# Nanoparticles - Emerging Replacement to Antimicrobials

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## Abstract

Nanoparticles (NPs) generate interest as substitutes for traditional antimicrobials because of their distinct physicochemical properties and wide-ranging effectiveness against fungi, viruses, and bacteria. NPs destroy microorganisms by disrupting membranes, producing Reactive Oxygen Species (ROS), interfering with enzymatic processes and DNA replication, and dissolving biofilms. Gold NPs (Au NPs) have been used in various fields, from engineering to medicine, in recent years. Au NPs' biocompatibility allowed them to be utilized in antibacterial treatments, cancer treatment, and arthritis treatment. Silver NPs (AgNPs) have potent antibacterial effects by breaking bacterial membranes and interfering with enzyme functions through the generation of ROS. Ag, Au, zinc oxide (ZnO), and titanium oxide metal NPs (MNPs) have special antibacterial properties. Their most intriguing feature is their ability to administer medicines in the intracellular space where the infection is located. As a result, they enhance medication stability, boost drug circulation, improve target delivery, and boost therapy efficacy. They also improve the antibacterial spectrum, reduce toxicity and side effects, reduce the duration of treatment, and reduce the dosage of necessary medications. In nanomedicine, the active substance is transported and released at its pharmacological target by the use of nanovectors. Therefore, adjusting the pharmacokinetic route and bioavailability improves the effectiveness of medications and reduces their side effects.

Keywords: Nanoparticles, Silver, Gold, Polymers, Metal Oxide, Antiviral, Drugs, Antibiotics

Cite this Article as: Faraz A, Arshad M, Asghar S, Zeeshan A, Dilshad M, Yaqoob R, Arif S, Kazmi SAA, Tahir I and Noor, 2025. Nanoparticles - Emerging replacement to antimicrobials. In: Nisa ZU, Altaf S, Zahra A and Saeed K (eds), Nanobiotech in Holistic Health: Innovations for Integrated Well-being. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 40-44. https://doi.org/10.47278/book.HH/2025.104



# Introduction

Antibiotics are drugs that have the ability to either kill or inhibit microorganisms (Baquero & Levin, 2021). Antibiotics are categorized as antiviral, antifungal, and antibacterial depending on their target population. The majority of antibacterial substances are commonly referred to as antibiotics. Antibiotics have supported a variety of medical procedures, such as chemical therapy and organ transplantation, and have been used since ancient times for both prevention and treatment of infections. Protein and RNA synthesis, membrane structure breakdown, inhibition of enzymes, and DNA disruption are the well-known antimicrobial pathways of antibiotics. Antibiotics have been created in a variety of groups or classes, depending on how multi-drug resistance develops. Therefore, it is nearly impossible to envision a world without antibiotics (Muteeb et al., 2023). Unfortunately, this might come to pass as a result of microbes becoming more resistant to antibiotics. Drug resistance in bacteria is directly caused by the misuse of antibiotics, high dosages of medications that increase toxicity, prolong hospital stays, and raise mortality, as well as by their widespread use in agriculture and the lack of new antibiotic research. Furthermore, the accessibility with which products and infected individuals can now travel around the world contributes to the unprecedented spread of infections. Antibiotic resistance (AMR) has been identified by the World Health Organization (WHO) as one of the main public health concerns. Antibiotic resistance in microorganisms can be prevented by decreasing the use of antimicrobial agents and improving drug release, changing the targets of antibiotics, creating medications that break down or modify the enzymes of microorganisms, creating a biofilm coating that includes the bacteria, and limiting exposure to antibiotics (Tang et al., 2023).

These changes will eventually result in less drug accumulation in microbial cells or a brief intracellular presence of medications that are

unable to reach therapeutic concentrations efficiently therapeutic concentrations. But at this time, larger dosages and frequent drug administration are common, which greatly increases the possibility of negative side effects in both humans and animals. Numerous antibiotics that are often used to treat harmful germs have caused resistance (Uddin et al., 2021). In addition, the process of developing and promoting new antibiotics is expensive and time-consuming, involving the production of novel chemicals, several clinical trials, and licensing. There is a chance that bacteria would quickly become resistant to entirely novel antibiotics, which would reduce antibiotic use and sales and worsen the state of the economy and public health. Therefore, the failure of antibiotic treatment would eventually lead to a greater chance of infection-related death. Modern remedies are therefore essential for overcoming these barriers. The most significant advancement in recent years, nanotechnology, has revolutionized medicine. The market for products that use nanotechnology is growing steadily. The advanced field of nanotechnology will influence initiatives to improve human health. Medical experts have looked into NPs' lifespan, efficacy, resilience, adaptability, and special physicochemical characteristics (Bhardwaj et al., 2023).

