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Silver nanoparticles: Synthesis, Applications, and Side Effects

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ABSTRACT

Silver nanoparticles (AgNPs) have garnered considerable interest recently due to their diverse applications and exceptional physicochemical properties. As AgNPs have distinct optical, electrical, catalytic, antibacterial, and antioxidant properties, they are widely used in commercial cosmetics, industrial electronics, medicinal applications such as drug delivery, wound and bone healing, biosensing, and cancer therapy, energy storage, and agricultural applications such as water filtration and treatment systems. Regardless of these benefits, AgNPs have toxic effects due to their accumulation in cellular tissues and organs, causing an increase in ROS, leading to oxidative stress, inflammation, and damage to vital organs like the liver, kidneys, spleen, and reproductive tissues. To get AgNPs' advantages, enhance biocompatibility, and mitigate their harmful effects, many strategies are applied as green synthesis methods, controlled dosage and exposure, size and shape modifications, composite nanoparticles, and surface coating. The appropriate application of AgNPs in industry and medicine depends on careful approaches that combine unique synthesis, safe delivery, and toxicity evaluation. In this review, we seek to gain a better knowledge of how to synthesize AgNPs in order to maximize their benefits while minimizing their toxicity.

1.Introduction

Nanoparticle technology is now having a significant impact on several industries due to its ability to alter material properties at the nanoscale. Apart from their industrial uses, nanoparticles are crucial in the medical field, especially for targeted drug administration **[1].** Numerous NP kinds are presently under investigation across a wide range of applications. Among these, AgNPs have attracted interest because of their effective properties, particularly their antibacterial activity. They can have virucidal, fungicidal, and bactericidal impacts **[2].** Because of their special optical, electrical, and antibacterial qualities, silver nanoparticles (AgNPs) are widely used in a variety of applications, such as biosensing, photonics, electronics, dental materials, cosmetics, food storage and packaging, textile coatings, catalysis, some environmental applications such as water disinfection, medical products, medical devices, antiviral coatings, and antimicrobial treatments **[3].** Although AgNPs have benefits, there is growing concern about their potential harm to human health and the environment. Previous research suggests that AgNPs may cause cytotoxicity, genetic disruption, oxidative damage, and inflammatory disorders in human cells, causing cancer, neurological issues, and respiratory infections **[4].** Silver nanoparticles tend to collect in organs, including the liver, lungs, and kidneys, causing harm to cells and tissues. Some people may be allergic to AgNPs, which can result in skin irritation, rashes, and other symptoms. The tendency of AgNPs to agglomerate increases their potential for toxicity **[5].** So, regulating the use and disposal of AgNPs is crucial to mitigate their environmental and human health impacts. So that researchers are exploring green synthesis methods to manufacture AgNPs from microbes or plant extracts. This approach is safer, more cost-effective, and ecologically friendlier than chemical synthesis, resulting in high-quality outcomes **[6].**

2.Silver nanoparticles applications

Nanotechnology is one of the key innovations that has effectively increased the utilization of silver ions. Multiple elemental ions are joined in an NP structure to create silver nanoparticles. The exceptional features of AgNPs, including their photocatalytic, optical, antiviral, antibacterial, and anti-inflammatory qualities, have been emphasized **[7].** Their biological activities are also greatly impacted by their distinct physicochemical properties, involving surface area, charge, shape, and localized surface plasmon resonance **[8].**

