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BACTERIAL, FUNGAL AND VIRUS MOLECULAR BIOLOGY - REVIEW

Bactericidal activity of silver nanoparticles in drug-resistant bacteria

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Abstract
Bacterial resistance to multiple drugs is a worldwide problem that afflicts public health. Various studies have shown that silver nanoparticles are good bactericidal agents against bacteria due to the adherence and penetration of the external bacterial membrane, preventing different vital functions and subsequently bacterial cell death. A systematic review of ScienceDirect, PubMed, and EBSCOhost was conducted to synthesize the literature evidence on the association between the bactericidal property of silver nanoparticles on both resistant Gram-positive and Gram-negative bacteria. Eligible studies were original, comparative observational studies that reported results on drug-resistant bacteria. Two independent reviewers extracted the relevant information. Out of the initial 1 420, 142 studies met the inclusion criteria and were included to form the basis of the analysis. Full-text screening led to the selection of 6 articles for review. The results of this systematic review showed that silver nanoparticles act primarily as bacteriostatic agents and subsequently as bactericides, both in Gram-positive and Gram-negative drug-resistant bacteria.

Keywords Drug-resistant bacteria · Gram-positive bacteria · Gram-negative bacteria

Introduction

One of the greatest challenges facing the global healthcare systems today is drug-resistant pathogenic species [1]. Drug-resistant bacterial infections are on the rise and pose a severe risk to the public's health [2]. Antimicrobial resistance (AMR) in strains is genetically determined and most mediated by the acquisition of extrachromosomal genetic elements through horizontal gene transfer, low outer membrane permeability, production of degradative enzymes, and target modification, as examples of mechanisms used by bacteria to resist antibiotic toxicity [3-5]. Bacterial resistance affects human and animal health worldwide, so new alternatives are being sought to help successfully address the different types of drug-resistant bacteria. AMR is a growing public health problem that is caused by the overuse and misuse of antibiotics. While antibiotics offer a safe and efficient treatment option for patients with bacterial infections, their availability also poses a risk of overuse, which can lead to the evolution of antibiotic-resistant bacteria at a population level [6]. Additionally, the widespread use of antibiotics in animal husbandry has also contributed to the development of AMR, as it creates an environment that selects for resistant bacteria [7, 8]. Other factors that contribute to the development of AMR include poor infection control practices, the lack of access to clean water and sanitation [9], and inadequate surveillance systems. In the same way, bacterial persistence also occurs. Persistent bacteria are a subpopulation of cells that are not killed by antibiotics [10-12]. This phenotype arises when bacteria enter a dormant state, making them less susceptible to antibiotics. Once the antibiotic concentration decreases, the dormant cells can resuscitate and regrow, potentially acquiring resistance genes in the process. Thus, understanding the mechanisms that contribute to bacterial persistence is crucial for developing new strategies to combat AMR.

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Most bacteria can be divided into two separate classifications according to their cell wall structure: Gram-positive and Gram-negative [13]. Gram-positive bacteria contain a thick peptidoglycan layer in their cell walls, while Gram-negative bacteria have a thin peptidoglycan layer with an additional outer membrane consisting of lipopolysaccharide [14]. The outer membrane of Gram-negative bacteria is a critical component that plays a significant role in the resistance of these bacteria to a wide range of antibiotics. The outer membrane acts as a protective barrier against various antibiotics, preventing them from entering the bacterial cell and exerting their antibacterial activity. As a result, the outer membrane is considered the primary factor responsible for the high level of drug resistance observed in Gram-negative bacteria. New treatments have been developed to fight against Gram-negative resistant bacteria such as β-lactamase inhibitor antibiotic adjuvants which deactivate the mechanism of resistance [15]. In the same sense, Gram-positive bacteria have shown an ability to acquire resistance to almost all clinically available antimicrobials. Mechanisms of resistance include alteration of bacterial structures, such as thickening of peptidoglycan, and efflux of drugs by overexpression of efflux pumps [16]. Research efforts have resulted in the discovery of innovative antibiotics and alternative treatments like peptidic benzimidazoles, quorum sensing (QS) inhibitors [17-20], and Ru complexes [21, 22] to target novel bacterial processes in Gram-negative bacteria, while teixobactin [23, 24], malacidins [25], nanostructured materials [26, 27], and microemulsions [28] have been studied in Gram-positive bacteria, and DCAP [29], odilorhabdins [30], and bacteriophages [31] have been studied in both [15, 16].

