## 2.2. Physicochemical properties of AgNPs

The physicochemical properties of AgNPs, such as size, shape, surface charge, and surface functionalization, play a critical role in their antimicrobial efficacy and interactions with both bacteria and host tissues. Zaman *et al.* highlighted the crucial influence of AgNP size on photocatalytic and antibacterial applications. Smaller nanoparticles exhibit enhanced efficacy against bacterial strains due to their higher surface-area-to-volume ratio and ability to penetrate bacterial cell barriers. Additionally, they demonstrated greater activity against Gram-negative bacterial strains.<sup>76</sup> Previous research has shown challenges in synthesizing highly monodisperse and stable AgNPs below 10 nm or above 50 nm using single reducing agents. Strong reducers like sodium borohydride (NaBH<sub>4</sub>) produce small, uniform particles but struggle with larger sizes, while weaker reducers like trisodium citrate (TSC) yield larger particles with wider size distributions and varied shapes. A co-reduction method using both NaBH<sub>4</sub> and TSC may offer better control over nucleation and growth, potentially addressing these limitations.<sup>77</sup>

In addition to size, the shape of AgNPs significantly influences their antibacterial effectiveness. AgNPs can be synthesized in various shapes, including spherical, triangular, cubic, rod-shaped, platelet, hexagonal, pyramidal, flower-shaped, octahedral, tetrahedral, cylindrical, and irregular configurations, each exhibiting unique physicochemical properties.<sup>78,79</sup> In a study, truncated-triangular nanoparticles appeared to be more effective for microbial killing. However, spherical nanoparticles are still considered to be the best-suited for practical applications in either colloidal form or immobilized state.<sup>77,80</sup> However, it's important to note that other factors also play crucial roles in determining antibacterial efficacy. Pokhrel *et al.* investigated the antibacterial efficacy of 5 nm positively charged amine (NH<sub>2</sub>)-functionalized AgNPs and 45 nm negatively charged citrate-AgNPs against *E. coli*. Positively charged AgNPs demonstrate greater antibacterial activity due to electrostatic attraction with negatively charged bacterial cell membranes.<sup>81</sup> Functionalization can prevent AgNP aggregation, enhancing their stability in various solvents. For example, poly(pentafluorostyrene) (PPFS)-modified AgNPs showed improved dispersion in organic solvents, while glycosylated PPFS-modified AgNPs were more easily dispersed in aqueous medium.<sup>82</sup> Surface modifications enable the targeted delivery of AgNPs to specific tissues or organs while potentially reducing toxicity concerns. Functionalizing AgNPs with biomolecules such as antibiotics, polymers, glycolipids, amino acids, and peptides enhances their stability, biocompatibility, and functionality for diverse applications.<sup>83</sup>

Depending on the desired local or systemic effect, AgNPs can be administered through topical applications or *via* intravenous injection.<sup>84,85</sup> He *et al.* developed an Ag-functionalized chitosan hydrogel dressing with sustained silver release and enhanced antibacterial capabilities. The hydrogel demonstrated significant wound healing acceleration, achieving a



99% healing rate in a mouse model, with improved re-epithelialization and reduced inflammation.<sup>86</sup> While effective against various conditions, AgNP cytotoxicity remains a concern for widespread use in medical applications. Studies are focusing on addressing safety concerns, optimizing efficacy, and developing novel applications to harness the full potential of AgNPs in biomedicine while ensuring their safe use.

### 2.3. Mechanism of antibacterial activity of AgNPs

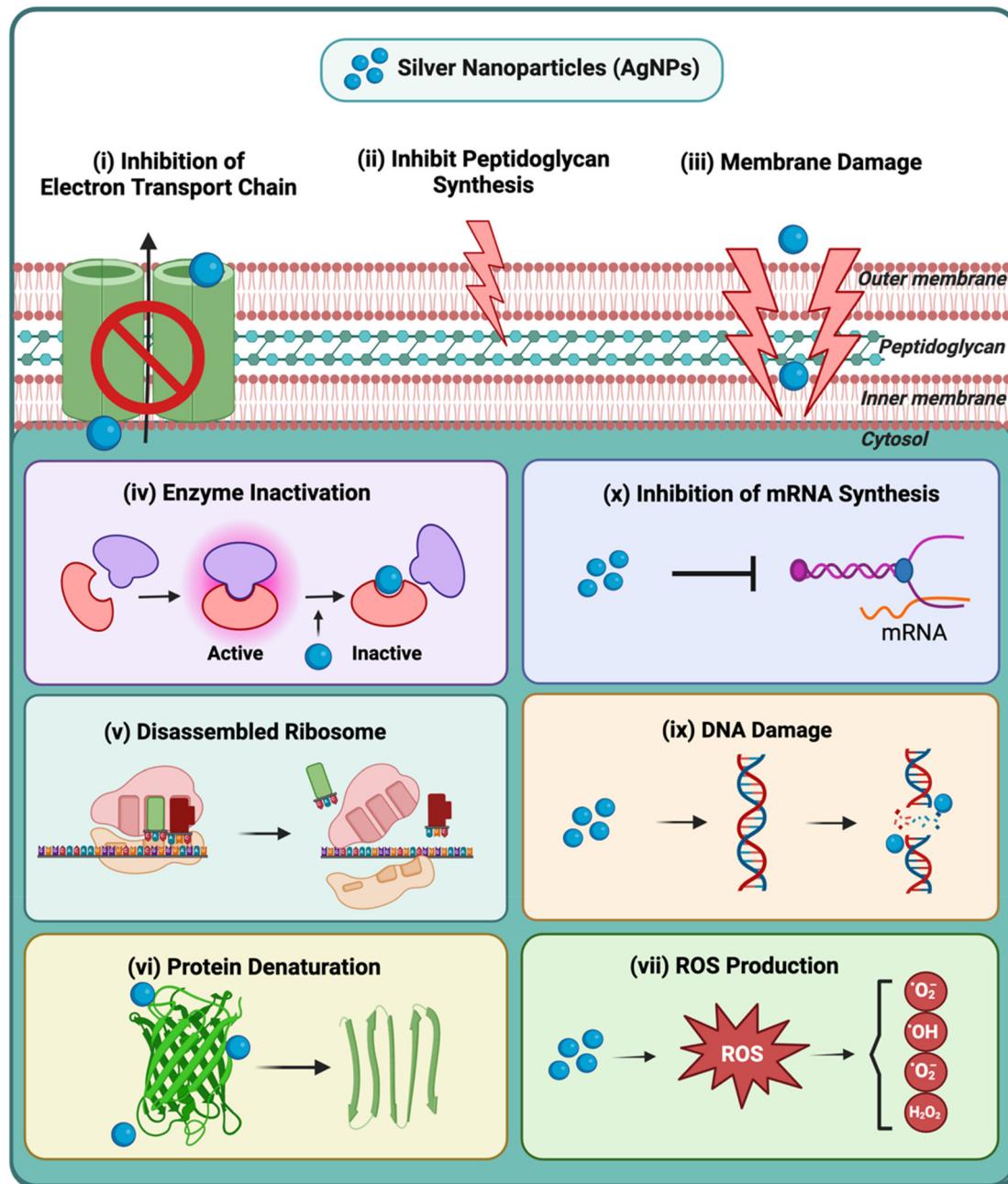
While the broad-spectrum antibacterial properties of AgNPs are well-known, the precise mechanisms behind their antimicrobial effects remain unclear. The antibacterial effectiveness of AgNPs mainly arises from the release of Ag<sup>+</sup> ions. These positively charged ions engage in electrostatic interactions with the negatively charged functional groups containing phosphorous and sulfur, such as phosphates (−PO<sub>4</sub><sup>3−</sup>) or sulfates (−SO<sub>4</sub><sup>2−</sup>) in cellular membranes, proteins, and DNA bases.<sup>87</sup> The presence of Ag<sup>+</sup> ions can enhance the permeability of the cytoplasmic membrane, potentially causing the bacterial envelope to rupture. Once the free Ag<sup>+</sup> ions are internalized, they can inhibit respiratory enzymes within the electron transport chain (ETC) and leading to the generation of ROS.<sup>88</sup> This oxidative stress can damage DNA and interrupt the metabolic activities of enzymes containing iron-sulfur clusters, such as aconitase in the tricarboxylic acid cycle (TCA), through Fenton chemistry.<sup>89,90</sup> Furthermore, Ag<sup>+</sup> ions can compromise the DNA's ability to replicate and disrupt protein synthesis by denaturing ribosomes in the cytoplasm.<sup>91</sup> It has also been noticed that AgNPs have antibacterial properties without the release of ions. AgNPs tend to accumulate in the pits that form on the cell wall. Subsequently, they attach to the cell membrane surface, altering its permeability by changing the cell potential and hindering cellular respiration.<sup>92</sup> The ability of AgNPs to interfere with bacterial signal transduction by dephosphorylating tyrosine residues on peptide substrates can induce apoptosis and halt cell multiplication.<sup>93</sup> AgNPs can also alter the morphology of bacteria by obstructing the synthesis of cell wall peptidoglycan and inhibiting bacterial growth by disrupting the functions of the cell division protein FtsZ and the chromosomal replication initiator protein DnaA.<sup>94</sup> Nevertheless, the potential mutagenic effects of AgNPs and the resistance mechanisms of target cells remain a subject of debate. Also, AgNPs have demonstrated the ability to disrupt biofilm formation by interfering with critical bacterial metabolic processes. They can hinder bacterial motility, impair iron uptake, induce oxidative stress, and disrupt respiration, which are crucial for bacterial survival.<sup>95</sup> Additionally, AgNPs can interfere with quorum sensing systems, which bacteria use to communicate and coordinate biofilm development.<sup>96</sup> Their small size also allows them to penetrate the exopolysaccharide layer *via* water channels, establishing direct contact with bacterial cells and inhibiting biofilm progression. This interaction leads to a reduction in membrane components,

