*Review*

# Antimicrobial Nanoparticles: applications and mechanisms of action

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## Abstract

Nanoparticle technology is rapidly advancing and is used for a wide range of applications in medicine. The potential of metal nanoparticles as antimicrobial agents is widely studied and is considered as an alternative approach to overcome the challenge posed by multidrug resistance in bacteria. This review discusses novel approaches to nanoparticle synthesis including green synthesis and the antimicrobial spectrum of nanoparticles. Approaches for enhancing antimicrobial potential of nanoparticles by surface modification and its potential as a vehicle for antibiotic delivery are also explored.

*Keywords: Nanoparticles, Antimicrobials, Drug delivery, Mode of action, Liposomes*

Nanoparticles (NP) have emerged as a novel alternative to overcome bacterial multidrug resistance encountered globally due to misuse of antibiotics. Use of nanoparticles as antimicrobial agents could overcome mechanisms of bacterial resistance as the microbicidal nature of nanoparticles result from direct contact with the bacterial cell wall, without the need to penetrate into the cell.[1] The development of antibacterial resistance to NPs are therefore less likely when compared to antibiotics. Nanoparticles therefore have potential to be developed into antimicrobial theranostics in medicine.

Nanoparticles are materials in which the basic unit in three-dimensional space falls within the nanometre scale range (1-100nm) or at least one dimension is within this range.[2] Nanomaterials have shown broad spectrum antimicrobial activity against Gram positive and Gram negative bacteria, mycobacteria and fungi.[1] The antibacterial activity of nanoparticles varies among the different types of nanoparticles. Although the specific antibacterial activity of nanoparticles is not well understood, it is suggested that multiple mechanisms may contribute to the antimicrobial mechanisms. The physical structure of the nanoparticle itself may have inherent antibacterial properties due to its membrane damaging abrasiveness, as seen in Graphene oxide nanoparticles. Enhanced release of antibacterial metal ions from the surface of nanoparticles is another

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mechanism which has been suggested. The low surface to volume ratio of the nanoparticles can increase the antimicrobial activity allowing greater interaction of the nanomaterial with the surrounding environment. Chemistry, particle size, particle shape, and zeta potential are among the most relevant variables affecting antibacterial activity.[1]

Heavy metals such as silver (Ag), copper (Cu), gold (Au), titanium (Ti), and zinc (Zn) have been known to have antimicrobial activity for centuries. The Rasashastra of the Ayurvedic system of medicine deals with medicines of mineral origin.[3] The properties of metal nanoparticles have been widely studied for their antimicrobial activity. Metal nanoparticles such as silver oxide ($Ag_2O$), titanium dioxide ($TiO_2$), silicon (Si), copper oxide (CuO), zinc oxide (ZnO), gold (Au), calcium oxide (CaO) and magnesium oxide (MgO) have demonstrated antimicrobial activity against a spectrum of microorganisms.[4] The toxicity of nanoparticles is not fully elucidated and requires in depth studies. Toxicity of the NPs are affected by multiple parameters, including the shape, size, surface charge, composition and the NPs stability. The toxic effect is also invariably dependant on the dose, route of administration and target tissue. The US Food and Drug Administration (FDA) has approved the use of several types of NPs including Ag and Titanium NPs for products such as antibacterial skin lotions and sunscreens which are in commercial use.

**Synthesis of nanoparticles**

Several approaches have been followed in the synthesis of nanoparticles. Physical methods generally employ high temperatures, but the disadvantages of this method include the time, required space and harmful environmental effects. The size of the NPs and the concentration of NPs vary with the heater surface temperature. The absence of solvent contamination and the uniformity of the distribution of NPs are the advantages of the physical synthesis methods in comparison with chemical processes. Laser ablation of metal bulk materials has also been used to generate nanoparticles in solution.[5]

Chemical reduction is the most common approach for synthesis of silver NPs by organic and inorganic reducing agents. The process requires three main components, the metal precursor, reducing agent and capping/stabilizing agent. Nucleation of metal ions is the first step, followed by agglomeration into oligomeric clusters which form the metallic colloidal NPs. Chemical reduction can be achieved in the presence of a variety of organic and inorganic reducing agents. Other chemical methods of NP synthesis include the micro emulsion method, UV initiated photo reduction, photo induced reduction, electrochemical synthetic methods and irradiation methods.[6] Chemical methods have the advantage of higher yield compared to physical methods.