Antibiotics are chemical substances used to treat bacterial infections. Antibiotics kill bacteria or inhibit their growth by blocking key cellular pathways [32]. They also allow our natural defenses, including the host immune system, to eliminate invading microorganisms [33, 34]. They target specific cellular components or processes in bacteria, disrupting their growth and replication. There are several main classes of antibiotics, each with different mechanisms of action and molecular targets. For example, beta-lactams, such as penicillins and cephalosporins, target bacterial cell wall synthesis by inhibiting the enzymes that cross-link peptidoglycan strands [35]. Aminoglycosides, like streptomycin and gentamicin, bind to bacterial ribosomes, inhibiting protein synthesis [36]. Tetracyclines, such as doxycycline, also target the bacterial ribosome, but at a different site than aminoglycosides [37]. Fluoroquinolones, such as ciprofloxacin and levofloxacin, inhibit bacterial DNA synthesis by binding to the enzyme DNA gyrase [38-40]. Macrolides, such as erythromycin and azithromycin, bind to the bacterial ribosome and inhibit protein synthesis by preventing peptide bond formation [41-44]. These are just a few examples of the different classes of antibiotics and their targets in bacteria. Long-term use of antibiotics leads to bacterial resistance. It is important to note that with the rise of antibiotic resistance, some antibiotics may no longer be effective against certain bacterial strains. Acquired resistance develops with genetic mutations or by external genetic acquisition from nearby resistant organisms through horizontal gene transfer [45] (Fig. 1).

Drug-resistant bacteria increase the risk of failure of conventional therapies, resulting in increased morbidity, higher mortality, longer duration of hospitalization, and higher treatment costs. Currently, researchers are focusing on the development of new antimicrobial agents [47] such as antimicrobial peptides and vaccines [48], combination therapy

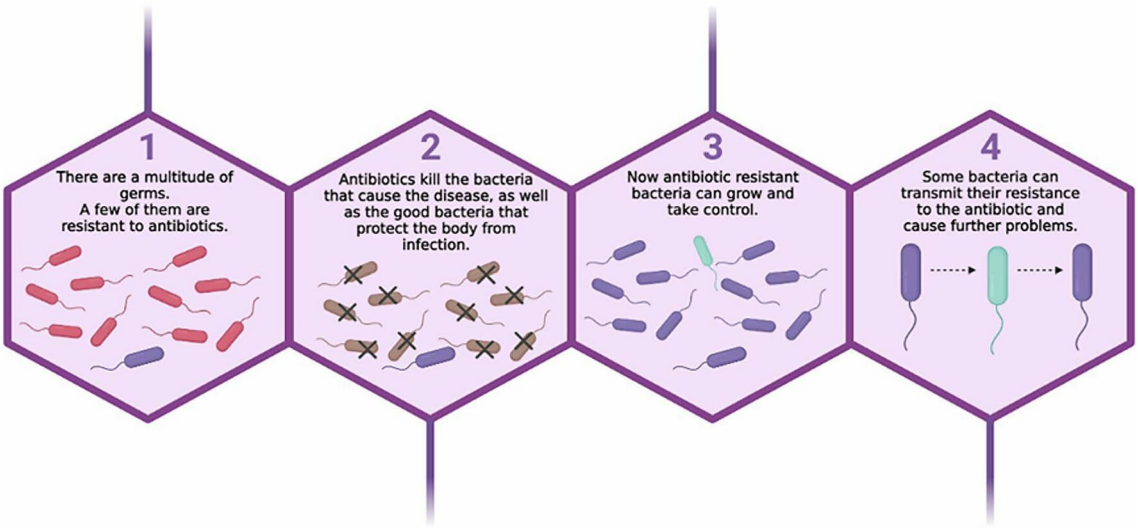

Fig. 1 Scheme of the mechanism by which bacteria transmit drug resistance [46]

[49], antibiotics hybrids [50], molecularly imprinted polymers [51], complex phytochemicals [52], carbon dot-based therapeutics [53], heterostructures 2D [54], nanoparticles [55] including silica-based nanosystems [56], alumina [57], and metallic nanoparticles [58]. For several years, silver nanoparticles (AgNP) have attracted attention and their antibacterial properties have been extensively investigated, although many of the studies are conducted in combination with other antimicrobial agents [59-63]. Therefore, it is necessary to elucidate their effectiveness on their own in drug-resistant bacteria.