including proteins, polysaccharides, lipids, and nucleic acids, gradually compromising membrane stability.<sup>97</sup> AgNPs exhibit potent antibacterial activity against a wide spectrum of bacterial species through multiple mechanisms. Fig. 3 illustrates key modes of action by which AgNPs combat bacterial pathogens, including disruption of cellular processes, membrane damage, and interference with biofilm formation.

### 2.4. Resistance mechanisms of AgNPs

Silver-resistant bacteria were initially identified following their emergence from a burn wound subjected to silver nitrate treatment.<sup>98,99</sup> Since then, these bacteria have been consistently detected in various environments, including clinical settings like hospitals and non-clinical environments such as mines and coastal waters.<sup>100,101</sup> The mechanism of silver resistance was best described in *S. typhimurium* carrying the multi-drug-resistant plasmid pMG101.<sup>99</sup> This plasmid contains the *sil* operon, which plays a vital role in exogenous silver resistance due to horizontal gene transfer. The *sil* operon encodes a sophisticated resistance mechanism involving multiple genes, notably *silCFBA*, *silE*, and *silRS*. The SilCBA complex forms an efflux pump that facilitates the transfer of silver ions out of the bacterial cell, while SilE acts as a periplasmic silver-binding protein, and SilRS functions as a two-component regulatory system.<sup>102–104</sup> The homolog sequences to the *sil* determinants have also been identified in numerous *E. coli* strains. The *cusCFBA* gene cluster, a component of the resistance-nodulation-division (RND) efflux system, is pivotal in the resistance mechanism against copper and silver.<sup>105</sup> Lok *et al.* demonstrated that disrupting the *cus* locus in the silver-resistant strain led to a substantial reduction in the MIC of Ag<sup>+</sup> from over 1000 μM to 12 μM.<sup>106</sup> Concerning the outer membrane, it has been documented that *E. coli* mutants lacking outer membrane porins exhibit more resistance to Ag<sup>+</sup> ions.<sup>107,108</sup> The resistance mechanisms can also involve a phenotypic change rather than a genetic alteration. Panáček *et al.* found that Gram-negative bacteria can generate flagellin, an adhesive protein found in flagella, which induces the aggregation of AgNPs.<sup>109</sup> The study proposed that suppressing flagellin production using pomegranate rind extract holds promise for overcoming resistance to AgNPs. Therefore, non-motile strains may exhibit increased susceptibility to AgNPs as the resistance mechanism is influenced by bacterial motility, particularly by the presence of the flagellum.<sup>110</sup> Numerous studies have documented the response of bacterial biofilms to silver-induced stress.<sup>111</sup> Gram-negative bacteria, particularly members of the Enterobacteriaceae family, appear more prone to developing silver resistance. Bacterial species exhibiting resistance to silver include *Enterobacter* spp.,<sup>112</sup> *Pseudomonas* spp.,<sup>113</sup> *E. coli*,<sup>114,115</sup> *Klebsiella* spp.,<sup>116</sup> *Acinetobacter* spp.,<sup>117</sup> *Citrobacter* spp.,<sup>118</sup> *Morganella* spp.,<sup>119</sup> *Proteus* spp.,<sup>120</sup> and *Cupriavidus* spp.,<sup>121</sup> among others. More recently, silver resistance has also been reported in some strains of *S. aureus*.<sup>122</sup> The prevalence and mechanisms of silver resistance can vary among different strains and species.





**Fig. 3** Mechanism of antibacterial activity of AgNPs. The primary antibacterial mechanisms of AgNPs include (i) inhibition of the ETC: AgNPs interfere with the components of ETC, impairing ATP production and cellular respiration; (ii) inhibition of peptidoglycan synthesis: AgNPs disrupt the synthesis of peptidoglycan, a vital component of the bacterial cell wall, thereby compromising its structural integrity; (iii) membrane damage: silver ions ( $\text{Ag}^+$ ) released from AgNPs attach to or penetrate the bacterial cell membranes, resulting in the leakage of cellular contents and causing structural damage; (iv) enzyme inactivation: AgNPs can shut down crucial bacterial enzymes, such as aconitase and succinyl coenzyme A synthetase, of the TCA cycle, thereby altering cellular metabolic status; (v) disassembled ribosomes:  $\text{Ag}^+$  ions binding to the 30S ribosome subunit can disassemble ribosomes, leading to alterations or abrupton of protein synthesis; (vi) protein denaturation: AgNPs can interact with proteins and enzymes, resulting in conformational changes in their tertiary structure, leading to loss of function and eventual cell death; (vii) ROS production: AgNPs can facilitate the production of ROS, such as superoxide radicals and hydrogen peroxide, leading to oxidative damage of proteins, lipids, and DNA in bacterial cells; (viii) DNA damage: AgNPs can enter bacterial cells and interact directly with DNA, leading to its denaturation or damage such as double-strand breaks, condensation, and mutations in crucial DNA repair genes. This interaction inhibits replication and results in cell death; (ix) inhibition of mRNA synthesis: AgNPs can inhibit mRNA synthesis, preventing the biosynthesis of proteins necessary for bacterial survival and growth. Created with BioRender.com.



