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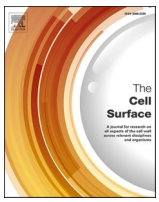

# Alternative mechanisms of action of metallic nanoparticles to mitigate the global spread of antibiotic-resistant bacteria

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A B S T R A C T

One of the biggest issues for medical professionals and a serious global concern is the emergence of multi-drug-resistant bacteria, which is the result of the overuse or misuse of antimicrobial agents. To combat this urgent problem, new drugs with alternative mechanisms of action are continuously replacing conventional antimicrobials. Nanotechnology-fueled innovations provide patients and medical professionals with hope for overcoming drug resistance. The aim of the present work was to document the antimicrobial potential and mechanisms of action of metallic nanoparticles against bacterial pathogens. Cell wall interaction and membrane penetration, reactive oxygen species (ROS) production, DNA damage, and protein synthesis inhibition were some of the generalised mechanisms recognised in the current study. In vitro and in vivo studies demonstrated that toxicity concerns and the development of bacterial resistance against nanoparticles (NPs) harden the use of metallic NP products for the treatment of drug-resistant bacterial pathogens. Therefore, researchers across the globe should actively engage in solving the above-mentioned issues.

## 1. Introduction

Pathogens that have developed antibiotic resistance have become a severe health concern, and as a result, several studies have been conducted to enhance the effectiveness of current antimicrobial medicines (Akram et al., 2022). It is also reported that over 70 % of bacterial diseases are resistant to one or more therapeutic agents that are commonly used to eradicate the causative agents (Dizaj et al., 2014). To overcome these urgent problems, novel agents with alternative mechanisms of action are needed for effective control of current bacterial pathogens. This has sparked a lot of interest in so-called "nanotechnology," an emerging area such as the technology of production, characterization, and application of materials at the nanoscale (any particle up to 100 nm).

Nanotechnology is a novel science that is applied and benefits different fields of study, including medicine. A variety of metallic nanoparticles (Dizaj et al., 2014; Franco et al., 2022; Malarkodi et al., 2014; Raghunath and Perumal, 2017) have drawn a lot of interest because of their potential antimicrobial properties, including silver (Ag), gold (Au), Ag oxide ($Ag_2O$), zinc oxide (ZnO), titanium dioxide ($TiO_2$), calcium oxide (CaO), copper oxide (CuO), and magnesium oxide (MgO) (Table 1). Even though, their antibacterial activities depend primarily on the size, shape, surface charge, pH, concentration, type of capping or stabilising agents, and bacterial gram-type. Several studies (Abbaszadegan et al., 2015; Almontasser et al., 2019; Dadi et al., 2019; Inam et al., 2019; Javed et al., 2016; Saliani et al., 2015) demonstrated that, small-sized, spherical-shaped, acidic-pH, positive-charged, capped, and high-concentration NPs and in gram-negative bacterial types had high antibacterial activity as compared to their counterparts.

Regarding mechanisms of action, metallic NPs have been shown to have antibacterial properties in various studies; however, the precise mechanism underlying their antimicrobial action against pathogenic microbes is still unknown. Numerous potential mechanisms, including nucleic acid damage, cell wall and cell membrane damage through pits and holes, disruption of normal cell structure and function, protein oxidation, interruption of electron transport, inhibition of cell division, formation of reactive oxygen species (ROS), degradation or inhibition of enzymes, inactivation or leakage of cellular materials, and loss of the flagella, cellular integrity, and cellular matrix, are the antibacterial mechanisms reported in the current study. Similar to the present study, (Dakal et al., 2016) reported that the following are some of the ways that metallic nanoparticles work: (i) attraction to bacterial cell walls due to opposite surface charges; (ii) membrane instability; (iii) production of reactive oxygen species (ROS); (iv) release of metal ions; and (v) modification of the signalling pathway. The unique mechanisms of different metallic nanoparticles and their toxicity are crucial for

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**Table 1**
Characteristics of metallic nanoparticles and their antibacterial activities.

