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# *Metal nanoparticles and their relationship with antimicrobial activity: A review*

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## Abstract

The global threat of antimicrobial resistance (AMR) has driven an urgent need to explore alternative strategies to combat resistant pathogens. Metal nanoparticles (NPs), owing to their unique physicochemical properties, have emerged as promising antimicrobial agents. This review highlights the diverse mechanisms of action exhibited by metal nanoparticles, including membrane disruption, reactive oxygen species (ROS) generation, and interference with intracellular processes. Particular emphasis is placed on silver, gold, copper, zinc oxide, and titanium dioxide nanoparticles due to their broad-spectrum antimicrobial activity and synergistic potential when combined with conventional antibiotics. Furthermore, the review discusses the role of nanoparticle synthesis methods, size, shape, and surface modifications in enhancing antimicrobial efficacy and reducing toxicity. While metal nanoparticles show immense potential in overcoming AMR, challenges such as scalability, biocompatibility, and long-term safety remain key considerations for clinical translation. This review underscores the need for further multidisciplinary research to harness the full potential of metal nanoparticles in addressing the AMR crisis.

**Keywords:** Antimicrobial resistance, Metal Nanoparticles; Sliver nanoparticles; Gold nanoparticles.

## Introduction

Antimicrobial resistance (AMR) represents a significant global health challenge in the 21st century, undermining the effectiveness of current therapeutic strategies and complicating the control of infectious diseases. In 2019, bacterial AMR was responsible for an estimated 1.27 million deaths worldwide and contributed to 4.95 million deaths. Among the key pathogens driving this crisis is the Gram-positive bacterium *Staphylococcus aureus*, a versatile organism responsible for a wide range of infections, from minor skin conditions to severe systemic diseases [47]. The 2022 Global Antimicrobial Resistance and Use Surveillance System (GLASS) report highlights alarming resistance rates among prevalent bacterial pathogens, with 35% of methicillin-resistant *Staphylococcus aureus* (MRSA) being particularly concerning[58]. The World Health Organization (WHO) and various organizations emphasize the urgent need

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for a coordinated global action plan to address the spread of AMR. Notably, *Staphylococcus aureus* is the leading cause of mortality due to antibiotic resistance [48], significantly contributing to deaths from bloodstream infections [49].

The emergence of methicillin-resistant strains and the presence of the mec cassette in the genome are significant events in *S. aureus's* acquisition of resistance, impacting its properties and facilitating resistance to other antibiotics [50]. Despite significant advancements in understanding the molecular mechanisms of antimicrobial resistance, the identification of new drug targets has not yet led to the development of effective new chemotherapeutic agents. This has necessitated the exploration of innovative approaches, with nanotechnology emerging as a promising frontier for advanced antimicrobial therapies. Nanoparticles, characterized by their high surface area-to-volume ratio and potential for functionalization with various biomolecules, offer ideal solutions for targeted drug delivery and enhanced antimicrobial activity [51].

Nanoparticles have emerged as a promising solution in addressing the global challenge of antimicrobial resistance (AMR), which has rendered many traditional antibiotics ineffective. Among these, metal nanoparticles such as silver, gold, and zinc oxide exhibit unique properties, including a high surface area-to-volume ratio and customizable functionalization, allowing for enhanced antimicrobial efficacy [1]. Additionally, their ability to disrupt microbial cell membranes, interfere with metabolic pathways, and generate reactive oxygen species makes them particularly effective against resistant strains [2]. However, despite their potential, concerns surrounding cytotoxicity and environmental impact necessitate further research into safer and more sustainable applications [3].