### 3. Vancomycin hydrochloride

Vancomycin, an amphoteric glycopeptide antibiotic, is frequently designated as the “drug of last resort”, typically administered after other antibiotics have failed.<sup>123,124</sup> During the 1950s, researchers at Eli Lilly and Company, including Dr E.C. Kornfeld, isolated vancomycin (compound 05865) from Bornean soil samples. Produced by *Streptomyces orientalis* (now *Amycolatopsis orientalis*), it proved effective against Gram-positive bacteria, including antibiotic-resistant *S. aureus*. Its name, derived from “vanquish”, reflects its potency against resistant strains.<sup>125,126</sup> Approved by the FDA in 1958, vancomycin’s early use was limited by impurities and toxicity concerns, including ototoxicity and nephrotoxicity.<sup>127</sup> Vancomycin is proven effective against *S. aureus* (MRSA), *S. epidermidis*, *C. difficile*, and it also has activity against other bacterial species, including *Streptococcus* spp., *Enterococcus* spp., *L. monocytogenes*, *Actinomyces* spp., *Lactobacillus* spp., and diphtheroids.<sup>128,129</sup> Nonetheless, following the emergence of vancomycin-resistant enterococci strains in the late 1980s, the incidence of resistance in both enterococci and staphylococci has continued to rise.<sup>130</sup>

#### 3.1. Mechanism of antibacterial activity of vancomycin

Each class of antibiotics targets specific components or processes essential for bacterial survival and growth. They disrupt these processes through various mechanisms, including inhibiting cell wall and protein biosynthesis, disrupting cell membranes, and interfering with nucleic acid metabolism.<sup>131</sup> The reported antibacterial mechanism for vancomycin is based on inhibiting the cross-linking of peptidoglycan chains, a vital structural element within the cell walls of bacteria.<sup>132</sup> Peptidoglycan is a polysaccharide consisting of sugars and amino acids, with repeating units of *N*-acetylglucosamine (NAG) and *N*-acetylmuramic acid (NAM) in its sugar backbone crosslinked by oligopeptides attached to the NAM subunits.<sup>133</sup> It is reported that vancomycin forms hydrogen bonds with the *D*-alanyl-*D*-alanine terminal (*D*-Ala-*D*-Ala) in the nascent peptidoglycan, thereby disrupting the synthesis of the bacterial cell wall.<sup>134,135</sup> Due to steric hindrance, this binding inhibits the activity of enzymes such as transpeptidases which are crucial for cell wall synthesis.<sup>136</sup> The lack of transpeptidation directly reduces the crosslinking density in the peptidoglycan matrix, resulting in decreased strength and stiffness in the cell, impairing the resistance to osmotic pressure, and leading to bacterial lysis.<sup>137,138</sup> *In vitro* evidence indicates that vancomycin also inhibits transglycosylation via binding to *D*-Ala-*D*-Ala moieties in peptidoglycan precursors such as lipid II, impeding the elongation of the peptidoglycan backbone.<sup>139,140</sup> Besides inhibiting peptidoglycan biosynthesis, vancomycin has been found to affect genes involved in autolysis and peptidoglycan hydrolase (SagB), accelerating cell death.<sup>141</sup> In addition, there are reports focusing on the effect of vancomycin on bacterial cell membranes, leading to alterations in membrane permeability and RNA synthesis.<sup>128</sup>

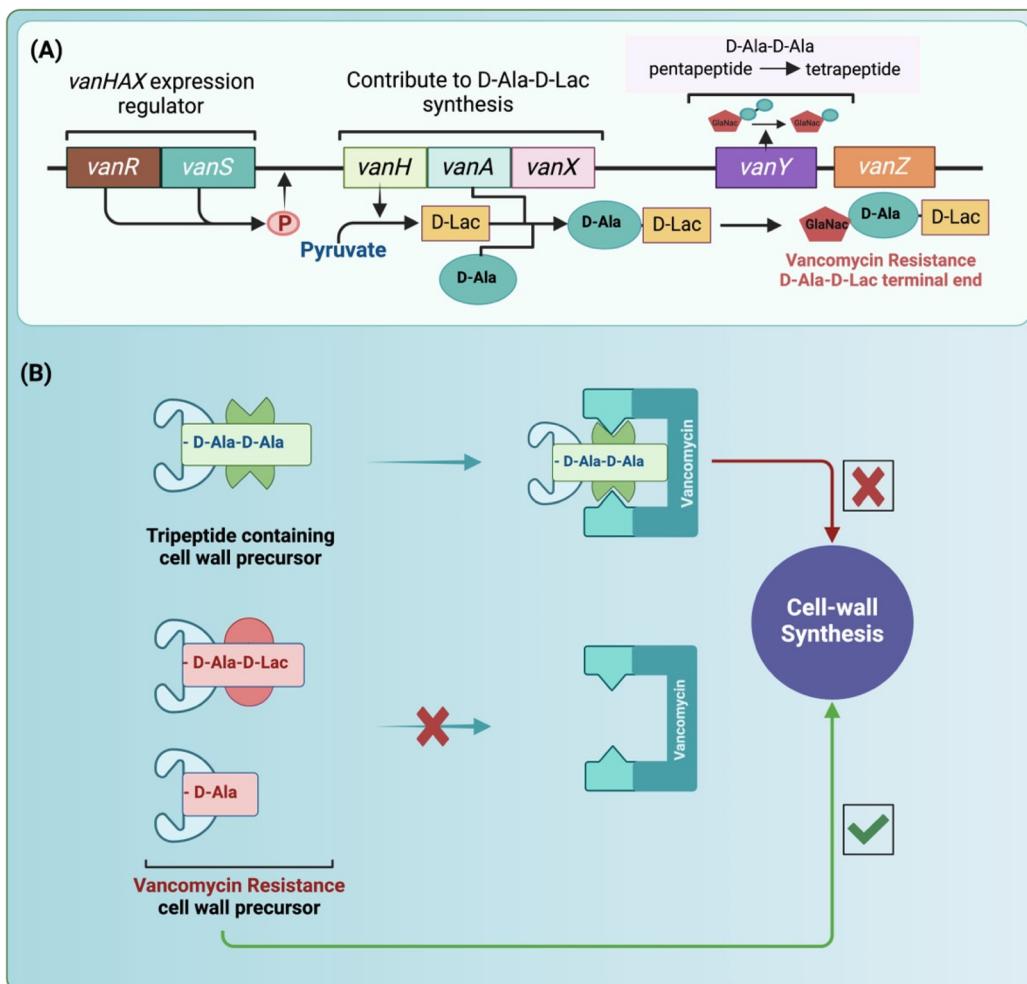
#### 3.2. Resistance mechanisms of vancomycin

