

Silver Nanoparticles and Their Antimicrobial Activity on Multidrug-Resistant Bacteria (AgNPs): A Literature Review

Maria HR Marques*, Eduarda S Fabri, Heitor AB Da Silva, Thiago R Silva, Lavinia M Barbosa, and Romulo DA Andrade*

Institute Superior of Education Brasilia, Department of Biomedicine, IESB, South Campus, Brasilia 72225-315, Brazil

*Corresponding author

Maria HR Marques and Romulo DA Andrade, Institute Superior of Education Brasilia, Department of Biomedicine, IESB, South Campus, Brasilia 72225-315, Brazil.

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ABSTRACT

The rise in antibiotic resistance has driven the search for new therapeutic strategies. It is estimated that antimicrobial resistance was associated with approximately 4.95 million deaths in 2019, 1.27 million of which were directly attributable to resistant bacteria. In current studies, silver nanoparticles have attracted significant scientific interest due to their ability to bind to components of the bacterial cell wall and membrane, making them susceptible to lysis, and promoting the release of silver ions, which induce oxidative stress and inhibit DNA replication a process that, in turn, causes oxidative imbalance and failure in genetic replication. The objective of this study was to review the antimicrobial potential of AgNPs against multidrug-resistant strains, as well as their potential efficacy in combination with conventional antibiotics already in use. The searches were conducted in PubMed and SciELO using subject-related keywords, restricted to studies published since 2019, addressing research on the antimicrobial activity and clinical and experimental applications of silver nanoparticles. It was indicated that nanoparticles effectively inhibit the growth of multidrug-resistant organisms through mechanisms involving cell membrane disruption and the induction of reactive oxygen species. Furthermore, their combination with antibiotics reduced the minimum inhibitory concentration, indicating a synergistic effect and greater clinical efficacy. These findings highlight the potential of silver nanoparticles in the treatment of resistant infections, both as a standalone therapy and as an adjunct in combination with commonly used antibiotics. Despite their efficacy, further studies are needed on safety, standardization, and production to enable the application of silver nanoparticles in clinical settings.

Keywords: silver nanoparticles; multidrug-resistant bacteria; antimicrobial activity;

Introduction

In the current global public health landscape, the rise of bacterial resistance to antibiotics poses a major challenge. The indiscriminate and prolonged use of antibiotics has exerted significant selective pressure on bacterial populations, favoring the emergence and spread of strains capable of resisting multiple classes of antimicrobial agents. Multidrug resistance complicates the treatment of severe infections, reduces treatment options, and leads to increased complications, deaths, and healthcare costs worldwide. [4]

According to Murray et al [3], antimicrobial resistance was associated with approximately 4.95 million deaths in 2019, with 1.27 million deaths directly attributable to resistant bacteria. Estimates indicate that, in the absence of effective measures, the annual economic impact could range from \$1

trillion to \$3.4 trillion by 2030 [4] Given this scenario of global urgency, international organizations such as the World Health Organization (WHO) classify antimicrobial resistance as one of the main threats to public health in the 21st century, demanding the urgent development of new therapeutic strategies.

In this context, nanotechnology has gained prominence as a potential ally in the development of innovative antimicrobial solutions. Silver nanoparticles (AgNPs) stand out for their ability to combat various types of microorganisms and for their capacity to act through multiple simultaneous mechanisms, which reduces the likelihood that bacteria will develop specific resistance to them [1]. Unlike conventional antibiotics, which typically target a single molecular pathway, AgNPs interact with various essential bacterial structures, making their mechanism of action considerably more complex to circumvent.

The antimicrobial properties of silver have long been utilized, having been used since ancient times for the preservation of food

and water [9]. Beyond this context, when used as nanoparticles, their effect becomes more potent due to the high surface-to-volume ratio of these structures [5]. The nanoparticles bind to the bacterial cell wall and membrane, weakening their structure, thereby facilitating their destruction; simultaneously, they release silver ions that induce oxidative stress through the generation of reactive oxygen species (ROS) and inhibit DNA replication, leading to bacterial death [1].

