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SILVER NANOPARTICLES: MULTIFUNCTIONAL AGENTS FOR BIOMEDICAL AND ENVIRONMENTAL APPLICATIONS

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ABSTRACT

Silver nanoparticles (AgNPs) have attracted significant attention due to their unique physicochemical and biological properties, enabling broad applications in medicine, pharmaceuticals, food, cosmetics, and environmental sciences. Their nanoscale size and high surface-to-volume ratio enhance antimicrobial, antioxidant, anti-inflammatory, and anticancer activities, even at low concentrations. Various synthesis methods—including physical, chemical, and biological approaches—have been developed, with eco-friendly green synthesis using plants and microorganisms emerging as a sustainable alternative to conventional methods. AgNPs demonstrate therapeutic potential in drug delivery, wound healing, diagnostics, and medical device coatings, with notable synergistic effects when combined with conventional antibiotics to combat multidrug-resistant pathogens. However, challenges regarding toxicity, stability, and environmental safety remain critical concerns. This review summarizes synthesis strategies, characterization techniques, biological applications, and safety considerations for AgNPs while emphasizing the importance of optimizing green synthesis approaches and comprehensive toxicity profiling to ensure safe and effective biomedical and industrial applications.

KEYWORDS: However, challenges regarding toxicity, stability, and environmental safety remain critical concerns.

INTRODUCTION

Silver nanoparticles (AgNPs) are nanoscale particles of silver typically ranging between 1–100 nanometers in size. Their exceptionally high surface area-to-volume ratio and unique physicochemical and biological properties impart significant antimicrobial, antioxidant, and catalytic activities. These nanoparticles can be synthesized using physical, chemical, and biological techniques, with green synthesis methods gaining increasing importance due to their environmental friendliness.[1-6]

Owing to their strong antibacterial and antiviral potential, AgNPs have found wide applications in medicine (wound healing, drug delivery, diagnostic tools), cosmetics, water purification, textiles, and electronics. Among zero-dimensional nanomaterials, AgNPs stand out as one of the most extensively explored materials for innovative applications, demonstrating promising results in pharmaceuticals, antimicrobial coatings, wound dressings, functional textiles, and food packaging.[7-9]

Numerous preclinical studies have highlighted the role of AgNPs in developing effective and advanced therapeutic strategies. However, thorough characterization of synthesized nanoparticles is essential, as their physicochemical properties strongly influence biological interactions and safety profiles. Proper characterization ensures their safe and efficient use in healthcare and nanomedicine applications.[10-12]

This review focuses on recent progress in the synthesis, characterization, physicochemical properties, and bio-applications of AgNPs, particularly their antibacterial, antifungal, antiviral, anti-inflammatory, anticancer, and anti-angiogenic activities. The mechanisms underlying their anticancer effects, therapeutic approaches, as well as existing challenges and limitations in cancer therapy, are also discussed, along with future perspectives.[13-14]

The antimicrobial effects of silver ions and AgNP suspensions are noteworthy, often surpassing those of conventional antibiotics such as penicillin and biomycin, especially against resistant microbial strains. Additionally, the versatility of AgNPs extends to applications in biomedicine, mosquito control, environmental remediation, wastewater treatment, agriculture, food safety, and packaging industries.[15-16]

With the growing emphasis on sustainability, eco-friendly synthesis methods that eliminate toxic chemicals—such as green synthesis approaches involving polysaccharides, polyoxometalates, Tollens processes, biological systems, and irradiation techniques—are becoming increasingly significant. Finally, nanobiotechnology, as a rapidly expanding domain, continues to enable the controlled synthesis of nanoparticles with tailored sizes, shapes, and compositions, reinforcing its importance within modern nanotechnology.

METHODS

Physical Methods

Physical methods for synthesizing silver nanoparticles mainly include mechanical processes and vapor-based processes, where different forms of energy are utilized to reduce the particle size. These energies include mechanical energy (ball milling)[60], electrical energy (arc-discharge), light energy (laser ablation), and thermal energy (physical vapor deposition).

