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EXPLORING SILVER NANOPARTICLES: STRATEGIES OF SYNTHESIS AND ITS DIVERSE APPLICATIONS

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ABSTRACT

Recent years have observed a significant increase in the scope of research focused on nanotechnology. The field of nanotechnology is multidisciplinary and includes significant overlap in the fields of nanomaterials, nanoelectronics, and nanobiotechnology. Nanoparticles have been able to resolve several fundamental issues with conventional small molecules or biomacromolecules (such as DNA, RNA, or protein) by facilitating targeted delivery and bypassing biological barriers in some disorders. Metallic nanoparticles are frequently employed in the fields of biology and engineering. The application of metallic nanoparticles in drug delivery systems provide significant benefits, including increased stability and drug carrier half-life in circulation for required biodistribution, and passive or active targeting into the desired target site. Therapeutic applications use a variety of metal nanoparticles, including gold, titanium oxide, and selenium nanoparticles. Silver is the most economically significant metal utilized in the production of nanoparticles and nanomaterials as antibacterial, antiviral, antifungal and antioxidant. They have exceptional physicochemical properties such as optical, thermal, electrical and catalytic properties, relative to bulk materials. There are several advantages of silver nanoparticles as drug carriers due to its size and shape, increased stability of surface-bound nucleic acids, transmembrane delivery without any requirement for a severe transfection agent, and protection of the connected

tissue. Further they prevent degradation and increase the possibility of better and controlled intracellular medication administration.

KEYWORDS: Silver nanoparticles, Green chemistry approach, Antibacterial, Antiviral, cancer therapy.

INTRODUCTION

Over the past century, nanotechnology has gained significance as a field of research. Nanotechnology is a science that deals with the preparation of nanosize particles ranging from 1 to 100 nm employing diverse synthetic strategies, particle structure and size modification. The ability to regulate materials at the nanoscale due to technological advancements has enabled significant improvements in medical and healthcare therapy. The high surface-to-volume ratio of nanoparticles, along with their capacity to interact with molecules and cells and potentially impact their functions, makes them highly appealing for a variety of biomedical applications.[8] A major advantage of nanoparticles which makes them an efficient delivery system is their submicron size which permits terminal occlusion and extravasations from blood vessels. High density of therapeutic agent can often be encapsulated, dispersed or dissolved these nanoparticles, the yield of which is dependent on the method of preparation, different properties and release characteristics of the entrapped agent.[38]

Reducing adverse effects and improving the effectiveness of chemotherapy therapy can be accomplished through the use of nanoscale drug delivery devices.[12] Materials such as metal nanoparticles, metal oxide nanoparticles, carbon nano-materials and their composites have been intensively used as new antibacterial agents as a result of their small high specific surface, unique chemical and physical characteristics, and particle size.[24]

Metallic nanoparticles (MNPs) are of great interest because of its optical properties such as the capacity to adjust the optical field of surface plasmon resonance (SPR) makes them potential candidates for biomedical application. Because of their tiny size, MNPs can more easily penetrate physiological or biological membranes, which are typically impermeable to other macromolecules.[8] Among the various MNPs, silver nanoparticles (AgNPs) are increasingly used in various fields due to their unique physical and chemical features including high electrical conductivity and optical, electrical, thermal and biological properties.[28] Due to their peculiar characteristics, they have found use in a wide range of

industries and products, such as food, medical devices, diagnostics, optical sensors, pharmaceutical as drug delivery agents, antibacterial agents and also enhancement of the tumor-killing properties of anticancer drugs.[6]

A number of methods for synthesis have been developed to fulfill the requirement for AgNPs.[6] Conventional chemical and physical methods are thought to be hazardous and expensive to use. Biological methods appear to be simple, quick, safe, dependable, and environmentally friendly among the several synthetic procedures for AgNPs as they can yield well-defined size and morphology under ideal conditions for clinical studies. Ultimately, a green chemical method for AgNP synthesis appears to have a lot of potential. To evaluate the synthesized nanomaterials, many analytical methods have been used, such as dynamic light scattering (DLS), scanning electron microscopy (SEM), transmission electron microscopy (TEM), Fourier transform infrared spectroscopy (FTIR), ultraviolet visible spectroscopy (UV-vis spectroscopy), and X-ray diffractometry (XRD).[6] The biological activity of AgNPs depends on factors including surface chemistry, size, size distribution, shape, particle morphology, particle composition, coating or capping, rate of agglomeration and dissolution, reactivity of particles in solution, ion release efficiency, cell type, and type of reducing agents employed in AgNP synthesis. Furthermore, the type of reducing agent used during AgNP synthesis plays a critical role in determining the particle's cytotoxicity. The physicochemical properties of nanoparticles may affect cellular absorption, biological distribution, penetration through biological barriers, and subsequent therapeutic effects.[8] On the other hand, they can increase the bioavailability of therapeutic drugs through both systemic and local delivery. For this reason, the creation of AgNPs with regulated structures that are consistent in size, shape, and functionality is crucial for a range of biomedical uses.[24]