They are used in many therapeutic techniques, including tumor identification, prognostic visual assessment of therapy, and targeted drug delivery. NPs were produced using several traditional methods, including chemical processes like photo-reduction, sol-gel, thermolysis, and micro-emulsion, as well as efficient methods like physical vapor deposition, laser ablation, sputtering, and mixing. These methods have the potential to make NPs unstable, cause dangerous substances to adhere to their surface, and produce dangerous byproducts. Biogenic NPs are made using environmentally friendly processes. Stable NPs, the use of a biomass-based coating on the surface that offers larger surface areas for biological interaction, the avoidance of hazardous byproduct formation, and more stabilizing or reducing factors that ultimately make the process cost-effective are some of the benefits of green synthesis. However, prolonged exposure to NPs at work could provide unexpected health risks to people. Additionally, breathing in NPs in the form of air pollutants might result in secondary exposure to NPs. Systemic health problems can arise when these inhaled NPs pass the immune system and spread throughout the body (Saratale et al., 2022). The antibacterial and antiviral properties of nanoparticles, such as AgNPs, AuNPs, quantum dots (QDs), carbon dots (C-dots), graphene oxide (GO), silicon materials, polymeric NPs, dendrimers, and polymers, are generally quite strong.

#### Role of Silver NPs in Antimicrobial Action

When AgNPs are exposed to bacteria, they have a tendency to assemble at the bacterial membrane, causing perforations that ultimately result in cellular death (Tripathi & Goshisht, 2022). The mechanisms of action between AgNP surfaces and biological elements also interact with different sizes (ranging from 1 nm to several 100 nm), as particle size may significantly suggest their action strategy without a secondary component. By inactivating bacterial enzymes and generating ROS, AgNPs produce cytotoxic activity. Ag+ species are given a prominent role by some other methods. In contrast to (metallic Silver Nanoparticles) Ag<sup>o</sup> Nps, some systems that contain originally Ag (+1) species, such as salts, zeolites, or ionomers, release ROS through ion exchange and dissolution (Varier et al., 2019). NPs serve as a reservoir for the monovalent Ag species, which turns into an antibacterial agent. The Ag ions are attracted to organic compounds, particularly phosphates, amines, and thiols, with which they establish a quasi-covalent bond (around sixty-five kcal/mol is the Ag–S binding energy).

Although these compounds are rather rare in the biological world, Ag+ has an equivalent affinity for selenol groups. Several substances, including cofactors, membrane-bound or intracellular peptides, and DNA, have been determined to be the ions' targets in the dying bacterium (Godoy-Gallardo et al., 2021). Any high-affinity moiety will be readily adsorbed by Ag+ ions unlike antibiotics that target a single component of the bacterial life cycle; therefore, it is unlikely that multiple pathways are impacted, leading to cellular death. Ag binds to a wide variety of sites in a non-specific manner, disrupting multiple elements of cell metabolism at once and ultimately causing cell death, which is far more likely. Some of the impacted pathways are extremely susceptible to even small amounts of Ag species. The antibacterial action of Ag NPs against a wide range of microbes may be explained in part by their capacity to interfere with a wide range of paths. Comparing Ag+ activity with and without oxygenic respiration revealed that more than half of the antibacterial activity was mediated by ROS (Kędziora et al., 2021).

Ag+ ions in nanoparticulate systems were also produced by oxidation and the discharge of ions that have been chemisorbed at the surface of particles. The antibacterial properties of *Urtica dioica*'s phytosynthesized AgNPs against a variety of harmful microbes were investigated. Compared to the controls, which were AgNO3 solution and leaf extracts, the AgNPs showed more activity. Furthermore, the increased concentration of AgNPs was observed to enhance the antibacterial properties. Compared to the controls, which were AgNO3 solution and leaf extracts, the AgNPs showed more activity. Furthermore, the increased extracts, the AgNPs showed more activity. Furthermore, the increased properties. Both biological and environmental systems include large amounts of chloride, which precipitates as the somewhat soluble compound AgCl (Sarvalkar et al., 2024).