| NPs | Shape | Size (nm) | Bacterial strains | Time | MIC | References |
|---|---|---|---|---|---|---|
| ZnO | Sphere-like | 19 | *E. coli* | 3 h | MIC = 50 μg/mL | (Li et al., 2011) |
| $TiO_2$ | Spherical | 12 | *E. coli* MG 1655 | 24 h | MIC = 100 μg/mL | (Simon-Deckers et al., 2009) |
| $Al2O_3$ | Spherical | 11 | *E. coli* MG 1655 | 24 h | MIC = 106 μg/mL | (Simon-Deckers et al., 2009) |
| Ag | Spherical | 7.1 | *E. coli* MTCC 062<br>*P. aeruginosa* MTCC 424 | 18 h | MIC = 3.6 μg/mL<br>MIC = 2.7 μg/mL | (Ramalingam et al., 2016) |
| Au | Spherical | 8.4 | *A. baumannii*, *E. coli* J96, *E. coli* O157:H7, MRSA, *P. aeruginosa*, *S. aureus*.<br>*E. faecium*<br>*E. faecalis* | 9 h | MIC = 8 μg/mL<br>MIC = 16 μg/mL<br>MIC = 32 μg/mL | (Lai et al., 2015) |
| $CeO_2$ | Ellipsoidal | 7 | *E. coli* RR | 13 h | MIC = 500 μg/mL | (Thill et al., 2006) |
| MgO | Cubic | 7 | *E. coli* and *S. aureus* | 24 h | MIC = 10 mg/mL | (Almontasser et al., 2019) |
| $Fe_3O_4$ (IO) | Spherical | 66 | *S. aureus, S. epidermis, V. cholerae, B. subtilis* and *E. coli, Bacillus licheniformis, Brevibacillus brevis* | 24 h | MIC = 50 mg/mL | (Behera et al., 2012) |

**MIC:** Minimum inhibitory concentration; **MRSA:** Methicillin-resistant *Staphylococcus aureus*.

decreasing drug-resistant bacterial pathogens. Furthermore, knowing their unique mechanisms of action against the current potential drug-resistant bacterial pathogens and their toxins is useful as a guide for both governmental and nongovernmental policymakers and stakeholders to control diseases causing bacterial infections.

## 2. Interaction with cellular (cell wall and membrane) compartments

Metallic NPs cling to cell walls and membranes after being exposed to bacteria (Fig. 1). Metallic NPs' positive surface charge is essential for attachment (Wang et al., 2017). The negatively charged cell membrane of the bacteria and the positively charged NPs are electrostatically attracted to one another, making metallic NP adhesion to cell membranes easier since they are positively charged in water. According to research by (Z. Li et al., 2019b), positively charged magnetic (NP + ) effectively attracted over 90 % of *E. coli*; however, negatively charged magnetic (NP-) did not exhibit any affinities. These results also imply that NPs + have a high potential for electrostatically attracting bacteria. Upon such interaction, morphological changes become obvious and can be distinguished by cytoplasmic shrinkage and membrane detachment, which ultimately result in cell wall rupture (Xie et al., 2011). According to transmission electron microscopy, the cell membrane of *E. coli* cells totally ruptures after a short period of contact with AgNPs. When AgNPs cause damage, the cell wall becomes circumferential, and TEM images show multiple electron-dense pits at those locations. For the microorganisms' *P. aeruginosa* and *S. aureus*, (Song et al., 2006) demonstrated plasmolysis and inhibition of the formation of the bacterial cell wall by AgNPs. Similarly, some scholars (Leung et al., 2014; Pan et al., 2013) have shown that MgO-NPs and $Mg(OH)_2$-NPs can destroy cells without entering the cell by electrostatic adsorption to the cell wall. In addition to electrostatic attraction, the interaction of metallic NPs with the proteins in the cell wall that contain sulphur results in irreversible changes in cell wall structure, which causes its destruction. This, in turn, has an impact on the cell membrane's permeability and lipid bilayer integrity. Increased membrane permeability as a result of morphological changes in cells has an impact on their capacity to control transport activities through the plasma membrane. The transport and release of potassium ($K^+$) ions from microbial cells can also be affected by metal ions. Similarly, a study found that superparamagnetic iron oxide interacts with microbial cells by directly penetrating the cell membrane and interfering in the transmission of transmembrane electrons. The increase in membrane permeability may have more severe repercussions than just impairing transport function, such as the loss of cellular contents through leakage, like ions, proteins, reducing sugars, and occasionally the cellular energy reserve, ATP (Dakal et al., 2016).

With regard to ion leaching and dissolution, several investigations have shown that environmental factors, such as pH and NP dissolving rate, can have a big impact on the antibacterial activity of metallic NPs. (Saliani et al., 2015), demonstrated that as pH declined from 7 to an acidic pH, the inhibition of bacterial growth caused by ZnO-NPs increased. Similar to this, (Moreau et al., 2007), discovered that ZnO-NPs dissolve more readily in acidic environments, indicating a larger release of Zn (2 + ) ions. According to (Peretyazhko et al., 2014), AgNPs undergo oxidative breakdown after being discharged into the aquatic system, which causes the release of Ag (+) ions and the induction of antibacterial activity. They also noticed that the size-dependent dissolution of AgNPs in acetic acid was greater than that in water.