In this review, we present different methods of preparation of AgNPs to develop cost-effective, eco-friendly, and highly effective colloidal silver nanoparticles and primarily examined the antibacterial, antifungal, antiviral, anti-inflammatory, anti-cancer, and anti-angiogenic capabilities of AgNPs, as well as recent advancements in their bio-applications.[38] This review is also emphasizes therapeutic approaches and the challenges and limitations of silver nanoparticles (AgNPs) and their future perspectives.

Method of preparation of silver nanoparticles (agnps)

Synthesis of silver nanoparticles by physical methods

Physical methods include the use of a tube for evaporation-condensation to produce nanoparticles. AgNPs have been synthesized using conventional physical techniques like pyrolysis and spark discharge as shown in Figure 1. Physical methods have the advantages of being rapid without involving any dangerous chemicals and use of radiations as a reducing agent. The downsides of physical methods are low yield and high energy consumption, solvent contamination and lack of uniform distribution.[28]

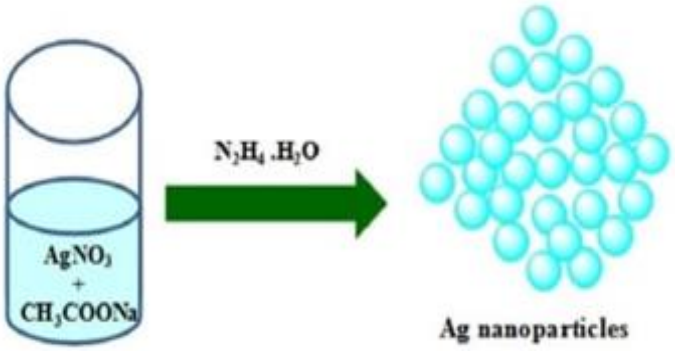

Figure 1: Synthesis of AgNPs by physical method.[5]

Synthesis of silver nanoparticles by chemical methods

Silver nanoparticles are prepared by chemical methods using organic solvents or water. Chemical methods make use of techniques such as cryochemical synthesis, laser ablation, lithography, electrochemical reduction, laser irradiation, sono-decomposition, thermal decomposition, and chemical reduction. Usually, this procedure includes three primary components: metal precursors, reducing agents, and stabilizing/capping agents. The reduction of silver salts involves preliminary nucleation followed by subsequent growth. In general, silver nanomaterials can be obtained by two methods, classified as “topdown” and “bottom-up” as shown in Figure 2. The mechanical grinding of bulk metals followed by stabilization with colloidal protective agents includes the "top-down" approach. Sono-decomposition, chemical reduction and electrochemical processes are examples of "bottom-up" techniques. The ease of use and high yield are the main benefits of chemically synthesized nanoparticles. The disadvantage, however, is that the method is extremely expensive. Additionally, toxic and hazardous chemicals like citrate, borohydride, thio-glycerol, and 2-mercaptoethanol are used in the synthesis of AgNPs.

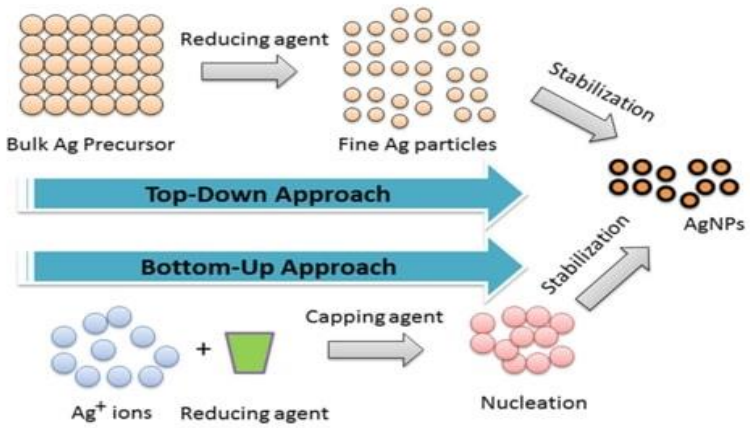

Figure 2: Synthesis of silver nanoparticles by chemical methods.[8]