Despite its effectiveness against Gram-positive bacteria, improper administration and excessive use of vancomycin can induce genetic alterations such as mutations or the acquisition of resistance genes. This culminates in the emergence of vancomycin-resistant strains like VRE, vancomycin-resistant *S. aureus* (VRSA), and vancomycin-intermediate *S. aureus* (VISA), characterized by higher MICs than non-mutated strains.<sup>142</sup> It has been found that vancomycin resistance is directly attributed to the expression of gene clusters named *van* operons. Several established *van* operons (such as *vanA*, *vanB*, and *vanD*) encode enzymes that alter the biosynthesis of peptidoglycan precursors.<sup>143</sup> This alteration produces substituted terminated precursors with less binding affinity to vancomycin, such as *D*-alanyl-*D*-lactate (*D*-Ala-*D*-Lac) and *D*-alanine-*D*-serine (*D*-Ala-*D*-Ser).<sup>144</sup> One representative *van* operon, *vanA*, is shown in Fig. 4. It is found in both VRE and VRSA and contributes to the formation of *D*-Ala-*D*-Lac residue for transpeptidation.<sup>145,146</sup> Upon activation, three enzymes, VanH, VanA, and VanX, are expressed from the *vanA* operon, which possess respective functions. The VanH reductase catalyzes the reduction of pyruvate to *D*-Lac, while the VanA ligase catalyzes the formation of a crucial bond between *D*-Lac and *D*-Ala through a covalent linkage.<sup>147</sup> The VanX dipeptidase hydrolyzes the peptide bond in *D*-Ala-*D*-Ala residue.<sup>148</sup> Additionally, the expression of the *vanA* cassette is controlled by a two-component regulatory system, VanR–VanS.<sup>149,150</sup> It is also reported that the structure of peptide residue correlates with the level of vancomycin resistance, in which *D*-Ala-*D*-Lac rather than *D*-Ala-*D*-Ser is present in highly resistant genotypes of VRE, as the former structure shows less binding affinity.<sup>151,152</sup> Besides *van* operons, there are also other reported genes associated with vancomycin resistance, such as *cls* and *mprf*, expressing enzymes to prevent vancomycin penetration via structural modifications of bacterial cell membranes.<sup>153–155</sup>

### 4. Combination approaches for vancomycin and silver nanoparticles

Several studies have reported enhanced bactericidal effects when the combination of vancomycin and AgNPs is administered, surpassing the efficacy observed with either agent alone. This enhanced activity is valuable in overcoming bacterial antibiotic resistance mechanisms, thereby rejuvenating the effectiveness of vancomycin against resistant strains. The susceptibility of *S. aureus* biofilms to AgNPs and vancomycin was examined individually and in combination. Hair *et al.* used ten distinct *S. aureus* isolates, each representing a range of biofilm-forming abilities, and employed a crystal violet assay to quantify the mass of the biofilms.<sup>156</sup> Treatment with 2  $\mu$ g mL<sup>-1</sup> vancomycin reduced the biofilm formation in 7 out of 10 isolates, encompassing 4 out of 5 methicillin-susceptible and 3 out of 5 methicillin-resistant *S. aureus* isolates. The AgNPs treatment demonstrated a decrease in 6 out of 10 isolates,





**Fig. 4** Mechanism of vancomycin activity and resistance. Vancomycin primarily inhibits peptidoglycan synthesis by binding to the D-Ala-D-Ala terminus of cell wall precursors. In response to vancomycin exposure, the sensor kinase VanS undergoes autophosphorylation and activates the response regulator VanR. This activation triggers the transcription of the *vanHAX* genes. VanH facilitates the reduction of pyruvate to D-lactate, serving as a substrate for the ATP-dependent D-Ala-D-lactate ligase VanA. VanX carries out the hydrolysis of the existing D-Ala-D-Ala peptide pool. Consequently, peptidoglycan precursors ending in D-Ala-D-Lac are incorporated into the growing cell wall instead of D-Ala-D-Ala, resulting in a substantial reduction in vancomycin binding and ultimately conferring resistance. (A) The VanA gene cluster responsible for vancomycin resistance, (B) mechanisms by which *S. aureus* develops resistance to vancomycin. Created with BioRender.com.

including 4 out of 5 MSSA and 2 out of 5 MRSA strains, whereas the combinatorial treatment had a substantial reduction in biofilm formation in 9 out of 10 isolates. In another study, the combination of AgNPs with vancomycin demonstrated enhanced efficacy in inhibiting MRSA biofilms, showcasing a synergistic approach to combat antibiotic-resistant pathogens.<sup>157</sup> AgNPs and vancomycin demonstrated promising synergistic antibiofilm activity with AgNP concentrations ranging from 2–4  $\mu\text{g mL}^{-1}$ , permitting non-cytotoxic application of the combination.

#### 4.1. Vancomycin conjugated to AgNPs

AgNP surface can be easily modified to increase its stability while offering an opportunity for drug conjugation. Thus, vancomycin can be conjugated to AgNPs based on the type of functional groups. Direct functionalization of AgNPs with van-

comycin demonstrates the potential for developing novel antibacterial agents with enhanced efficacy. Esmaeilou *et al.* utilized *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDC) and *N*-hydroxysuccinimide (NHS) to conjugate vancomycin to the terminal carboxy group of thioglycolic acid-stabilized AgNPs.<sup>21</sup> The resulting conjugate showed potent antibacterial activity, with MIC of 0.1  $\mu\text{g mL}^{-1}$  against VRE and 0.05  $\mu\text{g mL}^{-1}$  against *S. aureus*. Another study explored the use of polydopamine (pDA) coated AgNPs as a platform for vancomycin conjugation.<sup>158</sup> It was found that the size of pDA-AgNPs formulation increased from 24 nm to 33 nm with vancomycin concentration in the micromolar range, potentially enhancing its efficacy against vancomycin-resistant *E. faecalis* and inhibiting further resistance development. Wang *et al.* took a different approach, designing vancomycin-modified magnetic-based silver microflowers assembly with bactericidal ability.<sup>159</sup>

The microflowers were carboxy-capped and then conjugated with vancomycin. The hybrid micro composite exhibited synergistic effects of magnetic-based Ag microflower and vancomycin for sterilization. The magnetic microflowers were designed to offer magnetic responsiveness, featuring a flower-like Ag shell to facilitate more release of Ag<sup>+</sup> ions and bacterial contact, complemented by a vancomycin layer to enhance cell membrane permeability. The assembly demonstrated recyclability over five washing-and-reuse cycles and efficiently eradicated both *E. coli* and MRSA at low concentrations. In another study, poly(amidoamine) (PAMAM) dendrimers, conjugated with vancomycin *via* amide bonds and incorporating AgNPs, resulted in a 6–7 log reduction in colony-forming units (CFU) of a vancomycin-resistant bacterial strain *in vitro*.<sup>160</sup> This treatment did not induce resistance in vancomycin-susceptible strains. Moreover, *in vivo*, bacterial killing was demonstrated in an infected wound murine model with a low dose of Van-PAMAM–AgNPs dendrimers upon its single topical application.

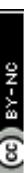
A multifunctional platform capable of simultaneously detecting, eliminating, and inactivating pathogenic bacteria was constructed by Yang and coworkers.<sup>161</sup> The electrochemical platform was fabricated using vancomycin-functionalized AgNPs/3D-ZnO nanorod array electrodes. AgNPs were functionalized with vancomycin using mercaptoacetic acid as a linker. This allowed for specific recognition and detection through hydrogen bonds between the peptidoglycan in the bacteria cell wall and the carbonyl and amine groups of vancomycin. This approach achieved a low detection limit of 330 CFU mL<sup>-1</sup> and demonstrated effective bacterial elimination, with 50% efficiency at low concentrations (1000–2000 CFU mL<sup>-1</sup>). The synergistic effect of the AgNPs and vancomycin provided high antibacterial activity (99.99%) against pathogenic bacteria. Building on this concept of multifunctionality, Zhou *et al.* developed a nanocomplex that integrates surface-enhanced Raman scattering (SERS) and antimicrobial photodynamic therapy (aPDT) for theranostic applications against vancomycin-resistant bacterial infections.<sup>162</sup> The nanocomplex was comprised of silver-coated gold nanoparticles encapsulated in silica functionalized with vancomycin and a near-infrared photosensitizer, silicon 2,3-naphthalocyanine dihydroxide. The SERS-active core facilitated sensitive SERS imaging of VRE strains, while the integrated photosensitizer generated ROS upon near-infrared light irradiation, resulting in the effective photodynamic killing of VRE. *In vitro* experiments demonstrated that the nano complex, when used at nanomolar concentrations, can significantly reduce bacterial populations by 4–5 log units upon photodynamic therapy.<sup>162</sup> This finding indicates the nano complex's potential as an alternative method for bacterial detection and elimination. In another study, Zhang *et al.* synthesized vancomycin functionalized TiO<sub>2</sub>/AgNPs using nanoparticle deposition and chemical crosslinking reactions.<sup>163</sup> These nanoparticles demonstrated remarkable efficacy in degrading methylene blue under ultraviolet (UV) illumination. The photocatalytic inactivation of sulfate-reducing bacteria *Desulfotomaculum* spp.

was investigated under UV irradiation, and prepared nanoparticle assembly was able to prevent bacterial cell growth under UV irradiation.