Biological methods of NP synthesis harness the reducing ability of microbial cells, enzymes and biological molecules. Bacteria, fungi and plants have recently gained much attention due to their ability to biosynthesize metal NPs by an environmentally friendly process. For example, silver nanoparticles have been successfully made from *Staphylococcus aureus*, *Pseudomonas aeruginosa*,[7] *Escherichia coli*, *Acinetobacter* species,[8] *Lactobacillus* species,[9] *Klebsiella pneumoniae*[10] and *Enterobacter cloacae*[11]. An advantage of biological synthesis methods is the higher stability of the AgNPs compared to chemically synthesized NPs.[5] Evidence suggest that the fungus *Fusarium* secretes a nitrate reductase enzyme which reduces the Ag ions and also secretes capping proteins, which contribute to the long term stability of the AgNPs.[12] Various plants have recently been employed for the biosynthesis of NPs.[13] The plant extracts are rich in

phytochemicals and enzymes, which facilitate the reduction of Ag ions into nano sized material. This method offers a renewable source for a cost effective, environmentally friendly alternative for large scale NP synthesis over the more environmentally unfavourable physical and chemical methods. Polyphenols, flavonoids, and phenolic biomolecules present in *Camellia sinensis* (green tea) and black tea leaf extracts are also reported to be responsible for the reducing of silver ions and stabilization of silver NPs.[14]

**Silver nanoparticles (AgNPs**)

Silver nanoparticles have been widely used for various applications due to their unique properties which facilitate numerous antimicrobial applications. Both chemically synthesized and biosynthesized silver nanoparticles have been shown to inhibit Gram negative and Gram positive bacteria as well as yeasts.[7] Stronger antimicrobial activity was shown against Gram negative bacteria which can be attributed to the thicker cell wall composition of Gram positive bacteria. A number of mechanisms have been attributed to the bactericidal activity of silver NPs. The AgNPs may alter the membrane permeability of the bacterium allowing inflow of AgNPs into the cell.[15] The interaction of the NPs with intracellular proteins, particularly sulphur containing membrane proteins and microbial DNA can interfere with cell division leading to cell death.[16] Bacterial replication is compromised due to the release of Ag ions from the AgNPs.[4]

Silver has displayed antibacterial, antiviral and antifungal properties when used in the nanoscale. AgNPs are widely used for coating of medical devices, disinfection of medical devices, home appliances and water purification.[17] AgNP incorporated fibres have been tested for production of textiles with antimicrobial properties.[18] They have also been used in coatings of refrigerators and food containers due to their antimicrobial properties.[19] AgNPs have electrochemical and bioluminescent properties which can be used as nanosensors, biological labels and for optical data storage.[20]

**Zinc nanoparticles (ZnONPs)**

Zinc oxide (ZnO) is a "generally recognized as safe" (GRAS) compound (U.S. FDA:21CFR182.8991) and exhibits minimal toxicity to humans. ZnONPs have high photo catalytic activity and are more biocompatible than $TiO_2$.[21]

Zinc oxide is used widely in the food industry to preserve colours and prevent spoilage due to its antimicrobial activity. ZnONPs have pronounced antimicrobial activity due to their high surface to volume ratio and surface abrasiveness of the nanostructures. ZnONPs can inhibit the growth of both Gram positive and Gram negative bacteria. Gram positive bacteria including *S. aureus*, *Streptococcus pyogenes* and *Enterococcus faecalis* have shown 95% growth inhibition in the presence of ZnO.[21] ZnONPs have potent antimicrobial activity against common food pathogens such as *Campylobacter jejuni, E. coli O157:H7, Salmonella spp., Listeria monocytogenes,* and *S. aureus* indicating its usefulness as a food preservative.[4] Applications of ZnO include antibacterial creams, lotions, ointments and deodorants. Further, self cleaning glass and ceramics consisting of ZnONPs is another novel application.[22] The antimicrobial properties of ZnONPs are attributed to the intracellular accumulation of ZnONPs which result in damage to the cell wall and disruption of DNA replication. Inside the cells, the NPs release metal ions, generate reactive oxygen species (ROS) and accumulate in the bacterial membrane. Studies have shown the strong ROS generating potential of ZnONPs, suggesting it has an important role in bacterial killing,