Resistance to nanomaterials is less likely to develop in bacteria [64, 65]. Therefore, there is a lot of interest in non-traditional antibacterial medicines to combat the resistance that diverse harmful microbes develop against the most common antibiotics. Although AgNP's strong antimicrobial impact has been extensively characterized, its mechanism of action is still not completely understood [66]. In fact, a complex mechanism by which nanoparticles interact with germs appears to relate to the strong antibacterial and broad-spectrum activity against morphologically and metabolically distinct microorganisms. Furthermore, their structure and various ways of interacting with bacterial surfaces may present a novel and underutilized antibacterial mechanism to take advantage of. The fabrication and synthesis parameters, such as temperature, the presence of a substrate, pH, and the flow velocity of the growth material, have a major impact on the morphology and structure of AgNPs [67]. AgNP nanoparticles have a crystalline structure and can be synthesized in various shapes and sizes, ranging from a few nanometers to hundreds of nanometers. The size of nanoparticles plays a critical role in their interaction with bacterial cell wall and membranes [68]. The size of nanoparticles can influence the surface area available for interaction with bacterial membranes [69]. Enhanced interaction with microorganisms and an amplified antimicrobial effect can be attributed to the larger surface area of nanoparticles. In addition, surface charge of nanoparticles can also influence their interaction with bacterial membranes. Positively charged nanoparticles can adhere to the negatively charged bacterial membrane and destabilize it, leading to bacterial cell death [70].

The purpose of this work is to determine the antibacterial efficacy of AgNPs, without combining with other agents, on resistant bacteria. Considering that the antibacterial effect of silver nanoparticles has been extensively studied and that there are several species of resistant bacteria that can be classified as Gram-positive or Gram-negative. Therefore, we pose the research question: In what type of drug-resistant bacteria (Gram-positive or Gram-negative) are silver nanoparticles more effective as bactericides? The results of this research, if validated by larger studies, may help to develop nanomaterials to mitigate the risk of infections by drug-resistant bacteria.

Methods

This systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and follows the protocol registered elsewhere [71]. A comprehensive search for relevant evidence was conducted following the search strategy ("Silver nanoparticles" OR AgNPs) AND ("Antibacterial activity" OR "Antimicrobial agents" OR "Bactericidal activity") AND ("Drug resistant" OR "Multidrug resistant") AND ("Gram positive" OR "Gram negative"). The following databases were searched: ScienceDirect, PubMed, and EBSCOhost. The paper that met the inclusion criteria was included in the review. The inclusion criteria were that it was a study applying silver nanoparticles in drug-resistant bacteria, that it clearly indicated the Gram-positive or Gram-negative classification of the strain used, that it had a publication date of 2015 onwards, that we had access to the full text, and that it was written in English. On the other hand, the paper was not included in the review if it met any exclusion criteria. The exclusion criteria determined that the paper was excluded if it was a publication other than a research article (e.g., reviews, book chapters, or editorials) or that silver nanoparticles were used in combination with any other component or drug in the study.

Records identified were exported to bibliographic software (Mendeley Reference Manager). Duplicate records were excluded. Titles and abstracts of all associated articles were screened for eligibility against the review selection criteria. Screening of articles and data extraction were independently carried out by two reviewers (C. C. G. and L. I. G. G), with a third reviewer asked in case of disagreement. Data were extracted on the characteristics of the AgNP, such as their synthesis method, the size, and morphology. In the same way, data such as the type of bacteria, Gram classification, incubation time, minimum inhibitory concentration, or zone of inhibition were also extracted from the sources of evidence. All the information on indicated variables of the included articles were listed in tables built in Microsoft Excel. Last of all, the content of those Excel tables was checked by a third reviewer (JMC-A), attesting the registry compliance.

