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Mechanism and Application of Metal Nanoparticles as Antimicrobial Agents

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ABSTRACT

Antimicrobial resistance (AMR) is one of the major concerns worldwide that has emerged as the leading source of mortality and morbidity due to bacterial infection because of their resistance to antibiotics. Overuse of antibiotics has led to the development of AMR due to the mutation of genes, the formation of biofilm, and the modification of enzymes. This alarming situation has caused the creation of new alternative antibacterial materials such as nanoparticles. Nanoparticles are emerging as a promising solution due to multiple and unique mechanisms of action to prevent bacteria from developing resistance and help to control the worldwide problem of bacterial resistance. Metal nanoparticles such as silver, gold, zinc, and titanium oxide have been synthesized by chemical, physical, and biological methods, and they have strong antibacterial properties. Mechanisms of nanoparticles include disruption of cell membrane integrity, DNA damage, destruction of biofilm production, and enzyme denaturation. They attach to DNA, inhibiting replication and transcription. But the usage of nanoparticles also exhibits toxicity. They harm the beneficial bacteria, accumulate in the body, cause organ damage, and develop neurotoxicity and hepatotoxicity. Further research is needed in the future to develop a more potent antimicrobial agent that has the potential to hinder the spread of antibiotic resistance against bacteria.

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INTRODUCTION

Bacteria and viruses are disease-causing agents that lead to mortality and morbidity in humans and animals (Paul, 2024). To prevent and control these pathogens, antimicrobial agents that inhibit and kill the growth of different microorganisms are used (Purssell, 2020). Various anti-microbial agents, such as antivirals and antibiotics, are used to effectively treat a wide range of infectious diseases (Nigam et al. 2014). In the 20th century, the biggest invention in the medical field was the discovery of antibiotics (Katz and Baltz, 2016). During the discovery of antibiotics, the clinical medicinal treatment and surgical procedures, such as organ transplants, cancer treatment, and childbirth, were considerably safer (Hutchings et al. 2019). In addition to antibiotics, antivirals are also used for the treatment of viral illnesses, such as the most recent coronavirus pandemic in 2019. The capacity of antivirals to regulate the human immunodeficiency virus (HIV) is one of their best pharmacological properties (Aljeldah, 2022). However, research on antibiotics did not start until 1928, with the accidental discovery of penicillin by Alexander Fleming, and the research reached its peak between the 1950s and 1960s. This period is known as the ‘golden age’ (Szollosi, 2023). Between 1930 and 1962, more than 20 classes of antibiotics were created, but now the development of resistant bacteria poses a challenge for the pharmaceutical industry to develop a new antibacterial activity compound (Verma et al. 2022).

Globally, antimicrobial resistance has become one of the most critical public health concerns (Mehmood and Ashraf, 2023; Bui et al. 2024). Overuse of antibiotics in agriculture, human, and animal health contributes to the development of resistance due to mutation in genes (Ahmed et al. 2024). Different mechanisms, such as biofilm formation and enzymatic modification, allow the pathogen to resist the antibiotic (Baquero et al. 2021; Rather et al. 2021; Dorgham et al. 2024). According to the 2019 antibiotic resistance threat report of the Centers for Disease Control and Prevention (CDC), annually, the US estimated 2.8 million people were affected by antimicrobial resistance, resulting in over 35000 deaths (Last-Resort Antibiotics 2022). AMR has a huge economic impact, with losses in the trillions of dollars and a severe financial burden on the healthcare and agriculture systems. Under these situations, the demand to find an antibiotic alternative to prevent and control microbial infection is increasing daily (Roope et al. 2019). One strategy is to use botanical potential as an alternative against antimicrobial resistance (Munir et al. 2023). Vaccines and traditional herbs were also used in conventional therapy and do not cause resistance. Vaccines no doubt have the potential to control bacterial infection, but due to the strain variability, they are not used worldwide. Herbs derived products such as plant extracts and essential oils contain terpenoids, alkaloids, steroids, tannins, flavonoids, and coumarines (Khameneh et al. 2021). Different types of bacteria are affected by plant extracts and essential oils from lovage, thyme, basil, and parsley by increasing cell permeability, changes to the bacterial cell wall and cell membrane, DNA damage, and inhibition of protein synthesis (Gălăţanu et al. 2022). However, the use of plant extracts and essential oils at high doses causes toxic effects such as headache, contact dermatitis, eye irritation, immunotoxicity, genotoxicity, and neurotoxicity (Mehdizadeh and Moghaddam, 2018; Asghar et al. 2024). So, now researchers and pharmaceutical companies are moving toward non-traditional medication, especially the nanotechnology industries, to develop nanoparticle drugs that are effective against resistant bacteria (Muteeb et al. 2023).