Since the 1950s, magnetic nanoparticles have garnered significant attention for their applications in hyperthermia, imaging, drug delivery, and enzyme immobilization, owing to their unique surface chemistry and magnetic properties [52]. Metal nanoparticles exhibit unique physicochemical properties, such as a high surface area-to-volume ratio, tunable size and shape, and the ability to generate reactive oxygen species (ROS), which contribute to their broad-spectrum antimicrobial activity [53]. These nanoparticles can disrupt bacterial membranes, interfere with cellular processes, and induce oxidative stress, leading to bacterial cell death. Additionally, their ability to bypass traditional resistance mechanisms makes them highly effective against multidrug-resistant (MDR) pathogens [51]. Commonly studied metal nanoparticles include silver (AgNPs), gold (AuNPs), copper (CuNPs), zinc oxide (ZnO-NPs), and titanium dioxide (TiO2-NPs), each of which exhibits distinct antimicrobial properties and potential applications.

A significant advantage of metal nanoparticles lies in their synergistic effects when combined with antibiotics. Studies have demonstrated that nanoparticles can enhance antibiotic efficacy by increasing cellular uptake and disrupting biofilms, a key defense mechanism employed by many pathogens [54]. Despite their potential, several challenges remain, including concerns about cytotoxicity, environmental safety, and the scalability of nanoparticle production for clinical use [55]. Addressing these challenges requires a multidisciplinary approach, integrating materials science, microbiology, and clinical medicine.

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This review aims to provide a comprehensive overview of metal nanoparticles and their mechanisms of antimicrobial action, with a focus on their applications in combating AMR. Additionally, it highlights the current challenges and future perspectives in utilizing metal nanoparticles as antimicrobial agents, providing insights into their potential role in addressing one of the most pressing healthcare issues of our time.

## Types of Metal Nanoparticles Used in Antimicrobial Applications

### Silver-Based Nanomaterials:

Silver nanoparticles (AgNPs) are particularly valued for their strong antimicrobial activity against bacteria, viruses, and fungi, and they are often used as disinfectants and to enhance the efficacy of antibiotics through synergistic effects [3]. In clinical settings, AgNPs are applied for treating chronic ulcers, burns, and antibiotic-resistant wounds, promoting collagen deposition for wound healing and demonstrating anti-inflammatory properties [4]. However, their cytotoxicity to human cells—especially for particles ≤ 10 nm—depends on factors like size, dose, and exposure time. To address this, researchers have immobilized AgNPs on support materials like polymers, activated carbon, and graphene oxide. Modifications with titanate nanotubes further enhance their antibacterial, catalytic, and photocatalytic properties by improving stability and altering their physicochemical characteristics [5].

### Gold-Based Nanomaterials:

Gold-based nanomaterials, such as nanorods, nanoclusters, and nanoshells, have been developed with antimicrobial activity in mind. Their properties can be optimized through structural modifications or conjugation with antimicrobial agents and antibodies. Antibiotic-conjugated gold nanoparticles (AuNPs) exhibit significant efficacy against bacteria, including antibiotic-resistant strains [6]. Gold nanoclusters (AuNCs) have shown excellent biocompatibility, photothermal stability, and polyvalent effects, making them ideal for biomedical applications like imaging, detection, and antimicrobial therapy [7]. In pharmacology, AuNPs are notable for their diverse activities, including anti-angiogenesis, anti-HIV, and anti-arthritic effects. They are widely used in gene therapy, drug delivery, and medical diagnostics due to their ease of surface functionalization and biocompatibility [8, 9].

### Titanium Dioxide (TiO2) Nanomaterials:

Titanium dioxide nanoparticles have gained attention due to their photocatalytic bactericidal activity, chemical stability, and low cost [10]. TiO2 is widely utilized in nanomedicine and environmental remediation, due to its non-toxic nature, good thermal stability, and high surface-area-to-volume ratio [11]. These nanoparticles exhibit broad-spectrum antimicrobial activity, making them effective against multidrug-resistant strains [12]. Furthermore, TiO2-based nanocomposites provide a non-contact biocidal effect[13], reducing the need to release potentially harmful nanoparticles into the environment while maintaining their disinfectant properties [14].