## 3. Binding to proteins

The alternative antibacterial mechanisms exhibited by metallic NPs (Godoy-Gallardo et al., 2021) are protein dysfunction and enzyme inactivation (Fig. 1). For example, it has been suggested that Ag (+) primarily exerts antibacterial activity through different modes of action, such as denaturing the 30-s ribosomal component and inhibiting the synthesis of proteins and enzymes necessary for the production of ATP via oxidation of amino acid side chains. For instance, protein deactivation results from persistent SAAg bonds formed when Ag (+) ions connect to thiol groups of proteins present in the cell membrane. AgNPs and Ag (+) ions interact with proteins to change their three-dimensional (3D) structure, disrupt disulfide bonds, and block active binding sites,

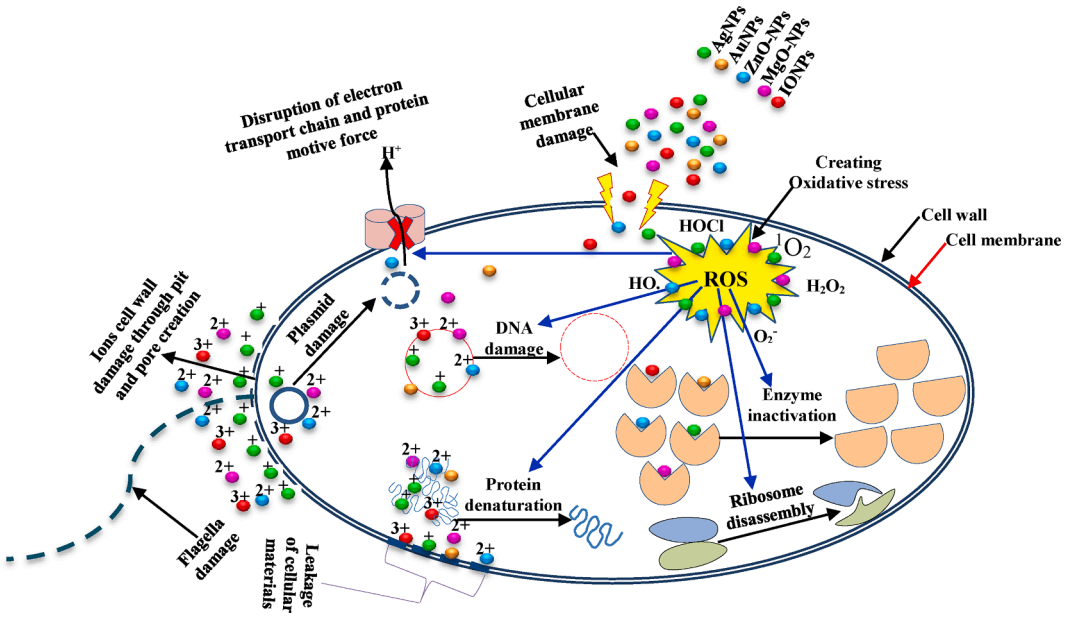


**Fig. 1.** The general mechanisms of metallic NPs against bacterial pathogens.

which causes general functional problems in the microorganism. Furthermore, inhibition of phosphorylation of proteins would inhibit their enzymatic activity, which in turn would result in inhibition of bacterial growth. Similarly, studies including the inactivation of cellular proteins, DNA damage, and disruption of metabolic enzymes can be implicated in the beneficial antimicrobial activities of NPs (Singh et al., 2013). This might be due to the fact that NPs have a significant potential to inactivate common activities or metabolic processes, such as permeability, respiration, and energy generation, in bacterial pathogens.