In addition to these drawbacks, the produced particles are not as pure as anticipated because chemical sedimentation was discovered on their surfaces. Furthermore, an excessive number of dangerous and toxic byproducts are eliminated throughout the synthesis process.[8,10]

Synthesis of silver nanoparticles by biological methods and Green chemistry approach

The physical and chemical methods of producing silver nanoparticles are costly, time-consuming and environmentally unfriendly. Therefore, it is crucial to develop a system that is both affordable and environmentally friendly. Biological approaches fill these gaps and provide a wide range of uses in the management of health by controlling different biological processes. Utilizing sources from plants as well as bacteria, yeasts, and fungi are examples of biological production techniques. It has been stated that plant and microbe-based nanoparticle production techniques are safe, cost-effective, and environmentally less hazardous than chemical synthesis. Moreover, inorganic metallic ions from the environment can be absorbed and accumulated by microbes and plants. Microorganisms and plant materials are mainly used for biological methods for synthesis of silver nanoparticles as shown in Figure 3.

Figure 3: Green chemistry approach for synthesis of AgNPs.[36]

Biological approaches have become effective ways to address the shortcomings of chemical methods. Several studies have documented the production of AgNPs without the use of hazardous chemicals in biological processes through the use of environmentally friendly, economical, and biocompatible methods. Pseudomonas stutzeri AG259, Lactobacillus strains, Bacillus licheniformis Escherichia coli (E. coli), Brevibacterium case, fungi, Ganoderma neo-japonicum Imazeki, Fusarium oxysporum, and plant extracts, Allophylus cobbe, Artemisia princeps, and Typha angustifolia were among the bacteria used in this green chemistry approach. In addition to these, several biomolecules, such as biopolymers, starch, fibrinolytic enzyme, and amino acids were used. Three components are required for the biological synthesis of nanoparticles: (a) the solvent; (b) the reducing agent; and (c) the non-toxic substance. The availability of amino acids, proteins, or secondary metabolites involved in the synthesis process, the removal of the extra step important to prevent particle aggregation, and the use of biological molecules for the pollution-free and environmentally friendly synthesis of AgNPs are the main advantages of biological methods. The size and form of the particles determines the morphology and structure of AgNPs, which in turns determines their biological activity. To achieve control over morphology and structure, an excess of strong reducing agent such as sodium borohydride ($NaBH_4$) was used for the synthesis of monodisperse and uniform-sized silver colloids. By optimizing the synthesis processes, such as the quantity of precursors, temperature, pH, and the amount of reducing and stabilizing agents, biological approaches yield nanoparticles with more adjustable shape, size, and distribution than chemical methods.[24] [36]

Synthesis of silver nanoparticles using polymer

A. Synthesis of silver nanoparticles using aqueous polymer

Polyvinylpyrrolidone (PVP) functions well as a dispersing agent to produce colloidal silver nanoparticles that are pure, homogenous, and stable AgNPs-A were prepared by dissolving PVP in deionized water by stirring at room temperature followed by addition of $AgNO_3$. The solution was then stirred. An aqueous solution of Na_3Ct (Trisodium citrate) in deionized water was added drop wise. Following the addition of the Na_3Ct solution, the reaction mixture was agitated for an hour at room temperature before receiving an aqueous solution of DMAE (Dimethylaminoethanol) in deionized water. The silver particles were separated from the solution by centrifugation, washed twice with deionized water, and then redispersed in deionized water. The significant advantages of this method are short reaction time and production of small and relatively uniform particles with a diameter less than 10 nm. The

reaction proceeds rapidly at room temperature and organic solvents are not used. The disadvantage of this method includes use of PVP used for protecting AgNPs which affects their electrical conductivity because the resin covered on nanoparticles has to be removed to obtain the electrical conductivity. The sintering process is desired to perform at low temperature.[28]

B. Synthesis of silver nanoparticles using low molecular weight compound as effective dispersing agent

AgNPs was prepared by the similar procedure as A. However, this method replaced PVP with sodium gluconate or DL-Malic acid disodium salt as a dispersant. Because sodium gluconate is low molecular weight compound and water-soluble, the formed AgNPs can be separated easily from the mixture. Furthermore, there is no great influence on the particle size with the amount of dispersing agents, which is very different from the above method. Compared with AgNPs prepared by using PVP, AgNPs prepared by sodium gluconate are smaller and more uniform in particle size, and exhibit almost the same level of electrical conductivity when sintered at 150°C and 200°C temperature. Table 1 shows that sodium gluconate can be used as a dispersant to decrease sintering temperature instead of PVP.[28]

Table 1: Comparsion of AgNPs between this two methods.

