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RESEARCH ARTICLE

# BIOMEDICAL ROLES OF SOME POTENT METALLIC NANOPARTICLES: A REVIEW

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## ABSTRACT

Anthropogenic activities may directly or indirectly influence global temperature and climatic patterns, leading to an increase in susceptibility to various diseases and disorders. Modern infrastructure and technology in the field of medicine have provided great relief in the treatment of diseases, but a lack of innovation in vaccines and drug resistance makes us vulnerable in to putting up a fight against pathogens and diseases. Under such circumstances, nanotechnology becomes a boon to our lives. In this regard, metallic nanoparticles emerge as a potential agent in the biomedical field. Their preferred structures, synthesis procedures, and vast applications make them a fascinating exploration zone for scientists. Metallic nanoparticles offer numerous applications in drug delivery and treatment of many lethal and chronic diseases like cancer and diabetes due to their unique properties, like high surface area and high specificity. They also exhibit antimicrobial properties, making them reliable for combating multidrug-resistant bacterial diseases. This article aims to give a general overview of some important metallic nanoparticles along with their properties and applications in the biomedical field.



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# INTRODUCTION

Nanotechnology is a special branch of modern science. The term nanotechnology stands for producing nano-sized particles and making them functional for multiple purposes. Nano-sized particles range from <1 to 100 nm. These nanoparticles possess unique physiochemical properties like their nanoscale size, high surface-to-volume ratio, size or surface modification, and so on. Their unique properties made them potent candidates in various fields like medicine, biotechnology, molecular biology, chemistry, and physics. Especially in biomedical fields, nanoparticles can be used as carriers to deliver drugs or other therapeutic agents (1). Additionally, nanoparticles offer prospective advantages over traditional pharmaceutical agents in the case of drug delivery systems (2). If we particularly focus on one of the most progressive areas of nanotechnology, the metallic nanoparticles (MNPs) come first. MNPs pose significant efficacy on drug delivery and imaging (3, 4). These nanoparticles are composed of pure forms of metal as core components (e.g., silver, copper, titanium, gold, copper, iron, platinum, and zinc) or oxide forms of metal such as silver oxide. These metallic nanoparticles are enticing research interest with their optical and photothermal characteristics (5). MNPs also display an exclusive property, resonance electron oscillation, called surface plasmon resonance (6). Their exceptionally small size makes it easy for them to cross any membrane partitions and get absorbed into the bloodstream smoothly (7). MNPs offer diverse applications in various fields (Fig_1). Metallic nanoparticles are well-known for their target-specific drug delivery, which is achieved by conjugation of nanoparticles with specific ligands, drugs, proteins, antibodies, and enzymes (8). Apart from their prominent role in drug delivery systems, metallic nanoparticles also exhibit antimicrobial effects against bacteria, parasites, and viruses. These noble MNPs are generally synthesized by the methods of chemical reduction, biological processes, and physical methods (9). Yet, these expensive chemical processes pose several risks to the ecosystems (10). The green approach can be a safer alternative for synthesizing metallic nanoparticles to enhance their effectiveness, biodegradability, or compatibility or to reduce their toxicity, making them an eco-friendlier option (11). Furthermore, biosynthesis of MNPs can also be mediated through microbes (e.g., bacteria, viruses, fungi) or plants, which become advantageous replacements over conventional methods (12). Apart from these, MNPs play a critical role in the targeted delivery of anticancer agents to the malignant tumor cells (13). The main purpose of this review is to portray the exclusive properties of metal-based nanoparticles. This review also explores the major metallic nanoparticles and their roles in drug delivery systems as well as therapeutic agents.