In addition to acting independently, AgNPs also offer benefits when used as adjuvants with conventional antibiotics, demonstrating a synergistic effect, as evidenced by a significant reduction in the minimum inhibitory concentration (MIC) required for bacterial inhibition [2]. This combination enhances the antimicrobial effect and has clinical relevance, as it suggests the possibility of achieving effective therapy even with lower doses of antibiotics, reducing adverse effects and lowering the chances of new resistant strains emerging.

Literature Review

The rise of antimicrobial resistance has become a major global public health problem, with an alarming number of multidrug-resistant bacteria responsible for an increasing number of infections that are becoming increasingly difficult to treat. The current situation is linked to the excessive and often inappropriate use of antibiotics, which promotes the spread of multidrug-resistant bacteria [6]. In light of these findings, researchers are seeking new forms of treatment and combinations of treatments, and nanotechnology has emerged as a promising alternative [1,2].

In this context, silver nanoparticles stand out for their potent antimicrobial action and their ability to target different types of bacteria, including the most resistant strains. Their efficacy has already been demonstrated in several studies, especially against clinically relevant bacteria. One of the major advantages of these nanoparticles is their ability to act in multiple ways simultaneously, targeting different structures of the bacteria, which hinders the development of resistance compared to conventional antibiotics [1].

The main mechanisms of bacterial resistance include: Among the primary strategies are the production of substances that inactivate the medication, such as beta-lactamases and carbapenemases; alteration and/or protection of the targets of antimicrobial action, hindering their effectiveness; efflux systems that expel antibiotics from the cell interior; and reduced uptake of these drugs due to changes in the bacterial membrane. In many cases, a single bacterium may exhibit several of these mechanisms simultaneously, as is the case with carbapenemase-producing *Klebsiella pneumoniae* (KPC) and multidrug-resistant *Pseudomonas aeruginosa*, which makes treatment much more difficult and severely limits available therapeutic options [6].

Species such as methicillin-resistant *Staphylococcus aureus* (MRSA), *Acinetobacter baumannii*, vancomycin-resistant *Enterococcus faecium*, and members of the Enterobacteriaceae family that produce ESBLs (extended-spectrum beta-lactamases) have become emblematic of this global phenomenon [6,12].

Silver nanoparticles are metallic nanomaterials with at least one dimension between 1 and 100 nm. What truly sets them apart is their surface-to-volume ratio, which allows for the controlled release of silver ions (Ag^+), making them more effective than ordinary silver [5]. They can be spherical, triangular, cubic, or even rod-shaped. Spherical nanoparticles are more common and effective in antimicrobial studies [10].

AgNPs can be produced using three main approaches: physical methods, such as laser ablation, which yield ultra-pure particles of precise size but require expensive equipment and consume a lot of energy [10]; chemical methods, which use reducing agents such as sodium borohydride. This is practical and allows for fine control of properties, but it generates toxic waste [9]; and the most modern method, green synthesis: extracts from medicinal plants, fungi, or bacteria perform the reduction using natural compounds; this is sustainable and produces particles that are less toxic to our bodies [7,9,11].

The mechanism of action of AgNPs involves direct interaction with the bacterial cell wall. Upon contact with bacterial cells, the nanoparticles adhere to membrane components, impairing their structural integrity and increasing their permeability, leading to the leakage of intracellular contents and, ultimately, to cell lysis. Simultaneously, AgNPs promote the release of silver ions into the intracellular environment, which further amplifies the bactericidal effect by inducing oxidative stress through the generation of reactive oxygen species (ROS). The ROS produced cause oxidative damage to essential cellular components, including membrane lipids, structural and functional proteins, and genetic material, compromising bacterial viability at multiple levels [1,5].