Silver nanoparticles	Dispersing agent	Average particle size	Sintering temperature	Volume resistivity
AgNPs-A	PVP	5-40 nm	200 ^{o}C	1.6*10^{-4}
AgNPs-B	Sodium gluconate	4-10 nm	150 ^{o}C	4.6*10^{-4}

Applications of silver nanoparticles

Silver nanoparticles for antibacterial activity

For thousands of years, compounds based on silver have been used as antimicrobial agents due to their proven ability to cross biological membranes and display both local and systemic effects.[16] As a result, these compounds have been employed for a variety of medical conditions, such as digestive and oral disorders, burns, and wound healing.[37] AgNPs have the potential to overcome bacterial resistance to antibiotics and appear to be an acceptable substitute for antibiotics as antibacterial agents.[16] Thus, the development of AgNPs as antibacterial agents is vital. AgNPs appear to be prospective antibacterial agents among the various promising nanomaterials because of their high surface-to-volume ratios and crystalline surface structure as seen in Table 2.[8,16] Higher doses of these chemicals are poisonous to human cells, which is their drawback despite their remarkable therapeutic

qualities. In addition, continuous application of compounds based on silver may cause the compounds to accumulate in the organism, impairing vital organs and causing skin coloration (argyria). Therefore, very low metallic concentrations and suitable delivery mechanisms will be required for goods incorporating silver compounds and nanoparticles to overcome cytotoxicity.[37] Specifically, numerous studies examined the effects of biomaterials based on nanosilver against representative Gram-negative and Gram-positive pathogens responsible for hospital-acquired and community-transmitted infectious diseases, *E. coli* and *S. aureus,* respectively.[8,16]

Additionally, silver nanoparticle's antibacterial effectiveness was shown to be shape-dependent. Compared to irregularly shaped nanoparticles, spherical biosynthesized nanosilver (40 nm) exhibited more potent bactericidal activity against strains of *E. coli and S. aureus.*[16,20] AgNP-induced cell death processes were observed in *E. coli* by means of lowering sugar and protein leaks. Moreover, AgNPs can cause numerous pits and gaps in bacterial membranes, destroying their permeability and suggesting that AgNPs may harm the bacterial cell membrane's structure.[8,23] Strong antibacterial activity was demonstrated by the silver nanocrystalline chlorhexidine (AgCHX) complex against the tested strains of methicillin-resistant Staphylococcus aureus (MRSA) and Gram-positive/negative bacteria. When applied to E. coli, the graphene oxide (GO)-Ag nanocomposite exhibited increased antibacterial activity. When used against methicillin-resistant *S. aureus, A. baumannii, E. faecalis, and E. coli*, the GO-Ag nanocomposite demonstrated outstanding antibacterial efficacy.[8] When compared to AgNPs derived from the culture supernatant of bacteria (B-AgNPs), AgNPs derived from fungal extracts as reducing agents (F-AgNPs) demonstrated greater antibacterial activity in both *Pseudomonas aeruginosa* and *Staphylococcus aureus.*[1,25] In a variety of bacterial, fungal, and virus-mediated illnesses, nano-silver interacts with peptides and functions as nanomedicine.[8]

Table 2: Effects of AgNPs against various bacterial pathogens.