Results and discussion

Our primary search identified a total of 1420 articles. The screening of the papers is depicted in Fig. 2. Database automation tools, such as publication date, filtering of records other than research articles, resulted in the removal of 1211 records. Duplicates screening led to 67

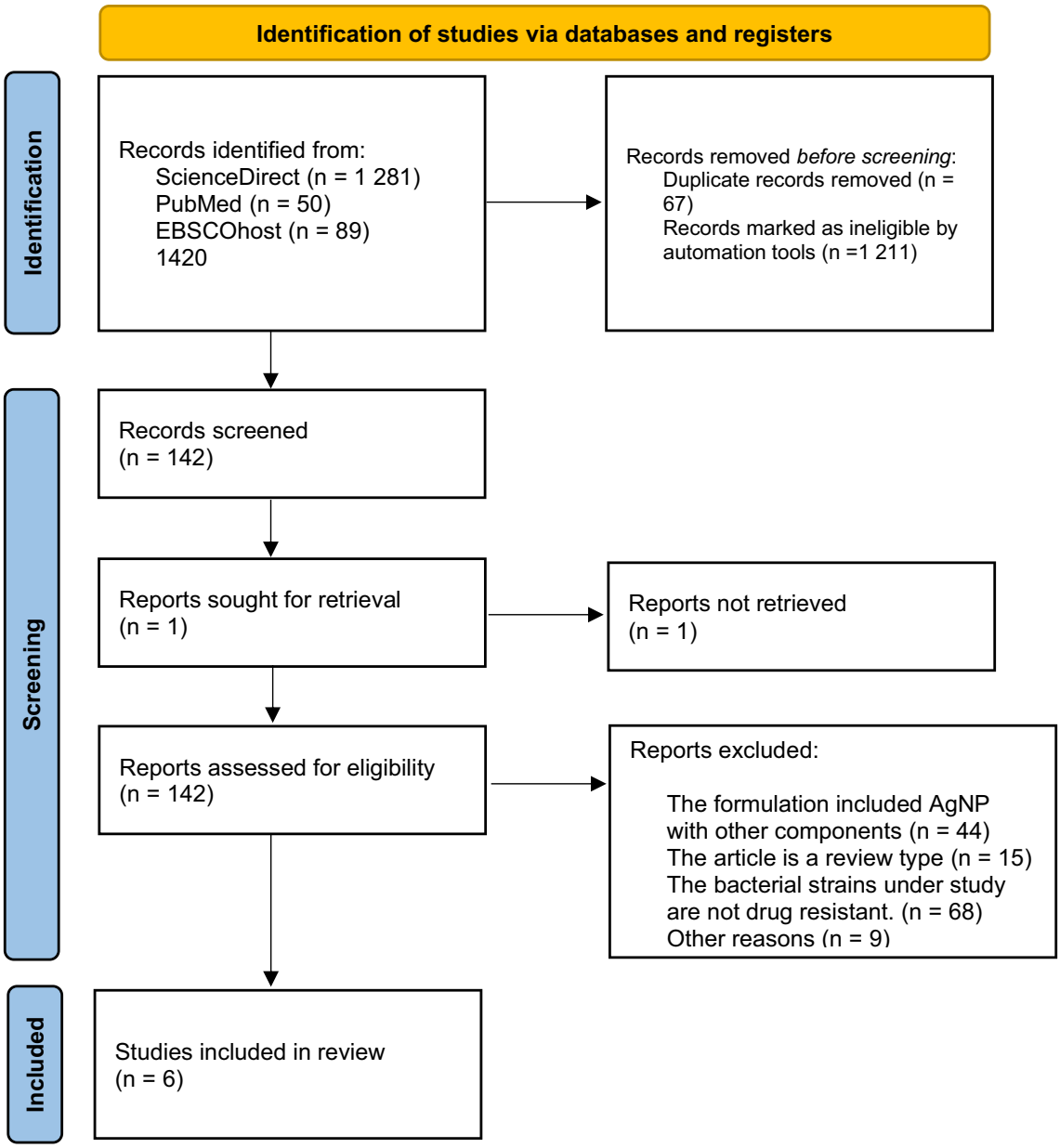

Fig. 2 PRISMA flowchart

articles being excluded resulting in 142 remaining for full-text screening. Full-text screening led to 6 articles being selected for the review.