Another ability of AgNPs is the disruption of biofilms, the protective communities that bacteria create to shield themselves from conventional antibiotics. AgNPs penetrate the polymeric matrix of the biofilm, composed mainly of polysaccharides, proteins, lipids, and DNA, and interfere with the adhesion between bacterial cells, preventing their organization and survival [6,12].

An additional mechanism is interference with DNA replication. Silver ions interact with bacterial genetic material, blocking DNA transcription and hindering its replication, thereby preventing cell multiplication. This set of actions contributes to the antibacterial effect of AgNPs and reinforces their potential as an alternative in combating infections [1].

Not all bacteria respond equally to AgNPs; the response depends on the structure of the cell wall. Gram-negative bacteria, which have a double membrane and lipopolysaccharides, tend to be slightly more resistant, requiring slightly higher minimum inhibitory concentrations (MICs); Gram-positive bacteria, which have a thick peptidoglycan cell wall, are more sensitive. However, AgNPs are effective against both groups, providing a broad spectrum of activity rarely seen with common antibiotics [5,12].

Studies show a consistent synergistic effect when AgNPs are combined with conventional antibiotics, reporting that when

AgNPs are used in combination with antibiotics, a significant reduction in bacterial counts is observed compared to the isolated use of each agent, indicating that AgNPs enhance the action of antibiotics, thereby increasing the efficacy of combination therapy. [1,2].

The proposed mechanism of synergy between the two components involves the ability of silver ions to weaken bacteria and compromise membrane integrity. As a result, antibiotic molecules penetrate the bacterial cell more easily (Fig.1). Given the highly promising synergistic strategy, especially in the treatment of infections caused by multidrug-resistant bacteria, in situations where antibiotics used alone have limited efficacy [2]. In clinical practice, this combination allows for the use of lower doses to achieve the same result, causing fewer adverse effects and reduced renal/hepatic toxicity, as well as less resistance, thereby delaying the emergence of new resistant strains and contributing to the long-term efficacy of antibiotics [4].

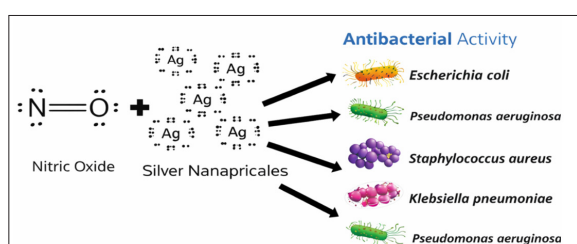


Figure 1: Mechanism by which silver nanoparticles attack bacteria.

Despite their antimicrobial potential, clinical application requires further studies and a thorough safety assessment, given that nanoparticles interact directly with both prokaryotic and eukaryotic cells. Mali et al. [13] identified three main mechanisms of cytotoxicity: genotoxicity—nuclear accumulation induces DNA breaks; mitochondrial dysfunction—dysregulation of intracellular calcium, leading to apoptosis; cytoskeletal damage—structural collapse due to alterations in microtubules. Toxicity is size-dependent: particles <20 nm penetrate more efficiently, exhibiting greater reactivity. However, therapeutic concentrations preserve >80% cell viability in fibroblasts and epithelial cells [13].

Systemic biodistribution shows accumulation in the liver (60%), spleen (20%), and kidneys (15%), with slow exocytosis suggesting a risk of chronic toxicity [14]. Systemic toxicity of AgNPs in the human body can occur through various routes of exposure, including dermal, intravenous, oral, and inhalation, and may affect various organs and systems, such as the eyes, the central nervous system, the skin, the respiratory system, the immune system, the hepatobiliary system, and the reproductive system [14].

Materials and Methods

This study is a narrative literature review. The search for studies was conducted in the PubMed and SciELO databases using the search terms “silver nanoparticles,” “multidrug-resistant bacteria,” “antimicrobial activity,” and “bacterial resistance,” both individually and in combination. Articles published between January 2022 and December 2025 were considered.