Inorganic particles with a nanometric size are the nanoparticles (NPs) that exhibit antiviral and antibacterial activity (Haleem et al. 2023; Naeem et al. 2023; Mehwish et al. 2024; Abbas et al. 2025; Ambrose et al. 2025). They can enter the membrane of microbes and interact with a particular target, producing free radicals (Akhreim et al. 2024; Tabassum et al. 2024). NPs have multiple and unique mechanisms of action to prevent bacteria from developing resistance and help to control the worldwide problem of bacterial resistance (Mba and Nweze, 2021). Metal NPs (MNPs) such as silver (Ag), gold (Au), zinc (Zn), and titanium (Ti) have special antibacterial properties. The chemical composition of MNPs has the potential for longer binding, active targeting of antibiotics to the target region, and defense against enzyme degradation (Kotrange et al. 2021; Aslam et al. 2023). Their most fascinating feature is that they can administer the antibiotic to the intracellular compartment where the pathogen is present. Through this, they promote the medication's potential, boost drug circulation, enhance absorption, and achieve effective therapy at the target site (Gao et al. 2018). This review highlights the antimicrobial resistance, its global impact, and the efficacy of the mechanism of NPs as an antimicrobial agent.

Synthesis of NPs

NPs are used in biomedical sciences for biological imaging and instruments, against pathogens, and in medicine (Rezić, 2022). To synthesize NPs, different chemical, physical, and biological methods are used. Certain techniques are developed for their production of particular sizes and shapes (Habibullah et al. 2021). The biochemical, microemulsion, template method, microwave-assisted synthesis, irradiation, photo-catalytic, ultrasonic-assisted, aqueous, and non-aqueous chemical reduction are additional chemical methods for the synthesis of NPs (Häffner and Malmsten, 2019; Liyanage et al. 2019). However, there are a variety of drawbacks linked with these chemical methods, such as high energy consumption, the formation of dangerous byproducts, and the use of toxic solvents, all of which pose a significant risk to human and animal health. The concern over the development of NPs with the help of sustainable and eco-friendly techniques is growing rapidly (Bhardwaj et al. 2020). An eco-friendly method that links nanotechnology and microbial biotechnology is the microbial production of NPs (Aithal and Aithal, 2021). It is documented that bacteria, fungi, actinomycetes, viruses, and yeast can cause the biosynthesis of Au, Ag, Au-Ag alloy, Ti, selenium (Se), platinum (Pt), silica (SiO_2), palladium (Pd), zirconia, uraninite, magnetite, and quantum dots NPs (Jyothikumari et al. 2023; Ibrahim et al. 2024). Biological properties are not uniform, and their synthesis rate is low, even if they are stable. Many factors, including microbial growing approaches, extraction procedures, and combinatorial approaches such as photo-biological techniques, are employed to solve these issues (Dawiec-Liśniewska et al. 2022). Different processes, such as cellular, biochemical, and molecular mechanisms that influence the synthesis of biological NPs are studied in detail to accelerate the synthesis and enhance the nanoparticles' characteristics (Das et al. 2017). The synthesis of MNPs also depends on the capacity to tolerate heavy metals. Therefore, it is now suggested that a major source of nanomaterial mining is the biological manufacture of MNPs by bacteria (Yan et al. 2025). Various methods to synthesize NPs have been shown in Fig. 1.