All 6 studies used both Gram-positive and Gram-negative bacteria for their respective investigations, which allowed a comparison between the results. Of the 6 studies, the one that obtained a smaller average size of AgNP corresponds to Yuan et al. 2017 [72] with an average of 11 nm, which was achieved by a green synthesis that was performed using quercetin. The influence of AgNP nanoparticle size on bacterial interaction and antimicrobial efficacy has been extensively studied in the literature. The literature suggests that nanoparticle size has a significant impact on their antimicrobial activity against bacteria [69]. However, it is important to note that other factors such as shape [73, 74] as well as surface charge [75] can also affect their interaction with bacterial cells. Studies have shown that smaller AgNPs have greater inhibitory activity compared to their counterparts. This is attributed to the fact that AgNPs with a size of approximately 10 nm can easily penetrate the nucleus of microorganisms, leading to an accumulation of envelope protein precursors in bacterial cells, which is indicative of the dissipation of the proton motive force, leading to bacterial death [76]. Other studies agree that the size close to

10 nm has a greater impact on antibacterial efficacy over the range 5–100 nm [77].

On the other hand, the Gram-negative bacterial strains that were repeated in more studies were *Pseudomonas aeruginosa*, being used by Cavassin et al. 2015 [78], Yuan et al. 2017 [72], Arul et al. 2017 [79], and Mahmod et al. 2021 [80] (Table 1). While in Gram positives all 6 studies used *Staphylococcus aureus*, as shown in Table 1. *Pseudomonas* and *Staphylococcus* are commonly found in various studies due to their high prevalence as pathogenic bacteria and their ability to develop resistance to antibiotics [81]. Several studies have shown that *Pseudomonas aeruginosa* and *Staphylococcus aureus* are two of the most common bacteria associated with hospital-acquired infections, and both are known for their high levels of antibiotic resistance [82-84]. The mechanisms of resistance in these bacteria have been extensively studied, and it has been found that they possess various genetic and biochemical mechanisms that allow them to resist the action of antibiotics [85-89]. In addition, *Pseudomonas* and *Staphylococcus* are both opportunistic pathogens, meaning they can cause infection in people with weakened immune systems, such as those with chronic diseases or who have undergone surgery [90, 91]. Therefore, it is important to study the interaction of AgNPs with these bacteria as they are responsible for a significant portion of hospital-acquired infections and are known for their resistance to antibiotics. In five of the studies included in the review the samples were incubated for 24 h after being exposed to AgNP [72, 78, 79, 92, 93] in which the minimum inhibitory concentration (MIC) was evaluated. Paosen et al. 2019 [93] reported the lowest MIC of 0.02–0.09 µg /mL against the Gram-negative *Acinetobacter baumannii* as well as for the Gram-positive *E. faecalis* and *S. aureus*. Regarding the results of Mahmod *e*t al. 2021 [80], Gram negative had an inhibition zone of 12 mm for both strains, while the Gram-positive *Staphylococcus* has an inhibition zone of 8.67 mm.

Table 2 presents the objectives and a summary of the findings of the 6 included studies. Overall, the main objectives of these studies were to successfully synthesize AgNP and then apply and evaluate their effectiveness on drug-resistant bacteria. The studies by Yuan et al. 2017 [72] and Paosen et al. 2019 [93] report that the bacteria suffered damage to the cell membrane, which causes them instability, thus inhibiting their respiration and thus preventing them from growing. Finally, AgNP in all 6 studies presents a greater effect on Gram-negative strains, according to the findings shown in Table 2.