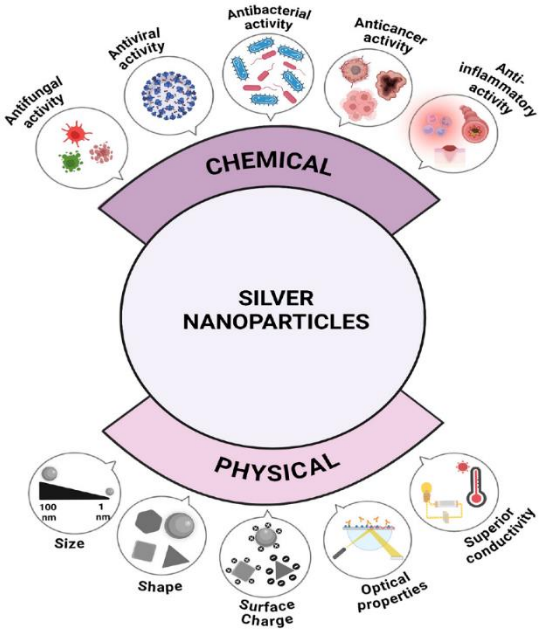

Fig 1. Characteristics of silver nanoparticles **[9].**

In the medical field, silver nanoparticles are used in the diagnosis of cancer cells and destroy them through photothermal treatment. Additionally, in cancer therapy, they help in targeted drug delivery for cancer treatment **[10].** Silver nanoparticles have anticancer effects, as high concentrations of AgNPs induce apoptosis by increasing membrane permeability, activating caspases, and causing nuclear condensation **[11].** Silver nanoparticles revealed efficient cytotoxicity against HT-29 human colon cancer cells **[12].** Biosynthesized AgNPs from Aspergillus Tereus demonstrated significant anticancer properties, especially in the MCF-7 breast cancer cell line **[13].** Utilizing AgNPs with chemotherapy can overcome radiation resistance and improve tumour treatment for several cancer types **[14].** Silver nanoparticles have a strong ability to mitigate bacterial proliferation and other microbes in the following ways: rupturing of the cell wall, lysis of the cell membrane, inhibition of protein synthesis, and bacterial reproduction. As a result of these abilities, AgNPs have potent antibacterial properties against both Gram-positive and Gram-negative bacteria [15**].** Numerous studies have shown that the smaller the size of NPs, the more effective the ability to penetrate the bacteria **[16].** The antibacterial activity of AgNPs against P. aeruginosa was proved **[17].** Silver nanoparticles have a great bactericidal effect on E. coli [18]. Silver-modified copper oxide (Ag-CuO) NPs have antibacterial activity against Gram-positive (S. aureus) and Gram-negative (E. coli) **[19].** It has been revealed that AgNPs support immune cells during inflammation, as detected in previous studies that biosynthesized AgNPs have enhanced antiviral activity against hepatitis C virus, HSV-1, and SARS-CoV-2 **[20].** Direct pulmonary administration of AgNPs enhances the immune system against the influenza virus and murine pneumonia virus by activating lymphoid cells [21]. It was revealed that chemically synthesized AgNPs interacted with swine coronavirus, which inhibited viral attachment by 12% **[22].** This is because AgNPs bind to virus spikes in glycoproteins without blocking virus attachment **[23].** Numerous studies have shown that green-synthesized AgNPs by plant extracts increase antioxidant potential by neutralizing free radicals and mitigating oxidative stress in biological systems, as the presence of bioactive phytochemicals further boosts their antioxidant potential through a synergistic effect, leading to strong radical scavenging activity **[24**]. It has been shown that Astragalus Sarcocolla (Anzaroot) extract-mediated AgNPs exhibited antioxidant properties and had an inhibitory effect on C. albicans and K. pneumonia **(25)**

. Biosynthesized AgNPs from Origanum Majorana L. extract show potential for use in food and medicinal applications due to their potent antioxidant properties **[26].** Silver nanoparticles are already being utilized in various medical applications, including coated medical equipment **[27],** dental materials **[28],** bone implants **[29],** and wound dressings by restoring the skin to its optimal physiological state **[30].**

2.**Methods of Silver Nanoparticle Synthesis**

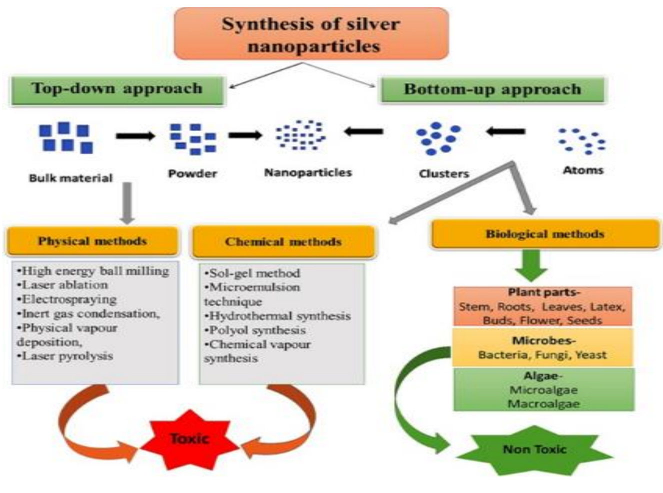

Fig 2. Techniques for synthesizing AgNPs [31].