**Fig. 1. Numerous applications of metallic nanoparticles in the biomedical field**

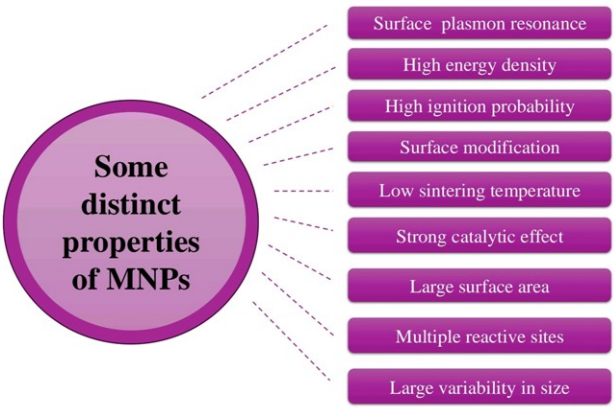


**Fig. 2. Different unique properties of metallic nanoparticles**

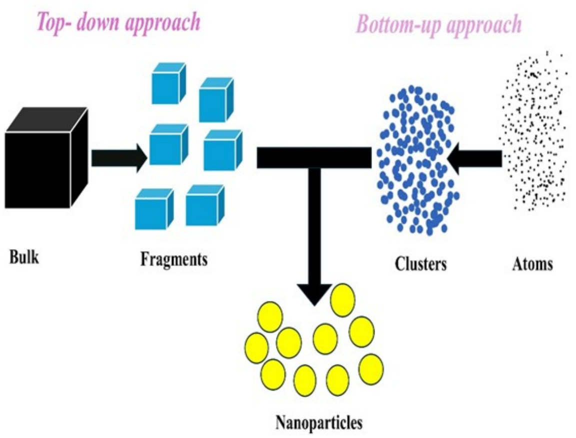


**Fig. 3. Schematic diagram representing an overview on synthesis methods of metallic nanoparticles**

**Properties:** Metallic nanoparticles (MNPs) are mainly metal oxides or metal monomers. These solid nanoparticles are composed of pure metals or their compounds produced by chemical or mechanical processes (14). The processes include chemical reduction, photochemical reduction and electrochemical changes. The selection procedures of manufacturing nanoparticles are crucial, as they can influence the size, structure, and other physiochemical properties. MNPs display distinct features that make them gain attention from scientists and researchers (Fig._2). These features include high

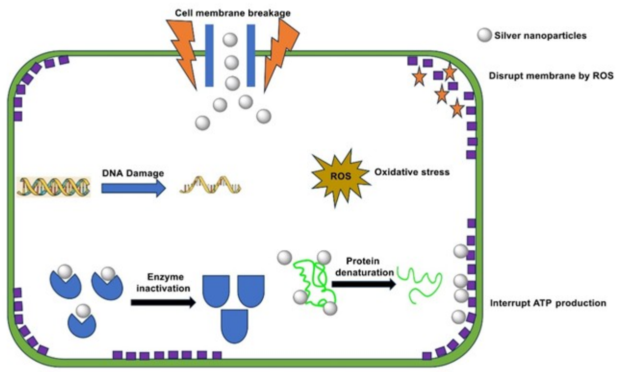


**Fig. 4. Pictorial representation of antibacterial activity of silver nanoparticles**

**Table 1. Antiparasitic activity of some potent metallic nanoparticles**

| Metal nanoparticles | Targeted parasite | References |
|---|---|---|
| Zinc oxide nanoparticles (ZnONPs) | *Leishmania tropica* | (52) |
| Silver nanoparticles (AgNPs) | *Leishmania amazniensis* (amastigotes) | (53) |
| Both AuNPs and AgNPs | *Trypanosoma brucei* | (53) |
| Silver nanoparticle (AgNPs) | *Plasmodium falciparum* | (54) |
| Metal oxide nanoparticles ($Fe_3O_4$, MgO, $ZrO_2$, $Al_2O_3$ and $CeO_2$) | *Plasmodium falciparum* | (55) |
| Gold nanoparticles (AuNPs) | *Schistosoma mansoni* | (56) |
| Polyaniline-coated silver nanoparticles | Helminth | (57) |
| Gold nanoparticles (AgNPs) | Helminth | (58) |

energy density, high ignition probability, strong catalytic effect, and low sintering temperature (15). MNPs also exhibit a unique optical feature, widely known as surface plasmon resonance (SPR). This unique feature makes them a potential tool in the biomedical field. MNPs show a large variability in size. The small size of MNPs brings the advantage of crossing the cell membranes more easily than impermeable macromolecules (16, 17). They can also interact with ligands stably. MNPs can bind with both water-fearing (hydrophobic) and water-loving (hydrophilic) substances. These advantageous qualities of MNPs make them desirable options in the case of target-specific or controlled delivery for disease therapy. The outer surface of MNPs can be modified according to desirable pharmacokinetic properties. Usually, polyethylene glycol (PEG) is used to coat the surface of MNPs to escape the one specific phagocytosis activity (11). Using PEG in the surface modification of MNPs also helps to reduce the absorption of nonspecific protein onto their membrane (11). Surface modification of MNPs is a progressive field in the field of nanotechnology. Surface modification not only increases the stability, biocompatibility, adhesive properties, and wettability but also prevents the uptake of toxic substances and agglomeration (18). Other than PEG, several other groups such as thiol groups, phosphines, amines, and disulfide ligands are also used for surface modification of MNPs. Another important property of metallic nanoparticles possess a large surface area. The large surface area leads to an increased number of reactive sites (19,20). The high surface area also leads to an increase in the surface energy (21). Having more surface area and a smaller size, the MNPs can easily overcome the physiological barriers of the body, interact with proteins or nucleic acids of cell membranes, and alter the function of any cell organelles by penetrating their nucleus (22, 23). MNPs can be synthesized by two different methods—dispersion method (top-down approach) and condensation method (bottom-up approach) (24) (Fig _3). Recently, green chemistry has become the talk of the town due to its eco-friendly and sustainable approaches. When green chemistry principles are applied to the synthesis of MNPs, it increases their biocompatibility and makes them healthier for our nature (25).