The findings of this systematic review indicate that more studies are needed to focus AgNP specifically on drug-resistant strains. It was also found that as new alternatives such as silver nanoparticles to combat bacterial resistance are found to be in demand to meet the needs of modern medicine, it is important to find ways to synthesize such nanoparticles in an environmentally friendly and cost-effective manner. Additionally, studies found different ways to perform green synthesis by bioresources such as extract of flowers, leaves, stems, plants, and even in microorganisms such as bacteria obtained from seawater as in the case of Arul et al. 2017 [79]. In the study of Mahmod et al. 2021 [80], it was found

Table 1 Summary of data on Gram-negative and Gram-positive bacteria extracted from evidence sources

Ref	Morphology, size (nm)	Type of test, hours of incubation	Drug-resistant bacteria used with their Gram classification and notable MIC or ZOI results
[72]	Well-dispersed and highly spherical in shape with an average size of 11 nm	MIC, 24	*P. aeruginosa* (−), 1 µg/ml *S. aureus* (+), 2 µg/ml
[78]	Spherical, 40 nm	MIC, 24	*A. baumannii* (−), 3.4 µg/ml *P. aeruginosa* (−), 3.4 µg/ml *S. aureus* (+),6.7 µg/ml
[79]	Spherical in shape and the sizes ranged between 24 and 46 nm	MIC, 24	*E. coli* (−), 6.25 µg /mL *K. pneumoniae* (−), 3.12 µg /mL *P. aeruginosa* (−), 3.12 µg /mL *S. aureus* (+),12.5 µg /mL
[80]	——	ZOI, 18	*K. pneumoniae* (−), 12.00 ± 0.58 mm *P. aeruginosa* (−), 12.00 ± 1.00 mm *S. aureus* (+), 7.00 ± 1.00 mm *S. mutans* (+), 8.67 ± 1.53 mm
[92]	Nearly triangular geometry with a mean size of 18 ± 3 nm	MIC, 24	*E. coli* (−), 4 µg /mL *S. aureus* (+), 8 µg /mL
[93]	Spherical shaped with an average size of 17.51 nm	MIC, 24	*A. baumannii* (−), 0.02–0.09 µg /mL *E. coli* (−), 0.04–0.18 µg /mL *E. faecalis* (+),0.09–0.36 µg /mL *S. aureus* (+),0.09–0.36 µg /mL

**MIC*, minimum inhibitory concentration; *ZOI*, zone of inhibition

Table 2 Summary of findings from selected records

Ref	Aims of the study	Summary of findings
[72]	The objectives of the study were to synthesize and characterize AgNP by means of the biomolecule quercetin as a reducing and stabilizing agent. In addition, to isolate and characterize the milk samples carrying the bacteria. And finally, to evaluate the effect of biologically synthesized AgNP on multidrug resistant Gram-negative and Gram-positive bacteria	A nanomaterial-based antimicrobial therapy was designed against *P. aeruginosa* and *S. aureus*, strains isolated from milk samples of mastitis-infected goats Successful biomolecule-assisted synthesis of AgNP using quercetin is demonstrated. AgNP were more effective against Gram-negative *P. aeruginosa* than Gram-positive *S. aureus*, which could be explained by differences in membrane structure and cell wall composition that influence bacterial accessibility to AgNP -AgNP exert antibacterial effects through loss of membrane stability and inactivation of respiratory chain dehydrogenases, which inhibit cell respiration and growth
[78]	The objective of this study was to evaluate the in vitro activity of AgNP stabilized with different compounds against MDR and Gram-positive and Gram-negative antimicrobial susceptible microorganisms, using different methods	-Different methods were used: agar diffusion, minimum inhibitory concentration, minimum bactericidal concentration and kill time -The activity of AgNP by solid media diffusion and MIC methods showed a similar effect against MDR and antimicrobial susceptible isolates, with a higher effect against Gram-negative strains -The best results were obtained with citrate and chitosan silver nanoparticle
[79]	The objective of the study focuses on the characterization and identification of the most effective marine bacterium against MDR pathogens, to synthesize and characterize AgNP from that strain and to evaluate the efficacy of the resulting AgNP against MDR pathogens	-A rapid method for the synthesis of AgNP was achieved using the halophilic bacterium, *Bacillus cereus* A30, isolated from marine waters -The AgNP were found to be highly stable and crystalline in nature -The AgNP showed significant activity on the pathogens tested, especially on Gram-negatives
[80]	This research aimed to investigate the medicinal value of *G. formosa* leaf and flower extracts in terms of antibacterial activity through the synthesis of AgNP against five drug-resistant pathogenic bacteria	-AgNP synthesized from *G. formosa* leaves and flower extract showed antibacterial activity against Gram-positive (*S. aureus*, *S. mutans*, and *S. epidermidis*) and Gram-negative (*K. pneumoniae* and *P. aeruginosa*) bacteria, where Gram-negative bacteria were more sensitive than Gram-positive bacteria
[92]	The aim of this study was to design the rapid biosynthesis of new AgNP with a simple, non-toxic, cost-effective, and environmentally friendly method under ambient conditions using the reduced property of *O. gratissimum* leaf extract, which shows enhanced efficacy against different Gram positive and Gram-negative bacteria even at low doses	-This study represents a successful synthesis method of AgNP through green synthesis using *O. gratissimum* leaf extract as a bio-reducer -The antibacterial activity of the particles was tested against multidrug resistant strains of *E. coli* and *S. aureus* -AgNPs were shown to exhibit antibacterial activity and were found to be most effective against *E. coli* (Gram negative) -AgNP was also found to be an effective inhibitor of biofilm formations in both types of strains
[93]	The aim of the present study was to broaden the spectrum of antimicrobial activity of AgNP on clinically isolated human pathogens	The results showed that AgNP caused more rapid bactericidal activity against Gram-negative bacteria than Gram-positive bacteria and possess excellent antimicrobial capacity against important hospital-acquired pathogens -AgNP caused a dramatic effect on their cell membrane resulting in rapid concentration-dependent membrane disruption and bacterial cell lysis, suggesting that these are the main targets of AgNP action in organisms -Mutational resistance to AgNP was not induced when bacteria are sequentially challenged with increasing concentrations of AgNP