#### 4.2. Vancomycin electrostatic binding to AgNPs

AgNPs synthesized using an ionic surfactant can achieve stability through an electrostatic stabilization mechanism, where the surfactant acts as a crucial intermediary between the drug and the AgNPs.<sup>164</sup> Notably, utilizing citrate capped AgNPs alongside vancomycin has yielded promising results, revealing a synergistic effect.<sup>165</sup> In that study, the combination exhibited enhanced efficacy compared to free vancomycin against Gram-positive (*S. aureus*) and Gram-negative (*E. coli*) bacterial species. Further investigations were carried out to explore the possible mechanism of interaction of vancomycin functionalized AgNPs complex with bacterial cell walls. Vancomycin inhibits the synthesis of bacterial cell walls by binding to the D-alanyl-D-alanine dipeptide within the peptidoglycan layer.<sup>166</sup> However, when combined with AgNPs, vancomycin exhibits a synergistic antibacterial effect through a four-step mechanism: (i) vancomycin binding to AgNPs, (ii) AgNPs–vancomycin complex interacting with bacteria, (iii) the release of Ag<sup>+</sup> ions or AgNPs, and (iv) AgNPs inducing toxicity by binding to bacterial DNA and proteins.<sup>165</sup> Another common approach involves the use of polymers or non-ionic surfactants, which interact with AgNPs through a steric repulsion mechanism.<sup>167,168</sup> For instance, polyvinylpyrrolidone (PVP), a non-ionic polymer surfactant, has been used with citrate to functionalize vancomycin to AgNPs.<sup>169</sup> Interestingly, citrate–AgNPs demonstrated better drug loading than PVP–AgNPs. Ma *et al.* loaded vancomycin on pDa nanoparticles through π–π stacking, electrostatic, and hydrogen-bonding interactions.<sup>170</sup> AgNO<sub>3</sub> was subsequently reduced *in situ* and embedded by the action of pDa from the pDa–vancomycin hybrid in a stable and facile process. Due to the robust interaction between pDa and vancomycin, the nanohybrid demonstrated sustained drug release during extended incubation periods. The incorporation of pDa helped stabilize the AgNPs, preventing their aggregation and thus maintaining their antibacterial effectiveness. *In vitro* testing using a spread plate assay revealed the superior antibacterial effect of the nanohybrid. While vancomycin and pDa–vancomycin treatments reduced bacterial colony numbers to 80.7% and 54.4%, respectively, the pDa–vancomycin–Ag nanohybrid group showed almost no bacterial colonies. This synergistic antibacterial effect was quantified by a low Combination Index (CI) value of 0.328. Additionally, the nanohybrid achieved hyperthermia-assisted bacterial inactivation due to the photothermal pDa. In *S. aureus*-infected mice, all wounds decreased in size over time, with the combined antibiotic–Ag treatment showing the most effective wound healing and significant reduction in wound area percentage. The authors suggested a possible antibacterial synergistic mechanism that disrupts the bacterial membrane and ROS generation.<sup>170</sup> In another study, Veriato *et al.* investigated the formation of a complex between vancomycin–cysteamine and AgNPs.<sup>171</sup> The synthesized nano-antibiotic exhibited potent



**Table 2** Summary of antibacterial activity of vancomycin and AgNPs in combination

Sr. no.	Formulation	Particle size (nm)	Bacterial strain	Antibacterial activity	Ref.
1	AgNPs and vancomycin	MRSA: M1, M6, M7, HA1, USA300 GA-92, MSSA: SA 29213, SA 12600, SA 4651, SA 25923, SA 6538	Out of 10 isolates, 9 showed a mean reduction in biofilm mass of $20.8 \pm 3.8\%$ after a combination treatment of $2 \mu\text{g mL}^{-1}$ AgNPs and $2 \mu\text{g mL}^{-1}$ vancomycin for 24 h	156	
2	AgNPs AgNPs and vancomycin	10	10 <i>S. aureus</i> isolates were recovered from 50 urine specimens (7/10 MRSA)	MICs of AgNPs against MRSA isolates range from $1-2 \mu\text{g mL}^{-1}$ . The AgNPs/vancomycin combination, used at MIC/ MIC and 2MIC/4MIC, was more effective when the concentration of vancomycin was above the subinhibitory level ( $\geq$ MIC)	157
3	Vancomycin-capped with thioglycolic acid-stabilized AgNPs	20 to 42	<i>S. aureus</i> , <i>E. faecalis</i> (VRE) <i>S. epidermidis</i> (MRSE), <i>P. aeruginosa</i> , <i>E. coli</i>	MIC for Vancomycin-capped AgNPs was $0.1 \mu\text{g mL}^{-1}$ for VRE, $\leq 0.02 \mu\text{g mL}^{-1}$ for MRSE, and $0.05 \mu\text{g mL}^{-1}$ for <i>S. aureus</i>	21
4	Vancomycin grafted polydopamine (pDA) coated AgNPs	16 to 25	Vancomycin-resistant <i>E. faecalis</i>	Vancomycin concentrations as low as $1-5 \mu\text{M}$ , when grafted to pDA-AgNPs, show a significant zone of inhibition and antibacterial efficacy compared to the standard high dose of vancomycin (13-54 mM)	158
5	AgNPs PDA-AgNPs Vancomycin-pDA-AgNPs	$12 \pm 1.5$ $24 \pm 1.4$ $33 \pm 1.6$	Vancomycin-modified magnetic-based silver micro flowers (Van/Fe <sub>3</sub> O <sub>4</sub> -SiO <sub>2</sub> -Ag)	MICs of the vancomycin-modified Fe <sub>3</sub> O <sub>4</sub> -SiO <sub>2</sub> -Ag microflowers were $10 \mu\text{g mL}^{-1}$ for <i>E. coli</i> and $20 \mu\text{g mL}^{-1}$ for MRSA	159
6	Fe <sub>3</sub> O <sub>4</sub> -SiO <sub>2</sub> -Ag micro flowers Poly-(amido-amine) (PAMAM) dendrimers with dual-conjugated vancomycin and AgNP (Van-PAMAM-AgNP)	700 to 900	<i>E. coli</i> (BL21) and MRSA clinical isolates	Van-PAMAM-AgNP dendrimers achieved 6 to 7 log-unit reductions at $1 \mu\text{g mL}^{-1}$ Ag and $2 \mu\text{g mL}^{-1}$ vancomycin concentrations, primarily through cell wall damage. In mice with superficial wounds infected by vancomycin-resistant <i>S. aureus</i> Xen36, irrigation with low-dose Van-PAMAM-AgNP significantly improved healing compared to vancomycin or PAMAM-AgNP	160
7	PAMAM-AgNP Van-PAMAM-AgNP dendrimers Vancomycin functionalized AgNPs/3D-ZnO nanorod array	38 68	<i>S. aureus</i> (ATCC12600) and <i>S. aureus</i> (Xen36) <i>E. coli</i> and <i>S. aureus</i>	Platform demonstrated high detection sensitivity for <i>S. aureus</i> with a low detection limit of $330 \text{ CFU mL}^{-1}$ and adaptable bacterial elimination efficiency (50%) at concentrations of $1000-2000 \text{ CFU mL}^{-1}$ . Additionally, it exhibited high antibacterial activity (99.99%) due to the synergistic gemmical effect of vancomycin and AgNPs	161
8	Silica-encapsulated silver-coated gold nanoparticles conjugated with 2,3-naphthalocyanine dihydioxide (Nc) and vancomycin (Au-AgNP-SiO <sub>2</sub> -Nc-Van)	110	<i>B. subtilis</i> (ATCC 6633), <i>E. faecium</i> (ATCC 51559), <i>VanA</i> , <i>E. faecalis</i> (ATCC 51299, VanB), and <i>E. coli</i> (ATCC 535868)	Au-AgNP-SiO <sub>2</sub> -Nc-Van showed a bacterial reduction of 99.999% upon irradiation with $54 \text{ J cm}^{-2}$ . Fast bacterial regression was observed during <i>in vivo</i> photodynamic therapy of mice with <i>E. faecalis</i> (VanB) infected wounds	162
9	Vancomycin functionalized silver-titanium oxide nanoparticles (Van-Ag-TiO <sub>2</sub> )	60	Sulphate-reducing bacteria ( <i>Desulfotomaculum</i> spp.)	Vancomycin-sensitive sulfate-reducing bacteria were nearly eradicated within 1 h using Van-Ag-TiO <sub>2</sub> under UV light irradiation, demonstrating high selective phototoxicity	163