including cell wall damage, increasing membrane permeability, internalization of NPs due to loss of proton motive force and uptake of toxic dissolved zinc ions.[21]

**Titanium nanoparticles ($TiO_2$NPs)**

$TiO_2$NPs have a wide spectrum of antimicrobial and anti-biofilm activity against a wide range of pathogenic microorganisms including bacteria, fungi, parasites and viruses. Recent uses of Titanium dioxide ($TiO_2$) have involved various applications which include the food industry. The FDA has approved the use of $TiO_2$ in human food, drugs and cosmetics. The unique photo catalytic activity of $TiO_2$NPs and the quantum size effects make it ideal in antimicrobial applications including air purification, water purification and antimicrobial coatings on biomedical devices.[4] The antimicrobial activity of $TiO_2$NPs against both Gram negative and Gram positive bacteria are well known. Further modification of $TiO_2$NPs with plant extracts such as *Garcinia zeylanica* extract results in enhanced bactericidal activity.[23] The antimicrobial activity of plant extracts in combination with the inherent antimicrobial activity and photo catalytic activity increases the potential of $TiO_2$NPs as microbicidal agents.

$TiO_2$NPs can destroy microorganisms upon illumination of light due to its photocatalytic properties. Reactive oxygen species generated by $TiO_2$NPs can oxidize the components of the cell membrane leading to destruction. Antimicrobial activity of $TiO_2$ observed in the absence of light indicate that apart from the photocatalytic activity, direct contact and adsorption of cells on to $TiO_2$ nanoparticles may cause a loss of membrane integrity.[4]

**Copper nanoparticles (CuNPs**)

Copper NP synthesis is challenging due to its extreme sensitivity to air, resulting in formation of an oxide layer which can cause a marked reduction in antimicrobial activity. Several attempts have been made to produce Cu nanoparticles chelated to various materials to obtain higher stability. Chelates are highly stable products capable of maintaining the surrounded metal ions from an organic molecule (chelating agent).[24] Copper-amino acids chelate demonstrated approximately ten times more antimicrobial activity compared to the copper nanoparticles. The antimicrobial specificity of Cu chelates may also differ - for example the copper-EDTA chelate had stronger antimicrobial effect against *E. faecalis* compared to both *E. coli* and *S. aureus.*[25]

The antimicrobial activity of copper NPs have been demonstrated against diverse species of bacteria, such as methicillin-resistant *S. aureus* (MRSA) and *Bacillus subtilis*, Gram-negative organisms such as *S. cholerasuis* and *P. aeruginosa*, and yeast species such as *Candida albicans.*[1] CuNPs have been used as applications for coating of medical devices due to their antimicrobial properties.[26] The bactericidal activity of Cu depends on the level of agglomeration which is a common issue with CuNPs. Minimizing agglomeration results in smaller sized NPs providing more available surface area for solubilisation of copper ions and for interaction with bacterial membranes which leads to more toxicity. Metallic and ionic forms of copper produce hydroxyl radicals that damage essential proteins and DNA.[24]

**Gold nanoparticles (AuNPs)**

Gold nanoparticles are reported to have weak antibacterial activity of varying degrees compared to the other metal nanoparticles mentioned above. In contrast, the bactericidal activity of low concentrations of Au(I) and Au(III) used as the starting material for NP synthesis is well established for Gram positive and Gram negative bacteria. Gold NPs less than 2nm have shown

strong antibacterial activity.[27] It is speculated that the antimicrobial activity of AuNPs reported in some studies may be due to the bactericidal activity of co-existing chemicals not completely removed from AuNPs during synthesis. However, photo thermal therapy (PTT) offers a promising new approach for improving the bactericidal potential of AuNPs.[28] Gold nanoparticles irradiated with laser energy release heat due to the excitation and oscillation of electrons, making them useful as anticancer or antibacterial agents. AuNPs treated *S. aureus* had enhanced bactericidal effect when exposed to laser energy.[28] Gold nanoparticles have been studied as potential drug and gene delivery systems in cancer therapy.