- Ball Milling Method: In this technique, high-speed collisions between hard balls such as ceramics, stainless steel, or flint pebbles generate localized high pressure, breaking down the bulk silver into very fine powders.[17]
- Electrical Arc-Discharge Method: Nanoparticles are produced using a DC-powered arc discharge device. The powder reagent layer serves as the anode, and the electrodes are immersed in dielectric liquids such as hydrocarbons, inert gases, or deionized water.[18]
- Laser Ablation Method: Here, a high-power laser beam ablates a metal target, and the energy absorbed leads to the formation of plasma. On cooling, nucleation and growth of metal particles occur, leading to nanoparticle formation.[9]
- Physical Vapor Deposition (PVD): Two main processes are used.
  - Sputtering: High-energy electrical charges bombard a target material, ejecting atoms or molecules that deposit on a substrate.
  - Evaporation: The material is heated in a vacuum to its boiling point; the vaporized atoms rise and condense on the substrate.

Although physical synthesis methods can produce large quantities of AgNPs with uniform size distribution and high purity, they often require complex equipment and significant energy input. Additionally, nanoparticles may aggregate, affecting their stability. To prevent this, stabilizers such as polyvinylpyrrolidone (PVP) or fructose are commonly used, ensuring long-term stability of colloidal AgNPs.[20-21]

Chemical Methods

Chemical synthesis is the most widely used approach for producing AgNPs. In this method, silver ions (Ag^+), usually supplied by a silver salt precursor, are reduced to elemental silver (AgNPs) through electron transfer under controlled conditions.

Common reducing agents include sodium borohydride ($NaBH_4$) and sodium citrate (TSC), which facilitate the conversion of Ag^+ to Ag^0. Additionally, chemical synthesis can be coupled with external energy sources such as photochemical, electrochemical, microwave-assisted, and sonochemical methods to enhance the reaction.[22-23]

The process typically occurs in two stages.

1. Nucleation: The concentration of silver monomers quickly rises above the critical supersaturation level, initiating a rapid "burst nucleation" process that leads to the formation of small nuclei.
2. Growth: As monomer levels decrease below the critical point, additional monomers attach to the existing nuclei, allowing them to grow into larger nanoparticles.

To prevent aggregation and ensure uniform distribution, stabilizers such as polyvinylpyrrolidone (PVP) and cetyltrimethylammonium bromide (CTAB) are often added during synthesis.

Although the chemical method is high-yield, time-efficient, and easily controllable, the use of chemical reagents raises concerns about environmental pollution and potential toxicity.[24-27]

Biological Methods

In recent years, various microorganism- and plant-mediated methods have been developed for the biological synthesis of AgNPs. Microorganisms possess metal tolerance genes and metal bioconcentration abilities that enable them to survive in environments rich in silver. Through adaptive mechanisms, they reduce the cytotoxicity of silver ions (Ag^+), and the formation of AgNPs occurs as a by-product of their resistance mechanism.

Similarly, plant-mediated synthesis relies on plant extracts containing functional groups such as O–H and =C–H in organic compounds, which help reduce Ag^+ to Ag^0. A wide range of plant parts—including bark, leaves, flowers, fruits, seeds, stems, peels, rhizomes, and callus tissues—have been used for this purpose.

In these biosynthetic processes, various biological molecules act as reducing agents.

- From microorganisms: exopolysaccharides, peptides, nitrate reductase, reducing cofactors, and c-type cytochromes.
- From plants: starch, cellulose, chitin, dextran, alginates.

However, the interactions between these organic components and AgNPs are complex, and further research is needed to fully understand their roles.

Compared to physical and chemical methods, biological synthesis is advantageous because it can be carried out under ambient temperature and pressure and does not require toxic or hazardous chemicals.[28-31]

Mechanism of Silver Nanoparticles

Despite the vast number of studies on the biosynthesis of AgNPs using organisms like **bacteria, fungi, lichens, algae,** and **higher plants**, the **exact mechanism** of this process is still not fully understood. Research shows that AgNP formation can occur both **extracellularly** and **intracellularly**, depending on the organism and conditions used.

Extracellular Biosynthesis

In **extracellular synthesis**, enzymes and proteins on the **cell wall** or secreted into the surrounding medium reduce **Ag^+ ions to Ag^0**, leading to nanoparticle formation. This mechanism has been observed in several **Gram-positive bacteria** such as *Bacillus pumilus*, *B. persicus*, *B. licheniformis*, *B. indicus*, *B. cecembensis*, *Planomicrobium* sp., *Streptomyces* sp., and *Rhodococcus* sp., as well as **Gram-negative bacteria** like *Klebsiella pneumoniae*, *Escherichia coli*, and *Acinetobacter calcoaceticus*. Similarly, fungi including *Rhizopus stolonifer*, *Aspergillus niger*, *Fusarium oxysporum*, *Fusarium* sp., and *A. flavus* also exhibit this pathway.