Table 2 (Contd.)

Sr. no.	Formulation	Particle size (nm)	Bacterial strain	Antibacterial activity	Ref.
10	Vancomycin loaded citrate-AgNPs (Van-citrate-AgNPs)	70 ± 3.3 86 ± 4.5 91 ± 2.3	<i>S. aureus</i> and <i>E. coli</i>	The zone of inhibition increased from 16 mm to 26.5 mm for <i>S. aureus</i> , while for <i>E. coli</i> , it increased from 0 mm to 7.5 mm	165
11	Van-citrate-AgNPs 0.1 mM Van-citrate-AgNPs 0.3 mM Vancomycin-cysteamine complexed AgNPs (Van-Cys-AgNPs)	—	<i>S. aureus</i> (ATCC 29213) and the clinical strains (SA-1, SA-2, and SA-3), <i>E. faecalis</i> (ATCC 29212) and the clinical strains (EF-1, EF-2, and EF-3)	For <i>S. aureus</i> ATCC 2913, both the MIC (2.00 to 0.25 µg mL <sup>-1</sup> ) and MBC (8 to 1 µg mL <sup>-1</sup> ) exhibited an 8-fold reduction with Van-Cys-AgNPs treatment. For <i>E. faecalis</i> ATCC 29212, the MIC demonstrated a 16-fold reduction (2.0 to 0.12 µg mL <sup>-1</sup> )	171
12	Vancomycin-encapsulated polydopamine with AgNPs (pDA-Van-Ag)	1.51 to 43.82	<i>E. coli</i> and <i>S. aureus</i>	Vancomycin and pDA-Van treatments reduced colony numbers by 80.7% and 54.4%, respectively, whereas nearly no bacterial colonies were observed in the pDA-Van-Ag nanohybrid group for <i>S. aureus</i> . The combination index (CI) value was 0.328, indicating synergistic effects. Significant bacteriakilling activity was also observed <i>in vivo</i> using an <i>S. aureus</i> -infected mouse skin defect model	170
13	pDA-Van-Ag Vancomycin-hybrid bimetallic nanoparticles (Au/AgNPs-Van)	290	<i>E. coli</i> ATCC 8099 and <i>S. aureus</i> ATCC 6538	MICs against <i>S. aureus</i> were reduced to 30–60 nmol mL <sup>-1</sup> for Au/AgNPs-Van-1 and AgNPs-Van, compared to 120 nmol mL <sup>-1</sup> for vancomycin and AuNP-Van	172
14	Ag/AuNPs-Van Vancomycin functionalized Au and Ag nanoparticles (Van-AuNPs) and (Van-AgNPs)	5 to 9	19 MRSA strains and 1 MSSA strain (ATCC 29213)	MIC values for Van-AgNPs (45.3–90.6 µg mL <sup>-1</sup> ) were lower than those of the Van-AuNPs (217.4 or >217.4 µg mL <sup>-1</sup> ). Van-AgNPs demonstrated 2.4 to 4.8-fold more significant activity compared to Van-AuNPs	173
15	Van-AuNPs Van-AgNPs	11.01 ± 3.62 12.08 ± 2.13	<i>E. coli</i> and <i>S. epidermidis</i>	MICs for <i>E. coli</i> and <i>S. epidermidis</i> were 15 and 10 µg mL <sup>-1</sup> , respectively, with the co-delivery system (SiNPs-Ag-Van) outperforming other formulations against both bacterial strains	174
16	AgNPs Silica NPs	10–25 200	Clinical MRSA isolates	<i>In vivo</i> studies with Sprague-Dawley rats showed that Ag-HA combined with vancomycin was the most effective treatment compared to HA, HA-vancomycin, and Ag-HA Van-Ag/LDHs platform demonstrated efficient antibacterial activity against <i>E. coli</i> and <i>S. aureus</i> , enabling simultaneous bacterial capture and disinfection	175
17	AgNPs and vancomycin co-modified layered double hydroxides (Van-Ag/LDHs)	—	<i>E. coli</i> and <i>S. aureus</i>	AgNPs	176
				30	

Table 2 (Contd.)

Sr. no.	Formulation	Particle size (nm)	Bacterial strain	Antibacterial activity	Ref.
18	Platelet membrane-camouflaged vancomycin-loaded Ag–metal organic frameworks (PLT/Ag-MOF–Van)	—	<i>E. coli</i> (ATCC 25922), <i>P. aeruginosa</i> (ATCC 27853), and <i>S. aureus</i> (ATCC 25923)	MIC of free vancomycin was $2 \mu\text{g mL}^{-1}$ , and Ag–MOF–Van was $1 \mu\text{g mL}^{-1}$ against MRSA, which was reduced to $0.5 \mu\text{g mL}^{-1}$ for PLT/Ag–MOF–Van. Encapsulation in the platelet membrane allowed it to bind effectively to MRSA bacteria and infection sites. PLT/Ag–MOF–Van showed significantly better anti-infective efficacy <i>in vivo</i> mouse MRSA pneumonia model compared to free vancomycin	177
19	PLT/Ag–MOF–Van	148	<i>S. aureus</i> 113, <i>S. epidermidis</i> 1457, and <i>E. coli</i>	MBC values for vancomycin and IPV were quasi-identical, highlighting the potential for use as biocompatible and self-protective antibacterial implant coatings	178
20	Bovine pericardium impregnated with vancomycin or AgNPs	—	10 clinical isolates of MSSA and MRSA, each AgNPs	Antibacterial effect were observed in an <i>in vivo</i> <i>S. aureus</i> infection mouse model following subcutaneous spine implantation, with minimal inflammatory response	179

Abbreviations: silver nanoparticles (AgNPs), minimum inhibitory effect (MIC), zone of inhibition (ZO), minimal bactericidal concentration (MBC), combination index (CI), methicillin-resistant *S. aureus* (MRSA), methicillin-Sensitive *S. aureus* (MSSA), vancomycin-resistant enterococci (VRE).

bacteriostatic activity against both *S. aureus* and *E. faecalis*, achieving a MIC of  $\leq 1 \mu\text{g mL}^{-1}$ . These findings indicate that the antibiotic coating on AgNPs enhances both bacteriostatic and bactericidal effects, suggesting this approach is a promising alternative for treating resistant strains.

