# Promises of nanomaterials as antimicrobial agents: A Review

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**Abstract:**

Prevalence of multi-drug resistant strains of pathogenic bacteria poses serious threat to human health. The over usage of antibiotics has led to the evolution of resistant pathogens are. This has created an urgent need to develop a new generation of antimicrobial agents. Nontraditional antimicrobial agents have been of tremendous interest in overcoming this problem of multidrug resistance developed by several pathogenic microorganisms against most of the commonly used antibiotics. These antimicrobial agents must be effective, safe and can be used for the cure of multidrug-resistant microbial infections. In recent times a lot many properties have been identified in metallic nanoparticles. They can offer effective solutions for these challenges. Several classes of antimicrobial nanoparticles have proven their effectiveness for treating antibiotics resistant infectious diseases. This review summarizes emerging efforts in combating against infectious diseases, particularly using antimicrobial NPs as new tools to tackle the current challenges in treating infectious diseases.

**Keywords:** Drug resistance, Nanoparticles, Pathogenic bacteria, Environment.

## Introduction

The presence of microbial pathogens in environmental reservoirs is a well known fact. These pathogens harbor virulent factors, responsible for the deadly diseases. Antimicrobial therapy has got boom and evolved drastically to cure such infectious diseases. The easy availability and indiscriminate use of antibiotics in clinical infections are the factors that contribute to the emergence and spread of multi-drug resistance in bacteria. In addition, the dissemination of antibiotic resistance genes among human and non-human pathogens is the paradigm for horizontal gene transfer on a global scale. It is likely that close contact of the human population with surface and potable water can enrich the environmental gene pool of pathogens

and lead to emergence of new pathogenic variants. In India and other developing countries, pathogen diagnostics based on antimicrobial agent resistance and virulence gene profiles of *E. coli* pathotypes particularly ETEC and EHEC of surface and potable water resources is not well established [1].

*Salmonellae* are one of the most common causes of water-borne illness in humans. Enteric fever in humans is most commonly caused by *Salmonellae*. *Salmonellae,* usually acquired by the consumption of contaminated water and food have been a major human pathogen since decades. In India, the typhoid occurs with an incidence ranging from 102 to 2,219 per 100,000 populations [2]. With the frequent use of antibiotics to kill *Salmonellae* in previous decades, the pathogen has evolved resistance mechanism to combat against them. As a result, the multidrug-resistant (MDR) *Salmonellae* strains have been prevalent in environment and spread worldwide, resulting in high rates of morbidity and mortality. The extensive use of antibiotics have generated and disseminated drug-resistant *S.* Typhi in the environment and potable water drinking system. The emergence of MDR *S.* Typhi strains to existing antibiotics such as ampicillin, chloramphenicol and co-trimoxazole has complicated the treatment of typhoid fever [3]. This leads to necessity for the development of potential new alternative materials in order to combat this problem.

## 2. Nanomaterials as potential antimicrobial agents

Nanomaterials have successful impact on biology and medicine. Due to the large surface-to-volume ratio the surface activity of nanoparticles (NPs) is higher, providing the ease of surface modification of NPs for enhanced aqueous solubility, biocompatibility or bio-conjugation. In drug targeting research, there is a need for the use of an alternative agent which does not generate resistance and presents a good bactericidal property. A number of studies have been performed to demonstrate the antimicrobial activity of silver nanoparticles (AgNPs). Unfortunately, due to the potent toxicity and cytotoxicity of silver AgNPs, they have not been recommended for the practical use. A potential alternative to this are the gold nanoparticles, which is biocompatible and donot pose toxic effects even when administered into the

cells. Due to their ability to interact with microorganisms GNPs can act as antibacterial agents. The synergistic effects of GNPs and GNP coated drugs can minimize the treatment durations and side effects of drugs with reference drugs and are potential thrust area to be explored.

### 2.1. Silver nanoparticles

Silver has a strong antimicrobial potential, which has been used since the ancient times. But with the advent of antibiotics progress, the medical applications of silver as antimicrobial were declined. Antimicrobial effects of silver can be increased by manipulating their size at nanolevel. Because of their change in physiochemical properties, silver nanoparticles have emerged as antimicrobial agents owing to their high surface-area-to-volume ratio and the unique chemical and physical properties. Silver nanoparticles having size in the range of 10– 100 nm showed strong bactericidal potential against both Gram-positive and Gram-negative bacteria .The bactericidal activity of silver nanoparticles against the pathogenic, MDR as well as multidrug susceptible strains of bacteria was studied by many scientists, and it was proved that the silver nanoparticles are the powerful weapons against the MDR bacteria such as *Pseudomonas aeruginosa*, ampicillin-resistant *Escherichia coli*, erythromycin-resistant *Streptococcus pyogenes*, methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Staphylococcus aureus* (VRSA).