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## Zinc and Zinc Oxide-Based Nanomaterials:

Zinc oxide (ZnO) nanomaterials are favored for their selectivity, low toxicity, and stability compared to organic antimicrobials. Their nanoscale dimensions increase the surface area, enhancing interactions with microbial cells and optimizing antimicrobial effectiveness [15]. Studies indicate that smaller ZnO nanoparticles demonstrate superior antibacterial activity [16.17]. ZnO is particularly valued in healthcare products for its UV-blocking properties and effectiveness against various bacteria [18]. Additionally, ZnO nanoparticles are utilized in medicine for their antimicrobial and fungicidal effects, anti-inflammatory properties, wound-healing abilities, and chemiluminescent features for bioimaging [19].

## Copper and Copper Oxide-Based Nanomaterials:

Copper and copper oxide nanomaterials (CuO NPs) are of interest for their versatility in applications like sensors, solar cells, catalysis, and antimicrobial uses [20]. Copper is a cost-effective, highly conductive material, and its oxide forms are thermodynamically stable, making CuO nanoparticles particularly valuable. The antibacterial activity of copper-based nanomaterials is primarily attributed to the release of $Cu^{2+}$ ions, which disrupt bacterial membranes and interfere with enzymatic functions, ultimately causing cell death [21]. CuO nanoparticles, as the simplest copper oxide structure, exhibit strong antimicrobial properties against bacteria, viruses, fungi, and algae [22]. They are widely employed in health applications, including biocides, pesticides, gas sensors, and medical technologies [23,24].

## Synthesis and Mechanism of Antimicrobial Nanomaterials:

Nanomaterials can be produced using various synthesis techniques and exhibit unique interactions with microbial cells through diverse mechanisms. Among metal nanomaterials, silver nanoparticles (AgNPs) are the most extensively studied. With advancements in nanotechnology, AgNPs have been synthesized and found to interact uniquely with fungal and bacterial species. While numerous methods are available for AgNP synthesis, conventional chemical and physical techniques are often costly and hazardous. In contrast, biological methods are considered straightforward, rapid, eco-friendly, and non-toxic, making them a promising green chemistry approach for AgNP production [25]. For instance, Nadagouda et al. demonstrated the green synthesis of microwave-assisted silver nanostructures [26]. Similarly, Ullah et al. reported an environmentally friendly, photo-irradiation-based method for synthesizing antibacterial AgNPs using *Gui Hua* leaves [27]. Additionally, Liu et al. employed leaf extracts from *Nageia nagi* for eco-friendly AgNP production [28], and Yu et al. developed integrated alginate fibers containing AgNPs synthesized from *Dolcetto* grape leaves [29].

Despite extensive research into the antimicrobial mechanisms of AgNPs, the exact process remains unclear. Evidence suggests that silver ions disrupt the peptidoglycan cell wall, leading to structural alterations, increased membrane permeability, and bacterial death. AgNPs may also interact with bacterial protein sulfhydryl groups, inhibiting DNA replication [30]. However, while AgNPs exhibit potent antimicrobial properties, they can also be toxic to higher organisms, including humans, oysters, zebrafish,

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and rodents. Studies in rodents reveal that AgNPs can accumulate in the body, cross the blood–brain barrier, and damage tissues, while research on human cells indicates potential genotoxicity [31].

Nanomaterials are advantageous as antibacterial agents due to their high surface area relative to size, which enables biofilm penetration and disrupts encapsulating exopolysaccharides and proteins. For example, titanium dioxide (TiO2) nanoparticles can irreversibly bind to hydroxyl groups in biofilm polysaccharide matrices, while iron oxide and silica nanoparticles can adhere to biofilms through electrostatic forces. Additionally, other nanomaterials release charged antimicrobial agents or use strategies such as core quenching to inhibit biofilm formation [32]. Despite these benefits, the toxicity of nanomaterials presents challenges. TiO2 nanoparticles, for instance, exhibit inconsistent cytotoxicity, with both toxic and non-toxic results reported [33,34]. Green synthesis methods are particularly valuable for reducing toxicity while providing cost-effective and energy-efficient nanoparticle production. Pushpamalini et al. demonstrated this approach by synthesizing TiO2 nanoparticles using four different leaf extracts [35]. The toxicity of gold nanoparticles (AuNPs) also remains debated; some studies suggest they are non-toxic, while others report adverse effects. Geetha et al. found that AuNPs synthesized using *C. Guianensis* flower extract exhibited anticancer activity [36].