The two basic methods for creating NPs are top-down and bottom-up approaches. These methods include fundamental techniques: chemical, physical, and biological. The physical method employs a top-down process; in contrast, the chemical and biological techniques often employ a bottom-up approach. To turn bulk materials into NPs, the top-down approach uses physical techniques such as electrical arc discharge, vapor condensation, grinding, milling, and laser ablation without chemical additions. These methods can create NPs with typical diameters between 10 and 100 nm. Nanoparticles that are physically generated usually have a consistent size and significant purity. The absence of stabilizers or capping agents, which are essential for avoiding aggregation because no potentially dangerous compounds are used, is a significant disadvantage of this approach. Atoms and molecules combine to create NPs from smaller building blocks in a bottom-up process. Some examples of bottom-up methods include chemical vapor deposition, laser pyrolysis, sol-gel processing, bioassisted synthesis, self-assembly of monomer molecules, plasma or flame spraying, and electrochemical precipitation **[32].**

Physical techniques usually entail creating and modifying AgNPs by applying external physical forces. These methods are highly preferred as they can generate NPs with precise size, shape, and crystallinity. They can be used for a range of biological and industrial purposes. These techniques also enable accurate control over the characteristics of NPs by modifying factors including temperature, pressure, and reaction time. Physical procedures commonly don't need complicated precursor materials or chemical reagents, which lowers the possibility of contamination and undesirable chemical byproducts, in contrast to chemical and biological processes. There are several examples of physical methods, such as vapor condensation, ball milling, sputtering, thermal decomposition, and electrospinning techniques **[33].** Although chemical and physical approaches are still employed for AgNPs synthesis, there is a pressing need to deal with sustainability concerns. Chemical solvent residues such as ethylene glycol, sodium citrate, oleyl amine, and liquid paraffin are commonly found on the surface of synthesized AgNPs. When AgNPs are utilized in drug administration, antimicrobial therapies, and human-body integration applications, these chemical carriers may be dangerous. The large-scale chemical production of AgNPs isn't sustainable. There is a critical need for an eco-friendly, cost-effective, and biological (green) synthesis alternative **[34].**

Green synthesis approaches utilize microorganisms (fungi, yeasts, bacteria, and actinomycetes), plant resources, and templates such as membranes, viral DNA, and diatoms **[35].** Natural extracts contain phytochemical compounds such as polysaccharides, polyphenolic compounds, vitamins, amides, alkaloids, terpenoids, tannins, organic acids, and aromatic dicarboxylic acids, which are utilized to reduce Ag^+ ions to AgNPs **[36].** Various plant species have been employed in the green synthesis of AgNPs, revealing the adaptability of plant-based methods. Plant metabolites differ by species, affecting the efficiency and properties of NP production. Secondary plant metabolites include flavonoids, phenolic acids, polyphenols, terpenoids, alkaloids, saponins, and tannins. The presence of hydroxyl (-OH) groups in these molecules stabilizes and reduces Ag^+ to Ag^0, enabling the nucleation and development of AgNPs. Phenolic compounds and flavonoids are known for their ability to donate electrons, making them efficient reducing agents **[37].**

4.Toxicity of Silver Nanoparticles

Despite their numerous benefits in various fields, AgNPs have the potential to be harmful. The severity of toxicity of AgNPs varies based on their doses and pathways of exposure, surface coating, aggregates, form, and size; particularly, AgNPs with a smaller size are more harmful than those with a bigger size **[38].** The toxicity of silver nanoparticles occurs by the production of reactive oxygen species (ROS), which can oxidize proteins and lipids and cause mitochondrial dysfunction and ribosome destabilization. Excessive ROS formation causes oxidative stress and inflammation, which can harm cell viability. Additionally, after adhesion of AgNPs to the cell membrane, they can lead to leakage of cellular components and cell death. The interaction of AgNPs with biological membranes, such as DNA, leads to genotoxicity expressed by DNA-based damage, mutations, and inhibition of transcription and replication **[39].** Exposure to AgNPs has been linked to increased oxidative stress markers in liver tissues and increased lipid peroxidation. Oxidative damage can rupture cell membranes and cause the release of liver enzymes, indicating hepatocellular injury. Silver nanoparticles have been related to renal injury growth. Elevated amounts of urea and creatinine, both metabolic wastes produced by the kidneys, may indicate liver and renal failure. The liver converts ammonia, a toxic byproduct of protein breakdown, into urea through the urea cycle **[40].** Silver nanoparticles produce ROS, causing cellular component damage and inflammation. Oxidative stress activates stress response pathways, leading to cell death. Animals exposed to AgNPs showed elevated lipid peroxidation indicators in their spleens **[41].**