#### Role of Gold NPs in Antimicrobial Action

Au NPs have been used in a wide range of fields, from engineering to medicine, in recent years (Hu et al., 2022). Au NPs' biocompatibility allowed them to be utilized in antibacterial treatments, cancer treatment, and arthritis treatment. Au NPs can detect cell receptors, tumor metabolites, and endocytosis under dark-field light-scattering microscopy. Additionally, biosensors, disease indicators, toxic metals, pesticides, and blood glucose measurements have all benefited from the usage of green-synthesized Au NPs. Additionally, Au NPs may be able to cleanse and break down harmful contaminants. Because of their reduced size, polyvalences, distinct surface chemistry, and photothermic nature, NPs also enhance a wide range of gene expressions associated with redox reactions that lead to microbial death. When Au NPs react with bases that include sulfur or phosphorus, they inactivate enzymes called NADH dehydrogenases (Mikhailova, 2021). These enzymes disrupt respiratory chains by producing a lot of free radicals, which kill cells. The composition of the cell wall also affects the antibacterial action. Compared to Gram-positive bacteria, Au NPs showed more activity. In addition to the structure of the bacterial cell wall, the antibacterial activity is also influenced by concentration, purifying techniques, and surface alteration (capping or coating materials). Antibiotic coatings, particularly aminoglycoside antibiotics, can increase the effectiveness of Au NPs in antibacterial activity. The fact that green-synthesized Au NPs exhibit effective antibacterial activity against specific bacterial strains when compared to chemically synthesized Au NPs is fascinating and could be the

result of the synergistic interaction between Au NPs and extracts (El-Borady et al., 2020).

#### Role of Metal Oxide NPs in Antimicrobial Action

Recently, ZnO has been employed for piezoelectric nanogenerators and nanoscale optoelectronics in addition to being a semiconductor with a broad bandgap (3.36 eV) that has a range of nanostructures and possible electronic uses. They are effectively employed to combat microbes. According to certain findings, the production of ROS on the surface of CaO, MgO, and ZnO exhibits significant antibacterial activity, as determined by a conductometric approach. After ZnO breaks down the cell membrane, ZnONps securely adheres to the deceased bacterium's surface, blocking additional antibacterial activity and releasing peroxides into the medium with strong bactericidal efficiency. Another study's findings showed that a smaller particle size increases activity because of its high surface area-to-volume ratio (Gökmen et al., 2024).

#### Role of Polymeric in Antimicrobial Action

Polymeric NPs, which are colloidal solids with a diameter of 10–1000 nm, are the most prevalent type of organic nanoparticle (Shrestha et al., 2020). Higher amounts at target places may result from the tiny size's ability to enhance capillary penetration and cell absorption. When delivered through polymeric NPs made of poly(ethylene glycol)-block-poly(lactide-co-glycolide) (PEG-PLGA), diphyllin, a vacuolar ATPase blocker, proved more successful than diphyllin alone in preventing feline infectious peritonitis (FIP), which is brought on by a mutant feline CoV. Mice also showed greater tolerance to NPs loaded with diphyllin. Consequently, a polymeric nanoparticle-based nanoformulation showed promising antiviral efficacy against FIP. Because of their flexible molecular structure and lengthy chains and branches, polymers have a strong antiviral potential. It is possible to develop polymers according to arbitrary requirements based on their viricidal properties. They can be utilized as co-factors for the management of viral infectious illnesses in addition to being effective antiviral medications. Antiviral drug-carrying polymers effectively increase the solubility of antiviral medications, extending their retention period and improving their cell uptake efficiency. Organotin compounds, for instance, were made according to the requirements of universal viral agents. By preventing viral reproduction, cisplatin and organotin-like polymers efficiently destroy viruses. Oligo-phenylene ethynylenes (OPE) and cationic conjugated polyelectrolytes (CPE) based on polyphenylene ethynylene (PPE) make up the polymers. When exposed to UV-visible light, the  $\pi$  bonding structure in the compound's backbone produces singlet oxygen species, which is how they work as antiviral medicines through the mechanism of oxidative stress. Proteins, RNA, and DNA are among the macromolecules that are harmed by oxidative stress (Thakur et al., 2024).

Expandable and water-soluble polymers comprise Polymeric nanogels that are created by joining hydrogel particles that readily break down into smaller pieces that are eliminated by renal clearance. By binding to the heparan sulfate proteoglycans on the surface of the host cell, these polymers can stop virus particles from entering the cell. These pliable nanogels are effective HSV-2 viral infection inhibitors.