Bacterial strain	Proposed system	Effects
Bacillus subtilis (B. subtilis)	AgNPs biosynthesized by petai, fig tree	Antibacterial activity due to size related cytotoxicity and phytochemicals [16,31]
	AgNPs biosynthesized by corrainder leaf extract.	Bacterial death due to cellular uptake and Ag+ mediated DNA damage[16,30]
Streptococcus mutans (S. mutans)	AgNPs biosynthesized with citrus (Citrus limetta) peel	Antibacterial effect due to size-related membrane

	extract	permeability alteration and anti-biofilm activity[16,11]
	SiO2 -coated AgNPs biosynthesized with green tea (Camellia sinensis) extract	Strong antibacterial and anti-biofilm activity[16,32]
Pseudomonas aeruginosa (P. aeruginosa)	AgNPs biosynthesized with eyebright (Euphrasia officinalis) leaf extract	Strong antibacterial and anti-biofilm activity[16,35]
	AgNPs biosynthesized with Lysiloma acapulcensis extract	Antibacterial effect due to size-related cytotoxicity and phytochemicals[16,15]
	AgNPs biosynthesized with sesame (Sesamum indicum) oil, horse chestnut (Aesculus hippocastanum) and stonebreaker (Phyllanthus niruri) extracts	Bacterial death due to cellular uptake and size-related intracellular toxicity[16,1]

Silver nanoparticles for antiviral activity

As in the case of antibacterial characteristics, the intrinsic antiviral mechanism of silver nanoparticles is not fully understood, requiring more complex structural, molecular, and immunological research.[16] AgNPs' antiviral effects are similar to their antibacterial activity in that they are dependent on their unique affinity for vital biomolecules (viral proteins and glycoproteins, enzymes, lipids, and nucleic acids) and Ag^{+}-mediated biostatic events, which include blocking cellular attachment and invasion, stopping intracellular viral replication or propagation, and preventing the production of extracellular virions.[37,17] AgNPs may prevent cell infection and exhibit antiviral activity against type 1 human immunodeficiency virus (HIV-1)-infected cells, as reported previously. HIV-1 replication was significantly inhibited by low quantities of silver nanorods coupled with sodium 2-mercaptoethane sulfonate. HIV-1 reverse transcriptase activity was reduced by AgNPs (10-30 nm) biosynthesised with Rhizophora lamarckii extract, an important viral replication enzyme.[8,29] It was discovered that positively charged nanosilver can combine with either certain peptides (macromolecules related to HIV-10 polyproteins) or HIV-1 protease, which can divide viral polyproteins into mature and infectious particles.[18,25] The most significant decrease in viral replication was caused by competitive interactions in the early presence of AgNPs.[25] Effective treatment effects against many clinically-relevant viruses, including rotavirus, human papilloma virus (HPV), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and other enteric viruses, have been demonstrated by nanosilver-based formulations.[33]

Silver nanoparticles for cancer therapy

As an epidemic of aggressive, treatment-deficient diseases linked to an increasing number of deaths globally, cancer poses a serious threat to public health. In contemporary anticancer therapy, silver nanoparticles play a unique role.[25] They are being investigated for regulated and externally triggered drug delivery systems, as well as for the detection and diagnostics of malignant tumours.[25,7] Similar to AgNPs' antimicrobial function, nanosilver must be absorbed by cells for it to be effective against cancer cells.[16] This can happen through diffusion, phagocytosis, pinocytosis, or receptor-mediated endocytosis. AgNPs' size, shape, and surface characteristics make them suitable for incorporation by cancer cells, which causes oxidative stress and the local release of silver ions.[16] These additional events lead to the death of cancer cells through two mechanisms: (i) apoptosis, which is brought on by changes in the mitochondria and the imbalance that results between proapoptotic kinases and antiapoptotic proteins, or (ii) structural and functional impairment of cellular substructures brought on by particular interactions with ions and silver nanoparticles as shown in Table 3.[6,19]

Table 3: Cytotoxicity of AgNPs against various cancers.

Malignant cells	Effects
Breast adenocarcinoma	Apoptosis induced by DNA damage Cell death evidenced on distinctive tumor cell lines[34]
Rhabdomyosarcoma	Cell death induced by ROS generation[21]
Bladder carcinoma	Apoptosis induced by DNA damage, reduced cellular migration and proliferation, tumor regression[14]
Hepatocellular carcinoma	Cell death induced by apoptotic and necrotic mechanisms[22]
Lung adenocarcinoma	Cell death induced by ROS generation and damage of cellular organelles[26]

AgNPs may go through certain processes in biological mediums, such as surface oxidation, biomolecule conjugation or attachment, and the release of surface metallic ions, which could affect their cytotoxicity. AgNPs (20–30 nm in size) that were well-dispersed and produced using tamarind fruit shell extract caused human breast cancer cells to undergo apoptosis.[17] Due to DNA damage and mitochondrial dysfunction caused by the localised increase of ROS, a dose-dependent anticancer effect was identified. After cellular treatment with AgNPs biosynthesised from extracts from the medicinal shrub Ochradenus arabicus and marine bacilli, the same cytotoxic effects were observed.[12] Using gemcitabine-loaded PVP-stabilised nanosilver and capecitabine-loaded citrate-capped AgNPs, synergistic toxicity against breast cancer cells was reported.[29]