While antimicrobial nanomaterials offer significant advantages in biomedical applications, challenges remain, particularly in the use of antimicrobial nanoparticle (AMNP)-coated medical implants. Protein contamination on implant surfaces can alter antimicrobial properties, and sterilization processes may exacerbate these changes. The successful production of AMNPs and coated implants depends on factors such as nanoparticle properties, cost-effectiveness, antimicrobial efficacy, and process complexity. Furthermore, evaluating AMNPs requires addressing polymicrobial populations involved in implant-related infections. Overcoming these challenges will require collaboration among clinicians, researchers, regulatory bodies, and industry professionals. Nonetheless, modifying the biological activity of nanometals holds promise for improving existing treatments. Multi-metal and metal oxide nanoparticles, including metal-doped nanocomposites and alloys, show potential in addressing issues like agglomeration and cytotoxicity. Surface modifications can enhance properties such as hydrophilicity and anti-caking, while doping metal/metal oxide nanoparticles with other metal ions may reduce toxicity and enhance their performance [37,38].

## Antibacterial Activity:

Nanomaterials offer a distinct antibacterial mechanism that addresses bacterial resistance, making them valuable in the biomedical field [39]. Unlike traditional antibiotics, they are less likely to induce bacterial resistance due to their unique characteristics, including (A) a small size with a large specific surface area [40]; (B) easy suspension in liquids; (C) the ability to penetrate cells and organelles; and (D) significant optical and magnetic variations [41]. These properties position nanomaterials as promising approaches for medical antibacterial drugs. In recent years, metal and metal oxide nanomaterials have been extensively applied in antibacterial research, yielding remarkable results. Several antibacterial mechanisms for nanoparticles have been identified, as summarized below:

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(a) **Biofilm disruption**: Nanomaterials can break down biofilms, which are key contributors to drug-resistant microorganisms. Biofilm formation significantly increases mortality, morbidity, and treatment duration. Traditional antibacterial agents are often ineffective against biofilms in human wounds [42], but nanomaterials show potential in overcoming bacterial resistance to antibiotics [43].

(b) **Generation of reactive oxygen species (ROS)**: Nanoparticles produce ROS that damage DNA, RNA, and proteins, ultimately destroying microorganisms [44].

(c) **Inhibition of DNA replication**: By binding to bacterial DNA, nanoparticles can prevent DNA replication. Smaller nanoparticles exhibit higher binding rates and greater antibacterial activity compared to larger ones [45].

(d) **Release of metal ions**: Metal nanoparticles release positively charged metal ions, which interact with the negatively charged microbial cell membrane. These ions penetrate the cell membrane, react with sulfhydryl groups (-SH) on microbial proteins, and inhibit protein and nucleic acid synthesis. The antibacterial properties of nanoparticles are influenced by their size and surface charge. Smaller nanoparticles with a larger surface-to-volume ratio demonstrate superior antibacterial effects without compromising the mechanical properties of materials [44, 46].

In addition to these mechanisms, nanoparticles can kill bacteria by releasing loaded antibacterial agents, offering an alternative approach to combating bacterial resistance [44].