#### Role of Liposome in Antimicrobial Action

Liposomes are spherical and typically range in size between twenty and thirty nm (Has & Sunthar, 2020). They are composed of a phospholipid bilayer enclosing an aqueous core. Liposomes are safe and biocompatible. HIV-1 production was stopped when liposomes containing antisense RNA targeted at T-cell receptors were contained in the HIV envelope region. By lowering cellular cholesterol, polyunsaturated fatty acids included in these PLs demonstrate independent antiviral action. One of the prospective goals of many viral systems, such as HCV, HBV, and HIV, is to target the manufacture of cholesterol within infected cells. In HCV, HBV, and HIV infections, PLs dramatically reduced viral production and infectivity. Without active medicinal components preloaded, stearylamine (SA)-loaded cationic liposomes reduced viral infectivity. Many mammalian cell lines, particularly A549 cells, showed reduced baculoviral infectivity when exposed to SA liposomes. By lowering cholesterol levels, the non-toxic SA liposomes may enhance their antiviral properties, which become more pronounced as they adhere more firmly to the cell membrane. SA liposomes are associated with the antiviral medication acyclovir and enhance the entrance of virus fragments into host cells (Pradhan et al., 2021).

#### Antiviral Mechanism of NPs

Nanoparticle antiviral mechanisms need to focus on virus adhesion, penetration, replication, and budding. Depending on the form and nature of the NPs utilized, potential mechanisms include limiting viral replication, preventing viruses avoiding adhering to host cells, and directly or indirectly inactivating the virus (Alavi et al., 2022). By changing the capsid protein's structure, NPs typically prevent the aforementioned processes and ultimately reduce virulence, which is associated with both physical and chemical strategies to reduce the amount of active virus. Broad-spectrum, non-toxic NPs can combat dengue, lentivirus, RSV, HSV, and human papillomavirus. Effective viral prevention was demonstrated by the scientists using a set of antiviral NPs with long, flexible linkers that resembled heparin sulfate proteoglycans, the highly repetitive focus of viral attachment ligands. The VAL repeating units were effectively bound by the virus, simulating a strong and multivalent binding. Local-field action against virus surface receptors is one of the primary and immediate mechanisms of the NPs-mediated antiviral effect (Zare et al., 2021). The membrane potential can be significantly changed in this process by the NPs deposited on the cell surface. In contrast, NPs' indirect antiviral method involves preventing the virus from entering the cell by altering the membrane potential.

According to these reports taken together, the primary mechanisms of nanoparticle antiviral activity include binding to the plasma membrane, inactivating viral particles before entry, binding competition between double-stranded DNA and viral particles, interference with viral attachment, reduction of virus-host cell adhesion and penetration, and the relationship with the virus and NPs for the host cell. The interaction between MNPs and viral particles prevents the virus from replicating. Viral replication is inhibited and viral particle release into host cells is prevented by the potential antiviral action of non-toxic NPs like Au. NPs can inhibit the neuraminidase enzyme, that breaks the connection between the hemagglutinin on the descendant virus and the recipient cell's sialic acid receptor (Chakraborty & Chauhan, 2024). NPs stop this cleavage process, obstruct the release of virus offspring from infected host cells, and stop the infection from spreading. Thus, suppression of hemagglutinin and neuraminidase activity may be the potential antiviral mechanism. Additionally, Au NPs prevent viruses from adhering to host cells.

Advantages

In nanomedicine, the active substance is transported and released at its pharmacological target by the use of nanovectors (Abou Bakr et al., 2023). Therefore, adjusting the pharmacokinetic route and bioavailability improves the effectiveness of medications and reduces their side effects. Ag, Au, ZnO, and titanium oxide MNPs have special antibacterial properties. Their ability to administer medicines in the intracellular space where the infection is located is their most intriguing feature. As a result, they enhance medication stability, boost drug circulation, improve target delivery, and boost therapy efficacy. They also improve the antibacterial spectrum, reduce toxicity and side effects, reduce the duration of treatment, and reduce the dosage of necessary medications. The most promising strategy to fight antibiotic medication resistance is to use them because of all these benefits. Bacterial infections predominantly caused by intracellular bacteria can be treated with nanobiotics, the next generation of antibiotics. Noble metals, mainly Cu and Ag, are used in daily life and have long been recognized for their antibacterial properties (Qin et al., 2021). For example, door handles in several hospitals have Cu coatings added to them to lessen the spread of bacteria in the medical setting. Antimicrobial properties against MDR species, including, Acinetobacter baumannii, ESKAPE pathogens (Staphylococcus aureus, Enterococcus faecalis, Klebsiella pneumoniae, Pseudomonas aeruginosa, and Enterobacter), have been demonstrated in vitro via nanoparticle studies. A study demonstrated the dose-dependent antibacterial efficacy of Ag Nps against enterobacteria such as Klebsiella pneumoniae and Escherichia coli, with an honorable MIC of about 1.4 µg/mL. Additionally, the antibacterial activity of cefotaxime, gentamicin, and meropenem against these species was enhanced when Ag Nps were present at the same time (Malawong et al., 2021). Other research has shown that it is effective against both Gram-positive and Gram-negative bacteria both in vitro and in vivo. Additionally, it can be a substitute for the treatment of tuberculosis, a serious illness that affects millions of people globally. Treatments for MDR TB include chemotherapy and second-line drugs like ethionamide (ETH), which can result from the misuse of first-line medications. However, patients frequently struggle to follow treatment plans that call for high ETH dosages. Synergistic medications could be encapsulated in the NPs, significantly streamlining treatment and improving patient compliance. Additionally, it can be a substitute for the treatment of tuberculosis, a serious illness that affects millions of people globally. MDR TB, which is managed with second-line drugs like ETH or chemotherapy, can result from the misuse of first-line medications. However, patients frequently struggle to follow treatment plans that call for high ETH dosages. Synergistic medications could be encapsulated in the NPs, significantly streamlining treatment and improving patient adherence. Antimicrobial medications (antibiotics, antivirals, and antifungals) can be made with the NPs. The most well-documented combination is with antibiotic compounds; they are known as nanobiotics. The MNPs are utilized because they are inexpensive, simple to synthesize, and straightforward to employ. The MNPs are based on several metals, primarily CuO, iron oxide (Fe3O4 or Fe2O3), ZnO, titanium dioxide (TiO2), Au, and Ag. Because of their special optical, biological, and catalytic qualities. Ag NPs are used in the veterinary and human sectors in addition to research labs (Hajra et al., 2024).