NPs Mechanism against Resistant Bacteria

Different types of MNPs show their effectiveness against resistant bacteria (Amaro et al. 2021; Younas et al. 2024). Nowadays, AgNPs are considered the antibiotic of the future due to their incredible effectiveness in reducing bacteria (More et al. 2023). Currently, AgNPs are one of the leading NPs among all the available nanomaterials (Aslam et al. 2023). They have the potential to reduce toxicity compared to other NPs, so their use as antimicrobial agents has been increasing over the years (Franci et al. 2015; Du et al. 2023).

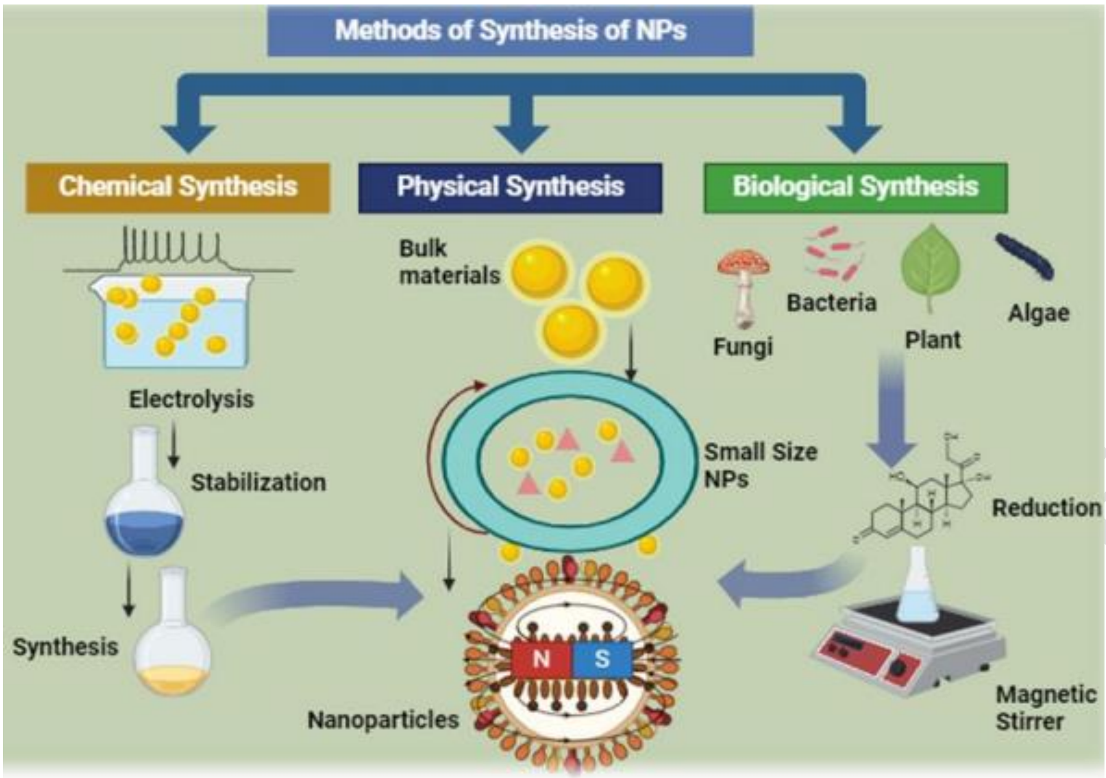

Fig. 1: Physical, chemical, and biological methods to synthesize metallic nanoparticles.

The cytotoxic mechanism of AgNPs typically begins with their attachment and penetration into the microbial membrane surface (Tripathi and Goshisht, 2022). The generated Ag ions promote the production of reactive oxygen species (ROS) and oxidative stress, which in turn damage the internal components. AgNPs and Ag ions interact with DNA (phosphorus-containing molecules), leading to protein inactivation and ultimate cell death (Kaiser et al. 2023). The emission of Ag ions is greatly affected by the interaction between sulphur, oxygen, thiols, and chlorine. Additionally, the size has a significant impact on the rate of emission of Ag ions (Randall, 2013). Small Ag ions can easily penetrate the cell wall. They also change the membrane shape and structural integrity, which increases the permeability and ultimately cell death (Xu et al. 2021). AgNPs activity is also influenced by the type of bacteria, due to different cell wall composition, thickness, and arrangement (Ahmed et al. 2018). According to Hamouda et al. (2019), the specific antibacterial action of AgNPs is linked to cell wall and plasma membrane damage along with the production of ROS. This is due to membrane lipid peroxidation and protein inactivation. These activities alter the integrity of the structural membrane and trigger the disorder of protein transport. In addition, metal-based NPs and metal oxide NPs are extensively used in the medical and veterinary field for anticancer and antibacterial research. Due to the different and changed properties of AgNPs, MNPs are becoming increasingly interesting in various fields.