Combining silver with other metals, such as gold, has been explored to enhance its antibacterial effects. Lu *et al.* prepared Au/Ag nanoparticles functionalized with vancomycin using a one-pot method.<sup>172</sup> They observed that the antibacterial activity increased with Ag content, specifically when the Ag–Au ratio remained below 2 : 1. Additionally, their study revealed that vancomycin could effectively enhance the adhesion between bacteria and the nanoparticles, effectively doubling it. The composite application showed lower bacterial resistance, with MIC values as low as  $30 \text{ nmol mL}^{-1}$ .<sup>172</sup> Hur and Park utilized a one-step, one-pot process to functionalize Au and Ag nanoparticles with vancomycin.<sup>173</sup> In this process, vancomycin served dual roles as both a reducing agent and a capping agent for the nanoparticles. The process employed a green synthesis route to prepare spherically shaped particles with an average diameter of around 12 nm. Their report indicated that vancomycin–AgNPs (MIC 45.3–90.6  $\mu\text{g mL}^{-1}$ ) have more antibacterial potential (2.4–4.8-fold increase) than vancomycin–AuNPs (MIC 217.4 or  $>217.4 \mu\text{g mL}^{-1}$ ).<sup>173</sup>

In addition, silica nanoparticles have been used as carriers to enhance antibacterial functions for the co-delivery of vancomycin and AgNPs.<sup>174</sup> The silica's porous structure facilitates a substantial loading capacity, whereas its spiky nano topography encourages pathogen interactions that enhance surface adhesion and localized delivery. A dual solvent method was employed to prepare Ag–silica nanoparticles, resulting in the uniform distribution of AgNPs measuring 10 to 25 nm on the surface of silica particles ( $\sim 200 \text{ nm}$ ) with a hollow core of approximately 110 nm, exhibiting no evident aggregation. Following this, vancomycin was loaded onto this composite, as shown demonstrating sustained release over two days and a synergistic bactericidal effect against both *E. coli* and *S. epidermidis*. The enhanced antibacterial effect of co-delivered nano-Ag and vancomycin using silica nanoparticles was explored through their interaction with bacterial membranes. Nano-Ag-decorated silica nanoparticles caused significant bacterial damage, effectively disrupting the membranes of *E. coli* and *S. epidermidis*.<sup>174</sup>

Hashimoto *et al.* explored the impact of a hydroxyapatite coating infused with silver (Ag–HA) and vancomycin on the MRSA biofilm formation.<sup>175</sup> The study demonstrated that the Ag–HA coating effectively inhibited the formation of MRSA biofilms and altered their architecture. The combination of Ag–HA coating and vancomycin synergistically reduced the formation of MRSA biofilms both *in vitro* and *in vivo*. Sun *et al.* utilized layered double hydroxides (LDHs) to capture and disinfect bacteria simultaneously.<sup>176</sup> The AgNPs were synthesized on the LDH surface *via* the reduction of  $\text{Ag}^+$  ions using glucose, followed by vancomycin adsorption onto the LDH sheets. The LDH nanocomposite demonstrated enhanced antibacterial activity against both Gram-positive and Gram-nega-

tive bacteria. In another study, Huang *et al.* developed pH-responsive platelet membrane-camouflaged nanoparticles of silver metal-organic framework (Ag-MOF) and vancomycin.<sup>177</sup> The Ag-MOF was synthesized with 2-methylimidazole as the ligand and silver nitrate as the ion source. The vancomycin encapsulation efficiency was 81%, while the loading efficiency reached 64.7%. The Ag-MOF loaded with vancomycin exhibited significant antibacterial activity against standard clinical isolates *in vitro*, surpassing the efficacy of free vancomycin. The platelet membrane facilitates adhesion to the *S. aureus* surface and targets MRSA infection sites. In a mouse-MRSA pneumonia model, the nanocomposite demonstrated a superior anti-infective effect compared to free vancomycin without apparent toxicity.<sup>177</sup>

Biomaterials play a crucial role in modern medicine; however, treating infections associated with these materials remains challenging due to the increased antibiotic resistance of bacterial biofilms. Varisco *et al.* developed a self-protective antimicrobial and biocompatible coating utilizing Ag<sup>+</sup> ions and a derivate of vancomycin, termed intelligent pyridinate vancomycin (IPV).<sup>178</sup> Recently, Collatusso, *et al.* created a novel biological membrane from bovine pericardium samples impregnated with AgNPs or vancomycin to mitigate the draw-

backs associated with antimicrobial properties in existing scaffold materials.<sup>179</sup> The membrane successfully decreased the *S. aureus* loads in murine infection model, while also demonstrating good biocompatibility and osteoconductivity, indicating its potential applications in various clinical settings, particularly as an antimicrobial coating for implants in orthopedic and spinal surgery. In another study, AgNPs and vancomycin-loaded collagen nanofibers were synthesized using the electrospinning method.<sup>180</sup> The synthesized nanofibers demonstrated antimicrobial activity against *E. coli* and *S. aureus*, emphasizing their promise for biomedical applications. Table 2 summarizes the antibacterial activity of vancomycin and AgNPs when used in combination.

AgNPs have been shown to enhance the efficacy of vancomycin through various mechanisms. This integrated system offers a powerful strategy to overcome antibiotic resistance, as highlighted in multiple studies. Specifically, AgNPs have been demonstrated to significantly reduce the MIC of vancomycin by increasing oxidative stress, disrupting bacterial membranes, and facilitating antibiotic uptake, thereby improving its effectiveness against resistant bacterial strains. Morones-Ramirez *et al.* demonstrated that AgNPs play an essential role in restoring the bactericidal action of vancomycin against Gram-nega-