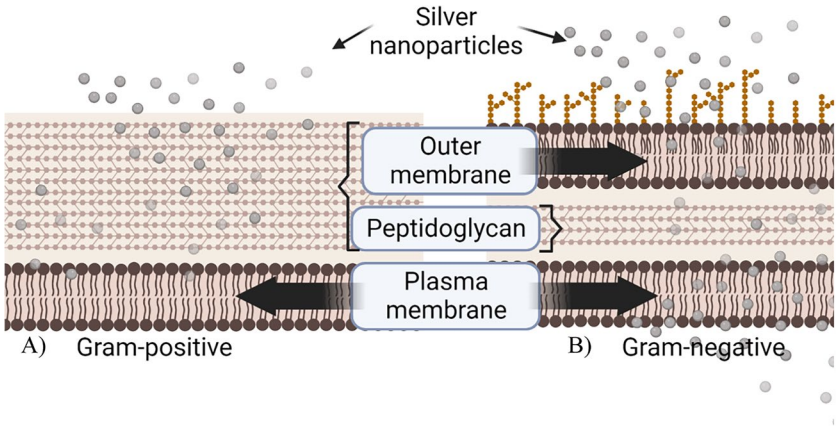

Fig. 3 Silver nanoparticle interaction with Gram-negative and Gram-positive bacteria. (**A**) Schematic representation of the interaction between silver nanoparticles and Gram-positive bacteria. The thick and cross-linked peptidoglycan layer in Gram-positive bacteria creates a formidable barrier for silver nanoparticles to traverse and interact with the cell membrane, resulting in lower efficacy compared to Gram-negative bacteria. (**B**) Schematic representation of the interaction between silver nanoparticles and Gram-negative bacteria. The small size of silver nanoparticles allows them to cross the outer membrane and interact with the cell wall and cytoplasmic membrane, leading to membrane damage and cell death

that with such bioactive natural compounds could serve as supporting materials for the formulation of new drugs against various bacterial infections.

Moreover, the size of nanoparticles was also found to influence the effectiveness on multidrug-resistant bacteria, according to Paosen et al. 2019 [93] smaller AgNP with larger specific surface area caused more damage to the cell membrane, which resulted in stronger antibacterial potency as they could achieve closer contact with bacterial cells. This can be observed in studies that successfully synthesized smaller nanoparticles, leading to improved results in tests conducted by Yuan et al. in 2017 [72] and Paosen et al. 2019 [93]. The results suggest that smaller-sized silver nanoparticles have greater ease of addition and penetration into bacteria, thus blocking cell respiration and inhibiting cell growth and reproduction, acting as a bacteriostatic agent, and followed by bactericidal activity.