The main advantage of AuNPs, which are thought to be the least hazardous MNP, is their ease of manufacturing and alteration by one or more thiol ligands with distinct chemical properties. MNPs facilitate the delivery of antibiotics to the cell surface because they function as drug carriers. The concentration of antimicrobial medications is increased at particular sites on the cell membrane as a result of the interaction between the antibiotics and NPs. In particular, AgNPs and AuNPs' affinity for sulfur-containing proteins in bacterial cell membranes enhances their interactions with cells and increases the permeability of the membranes. The antibiotics can enter the cell more easily as a result (Tripathi & Goshisht, 2022).

#### Limitations

NPs pose a health danger to people with their many benefits and wide range of uses.MNPs have limited applications both in vivo and in vitro, and research has indicated that they can enter cells and result in DNA damage, inflammation, organ toxicity, and oxidative stress. NPs pose a health danger to people with their many benefits and wide range of uses (Khan et al., 2021) The primary characteristics of MNPs have been linked to their toxicological effect as a result of their ability to penetrate the two hundred nm blood-brain barrier and their rapid penetration into human cells. NPs smaller than ten nm frequently have strong antibacterial action together with high cytotoxicity, agglomeration facilitates deposition and delays NP diffusion, increasing effective doses. Protein binding to NPs, cellular absorption, oxidative stress, autophagy, inflammation, and apoptosis are all regulated by surface charge. MNPs can be made less harmful to people. For maximum effectiveness, the size can be adjusted, and capping agents can be employed to improve ion release, minimize agglomeration, and stop unwanted NPs from oxidizing. polyacrylic acid, Oleic acid, polyvinyl alcohol (PVA), polyethylene glycol (PEG), and polyvinylpyrrolidone (PVP) are capping agents that are frequently employed (Liu & Tang, 2020).

#### Conclusion

NPs have distinct processes that include altering bacteria membranes, enzyme activity, and DNA synthesis, they present a promising option to control AMR. They are better than conventional antibiotics because of their tailored delivery, which incr eases efficacy while lowering dosage and adverse effects. Liposomes, polymeric NPs, Ag, and Au have all exhibited exceptional antibacterial properties. Ag NPs and gold Au NPs are two of the most notable nanoparticles due to their strong antibacterial properties and outstanding biocompatibility. Other metal-based nanoparticles, like ZnO further enhance the antibacterial arsenal and titanium oxide, which can efficiently target intracellular pathogens. Beyond their antibacterial qualities, nanoparticle-based treatments have further benefits. Nanoparticles maximize therapeutic drug pharmacokinetic profile and bioavailability by facilitating targeted drug distribution, increasing circulation time, and boosting drug stability. This lowers the necessary dosage and length of therapy, minimizes toxicity, and lessens adverse effects. The ability of nanoparticles to improve healthcare is highlighted by nanomedicine's novel method of medication delivery and its capacity to solve current problems in antimicrobial therapy. Therapeutic options for combating infectious diseases and antibiotic resistance that are more efficient, secure, and sustainable are probably going to be made possible by ongoing studies and research in this area.

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