Silver nanoparticles have important biological properties as follows: they are effective bactericidal agents against broad spectrum of bacteria, including antibiotic resistant strains, fast-acting fungicide against common fungi including *Aspergillus*, *Candida* and *Saccharomyces*. Silver nanoparticles of 5–20 nm diameters can inhibit HIV-1 virus replication. [4].These can not only alter the expression proteinases, which are important in inflammatory and repair processes, but also suppress tumour necrosis factor (TNF), interleukin (IL)-12 and IL- 1b and induce apoptosis of inflammatory cells. Moreover, silver nanoparticles are also responsible for cytokine modulation in wound healing and inhibition of the biofilm formation.

Silver nanoparticles are used as effective antimicrobial agents. They have bactericidal potential against MDR

organisms. Colloidal silver nanoparticles are found to possess significant bactericidal potential against MRSA and Gram-positive and Gram-negative bacteria. Gram-negative bacteria include members of the genera *Acinetobacter, Escherichia, Pseudomonas, Salmonella* and *Vibrio*. Gram-positive bacteria include *Bacillus, Clostridium, Enterococcus, Listeria, Staphylococcus* and *Streptococcus*. Antibiotic-resistant bacteria include methicillin-and vancomycin-resistant *Staphylococcus aureus* (MRSA and VRSA) and *Enterococcus faecium*, by preventing biofilm formation, which act as efficient barriers against antimicrobial agents and the host immune system to protect the bacterial colony.

Nanoparticles (NPs) are becoming widespread for their use in consumer products and medical applications; with potential for utilization as therapeutic compounds, transfection vectors, anti-microbial agents and fluorescent labels. Silver NPs are the most commercialized and prominent group of nano-compounds, attributed to their diverse applications in the health sector due to their physical as well as biological properties. Silver, in a colloidal form, is used for the treatment of bacterial infections in open wounds, and preparation of ointments, bandages and wound dressings [5]. Additionally, nanosilver has been used as a contraceptive, and marketed as a water disinfectant. Silver NPs are now being exploited for the treatment of various diseases such as retinal and acquired immunodeficiency syndrome as a result of human immunodeficiency virus [6]. Additionally, AgNPs are well known for their anti-microbial properties and are used as antiviral agents against hepatitis B, herpes Simplex virus type 1, monkey pox virus and respiratory syncytial virus [7]. Concerns on environmental exposure to AgNPs have initiated toxicity studies. Silver NP-hydrogel induced DNA damage and the production of reactive oxygen species (ROS) in cultured HeLa cells [18]. A study using human lymphocytes revealed that AgNPs caused DNA damage and cell death. Additionally, AgNPs induced oxidative stress and caused impairment of nuclear DNA in Swiss albino mice. Recently, the use of AgNPs as anti-cancer agents has proved promising. Various attempts to incorporate AgNPs into cancer treatments have been made, with positive outcomes. Although the induction of oxidative stress

by AgNP induced mt damage has been observed as the general mode of AgNP toxicity, mechanistic pathways remain unclear [8].

**2.2 Platinum nanoparticles**

The medicinal use of platinum is mainly focused on platinum compounds, but not nanoparticles. The best known platinum compound for anticancer agents is cisplatin (cis-diaminedichloroplatinum) [9]. Platinum nanoparticles (PtNPs) have recently been used for cancer treatments as well. Porcel *et al* showed that PtNPs strongly enhanced the biological efficacy of radiation. The combination of fast ion radiation (hadron therapy) with PtNPs resulted in enhanced DNA strand breakage. Fast carbon ion irradiation of platinum led to the production of radicals that amplified the lethal damage to DNA. In another study, human colon carcinoma cells (HT29) showed a concentration- and time-dependent response when exposed to PtNPs [10]. The efficacy comes from the PtNPs adsorbing the intracellular glutathione (GSH), causing levels to be reduced, while the soluble Pt species impair DNA integrity.

**2.3. Zinc oxide nanoparticles**

Zinc oxide (ZnO) has some similar properties to $TiO_2$ (i.e. its nanoparticles scatter light so it can be used for transparent UV filters, in creams or coatings). Like $TiO_2$, it is used for solar photocatalytic remediation but, compared to $TiO_2$, it has a weaker photocatalytic effect. Zinc oxide also suffers from the same limitation of absorbing only a fraction of the solar spectrum so research is underway to increase its photoresponse.