Intracellular Biosynthesis

In intracellular synthesis, silver ions enter the cells through membrane proteins and are reduced inside the cytoplasm. Examples include *Enterobacter cloacae*, *Pseudomonas stutzeri*, *Corynebacterium* sp, *Streptomyces* sp, and the fungus *Verticillium* sp. Some microorganisms like *Bacillus* strain CS11 and *Proteus mirabilis* can perform both intracellular and extracellular synthesis.[32-34]

Role of Enzymes and Biomolecules

Enzymes, especially NADH-dependent nitrate reductase, play a central role by transferring electrons from nitrate molecules to silver ions, reducing them to elemental silver. Other enzymes such as keratinase B from *Bacillus safensis* have also been implicated in AgNP formation. Additionally, proteins, peptides, sugars, and amino acids like arginine, cysteine, lysine, aspartic acid, methionine, and glutamic acid participate in silver reduction and nanoparticle stabilization.[35-38]

The process is influenced by environmental conditions such as pH and light exposure. Higher pH levels activate oxidoreductase enzymes, while light can enhance electron release from reducing agents, accelerating Ag^+ reduction. Some bacteria even use a transmembrane proton gradient and ATP hydrolysis to transport and reduce silver ions inside the cell.

Stabilization and Capping Agents

After synthesis, capping agents—including peptides, proteins, enzymes, carboxylic acids, aldehydes, ketones, rhamnose sugars, rhamnolipids, flavonoids, terpenoids, and polyols—bind to the nanoparticle surface. These agents:

- Prevent aggregation of nanoparticles,
- Reduce toxicity,
- Enhance antimicrobial properties, and
- Often contribute additional antioxidant, anti-inflammatory, or antitumor activities.

In plants, metabolites such as alkaloids, phenols, polyphenols, sugars (e.g., sucrose, fructose), glycosides, and saponins act as both reducing and stabilizing agents, producing nanoparticles under mild, eco-friendly conditions. These compounds also make the nanoparticles colloidally stable in aqueous media and improve their biological efficacy.[39-41]

Toxicity of Silver Nanoparticles

Nanosilver has gained considerable attention for modern biomedical applications due to its ability to interact with living cells, potentially affecting cytoskeleton organization, molecular adhesion, and cell proliferation . Howver, its toxicity mechanisms involve multiple pathways.

1. Disruption of energy-dependent processes and DNA replication due to free silver ion uptake.
2. Excessive generation of reactive oxygen species (ROS) and free radicals.
3. Cell membrane damage caused by direct interaction with AgNPs.

Impact of Coatings and Surface Modifications

- CTAB- and PEG-coated AgNPs showed dose-dependent effects on red blood cells (RBCs), but were non-hemolytic at concentrations below 100 µg/mL, indicating good blood compatibility.
- Polymer-coated AgNPs (e.g., PVA–PEG, poly(3-aminophenyl boronic acid)) were stable, conductive, and non-toxic to human RBCs at bactericidal levels.
- Chitosan-coated AgNPs demonstrated anticoagulant, antiplatelet, and thrombolytic effects in animal models while maintaining low cytotoxicity.

Size-Dependent Cytotoxicity

- Small-sized AgNPs (4 nm) triggered high ROS levels and inflammatory responses in macrophages, while larger particles (20–70 nm) exhibited lower toxicity.
- PVP-stabilized AgNPs allowed cellular recovery after acute exposure and showed no toxicity against macrophages or vital organs at bactericidal levels.
- 10 nm AgNPs induced toxicity in neural stem cells through ROS-mediated oxidative stress and DNA damage, leading to apoptosis or necrosis.
- 20 nm PVP-coated AgNPs caused cytoskeletal alterations and dopamine dysregulation in neural cells, unlike 70 nm particles.[42-45]

Effects on Different Cell Types and Models

- Sorrel flower extract-mediated AgNPs induced apoptosis in human endothelial cells and caused cell malformations in zebrafish due to oxidative stress.
- Some studies reported higher cytotoxicity against cancer cells compared to normal cells.
- Silica-coated AgNPs showed no genotoxicity in fibroblast cultures, while coatings with PVA and CMC were biocompatible; however, SDS- or oleate-coated AgNPs were cytotoxic.
- Ayurvedic herb extract- and oxidized amylose/curcumin-based AgNPs exhibited low toxicity at concentrations up to 2.5 mg/mL, with enhanced antioxidant and antibacterial properties.
- Lecithin-modified montmorillonite composites with AgNPs showed no fibroblast toxicity and good skin compatibility.