Copper (Cu) and its different nanomaterials have mechanisms as antibiotics to combat illness (Nisar et al. 2019). Cu and copper oxide NPs (CuNPs/CuONPs) also have antibacterial properties (Bhuvaneshwari et al. 2022). Electrostatic attraction between the cell and NPs causes the derivation of antibacterial activity. Cu ions can pass through the lipid bilayer and enter the cell, causing the production of ROS (Fan et al. 2021). According to Badetti et al. (2019), a recent study found that the CuONPs interaction with amino acids significantly shows the effect against resistant bacteria. AuNPs are among the most extensively explored NPs with antibacterial properties. According to the report of Smitha and Gopchandran (2013), AuNPs with triangular shapes have strong antibacterial activity as compared to spherically shaped AuNPs. They disrupt the membrane integrity by adhering to the membrane through electrostatic attraction. They attach to DNA, preventing transcription and replication. They can also cause the reduction of biofilm production, and interaction between AuNPs causes ROS production, which is essential for cell death (Soliman et al. 2023). The antibacterial activity of other NPs is summarized in Table 1.

Silver, copper, iron, nickel, gold, zinc, mercury, manganese, and cadmium have all been used as antimicrobial agents from ancient times (Sharma et al. 2022; Altaf et al. 2024). Metal affects the cell by inactivating the enzyme, releasing ROS, and disrupting the electron transport chain. Metal ions have good bactericidal properties, but their use is limited due to safety issues (Godoy-Gallardo et al. 2021). However, different research reports declare that the lethal effect of metallic nanomaterials is mostly due to particle-mediated membrane disruption rather than ion release (Xie et al. 2023). Hu et al. discovered that increasing the concentration of AgNPs increased the rate of lipid flip-flop, while Vishnupriya et al. (2013) used Raman spectroscopy to show that AgNPs could penetrate the bactericidal cells and interact with exocyclic nitrogen of guanine, adenine, and cytosine bases, causing DNA damage. Recently, increasing research has found that the bactericidal activity