The inclusion criteria were original articles, literature reviews, and clinical case reports published in Portuguese and English that addressed the antimicrobial activity of AgNPs against multidrug-resistant bacteria in clinical or experimental contexts. Studies investigating the mechanisms of action of these nanoparticles or their use in combination with conventional antibiotics were also included. Studies that were not directly related to the study’s objectives were excluded based on a review of titles and abstracts, as were duplicate publications and non-peer-reviewed studies.

Article selection was conducted in two consecutive stages: initial screening based on a review of titles and abstracts, followed by a full reading of the preselected articles. Data extraction was performed qualitatively, with an emphasis on the mechanisms of action of AgNPs, the reported antimicrobial activity results against multidrug-resistant strains, and findings related to synergism with conventional antibiotics.

Results and Discussion

The reviewed studies consistently demonstrate that AgNPs exhibit significant antimicrobial activity against multidrug-resistant bacteria through multiple simultaneous mechanisms, as summarized in Table 1. Among the main mechanisms, cell membrane damage stands out, where silver ions disrupt membrane integrity, leading to bacterial lysis; oxidative stress (EROs), which causes damage to proteins, lipids, and DNA; and the inhibition of DNA replication [1,5,12].

The synergistic effect observed in the combination of silver nanoparticles with antibiotics also has considerable clinical relevance. The reduction in the minimum inhibitory concentration (MIC) associated with this strategy indicates that lower doses of antibiotics, when combined with AgNPs, may be sufficient. Casals et al [2] describe how silver ions compromise the integrity of the bacterial membrane, facilitating the penetration and accumulation of antibiotics, and how they weaken the bacterial response to silver-induced stress, which overloads the defenses and increases sensitivity to antimicrobials. This is significant because reducing doses minimizes adverse effects in patients while simultaneously delaying the emergence of new resistant strains.

The results from the reviewed studies also confirm the superiority of green synthesis for therapeutic applications. Tadesse et al. [7] reported that biosynthesized AgNPs (<100 nm) exhibited MICs ranging from 2.50 µg/mL to 100 µg/mL and MBCs between 3.8 µg/mL and 2.5 mg/mL against multidrug-resistant pathogens, reflecting the diversity of formulations tested. Crisan et al. [6] demonstrated significant inhibitory activity at 10 and 100 µg/mL against critical clinical isolates, including MRSA and pan-resistant *Klebsiella pneumoniae*, with interpretation standardized according to the EUCAST 2023–2024 criteria, the European gold standard for the interpretation of microbiological tests.

The toxicity of AgNPs in human cells is predominantly concentration-dependent, varying according to the synthesis method and particle size. [13] Green-synthesized AgNPs exhibit lower cytotoxicity than chemically synthesized AgNPs [7,11].

Taken together, the results demonstrate that AgNPs are broad-spectrum antimicrobial agents with a multifactorial mechanism

of action, effective against clinically relevant multidrug-resistant bacteria. Combining them with conventional antibiotics enhances their efficacy, reducing the required doses and the risk of further resistance. The safety profile, although promising, requires further clinical validation before widespread therapeutic incorporation [3-7].

Table 1: Characteristics of the studies included in the literature review on silver nanoparticles and their antimicrobial activity against multidrug-resistant bacteria.