A peculiarity of ZnO is that it has a tendency to grow in self-organised nanostructures. By controlling crystal growth conditions, a variety of crystal shapes are possible. Researchers have been able to grow nanoscale wires, rods, rings, etc. The bactericidal mechanism of ZnO NPs is complex and still under investigation. However, it is believed to involve the release of $Zn^{2+}$ ions leading to the generation of hydrogen peroxide [11]. Huang *et al* showed that ZnO NPs attached to the cell walls of both gram-positive and gram negative bacteria, resulting in membrane disorganization, elevated membrane permeability, and cell damage [12]. Biocidal effects and cellular internalization of ZnO NPs on *E. coli* were also reported. ZnO NPs were synthesized in di (ethylene glycol) (DEG) medium through the hydrolysis of ionic

Zn salts. *E. coli* cells were damaged, showing membrane disorganization of gram-negative triple layer units after the contact with DEG and ZnO. This behavior caused an increase of membrane permeability, leading to accumulation of ZnO NPs in the bacterial membrane as well as cellular internalization of NPs. In another study, bactericidal effects of ZnO NPs (bare and thioglycerol (TG)-capped ZnO NPs) were also confirmed to result from membrane lipid peroxidation caused by ROS which is generated during the interaction of ZnO NPs with the culture medium [13]. Reactivity of nanoparticles toward bacteria depends on their size and shape. In general, toxicity is inversely proportional to particle size. Just as smaller-sized AgNPs release more $Ag^+$ ions against *E. coli*. Recent results suggest that the surface charge of nanoparticles affects the toxicity of AgNPs. Negatively charged nanoparticles do not adsorb to negatively charged cell membranes due to electrostatic repulsion, thus their cellular internalization is greatly inhibited [14].

## 3. Applications of inorganic Nanoparticles as therapeutic agents

Recent advances in nanotechnology are expected to help solve many key issues in biological disorders. In fact, many functional elements of biological systems are at the nanometer scale; therefore, nanomaterials can be ideally sized to assume some biological functionality at the molecular level [15]. Furthermore, nanomaterials with a size of 2–100 nm exhibit unique electronic, optical, chemical, and magnetic properties distinct from larger particles of the same material [16]. Therefore, biological phenomena can be explored by precisely controlling and harnessing these unique properties of nanomaterials, and various functional nanomaterials have been extensively applied to biomedical areas, including imaging, diagnosis, and therapy. Nanoparticles have been investigated as potential drug and gene delivery systems because they can overcome some intrinsic problems of drug efficacy by allowing targeted delivery and passage through biological barriers [17]. Active targeting can be achieved through conjugation with molecules such as folic acid (FA) or methotrexate (MTX) for recognition by the folate receptor, which is overexpressed on the surface of many cancer cells, or peptides such as arginine–glycine–aspartate (RGD) for targeting

integrins on the tumor endothelium [18]. Furthermore, various tailored nanomaterials, including core–shell structured nanoparticles or mesoporous structured nanoparticles, can perform additional functions related to imaging or controlled drug release. Considering the size-dependent physicochemical properties of nanomaterials along with their demonstrated ability to interact with biological systems, inorganic nanoparticles are promising candidates for biomedical applications [19]. Inorganic nanoparticles are formed by the crystallization of inorganic salts, forming a three-dimensional arrangement with linked atoms. The nature of the binding atoms is mainly covalent or metallic. These particles are highly ordered and rigid with little influence by the body. Organic nanoparticles, on the other hand, are mainly formed by spontaneous aggregation, as with micelles or vesicles. These systems are dynamic due to the weak nature of the cohesive interactions. Therefore, the size and geometry of organic aggregates are difficult to maintain below a certain size threshold, particularly in living systems. Although colloidal metals have been used in medicine since ancient times, their action mechanisms have been elucidated very recently. Now colloidal metal nanoparticle-based therapeutics is again attracting attention as an alternative to organic therapies in clinical settings. The development of highly uniform and biocompatible inorganic nanoparticles with optimized functional properties is critical. In the past decades, various inorganic nanoparticles have been successfully prepared by many different synthetic methods. One is the precipitation of salts in aqueous media [20]. Through this method, it is possible to synthesize a large number of nanoparticles of metals and oxides in a very simple and inexpensive manner, although it is hard to achieve good particle crystallinity and consistent size control. A second method, the hydrothermal process, uses water as a solvent and utilizes high pressure and temperature to increase the solubility of the precursors and reduce the reaction time. This synthesis can be performed above or below the supercritical point of water.

**Conclusion**

Antimicrobial agents must be effective, safe and can be used for the cure of multidrug-resistant microbial infections.

A number of antimicrobial nanoparticles have proven their effectiveness for treating antibiotics resistant infectious diseases. The behavior and fate of nanoparticles in vivo is hard to predict due to the complexity of biological systems. Systematic evaluation of whole-body effects by considering exposure concentration, accumulation and excretion, tissue and organ distribution, and potential chronic effects needs to be undertaken.

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