**Some potent metallic nanoparticles and their roles in biomedical field**

**Silver nanoparticles (AgNPs):** Among other metallic nanoparticles, silver nanoparticles are one of the most indispensable and engrossing nanomaterials in biomedical applications. These particular nanoparticles cover a wide range of areas, including household, industry, orthopaedic, cosmetic industry, drug delivery, and the food industry (26). In general, the biological method of synthesizing AgNPs is more cost-effective and secure than traditional physical and chemical methods (27). In the last few years, bacterial resistance against antibiotics has become an omnipresent issue. In such a scenario, AgNPs appear to be a potent antibacterial agent. Although the unambiguous action of AgNPs against bacteria is still unclear. It is believed that the activity of AgNPs shows three possible outcomes, such as cell wall and membrane disruption, generating oxidative stress, and intracellular penetration. During oxidative stress, the production of reactive oxygen species induces toxicity against bacteria by disrupting the cell wall and membrane and penetrating the bacterial cell, which leads to protein denaturation, DNA damage, enzyme inactivation, and disruption of ATP production (28) (Fig_ 4). Moreover, the antibacterial activity of AgNPs depends upon both shape and size (29). In research work to find out the antimicrobial properties of AgNPs, it was shown that the growth of yeast and *E. coli* is completely inhibited at low concentrations of AgNPs. Whereas AgNPs show a mild effect against *Staphylococcus aureus* (30). AgNPs also show an impact on bacterial cell membranes, generating many pits and gaps to damage the bacterial membrane (31). Furthermore, biologically synthesized AgNPs exhibit antifungal activity against virulent fungi to humans and plants along with indoor fungal species like *Cladosporium cladosporioides, Stachybotrys chartarum*, *Chaetomium globosum*, *Aspergillus fumigatus*, *Mortierella alpine*, and *Penicillium brevicompactum* that are cultured in agar media (32). Inhibitory antiviral effects of AgNPs are also documented against HIV and hepatitis B virus (33). Apart from these, AgNPs can also exhibit potent anti-cancer effects (34).

**Gold Nanoparticles (AuNPs):** Gold—this precious metal has been studied and applied in various fields for several thousand years. Gold-based nanoparticles are used vigorously in modern medicine due to their unique physiochemical properties. AuNPs become a robust agent in bioimaging and visualization. For example, to detect microbial cells or their metabolites, AuNPs are applied in dark field microscopy (35). AuNPs can also act as efficacious radiosensitizers in cancer therapy or drug delivery (36). Gold nanoparticles are usually conjugated with other antibiotics or antibacterial agents for the treatment of bacterial infections. For example, gold nanoparticles exhibit high efficacy against several enteropathogens such as *Enterococcus faecalis*, *Escherichia coli*, and *Enterococcus faecium* when colloidal gold and vancomycin form a stable complex (37). In cancer therapy, gold nanoparticles act as a novel factor by reducing the chance of side effects and damage to healthy cells (38). Recent studies have demonstrated that AuNPs can prevent degradation of nucleic acids from nucleases (39). To transfer various drugs prominently, AuNPs can be modified or conjugated with other drugs. The modified AuNPs reduced the risk of cancer developing drug resistance and systemic drug toxicity (40).

**Iron oxide nanoparticles (IONPs):** Oxides of iron possess some unique properties, such as biocompatibility, ultrafine size, and superparamagnetic iron oxide nanoparticles (SPION), which make them promising candidates in the field of medicine. Behera et al. developed iron oxide nanoparticles that exhibit efficacy against both Gram-positive and Gram-negative bacteria (41). Iron oxide nanoparticles show antibacterial activity through oxidative stress, generating ROS that leads to the damage of DNA and proteins of bacteria (42).

**Copper nanoparticles (CuNPs):** Copper nanoparticles have been utilized as antifungal and antibacterial agents for several decades. Their cost-effective price and availability as compared to gold and silver make them useful in a wide range of applications. As compared to silver, copper is a weaker antibacterial agent, but it has a wide range of activity, specifically against fungi (43). Kamble et al. have demonstrated a comparative study between native curcumin and curcumin-capped copper nanoparticles in which curcumin-capped CuNPs show possible inhibitory effects against breast cancer cells and angiogenesis in humans (44).