## 4. Formation of reactive oxygen species

Regarding ROS, it is thought that metallic NPs could enter the bacterium and inactivate the respiratory enzymes by accelerating the production of free radical species such as hydrogen peroxide ($H_2O_2$), superoxide anion ($O_2^-$), hydroxyl radical (HO.), hypochlorous acid (HOCl), and singlet oxygen ($^1O_2$), which ultimately results in bacterial death (Raffi et al., 2008). According to Yu et al. (Yu et al., 2020), the excessive ROS produced by nanoparticles can damage biomolecules and organelle structures because of their high oxidation potential. This damage includes protein oxidative carbonylation, lipid peroxidation, DNA/RNA breakage, enzyme inhibition, and membrane structure destruction, all of which can result in necrosis, apoptosis, or even mutagenesis. According to (Maji et al., 2020), ROS are very reactive entities that cause damage to cell walls and membranes by breaking the carbonyl group of peptide bonds against *Bacillus* spp. and *E. coli* at an MIC of 6 and 7.5 μg/ml, respectively. Moreover, ROS are beneficial for increasing the gene expression levels of oxidative proteins, which is a key mechanism in bacterial cell apoptosis (Fig. 1). For example, the hydroxyl radical (OH.), one of the most potent radicals, is known to react with all components of DNA, causing single-strand breakage via the formation of an 8-hydroxyl-2′-deoxyguanosine (8-OHdG) DNA adduct (Valavanidis et al., 2009). This could be due to the silver ions that AgNPs inject into the bacterial cells, increasing their bactericidal activity. It has also been suggested that AgNPs specifically target and disrupt the respiratory chain by interacting with the thiol groups found in enzymes like NADH dehydrogenases, ultimately causing cell death (Singh et al., 2013). As a result, it is anticipated that increasing levels of Ag (+) ions may enhance oxidative stress, which has both cytotoxic and genotoxic effects. The rise of cellular oxidative stress in microorganisms is a sign of the harmful effects of heavy metal ions like Ag (+). This toxic effect may be due to the binding of Ag (+) ions onto the cell membrane of the microbes, which consequently relays signalling and blocks the respiratory function of the microbes. The Ag (+) ion is known to cause dysfunction in the respiratory electron transport chain by uncoupling it from oxidative phosphorylation and inhibiting respiratory chain enzymes.

## 5. Interaction with DNA

Microbial cells exposed to metallic NPs also undergo genomic alterations, such as condensation of genetic materials, particularly genomic and plasmid DNA (Fig. 1). As a consequence, various important cellular functions get suppressed, which ultimately leads to cell necrosis and death. According to (Rai et al., 2009), metallic NPs have a high affinity for interaction with substances containing sulphur and phosphorus, such as DNA and proteins on bacterial cell membranes, alter membrane permeability, damage the respiratory chain and cell division machinery, and ultimately cause cell death.

Furthermore, the interaction of AgNPs with DNA may result in DNA shearing or denaturation as well as a disruption of cell division. NP-induced genotoxicity includes chromosomal aberrations such as mutations, DNA strand breaks, and oxidative DNA base damage. In *E. coli*, AgNPs result in DNA damage (such as strand breaks) and mutations in crucial DNA repair genes (mutY, mutS, mutM, mutT, and nth), rendering mutant strains more vulnerable to AgNP-based antimicrobial treatment than wild-type strains (Radzig et al., 2013). The H-bonds between base pairs of the anti-parallel DNA strands are broken when the Ag (+) ion intercalates between purine and pyrimidine base pairs, causing the double helical shape to be broken. In microorganisms, intercalation of AgNPs in the DNA helix may prevent the transcription of some genes. Additionally, AgNPs cause the DNA molecule to transition from its relaxed state to its compacted shape, which impairs DNA replication. The first stages of cell division are decreased when AgNPs connect with *S. aureus*, indicating that the interaction of the Ag (+) ions with DNA may play a role in inhibiting cell division and reproduction (Jung et al., 2008). Additionally, the bactericidal action of gold (Au) NPs against *E. coli* was shown to involve the inhibition of ribosome subunits, in addition to the alteration of membrane and ATPase activities.

**Table 2**
Toxicity effect studies of metallic nanoparticles.

| Nps | Dose | Test organism/cell type | Lab | Exposed time | Toxic effects | References |
|---|---|---|---|---|---|---|
| IO | 300, 400, & 600 mg/ml | C17.2 neural progenitor cells, PC12 rat pheochromocytoma cells and human blood outgrowth endothelial cells | In-vitro | 0, 3 & 6 days | Affect cell spreading and labelling and have effect on cell homeostasis. | (Soenen et al., 2011) |
| Ag | 0, 10,20, 30, 40, & 50 μM | A549 | In-vitro | 24 h | Apoptosis due to ROS creation, LDH leakage, mitochondria dysfunction, DNA fragmentation | (Gurunathan et al., 2018) |
| ZnO | 5.6 ± 0.55, 11.75 ± 0.8, 17.45 ± 1.1, & 21.7 ± 1.3 μg/mL | Murine Cell Lines | In-vitro | 24, 48, & 72 h | Membrane blebbing, nuclear condensation, nuclear fragmentation, and apoptotic body formation. | (Namvar et al., 2015) |
| MgO | 131.5 & 263 mg/kg | Reproductive organs of rats | In-vivo | 4 weeks | Produced considerable changes in sex hormones and stress parameters in both male and female rats. | (Naguib et al., 2023) |
| Au | 72, 180, & 720 ng/mL | Mammalian cell lines | In-vitro | 24, 48, & 72 h | DNA damage and repair responses, cell-cycle regulation, and oxidative stress in AuNP-induced cytotoxicity and genotoxicity effects | (Chueh et al., 2014) |
| $TiO_2$ | 20, 50, 80, 110, 140, 170 & 200 μg/ml | MCF-7 | In-vitro | 24, 48, & 72 h | Results showed significant effect on WBC cells. TiO2 NPs dose and time-dependently suppressed the proliferation of MCF-7 cells | (Lotfian and Nemati, 2016) |
| CuO | 4, 8, 80, & 400 μg/$cm^2$ | Airway epithelial cells | In-vitro | 5 h | Cell viability decreased in a dose-dependent manner following exposure to CuO nanoparticles | (Fahmy and Cormier, 2009) |