Author/Year	Study Type	Synthesis/Size	Tested Bacteria	MIC / Result	Synergism with Antibiotics
Bruna et al., 2021 [1]	Literature review	Multiple methods; 1–100 nm	<i>S. aureus</i> , <i>E. coli</i> , <i>P. aeruginosa</i> , <i>K. pneumoniae</i>	Variable depending on strain and method	Yes – enhances activity of beta-lactams and aminoglycosides
Casals et al., 2025 [2]	Literature review	Controlled chemical synthesis	MDR pathogens (Gram+ and Gram–)	MIC reduction observed in combination	Yes – controlled Ag ⁺ release restores antibiotic efficacy
Murray et al., 2022 [3]	Global systematic analysis	Not applicable	All relevant MDR species	Not applicable	Not applicable – epidemiological study
Poudel et al., 2023 [4]	Systematic review and meta-analysis	Not applicable	MDR bacteria in general	Not applicable	Not applicable
More et al., 2023 [5]	Literature review	Chemical and green synthesis; <100 nm	MRSA, <i>E. coli</i> , <i>K. pneumoniae</i> , <i>P. aeruginosa</i>	Variable; broad-spectrum activity confirmed	Yes – enzymatic and membrane inhibition enhance activity
Crisan et al., 2024 [6]	In vitro study	Chemical synthesis; size not specified	MRSA, <i>K. pneumoniae</i> (pan-resistant), <i>E. coli</i> , <i>P. aeruginosa</i> , <i>E. faecalis</i>	Inhibitory activity at 10 and 100 µg/mL	Yes – combination with antibiotics increased activity
Tadesse et al., 2024 [7]	Systematic review	Green synthesis (plant/microbial extracts); <100 nm	Gram+ and Gram– MDR pathogens	MIC: 2.50 µg/mL–100 mg/mL; MBC: 3.8 µg/mL–2.5 mg/mL; ZOI: 4–25 mm	Yes – lower cytotoxicity with green synthesis
Naghavi et al., 2024 [8]	Global systematic analysis	Not applicable	All relevant MDR species	Not applicable	Not applicable – epidemiological projections until 2050
Xu et al., 2023 [9]	Literature review	Green synthesis (algae, flowers, microorganisms)	<i>S. aureus</i> , <i>E. coli</i> , <i>C. albicans</i> , others	Variable depending on extract and strain	Not directly evaluated
Wasilewska et al., 2023 [10]	Experimental study	Green synthesis (fruit/vegetable extracts); 9–30 nm	<i>S. aureus</i> , <i>B. cereus</i> , <i>E. coli</i> , <i>C. krusei</i>	Variable; best with potato extract	Not evaluated
Almatroudi, 2022 [11]	Literature review	Green synthesis (plants, bacteria, fungi)	<i>S. aureus</i> , <i>S. epidermidis</i> , <i>P. aeruginosa</i> , <i>E. coli</i>	Variable MIC/ MBC; ZOI 18.3–20.4 mm	Yes – combination described
Almeida et al., 2024 [12]	Comprehensive review	Green synthesis (phyto- and biosynthesis)	<i>A. baumannii</i> , <i>E. coli</i> , <i>S. aureus</i> , <i>K. pneumoniae</i> , <i>P. aeruginosa</i>	Broad-spectrum; antibiofilm confirmed	Yes – combination with bioactive agents
Mali & Ranade, 2025 [13]	Comprehensive review	Physical, chemical, and green	Various Gram+ and Gram– species	Variable; concentration-dependent toxicity	Not evaluated
AlAtawi et al., 2024 [14]	Systematic review	Not specified	Systemic toxicity focus	Not applicable	Not evaluated
Zhang et al., 2021 [15]	Literature review	Physical, chemical, and green; 1–100 nm	<i>S. aureus</i> , <i>E. coli</i> , <i>P. aeruginosa</i>	Variable depending on formulation	Yes – combined therapeutic approaches

The rise of antimicrobial resistance has imposed increasing limitations on conventional therapy, with a direct impact on mortality and the efficiency of healthcare systems [3,4,8]. The difficulty in curbing this trend is largely related to the specificity of the mechanisms of action of traditional antibiotics, which favors the selection of adapted strains. In this scenario, approaches based on multiple cellular targets offer a strategic advantage.

The studies included in this review indicate that silver nanoparticles act simultaneously on different bacterial components, compromising membrane integrity, inducing oxidative stress, and interfering with essential replication processes [1,5]. This set of interactions not only reduces cellular viability but also hinders the organization of efficient adaptive responses by bacteria, particularly in multidrug-resistant strains. Unlike what is observed with conventional antimicrobials, there is no single, clearly defined point of selective pressure.