Table 1: Recent studies of nanoparticle source, shape, and size, and mechanism

NPs	Source	Size (nm)	Shape	Resistant bacteria	Mechanism	Reference
Silver nanoparticle (AgNPs)	*Pseudoduganella eburnean*	8-24	Spherical	*Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa*	Membrane instability,	(Huq 2020; Bui et al. 2024)
AgNPs	Plants	10-5	Spherical	*Vibrio natriegens*	ROS causes membrane damage	(Dong et al. 2019)
AgNPs	*Fusarium scirpi*	2-20	Quasi-spherical	*E. coli*	Inhibit the pathogen biofilm, destruction	(Rodríguez-Serrano et al. 2020; Ali et al. 2023)
AgNPs	*Adrographis paniculata* stem	24.90 25.2	Spherical	*Bacillus cereus*, *E. coli*, *V. cholerae*, *S. typhi*, *E. faecalis*	cytotoxicity mechanism	(Hossain et al. 2019)
AgNPs	*Sphingobium*	7-23	Spherical	*E. coli*, *S. aureus*, *P. aeruginosa*	Destroy membrane integrity and change the morphological structure	(Akter and Huq, 2020)
AgNPs	*Acacia rigidula*	15-22	Spherical	*E. coli*, *P. aeruginosa* and *Bacillus subtilis*	Exhibited the antimicrobial effect	(Escárcega-González et al. 2018)
AgNPs	*Oscillatoria* spp.	10	Spherical	*E. coli*, *P. aeruginosa*, *Citrobacter* spp., *B. cereus*	Acts as an antibiofilm, causes the highest mortality	(Adebayo-Tayo et al. 2019)
AgNPs	Black pomegranate peels	32-85	Spherical	*P. aeruginosa*	Showed strong inhibition of biofilm formation	(Habibipour et al. 2019)
AgNPs	*Fusarium solani*	13.70	Spherical	*S. aureus*, *P. aeruginosa*	The formation of cracks and holes in the cell wall	(El Sayed and El-Sayed, 2019)
AgNPs	*Cyanobacterium Oscillatoria*	3.20-17.98	Spherical	*E. coli*, *B. cereus*	Cytoplasm leakage, Internal diffusion, cell rupturing, membrane detaches from the cell	(Hamouda et al. 2019)
AuNPs	*Annona muricata*	25.5	Spherical	*E. faecalis*, *S. aureus*, *Clostridium sporogenes*	Antimicrobial activity	(Folorunso et al. 2019)
AuNPs	*Euprasia officinalis*	49.73-1.2	Quais-spherical	*E. coli*, *S. aureus*, *P. aeruginosa*, and *V. parahaemolyticus*	Good antibacterial activity	(Singh et al. 2018)
CuONPs	*Abutilon indicum*	-	Quartzite, hexagonal, & sponge crystal structure	*E. coli*, *S. aureus*, *Klebsiella*, *Bacillus subtilis*	Disruption of membrane integrity against *Klebsiella*, *S. aureus, and B. subtilis* by	(Ijaz et al. 2017)
CuONPs	*Aloe barbadensis*	33.4-64.9	Spherical	*E. coli*, *Pseudomonas*, *Klebsiella*, *Staphylococcus*	Enzyme denaturation generates ROS and causes cell damage	(Thakur and Kumar, 2019; Mohammed et al. 2024)
MgONPs	*Swertia chirayaita*	20	Spherical	*K. pneumonia*, *E. coli*, *S. epidermidis*, *S. aureus*	Dose-dependent antimicrobial activity. Causes the reduction of biofilm formation	(Sharma et al. 2017)
MgONPs	Commercial	20	Polyhedral	*E. coli*, *S. aureus*, *P. aeruginosa and S. epidermidis*	Generation of ROS, Ca^{2+} concentration, reduction in attachment, & destruction of biofilm	(Nguyen et al. 2018)
ZnONPs	*Bacillus haynesii*	5-20	Spherical	*S. aureus*, *E. coli*	Release Zn^{2+} ions that disrupt the bacterial membrane, and enzymatic inhibition	(Rehman et al. 2019; Shahid et al.2023)
TiO_2NPs	Laser ablation	36	Round or circular	*S. aureus*, *E. coli*	Degradation of protein	(Abdul-Hassan et al. 2018)
TiO_2NPs	*S. aureus*	20-30	Spherical	*S. aureus*, *E. coli*, *B. cereus*	Act as an antibiofilm against pathogens	(Landage et al. 2020; Nadi et al. 2024)

of metallic nanomaterials is influenced by both ion and particle impact (Champati et al. 2025). These NPs are rarely used in clinics but are widely applied in environments to prevent biofilm formation and provide long-term bactericidal effects (Parvin et al. 2025). The mechanism of NPs as an antimicrobial agent is also demonstrated in Fig. 2.

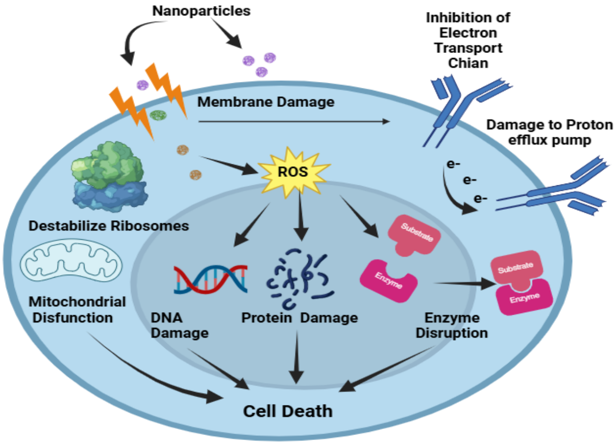

Fig. 2: Mechanism of metallic nanoparticles against bacterial cells.