**Other metal nanoparticles with antimicrobial activity**

Silicon (Si) nanoparticles are considered as nontoxic and have good biocompatibility. Silica nanowires can be biocidal by interrupting cell functions such as cell differentiation, adhesion and spreading of bacteria. Moreover, Si nanoparticles could inhibit the adhesion of bacteria to oral biofilms. Silica nanoparticles offer antimicrobial action and act as carriers of antimicrobials in biomedical applications.[29]

CaO and MgO NPs also display strong antibacterial activity, mediated by generation of superoxide on the surface of these particles, and also by increased pH due to the hydration of CaO and MgO with water. $Al_2O_3$NPs have a strong tendency to bind to and damage the bacterial cell wall which increases cell wall permeability.[30]

**Carbon-based nanomaterials**

Carbon nanostructures (CNSs) such as fullerene, carbon nanotubes (CNTs), graphene and diamond-like carbon (DLC) have potent broad-spectrum antibacterial activities. The mechanism by which CNSs cause bacterial lysis is complex. Fullerene induces cell membrane disruption, DNA damage and influences the energy metabolic pathways to inactivate microorganisms. It also has photochemical activity which results in generation of ROS upon exposure to light which contributes to antimicrobial activity.[31] Single and multi-walled Carbon nanotubes have a more potent antimicrobial activity than fullerene according to recent studies.[31] The antimicrobial effectiveness of CNTs depends on the length, diameter, residual catalyst, electronic structure, surface functional group, surface chemistry and coatings. CNTs with a length of more than 50 µm may wrap around the bacterial cell during the antimicrobial activity.[32] Long nanotube aggregates in liquid medium are known to be more bioactive and have potent antibiofilm activity, especially during the early phase of biofilm formation.[33] Carbon nanostructures may cause physical abrasions and structural damage to the bacterial cell walls and cell membranes. Graphene sheets can isolate bacteria from the microenvironment which is inimical for survival. Several forms of graphene nanoparticles have been reported, including graphene oxide (GO), reduced graphene oxide, graphite and graphene nanosheets. In general GO has strong antibacterial activity. Various factors including sheet sizes, layer number, nanopores, shapes, and presence of functional groups influence the antimicrobial mechanisms and activity.[31] Chemical interactions between the nanomaterial and the surface of the bacterial cell can lead to the generation of reactive oxygen species. Removal of electrons from the microbial surface into the carbon nanomaterial is also suggested as a cause of ROS-independent oxidative stress. These

complex interactions together can account for the broad spectrum antibacterial properties of the carbon-based nanoparticles.[31]

**Modification**

Surface modification of nanoparticles can be used to improve the stability and antimicrobial potential of the nanomaterial. Conjugation of different compounds, such as polyethylenimine, amoxicillin, polysaccharides, peptides, surfactants, and polymers to nanoparticles can result in synergistic antimicrobial effects. Increased antimicrobial activity is observed for antibiotics and antimicrobial peptides when conjugated to metal nanoparticles: for example, silver nanoparticles conjugated to the cationic antimicrobial peptide ubiquicidin have increased antibacterial activity against Gram-negative bacteria, providing a promising alternative therapy for topical infections.[34] Titanium oxide nanoparticles modified with pericarp extract of *Garcinia zeylanica* showed enhanced antimicrobial activity against methicillin resistant *S. aureus*.[23] Capping of nanoparticles to obtain enhanced stability leads to the alteration of the surface chemistry and biological properties. Capping agents such as citrate, chitosan, polyethylenimine, polyvinylpyrrolidone (PVP), polysaccharides, carbon, hydrocarbons, starch, peptides, and bovine serum albumin can all have an effect on inducing oxidative stress, DNA damage, and apoptosis of mammalian cells.[35]