Concentration and Coating Effects

- PEG-coated AgNPs below 10 µM were safe for keratinocytes, while higher doses caused significant cytotoxicity.
- PVP-coated silver nanoprisms showed preferential uptake in mesenchymal stem cells compared to spherical particles.
- Fungi-derived AgNPs exhibited strong antimicrobial activity with low toxicity against human melanocytes.
- Electrochemically synthesized AgNPs were non-toxic to muscle cells at ≤100 ppm but displayed antiviral activity.

Organ and Systemic Effects

- Pulmonary exposure in rodents caused mild lung inflammation and dose-dependent cardiovascular effects such as DNA damage, oxidative stress, apoptosis, and prothrombotic events.
- Smaller AgNPs were shown to penetrate cells more easily, affecting cytoplasm, mitochondria, and DNA.
- Apoptosis induction is another major mechanism of toxicity.

Developmental and Hepatic Effects

- Embryonic stem cell differentiation into hepatocytes and cardiomyocytes was dose-dependently affected by AgNPs.
- Citrate-coated AgNPs caused hepatic inflammation and enzyme downregulation in mice, highlighting the need for hepatoprotective coatings.
- CS-coated nanoparticles crossed the placenta but showed minimal fetal toxicity, while uncoated particles caused severe hepatotoxicity.

Surface Charge and Toxicity Correlation

- Neutral coatings (silicate, PVP) induced lower inflammation and genotoxicity than positively charged PEI or negatively charged citrate coatings.
- PEI-coated 80 nm particles were internalized at a higher rate, causing mitochondrial damage compared to PEG, PVP, or citrate-coated AgNPs.
- EG-coated particles showed antioxidant effects, while PVP-EG coatings caused pro-oxidant stress in rat models.[46-48]

Silver Nanoparticles for Antibacterial Applications

The growing problem of drug-resistant microorganisms in healthcare has made conventional monotherapies increasingly ineffective. Bacterial infections and related complications remain a major cause of death worldwide. To address this issue, researchers have focused on understanding antibacterial resistance mechanisms and developing novel, more effective therapeutic strategies.

Many bacterial strains have developed resistance to standard antibiotics due to their adaptive capabilities and the overuse of these drugs. This situation has led to the urgent need for new bactericidal agents, particularly those effective against biofilm-associated pathogens, which are notoriously difficult to treat. Nanomaterial-based formulations, especially those involving silver nanoparticles (AgNPs), have emerged as promising alternatives.

Silver has been used as an antimicrobial agent for centuries because it can penetrate biological membranes and exert both local and systemic effects. Historically, silver compounds have been applied in treating dental infections, gastrointestinal conditions, wound healing, and burns. However, their toxicity to human cells at high concentrations and the risk of accumulation leading to conditions like argyria have limited their usage. To overcome these drawbacks, modern approaches focus on using low concentrations of silver in biocompatible delivery systems, such as nanosilver formulations.

Studies have demonstrated that AgNPs are highly effective against various clinically important bacteria, including *Escherichia coli* (E. coli) and *Staphylococcus aureus* (S. aureus). E. coli is more sensitive to AgNPs than S. aureus due to its thinner peptidoglycan layer and outer lipopolysaccharide membrane, which make it more vulnerable to nanoparticle penetration and membrane destabilization. AgNPs exhibit antibacterial effects through multiple mechanisms, including.

- Interaction with bacterial membranes and disruption of cell integrity
- Generation of reactive oxygen species (ROS) leading to oxidative stress
- Release of silver ions (Ag^+) that inactivate vital enzymes, proteins, and nucleic acids

These mechanisms collectively cause cell damage, leakage of cellular contents, and ultimately bacterial death.