**Table 3**
Bacterial strains resistance evidence against some nanoparticles.

| NPs | Resistant *E. coli* strains | Required time or generations | Changes observed | References |
|---|---|---|---|---|
| IO | *E. coli* | 25 days | Increased cell length, selective sweeps in *rpoA & rpoC* | (Ewunkem et al., 2021) |
| Ag | *E. coli* K-12 MG1655 | 225 generations | Mutation in *cusS, purI, rpoB, ompR* | (Graves Jr et al., 2015) |
| ZnO | *E. coli* | 25 generations | Changes in cell shape-rod to oval probably due to low expression of membrane protein RodZ, porins | (Zhang et al., 2018) |
| $Ag_2S$ | *E. coli* | >200 days | Upregulation of MDR genes, Cu efflux transporter genes | (M. Li et al., 2019a) |

## 6. Current challenges and future prospects

Despite the high benefits and frequent use of these particles, their specific mechanisms of toxic consequences are still unknown. The biggest challenge is the toxicity of metallic NPs (inhaling specific NPs may cause gene alterations, allergic reactions, or localised lung inflammation) (Table 2). When the concentration of NPs increases, it can lead to an increase in cytotoxicity to mammalian cells and tissues, beneficial microbes in humans, as well as the environment (Shin et al., 2020). AgNPs are widely known for their capacity to pass the blood–-brain barrier and accumulate in the human body and many organs, particularly the brain. AgNP was additionally identified in the brain, liver, kidneys, spleen, lungs, and spleen of the subjected rats (Ivask et al., 2014). Zinc-based NPs have been demonstrated to cause toxicity, membrane damage, and increased oxidative stress in mammalian cell lines (Saptarshi et al., 2015). To reduce the toxicity of nanoparticles in human cells, it is advised to size-reduce, encapsulate, and surface-functionalize metallic nanoparticles. It is also advised to use in vitro and in vivo assessment methodologies.

Regarding bacterial resistance, it was previously believed that because NPs have a variety of ways of acting on different cell components of bacteria, they could not quickly acquire resistance to NPs (Amaro et al., 2021). However, recent studies have demonstrated that continuous exposure to metallic nanoparticles might cause bacteria to develop stable resistance mechanisms. According to (Gómez-Núñez et al., 2020; Niño-Martínez et al., 2019; Raza et al., 2021), it has been discovered that microbial adaptation to nanoparticles occurs through efflux pumps, electrostatic repulsion, biofilms and other extracellular polymeric materials, enzyme detoxification, volatilization, and genetic alterations (Table 3). A recent study (Kamat and Kumari, 2023) found that some bacterial pathogens can become resistant to antimicrobial nanoparticles through a variety of mechanisms, including oxidative stress brought on by nanoparticle transformation, membrane alterations, reversible adaptive resistance, irreversible alterations to cell division, and modifications to bacterial motility and resistance. Modify the surface corona of nanoparticles, as well as strict regulation regarding the use and disposal of nanowaste across the globe, firm knowledge of microbe-nanoparticle interaction, and the regulated disposal of nanoparticles in soil and water, are required to prevent microbes from developing nanoparticle resistance.

## 7. Conclusion

Cell wall interaction and membrane penetration, ROS production, DNA damage, and protein synthesis inhibition were some of the generalised mechanisms recognised in the current study. This makes metallic NPs a promising candidate for the development of new antibacterial agents that can combat bacterial resistant pathogens. However, further research is needed to fully understand the potential toxicity risks and benefits of using metallic NPs as antibacterial agents.

### CRediT authorship contribution statement

**Abayeneh Girma:** Conceptualization, Investigation, Writing – original draft, Visualization, Writing – review & editing.

### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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