Organic-inorganic hybrid nanoparticles are another emerging area of study. Organic-inorganic hybrids refer to materials with an inorganic component which is "dispersed" in a major organic, and typically polymeric, component. A study based on lipoic acid organic nanoparticles (ONPs) using ONP/Ag and ONP/Au showed improved antimicrobial activity, suggesting the potential for future investigation.[36] Multi-walled carbon nanotube hybrids with AgNPs have shown good stability and good antimicrobial activity, suggesting that these novel hybrids hold promise for future innovations.

**NP based antibiotic delivery systems**

Nanoparticles can act as a medium or a carrier for improved drug delivery. Several groups have reported nanoparticles used in drug delivery, including liposomal NPs, solid lipid NPs, polymer based NPs, terpenoid based NPs etc. Magnetic nanoparticles, mesoporous silica NPs, carbon nanoparticles and quantum dots have potential as inorganic nanodrug carriers. The small sizes of the nanoparticles make them suitable for antimicrobial purposes and combating intracellular bacteria.[1]

With a view to enhancing bioavailability, antibiotics have been coupled with liposomes or nanoparticles. Liposomes, because of their composition and compatibility with biological constituents are the more favoured carrier.[37] Colloidal particles, which are biodegradable polymers, have also shown promise for future applications in antimicrobial chemotherapy. However due to their polymeric nature, nanoparticles are likely to be more stable than liposomes in biological fluids and during storage. Recently, several studies have focused on antibiotic delivery by liposomes or nanoparticles. Amphotericin B loaded liposomes have been shown to

have better tolerance and higher efficacy than the antibiotic amphotericin B deoxycholate and is used in treatment of disseminated histoplasmosis in patients with acquired immunodeficiency syndrome (AIDS).[38] The advantages of such targeted therapy include improved treatment of intracellular infections compared to treatment using free antibiotics. Additionally, encapsulation of antibiotics will modify their pharmacokinetics, increasing the serum half-life or by reducing their toxicity, allow an increase in the maximum tolerated dose (eg: liposomal amphotericin). An improved therapeutic index is expected when compared with free antibiotics. Toxic side effects such as hepatotoxicity and nephrotoxicity are anticipated to be less when compared to free antibiotics. An additional advantage of nanoparticles targeted to a specific organism is the preservation of the microbiome, unlike free antibiotics which can adversely affect the microbiome.[37]

Exposure to nanoparticles such as AgNPs, AlNPs may promote bacterial resistance in certain situations. For example exposure to sublethal concentrations of AgNP resulted in alteration of the membrane lipids in *Pseudomonas putida*.[39] Kaweeteerawat, et al. showed that prolonged exposure of *E. coli* and *S. aureus* to AgNPs led to development of resistance to AgNP due to the selective proliferation of surviving resistant cells.[40] AgNP treatment was also suggested to cause physiological changes in bacteria leading to antibiotic resistance.[40] Furthermore, aluminium nanoparticles have been shown to promote conjugative transfer of plasmids, including those with antibiotic resistance genes, resulting in dissemination of these genes within the species as well as to other species of the genus.

The progress in nanotechnology and synthesis of nanomaterial has paved the way for innovative approaches for development of novel antimicrobial agents. Nanoparticles exert antimicrobial activity using a multitude of mechanisms which may vary with individual properties such as size, morphology, electrical charge, surface coatings etc. enabling scientists to design novel composite antimicrobial agents for various applications. The antimicrobial activity, specially of the heavy metal-based nanoparticles and carbon-based nanoparticles, can find many applications in the field of medicine and industry in the future and provide a solution to the current challenges of antimicrobial resistance to conventional treatment methods. Further, nanomaterials provide vast opportunities for prevention, diagnosis and treatment of infections as well as control of biofilms. However, it is imperative to carry out extensive studies on these nanomaterials to determine their impact on normal tissues prior to wide scale industrial applications and to evaluate the impact on humans and the environment.

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