**Table 3** Some of the metallic nanoparticles with vancomycin

Metal	Formulation	Size (nm)	Bacterial strain	Antibacterial activity	Ref.
Silver	Vancomycin-cysteamine complexed AgNPs (Van-Cys-AgNPs)	1.51 to 43.82	<i>S. aureus</i> (ATCC 29213) and the clinical strains (SA-1, SA-2, and SA-3), <i>E. faecalis</i> (ATCC 29212) and the clinical strains (EF-1, EF-2, and EF-3)	For <i>S. aureus</i> ATCC 2913, both the MIC (2.00 to 0.25) and MBC (8 to 1) exhibited an 8-fold reduction with Van-Cys-AgNPs treatment. For <i>E. faecalis</i> ATCC 29212, the MIC demonstrated a 16-fold reduction (2.0 to 0.12)	171
Gold	AgNPs Vancomycin-functionalized gold nanoparticles (V-GNPs)	24 to 77	<i>E. coli</i> (ATCC 25923), <i>K. oxytoca</i> (ATCC 43165), <i>P. aeruginosa</i> (NCIM 2036), <i>S. aureus</i> (ATCC 14222)	The observed antibacterial activities of V-GNPs were 1.4-, 1.6-, 1.8-, and 1.6-fold higher against <i>E. coli</i> , <i>K. oxytoca</i> , <i>P. aeruginosa</i> , and <i>S. aureus</i> , respectively, compared to pure vancomycin	184
Copper	Vancomycin-modified copper sulfide nanoparticles (CuS-Van)	15 ± 5	<i>Van-resistant E. faecium</i> (ATCC51559, VanA), <i>E. faecalis</i> (ATCC 51299, VanB)	CuS-Van with NIR irradiation demonstrated the highest antibacterial efficacy and the fastest infection regression in the <i>in vivo</i> study compared to the control groups	185
Iron	Vancomycin and nisin-modified magnetite ( $Fe_3O_4$ )– $SiO_2$ nano-structures coated with chitosan	22–47	<i>S. aureus</i> ATCC 33591 (MRSA), <i>S. aureus</i> ATCC 25923 (MSSA)	Vancomycin-functionalized nanocomposites exhibited to be more efficient in eradicating bacterial cells both <i>in vitro</i> and <i>in vivo</i>	186
Gallium	Vancomycin and gallium nitrate ( $Ga(NO_3)_3$ )	—	MSSA (ATCC 25 923) and MRSA (ATCC 33 591)	The combination of vancomycin and $Ga(NO_3)_3$ reduced the MIC of vancomycin in MRSA, exhibiting an additive effect while also inhibiting biofilm formation and enhancing biofilm destruction, particularly in the MRSA strain	187
Nickel	Vancomycin-modified gold nanoparticles combined with magnetic nickel oxide nanoparticles (NiO NPs–AuNPs–Van)	193.08 ± 1.61	MRSA (800 926)	Combination therapy accelerated wound healing in MRSA-infected mice by promoting collagen coverage, reducing IL-6 and TNF- $\alpha$ cytokines, and upregulating VEGF expression	188
Zinc	Vancomycin and zinc oxide nanoparticles	20–150	<i>S. aureus</i> clinical isolates	Decrease in vancomycin MICs from 2500–5000 $\mu$ g mL <sup>-1</sup> to 39–78.125 $\mu$ g mL <sup>-1</sup> when mixed with ZnO NPs	189



tive bacteria. The mechanism involved AgNPs increasing bacterial membrane permeability, allowing vancomycin to penetrate and become effective against Gram-negative pathogens. The combination therapy demonstrated significant reductions in bacterial cell counts. *In vivo* studies using mild and acute peritonitis models revealed that the combination of Ag<sup>+</sup> and vancomycin significantly reduced *E. coli* cell counts, while individual treatments had limited effect.<sup>181</sup> These findings suggest that combining AgNPs with vancomycin is a promising strategy to combat antibiotic-resistant infections and potentially repurpose existing antibiotics for broader application.

While combining AgNPs and vancomycin shows promise in enhancing antibacterial activity, there are several potential challenges to consider. The intricate synthesis process required to create a stable and effective AgNP vancomycin system poses technical hurdles, while concerns regarding the potential toxicity of these hybrid structures to human cells and tissues remain at the forefront of safety considerations. Moreover, the variable efficacy observed across different bacterial strains underscores the need for comprehensive testing and optimization to ensure broad-spectrum applicability. Long-term bacterial resistance development should also be considered. Regulatory approval and clinical translation present additional hurdles due to the novel nature of this nanomedicine approach. Addressing these challenges are essential to harness the full potential of combining AgNPs and vancomycin in combating antibiotic-resistant bacteria.

#### 4.3. Other metal nanoparticles in enhancing antibiotic efficacy

The role of nanoparticles in combating bacterial resistance extends beyond silver, encompassing various metal nanoparticles such as copper, gold, and zinc. These nanoparticles, when combined with antibiotics, offer promising avenues for addressing antimicrobial resistance. Copper nanoparticles, for example, have shown strong antimicrobial activity against biofilm-forming pathogens,<sup>182</sup> while gold nanoparticles are known for their ease of surface modification.<sup>183</sup> These properties position other metallic nanoparticles as an attractive option for enhancing antibiotic delivery, similar to AgNPs. Table 3 presents some of the combinations of metallic nanoparticles with vancomycin.

## 5. Conclusion and future outlook

By pairing specialized properties of metallic nanoparticles with antibiotics, this method offers a dynamic approach to counteracting the growing threat of bacterial resistance. Metallic nanoparticles, including silver, copper, and gold, possess intrinsic antimicrobial properties that can augment the effectiveness of antibiotics. These nanoparticles work through mechanisms such as disrupting bacterial cell membranes, interfering with essential cellular processes, and inducing oxidative stress. This review highlights the synergistic potential of AgNPs combined with vancomycin as an effective

approach to combat antibiotic-resistant pathogens. Insights gained from this combination can be applied more broadly to other antibiotics, enhancing their efficacy against resistant bacteria, particularly those residing in biofilms. Future research should focus on unraveling the molecular mechanisms behind how AgNPs boost antibiotic activity in resistant strains. Understanding the interactions between AgNPs and bacterial membranes, enzymes, and genetic pathways responsible for resistance will provide critical insights into optimizing these combinations. Additionally, studies should explore strategies to fine-tune nanoparticle size, surface charge, and coating materials to improve targeted drug delivery, minimize cytotoxicity, and ensure compatibility with specific antibiotics. From a clinical standpoint, comprehensive preclinical and clinical investigations are essential to assess the safety, efficacy, and optimal dosing of AgNPs in antibiotic formulations for both systemic and topical applications. Addressing concerns such as nanoparticle toxicity, long-term tissue accumulation, and environmental impact will be pivotal for securing regulatory approval and ensuring successful clinical translation. Collaborative efforts among researchers and clinicians are important to ensuring the stability, scalability, and cost-effectiveness of these technologies for widespread clinical adoption.

In summary, ongoing research and optimization of metallic nanoparticle-antibiotic combinations have the potential to transform the treatment of antibiotic-resistant infections. By providing novel, effective therapeutic options, these strategies have the potential to improve treatment outcomes, alleviate healthcare burdens, and significantly enhance patient care in the face of the growing threat of antimicrobial resistance.

## Abbreviations

AgNPs	Silver nanoparticles
aPDT	Antimicrobial photodynamic therapy
CDC	Disease control and prevention
CFU	Colony-forming units
CI	Combination index
EDC	<i>N</i> -(3-Dimethylaminopropyl)- <i>N'</i> -ethylcarbodiimide hydrochloride
ETC	Electron transport chain
FDA	Food and Drug Administration
GLASS	Global antimicrobial resistance and use surveillance system
IPV	Intelligent pyridinate vancomycin
LDHs	Layered double hydroxides
MDR	Multidrug-resistant
MICs	Minimum inhibitory concentrations
MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
MRSE	Methicillin-resistant <i>Staphylococcus epidermidis</i>
NAM	<i>N</i> -Acetylmuramic acid
NAG	<i>N</i> -Acetylglucosamine
NHS	<i>N</i> -Hydroxysuccinimide



OECD	Organization for Economic Cooperation and Development
PAMAM	Poly(amidoamine)
PVP	Polypyrrolidine
RND	Resistance-nodulation-division
ROS	Reactive oxygen species
SEM	Scanning electron microscopy
SERS	Surface-enhanced Raman scattering
TCA	Tricarboxylic acid cycle
UV	Ultraviolet
VISA	vancomycin-intermediate <i>S. aureus</i>
VRE	Vancomycin-resistant enterococci
VRSA	Vancomycin-resistant <i>S. aureus</i>
WHO	World Health Organization

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## Data availability

This review does not involve the analysis of primary research data, software, or code. The data tables presented in this study are compiled from publicly available sources in open-access journals cited throughout the manuscript. Full references to these sources are provided in the text. Additional data, supporting materials, or further clarifications will be made available upon reasonable request to the corresponding author.

## Conflicts of interest

The authors declare no competing interests.

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