**Platinum nanoparticles (PtNPs):** Platinum nanoparticles exhibit some distinct properties, like hydrogenation and dehydrogenation of several important molecules and catalyzing partial oxidation, making them appealing candidates in various industrial applications (45). PtNPs also show promising results in treating cancer. The effects of PtNPs were investigated on several cancer cell lines, and their cytotoxic effects on HepG-2 and MCF-7 cell lines were also studied through MTT assay (46). Several studies were also reported about the role of PtNPs in bone allografts. It was revealed that PtNPs can protect cells from oxidation-induced inflammation, leading to inhibition of pulmonary inflammation and induced bone loss by reducing osteoclastogenesis (47). Reactive oxygen species, or ROS, are small molecules of free radicals, peroxide, or oxide ions that are produced during normal body functions. Excessive production of ROS is associated with several body disorders like asthma, aging, neurodegenerative disorders, diabetes, and arthritis (48). PtNPs exhibit promising antioxidant effects. PtNPs can give protection against bone loss by modulating oxidative stress (49). However, it was reported that PtNPs can exhibit toxicity on normal living cell lines. Therefore, preparation of biocompatible PtNPs for cancer therapy is a challenging task (50). Apart from the toxicity, platinum group metals show promising potential to treat parasitic diseases in the future (51). Table 1 summarizes some metallic nanoparticles and their actions against specific parasites.

**Titanium nanoparticles ($TiO_2$NPs):** Titanium (Ti) is the ninth most plentiful element found in the crust of Earth. The oxide form of titanium metal is well known as $TiO_2$ or titania. Titanium dioxide nanoparticles ($TiO_2$ NPs) show some distinct properties like a high refractive index, strong oxidation properties, cost-effectiveness, formidable oxidation properties, and chemical stability, making them ideal for various applications (59). $TiO_2$ NPs exhibit a synergistic effect on breast cancer cell lines when they are conjugated with doxorubicin (60). The $TiO_2$ NPs also serve as a photoactive carrier for various drug deliveries because of their low cost, availability, high surface area, and surface modification (61). Recently, $TiO_2$ NPs have also utilized as an anticoagulant in the medicinal field (62). $TiO_2$-based biosensors are also used to detect protein, DNA, RNA, lipid, and metabolite biomarkers (63). At present, the usage of multi-layered $TiO_2$ NPs has been introduced in dental implants (64).

**Zinc oxide nanoparticles (ZnO NPs):** Due to their low toxicity and biocompatibility, Zinc oxide nanoparticles (ZnO NPs) have gained popularity over the last 20 years. ZnO NPs have been employed in several biomedical applications, including wound healing, tissue engineering, bio-imaging, and the formation of anti-cancer drugs (64). ZnO NPs also show influence to control foodborne pathogens (66). In addition, zinc oxide nanoparticles can be used to treat diabetes due to their biocompatibility and physicochemical properties (67). Additionally, ZnO nanoparticles also exhibit substantial toxicity to cancer cells *in* vitro as well as activated T cells (68). Furthermore, ZnO NPs may induce ROS that specifically cause damage to harmful bacterial cells (69).

# CONCLUSION

In this review, we have given insights about metallic nanoparticles, their unique properties, and their vital role in biomedical fields. The rapid development of MNPs and their diversified roles gives a glimmer of hope for a better quality of life. Their robust roles as nanocarriers for drug delivery establish them as new pharmaceutical tools, especially in the case of cancer, inflammatory diseases, diabetes, and microbial diseases. Although there are some reports about the toxic effects of MNPs on their surroundings or living systems. Apart from their multidimensional role, it becomes a hindrance to improving their efficacy by reducing their toxic effects. Moreover, nanotechnology is continuously working to find out efficient metal-based nanoparticles with improved formulas through modifying their size, shape, and surface coating to reduce the toxicity of MNPs. It is also well established that metallic nanoparticles have huge applications in different biomedical fields, but keeping in mind their toxicity and effectiveness, modern-day nanoscientists are trying to synthesize MNPs from different green sources to increase their effectiveness and diminish their toxicity. However, in recent times, the application of nanoparticles in the biomedical field is still in its early phase. Their infallible utilization in medicine, especially in drug delivery systems, requires in-depth research and further exploration.

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**Key Points**

- Metallic nanoparticles such as AgNPs, AuNPs,ZnNPs exhibit some unique physicochemical properties which make them functionalized in various aspects of biomedicinal fields.
- Metallic nanoparticles are used for multifarious applications, including antimicrobial agents, bioimaging, drug delivery, and therapeutics.
- The multidimensional role, efficiency and target specific properties of metallic nanoparticles make them a potent agent in a specific drug delivery system for many diseases.

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