The data summarized in Table 1 support this observation by demonstrating consistent antimicrobial activity across different experimental settings. *In vitro* studies, such as that by Crisan et al. [6], show significant inhibition at concentrations of 10 and 100 µg/mL against critical pathogens, while systematic reviews, such as that by Tadesse et al. [7], report a wide range of MICs, reflecting differences in synthesis methods and particle characteristics. This variability, although expected, highlights an unresolved issue in the literature: the lack of standardization that would allow for direct comparisons between studies.

The combination of silver nanoparticles and conventional antibiotics has implications that go beyond the synergistic effect described. The reduction in the minimum inhibitory concentration observed in different studies [2,6] suggests a change in the dynamics of the interaction between the drug and the bacterial cell, possibly related to increased membrane permeability. In practice, this allows for the use of lower doses of antibiotics, with the potential to reduce adverse effects and exert less selective pressure on bacterial populations. Furthermore, this strategy may contribute to the repositioning of drugs whose efficacy has been compromised over time.

The difference in response between Gram-positive and Gram-negative bacteria also remains evident. The presence of an outer membrane in Gram-negative bacteria acts as an additional barrier, which may explain the need for higher concentrations to achieve a similar effect [5,12]. Nevertheless, the antimicrobial activity observed in both groups reinforces the broad-spectrum nature of AgNPs, a relevant characteristic in infections of mixed or undefined etiology.

Despite these advances, the clinical application of silver nanoparticles still depends on a deeper understanding of safety and biodistribution. Evidence indicates that toxicity is directly associated with particle size, concentration, and synthesis method, with greater reactivity observed in smaller particles [13]. In this regard, studies employing green synthesis [7,11] point to a reduction in cytotoxicity, possibly due to stabilizing compounds of biological origin. However, studies evaluating these systems in long-term *in vivo* models remain limited, representing a significant gap.

Another recurring limitation in the literature concerns the lack of methodological standardization, both in the physicochemical characterization of nanoparticles and in the microbiological protocols employed. The variation observed in MIC and MPC values, as shown in Table 1, makes it difficult to compare studies and establish consistent therapeutic parameters. Furthermore, clinical studies validating the experimental findings remain scarce, which largely restricts the application of these nanoparticles to the laboratory setting.

Given this body of evidence, silver nanoparticles are emerging as a promising alternative in combating infections caused by multidrug-resistant bacteria, especially when used in combination with conventional antibiotics. However, the consolidation of this approach in clinical practice depends on advances in the standardization of synthesis processes, the reproducibility of results, and validation through controlled clinical studies. The transition from experimental potential to therapeutic application still requires a more robust evidence base.

Conclusion

Silver nanoparticles hold great potential for combating multidrug-resistant bacteria that cause bacterial resistance. AgNPs employ various mechanisms of attack: they penetrate the cell membrane, damage DNA and proteins, block essential enzymes, and inhibit DNA replication. This makes it difficult for bacteria to develop resistance, unlike conventional antibiotics, which have only one target. When combined with antibiotics, AgNPs enhance the effect and allow for the use of much smaller doses, reducing side effects for patients and helping to preserve the efficacy of drugs that are still effective. Furthermore, they inhibit the formation and maturation of biofilms, where common antibiotics fail. Green synthesis produces particles that are safer for our bodies and have a lower environmental impact. Despite their efficacy, further studies are needed on safety, standardization, and production to enable the application of silver nanoparticles in clinical settings.

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Authors' Contributions

Conceptualization, E.S.F. and M.H.R.M.; methodology, T.R.S. and L.M.B.; validation, R.D.A.A. and E.S.F.; investigation, H.A.B.D.S.; drafting of the original manuscript, E.S.F.; review and editing, all authors. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

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