Research has shown that the antibacterial activity of AgNPs is size-dependent—smaller particles (<20 nm) have greater surface area, enhanced reactivity, and stronger bactericidal effects. For example, ultrasmall AgNPs (1–5 nm) exhibited stronger activity against E. coli and S. aureus than larger nanoparticles. Similarly, shape-dependent effects have been observed—spherical AgNPs generally show stronger antibacterial activity compared to irregular, disk-shaped, or triangular nanoparticles due to higher ion release and greater surface reactivity.

Moreover, AgNPs synthesized using various biological extracts (e.g., plants, fungi, bacteria) and stabilizers like PVP, pectin, or chitosan have shown excellent antibacterial properties against multiple strains beyond E. coli and S. aureus, including *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Streptococcus* species.

Another promising approach involves synergistic treatments combining AgNPs with antibiotics, essential oils, or light irradiation. Such combinations have significantly enhanced bactericidal effects, even against drug-resistant strains. Examples include.

- AgNPs with antibiotics like gentamicin, vancomycin, or ampicillin.
- AgNPs with natural compounds like curcumin or essential oils.
- AgNPs combined with light irradiation, which further boosts ROS production and antibacterial activity.

These synergistic strategies not only improve antibacterial efficacy but also help reduce the required dosage of antibiotics, potentially slowing down the emergence of resistance.[49-51]

Advantage

1. Broad-Spectrum Antimicrobial Action

- Silver nanoparticles (AgNPs) show strong activity against a wide range of microorganisms, including antibiotic-resistant strains such as MRSA.
- Their mechanisms involve disrupting cell membranes, producing reactive oxygen species (ROS), and interfering with microbial genetic material.

2. Improved Wound Healing

- AgNPs accelerate tissue repair and minimize infection risks in wound management.
- They are incorporated into dressings and gels to maintain sterility and control inflammation.

3. High Surface-to-Volume Ratio

- Their nanoscale size provides a larger surface area, enabling greater interaction with pathogens at lower doses for enhanced efficacy.

4. Role in Drug Delivery

- AgNPs can serve as carriers for targeted drug delivery, improving drug absorption while minimizing adverse effects.
- They allow functionalization for controlled release and site-specific targeting.

5. Antioxidant Activity

- Silver nanoparticles possess free-radical scavenging properties that help reduce oxidative stress in biological systems.

6. Use in Cosmetics and Personal Care

- Incorporated into lotions, creams, and deodorants, AgNPs provide antimicrobial protection, enhance product shelf-life, and support skin health.

7. Medical Device Applications

- Coating implants and surgical instruments with AgNPs prevents biofilm formation and lowers the risk of post-operative infections.

8. Environmental Applications

- AgNPs are used in water purification for their antimicrobial and catalytic properties.
- They are also integrated into sensors to detect environmental pollutants and pathogens.

9. Anti-Inflammatory Benefits

- By reducing pro-inflammatory cytokine production, AgNPs help alleviate inflammation in skin and tissue therapies.

CONCLUSION

- Silver nanoparticles (AgNPs) are highly versatile nanomaterials with exceptional physicochemical and biological properties. Their antimicrobial, antioxidant, anti-inflammatory, and anticancer activities make them valuable in medicine, pharmaceuticals, food preservation, cosmetics, and environmental protection. Owing to their nanoscale size and large surface-to-volume ratio, AgNPs exhibit enhanced bioactivity even at low concentrations, enabling applications in drug delivery, wound care, diagnostics, and medical device coatings. Additionally, their synergistic effects with conventional antibiotics offer promising solutions against multidrug-resistant pathogens.
- However, certain limitations persist, particularly concerning toxicity, stability, and environmental safety. The biological behaviour of AgNPs is influenced by factors such as size, shape, surface properties, and synthesis methods, all of which affect both therapeutic outcomes and safety profiles. While traditional physical and chemical synthesis methods are efficient, they often rely on hazardous chemicals, emphasizing the importance of eco-friendly and cost-effective green synthesis approaches using plants and microorganisms.
- Future studies should focus on refining synthesis techniques, precisely controlling nanoparticle properties, and conducting comprehensive toxicity evaluations to ensure clinical safety. With sustainable development, AgNPs have the potential

to transform healthcare and industry by offering innovative solutions to current biomedical and environmental challenges.

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