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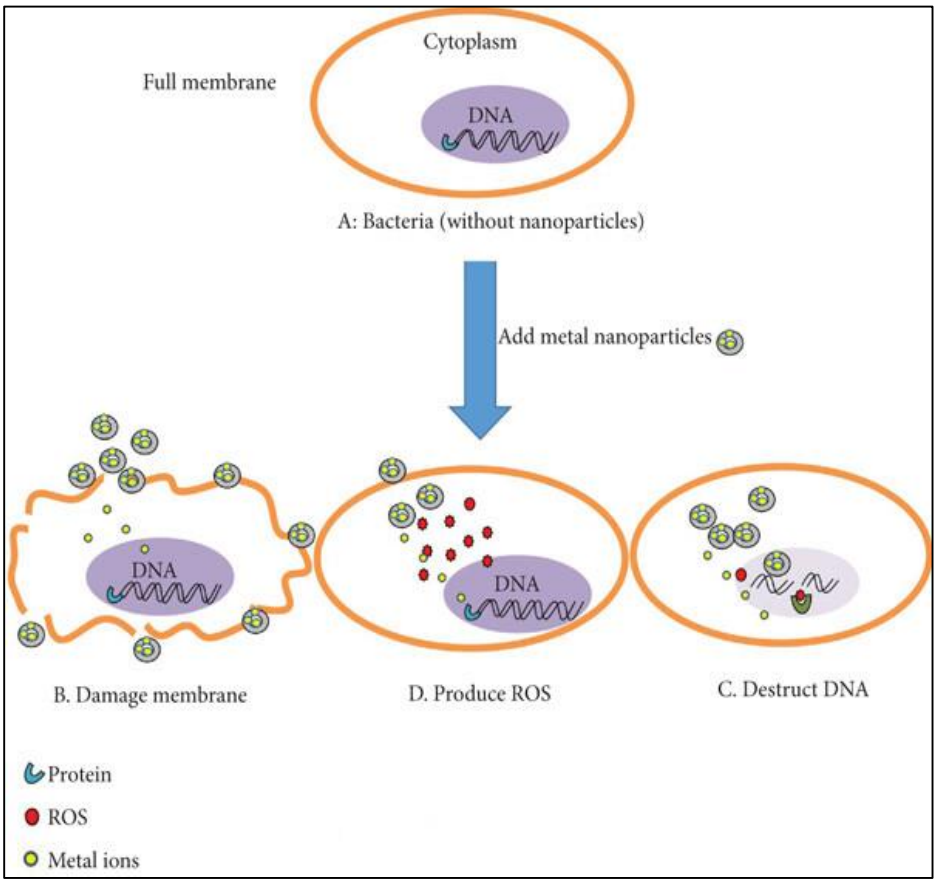


**Figure (1): The antimicrobial action of metal nanoparticles involves several steps: (a) Bacteria in their natural state, without exposure to metal nanoparticles. (b) Metal nanoparticles compromise the integrity of the bacterial cell membrane. (c) These nanoparticles disrupt bacterial DNA. (d) Metal nanoparticles generate reactive oxygen species (ROS) [56].**

## Conclusions

Metal nanoparticles have demonstrated remarkable antimicrobial activity, offering a novel and effective approach to combat resistant pathogens. Their versatile mechanisms, such as membrane damage, ROS generation, and intracellular disruption, make them promising therapeutic approaches in addressing the AMR crisis. Moreover, their synergistic interaction with antibiotics has the potential to restore the efficacy of existing drugs against resistant strains, providing a dual advantage in combating infections. However, despite their significant promise, challenges related to nanoparticle toxicity, environmental impact, and scalability in production must be addressed to enable safe and widespread clinical applications. Future research should focus on optimizing nanoparticle synthesis, functionalization, and delivery systems to enhance therapeutic outcomes. By integrating nanotechnology with existing antimicrobial strategies, metal nanoparticles can play a pivotal role in mitigating the global threat of AMR, marking a transformative shift in modern antimicrobial therapy.

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## Author's Declaration

- Obtained ethical clearance for our study from the local ethical committee at [Al-Nahrain University/College of Biotechnology]. This approval underscores our commitment to ethical research practices and the well-being of our participants.

## Author's Contribution Statement

Zainab H. Jassim: Contributed to the conception and design of the study, conducted some experiments, data rearrangement and drafted the initial manuscript.

Ali Z. Al-Saffar: conducted some experiments, collection a part of literature review and conducted some characteristics of the products.

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