Silver nanoparticles as anti-fungal agents

Immunosuppressed patients are more susceptible to fungal infections and treating fungi-mediated illnesses might be difficult due to the lack of antifungal medicines.[8] AgNPs are effective anti-fungal drugs that treat a range of fungal-related disorders. AgNPs have been reported to have strong antifungal activity against *Candida albicans* and *Aspergillus niger*, with a minimum inhibitory concentration (MIC) of 25 μg/mL.[8,5] As compared to conventional antifungal treatments, AgNPs stabilised by sodium dodecyl sulphate show increased antifungal activity against *Candida albicans*.[5,11] AgNPs that were biologically produced showed antifungal effectiveness against a variety of phytopathogenic fungi, such as *Sclerotinia sclerotiorum* and *Alternaria alternata*. AgNPs inhibit not only plant and human pathogenic fungi but also indoor fungal species grown on agar media, including *Aspergillus fumigatus, Penicillium brevicompactum, Cladosporium cladosporoides, Chaetomium globosum, Stachybotrys chartarum* and *Mortierella alpine*.[8,5]

Silver nanoparticles as anti-inflammatory agents

Inflammation is initiated by tissues as an early immunological response to foreign particles, which is reinforced by increased pro-inflammatory cytokine production, immune system activation, and prostaglandin release along with chemotactic substances like complement factors, interleukin-1 (IL-1), TNF-α, and TGF-β. AgNPs have become more significant in the anti-inflammatory sector recently. Although AgNPs have a history of being antibacterial, their anti-inflammatory effects are still rather limited. It was reported that colonic inflammation was greatly reduced in rats given 40 mg/kg of nanocrystalline silver (NPI 32101) orally or 4 mg/kg intracolonically. AgNP-treated mice exhibited dose-dependent improvements in inflammation and quick recovery. AgNPs may also inhibit inflammatory processes during the initial stages of wound healing.[37,25]

Limitations of silver nanoparticles

Among the most widely employed metal nanoparticles (NPs), AgNPs have been important in a variety of pharmaceutical and biomedical fields. AgNPs' reduced size makes it easier for them to cross biological membranes and enter cells, where they cause varying degrees of toxicity based on the exacerbated microorganisms.[25] It has been found that the AgNPs' size, shape, quantity, accumulation, surface charge, and manufacturing techniques are related to their toxicity.[1,20] The bacterial species' exposure to culture media has a significant impact on the bacterial response in toxicity assessments.[23] It is primarily assumed that AgNPs and Ag^{+}

ions that are produced from AgNPs cause toxicity by inducing membrane impairment, reactive oxygen species (ROS) production, protein oxidation and denaturation, mitochondrial malfunction, DNA damage, and disruption of cell division.[36] The additional causes of cytotoxicity, according to them, were inflammation and oxidative stress brought on by the production of ROS.[12]

CONCLUSION

Silver nanoparticles (AgNPs) hold tremendous potential in various biomedical applications, including antibacterial, antiviral, antifungal, anti-inflammatory, and anticancer therapies. Silver nanoparticles (AgNPs) offer immense potential in diverse biomedical and therapeutic applications due to their unique physicochemical and biological properties. The future development of AgNPs will focus on enhancing their biocompatibility, minimizing cytotoxicity, and ensuring environmental sustainability through green synthesis techniques. Advancements in nanotechnology will allow precise control over particle size, shape, and surface functionalization, enabling targeted drug delivery and enhanced therapeutic outcomes. In healthcare, AgNP-based formulations are poised to combat multidrug-resistant infections, improve antiviral therapies, and revolutionize cancer treatment with synergistic drug-nanoparticle approaches. Moreover, the exploration of AgNPs as anti-inflammatory agents holds promise for novel wound-healing and regenerative therapies. However, addressing challenges such as toxicity, stability, and long-term environmental impact is critical to their successful integration into clinical practice. Collaborative research focusing on scalable, cost-effective synthesis methods and rigorous evaluation of their safety profiles will shape the future of applications of silver nanoparticle across medicine, agriculture, and various industries.

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