Toxicity and safety considerations

Toxicity is the main issue in the use of NPs (Sengul and Asmatulu, 2020). There are some regional and global toxic effects to could potentially harm the beneficial bacteria in humans, which is a major concern (Serwecińska, 2020). NPs and their breakdown product disrupt blood circulation by causing haemolysis. They are delivered intravenously and accumulate in various organs throughout the body. Then causes malfunction and damage to organs (Chenthamara et al. 2019). The size and shape of NPs also have a great influence on toxicity. Larger-sized NPs are more harmful to biological systems than smaller-sized ones (Egbuna et al. 2021). The use of CuONPs, ZnONPs, and Ti2ONPs is limited due to DNA damage and oxidative stress (Ahmed and Nawaz, 2024; Hemeg, 2017). By interacting with cellular components, CuONPs can trigger hepatoxicity and nephrotoxicity (Baptista et al. 2018). Some studies have reported that they may not pose life-threatening toxicity in vivo, but their accumulation harms the cell (Sengupta et al. 2014; Wei et al. 2015; Mba and Nweze, 2021). Evaluating the toxicity at cellular and systemic levels is critical for clinical applications. The following safety guidelines are recommended to prevent the toxicity of nanoparticles, including such as evaluating the properties of nanoparticles' size, distribution, redox potential, and surface modification (Abbasi et al. 2023).

Current Challenges and Future Direction

One drawback of previous research on the antibacterial process of NPs is the lack of unified criteria. Specifically, different bacterial strains, action timing, and NPs properties are investigated in various research studies, making it impossible to compare the antibacterial activity. Furthermore, no single method meets all the requirements for gaining information regarding the antibacterial mechanism of NPs. A complete investigation is suggested for examining the potential antibacterial pathway, because different types of NPs have diverse antibacterial effects. Many questions remain unsolved about neurotoxicity, including how NPs pass the bacterial cell membrane. The size of all NPs will limit their ability to be transported. According to many scholars, prions may be able to facilitate the passage of NPs across the bacterial cell membrane, which have a size between 1-9nm. Similar to that seen in eukaryotic cells, endocytosis of bacteria is regarded as an additional mechanism of NPs transport. However, no finding is reported on this topic. Furthermore, there are a few studies that address the intracellular inhibitory process. Few studies have examined how NPs affect the bacterial cell gene expression, protein synthesis, and oxidative stress induced by NPs demands assessments. Metallic NPs can potentially be an effective alternative source of antimicrobial agents in the future. The current work reported findings on the in vitro antibacterial properties of nanoparticles. Most NPs are metallic and may promote the absorption and accumulation, so for the positive outcomes, careful selection of nanomaterial types, suitable dosage, and administration is critical. Before introducing them as safe and effective antimicrobial agents, it is necessary to consider the management of the environmental issues, health and safety elements, potential toxicity, and challenges. According to the current study, metallic NPs and their composite may be used in the future to create more potent antimicrobial agents that stop the development and spread of bacterial resistance to traditional antibiotics.

Conclusion

Antimicrobial resistance is one of the global issues and has a great impact on public health. This resistance developed due to irrational and continuous use of antibiotics against infection or illness. Metallic NPs are used as an antibiotic against resistant bacteria. NPs emerged as an antimicrobial agent, managing the issue of antibiotic resistance, which is getting worse. They have unique physicochemical properties such as variable shape, emit ROS, and a high surface area to volume ratio, which makes them effective against microbes. Enzyme denaturation, disruption of cell membrane integrity, DNA damage, and destruction of biofilm production are mechanisms of action. Different metallic NPs, such as zinc, silver, magnesium, iron, and copper, exhibit a strong antibacterial effect. Despite their activities, more studies are needed on issues like environmental risk, organ damage, and toxicity. Antimicrobial-based NPs will be safer and more effective in the future due to advancements in targeted delivery methods, functionalization, and biological stability.

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