Furthermore, AgNPs can destroy the endoplasmic reticulum, which can alter the structure of liver tissue and affect organ function and metabolism **[42].** Additionally, lysosome frequency may rise as a result of AgNPs exposure, reflecting cellular disintegration or repair mechanisms in reaction to stress or injury from the nanoparticles **[43].**

5-How to reduce the side effects of Ag NPs

To limit environmental and human health risks while harnessing their positive qualities, future studies should examine the elements that influence AgNPs' toxicity and the underlying mechanisms. Understanding toxicity pathways is critical for safe use in the future **[44].** The toxicity of AgNPs has been decreased using a variety of techniques. These include applying biocompatible coatings to the surface, controlling their size and form, using biodegradable materials, choosing safe and neutral core materials, conducting extensive toxicity tests, and managing dosage and exposure [45]. Green synthesis of AgNPs by using plants is one of the approaches that has been proposed to overcome the toxicity induced by AgNPs, as plant extracts are a rich source of secondary metabolites as reducing and capping agents **[46].** Another efficient method for lowering AgNPs' toxicity is the modification of surface chemistry and properties **[47].** Altering AgNPs' surface with biocompatible materials such as polyethylene glycol (PEG), chitosan, silica, or polyvinyl alcohol. To reduce the amount of harmful Ag^+ ions released, several changes have been made **[48].** These surface modifications improve AgNPs' biocompatibility, stability, and reactivity and make them appropriate for application in biomedicine. The type of coating, particle size, and ambient conditions all affect how effective all techniques are. Aggregation and disintegration of AgNPs are inhibited by effective coating, which affects bioavailability and biological interactions **[49].** Factors controlling AgNPs' toxicity, including size, shape, dosage, and release, should be managed to lessen their severity **[50].** Additionally, administration of antioxidants mitigates the toxic effect of AgNPs, as they are capable of protecting various biological systems against oxidative damage by scavenging and neutralizing free radicals and reactive oxygen and nitrogen species and repairing new antioxidants. Exogenous nonenzymatic antioxidants, including mineral elements, vitamins, dietary supplements, and plant antioxidants, play a crucial role in supporting the human defence system and preventing oxidative stress-induced damage. Long-term usage of high doses of antioxidant supplements (vitamins A, C, and E, quercetin, curcumin, N-acetylcysteine, and β-carotene) may be applied to reduce the toxicity of AgNPs **[51].** Vitamin C, a natural antioxidant scavenger, can neutralize intracellular ROS, reducing lipid oxidation and mitochondrial permeability. It plays an important role in protecting cells from oxidative damage and decreasing the toxic impacts of AgNPs **[52].** Vitamin E supplementation had beneficial protective effects against AgNPs' toxicity and apoptotic alterations in the tongue papillae due to its ability to neutralize ROS and reduce lipid peroxidation occurring within the body **[53].** In another study, it has been proven that increased vitamin E dosages were able to restore all essential parameters and considerably shield the body from AgNPs' effect **[54].** Usage of curcumin for the synthesis of biosynthesized AgNPs elevated the antibacterial and antibiofilm activities and reduced the toxic effect of AgNPs **[55].**

5-Conclusion

In conclusion, silver nanoparticles (AgNPs) are a versatile and promising substance with numerous applications in biomedicine, agriculture, environmental pollution control, and industry due to their broad-spectrum antibacterial, anticancer, and biological properties. However, AgNPs' exposure without control is accompanied by toxic hazards such as oxidative stress, DNA damage, hepatotoxicity, nephrotoxicity, and neurotoxicity resulting from the generation of excessive ROS. Green synthesis, surface coating, dosage and size control, co-administration with antioxidants, and targeted delivery can significantly reduce the negative effects of AgNPs. These techniques reduce cytotoxicity, improve nanoparticle stability, and increase therapeutic efficacy. Researchers may fully exploit their potential while protecting human health and the environment by prioritizing biocompatibility and sustainability in the creation and utilization of silver nanoparticles.

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