A positive response was found in the studies regarding the effectiveness of silver nanoparticles on drug-resistant bacteria, both in Gram-positive and Gram-negative bacteria. According to the findings of the studies shown in Table 2, AgNP nanoparticles have demonstrated a greater efficacy against drug-resistant Gram-negative bacteria, mainly attributed to the structural differences between Gram-positive and Gram-negative bacterial cells. Even in studies such as Cavassin et al. 2015 [78] where AgNP obtained by different methods were compared, drug-resistant Gram-negative bacteria showed a greater effect than on drug-resistant Gram-positive bacteria. According to Das et al. 2015 [92], these results can be explained based on differences in the cell wall of each strain; the cell wall of Gram-positive strains is wider than the cell membrane of Gram-negative strains.

It is well known that Gram-negative bacteria possess an outer membrane outside the peptidoglycan layer, which is not present in Gram-positive organisms [94]. The outer membrane of Gram-negative bacteria is composed of lipopolysaccharides and phospholipids, which creates a formidable barrier for compounds to penetrate and reach the cytoplasm [95]. The important role of the outer membrane is to serve as a selective permeability barrier to protect bacteria from harmful agents such as detergents, drugs, toxins, degrading enzymes, and penetrating nutrients to sustain bacterial growth [96]. However, AgNPs can traverse this membrane due to their small size and interact with the cell wall and cytoplasmic membrane. This implies that in drug-resistant bacteria again the outer cell membrane plays an important role in the interaction with silver nanoparticles. This interaction leads to the disruption of membrane integrity, resulting in the release of intracellular contents and cell death. Additionally, AgNPs have been found to attach to the negatively charged cell surface of Gram-negative bacteria, increasing their uptake and accumulation within the cells. These unique properties make AgNPs an attractive therapeutic option for targeting Gram-negative bacteria, which are often more resilient to antibiotics due to their outer membrane barrier. In Gram-positive bacteria, the peptidoglycan layer is thick and directly exposed to the extracellular environment, whereas in Gram-negative bacteria, the peptidoglycan layer is thinner. The peptidoglycan layer in both Gram-positive and Gram-negative bacteria contains cross-linked peptides and polysaccharide chains. The structural difference in the polysaccharide chains of Gram-negative and Gram-positive bacteria

may also explain why silver nanoparticles have a harder time penetrating the peptidoglycan layer in Gram-positive bacteria. The peptidoglycan layer in Gram-positive bacteria is thicker and more cross-linked, making it more difficult for silver nanoparticles to traverse this layer and interact with the cell membrane. This may explain why silver nanoparticles are generally less effective against Gram-positive bacteria compared to Gram-negative bacteria (Fig. 3).

Conclusion

The overall evidence is not sufficiently conclusive to affirm that silver nanoparticles, applied specifically to drug-resistant bacteria, are a reliable option for use as antimicrobial agents against infections caused by these microorganisms. Most of the studies included in this review performed a green synthesis to obtain the AgNP, which uses different plant extracts to obtain these nanoparticles. The findings of these studies indicated that these synthesized AgNP inhibited the growth of Gram-negative bacteria more than that of Gram-positive bacteria. Although biosynthesis is environmentally sustainable and less toxic than other syntheses such as chemical synthesis, more research working on this type of synthesis is still required to better understand it and to exploit its potential in various health applications. No records were found in the studies suggesting or mentioning a possible generation of bacterial resistance to silver nanoparticles. However, it has been objectively demonstrated that silver nanoparticles have both a bactericidal and bacteriostatic effect against multidrug-resistant bacteria. These metallic nanoparticles have a greater effect on Gram-negative bacteria. This is since AgNP exert antibacterial effects more easily on these bacteria because they cause a greater loss of cell membrane stability in Gram-negative strains, causing the inactivation of vital functions of the microorganism, such as respiration and growth, which ultimately leads to the death of the bacteria. Therefore, it is concluded that AgNP are more effective in drug-resistant Gram-negative strains, which concretely answers the initial research question.

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Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest The authors declare no competing interests.

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