INTERNATIONAL JOURNAL ON ORANGE TECHNOLOGY

https://journals.researchparks.org/index.php/IJOT e-ISSN: 2615-8140 | p-ISSN: 2615-7071

Volume: 4 Issue: 10 | October 2022

Biomedical Potential of Silver Nano Particles: An Overview

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Annotation: During the past few years, silver nanoparticles (AgNPs) became one of the most investigated and explored nanotechnology-derived nanostructures, given the fact that nanosilver-based materials proved to have interesting, challenging, and promising characteristics suitable for various biomedical applications. Among modern biomedical potential of AgNPs, tremendous interest is oriented toward the therapeutically enhanced personalized healthcare practice. AgNPs proved to have genuine features and impressive potential for the development of novel antimicrobial agents, drug-delivery formulations, detection and diagnosis platforms, biomaterial and medical device coatings, tissue restoration and regeneration materials, complex healthcare condition strategies, and performance-enhanced therapeutic alternatives. Given the impressive biomedical-related potential applications of AgNPs, impressive efforts were undertaken on understanding the intricate mechanisms of their biological interactions and possible toxic effects. Within this review, we focused on the latest data regarding the biomedical use of AgNP-based nanostructures, including aspects related to their potential toxicity, unique physiochemical properties, and biofunctional behaviors, discussing herein the intrinsic anti-inflammatory, antibacterial, antiviral, and antifungal activities of silver-based nanostructures.

Keywords: silver, nano, particles, toxic, drug-delivery, coatings, biomedical.

Introduction

Nanotechnology is a branch of science and engineering dedicated to materials, having dimensions in the order of nanometer scale and it has been widely used for the development of more efficient technology. [1,2]Nanoparticles offer many benefits to bulk particles such as increased surface-to-volume ratio, and increased magnetic properties. In recent years, nanotechnology has been embraced by industrial sectors due to its applications in the field of electronic storage systems, biotechnology, magnetic separation and pre concentration of target analytes, targeted drug delivery, and vehicles for gene and drug delivery. Over the year's nanomaterials such as nanoparticles, nanoclusters, nanoreods, nanoshells, and nanocages have been continuously used and modified to enable their use as a diagnostic and therapeutic agent in biomedical applications. The green synthesis of silver nanoparticles (AgNPs) is a good approach to avoiding the drawbacks associated with by-products formed in chemical synthesis. The present investigation was intended to synthesize AgNPs using gallnut extract as reducing agent and evaluate their potential biomedical applications. The ultraviolet-visible spectroscopy provided a preliminary indication of AgNP synthesis. Changing the pH of the reaction mixture from pH 3 to 10 revealed a significant impact of pH on the synthesis of AgNPs with the wavelength shift from red to blue. [3,4]Transmission electron microscope characterizations showed that the synthesized AgNPs at pH 3-10 were spherical with average sizes of 51, 27, 18, 30, 10, 8, 5 and 4nm. The synthesized AgNPs were further characterized by different techniques such as Fourier transform infrared spectroscopy, scanning electron microscopy, energy-dispersive X-ray spectrometry, X-ray photoelectron spectroscopy and powder X-ray diffraction. The AgNPs biosynthesized using gallnut extract showed higher antioxidant activity (81%) than AgNPs chemically synthesized using sodium borohydride (56%), indicating that AgNP-capping molecules such as tannic acid play an important role in antioxidant function. The biosynthesized AgNPs showed potent anticancer activity on four cervical cancer cell lines, namely, ME180, SiHa, HeLa and CaSki.[5,6]

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At present, the nanosized particles of less than 100 nm are the main focus of researchers which provide excellent results comparing with larger-sized particles. Among the various metal nanoparticles, the silver nanoparticles (AgNPs) have unique properties such as optical, catalytic, and electromagnetic properties which is dependent on the size, shape, and surface plasmon resonance of the AgNPs. It has been reported that the AgNPs have excellent biomedical applications by generating reactive oxygen species and regulating various signaling pathways. With this background, this chapter presents the overview about the method for synthesis of AgNPs and its mechanism of application in various field such as antimicrobial, antimalarial, antibiofilm, antioxidant, and anticancer activity.

Silver nanoparticles have high conductivity, powerful signal capacity, and biocompatibility. Due to the properties, they have an important role in electrochemical sensor platforms. Over the last 20 years scientists put a huge effort for design the novel methods for biomedical applications with using the silver NPs and their composites[7,8]

Silver nanoparticles are also effective against various fungi, virii, and algae. For example, silver nanoparticles restrain the growth of *A. niger* when stabilized with hyperbranched polymers. Further, the Myramistin stabilized silver particles with different sizes also showed toxic effects for other bacteria such as *S. cerevisiae*, *T. mentagrophytes*, and *C. albanicans*. The silver nanoparticles have also been used to disrupt the cell membrane structure that restrains the reproduction process, thus showing the antifungal activity against *C. albanicans*

Antiviral effects of silver nanoparticles are also explored by various research groups. For example, the replications properties of hepatitis B virus can be inhibited by silver nanoparticles of 10 nm size. Further, the PVP-coated silver nanoparticles (sizes 1–10 nm) restrains the attachment of the HIV-1 virus to host cells. The similar PVP-coated silver nanoparticles were found to reduce the respiratory syncytial virus infection by 44% in another study. Silver nanoparticles of different sizes (1–70 nm) lead to enhance virus removal when impregnated to polysulfone ultrafiltration membranes . This particular ability of silver nanoparticles helps to improve water disinfection by low-pressure membrane filtration.[9,10]

The properties of silver nanoparticles are broadening its usage in drugs, medicinal devices, and medicines. The compounds in silver ion (hygienic compounds) are proven to have the ability of curing health related issues. Over time, the need to use silver ions has expended the application of silver in the field of medicine and analytical purposes. The emerging nanobiotechnology with silver ion is utilized. Silver nanoparticle has shown its vast functionalization within everyday consumer products from home to medicinal appliances. The advanced silver nanobiotechnology has proven that silver nanoparticles are used in biosensor and imaging of nanomaterials and objects due to its unique optical scattering and plasmon-resonance properties

Discussion

Silver NPs exhibit antimicrobial activity compared to other metals due to their extremely large surface area and better contact with the microorganisms . NPs of silver attached to bacterial cell membrane can penetrate the bacteria. The cell membrane contains sulfur-containing proteins. The silver NPs interact with these proteins as well as with phosphorus containing compounds like DNA. They also enter the bacterial cell and attack the respiratory chain leading to hindered cell division and cell death . Resistance to microorganisms is necessary for wound healing, which otherwise could result in infection and delayed healing. Chitosan scaffolds with silver NPs could be used to treat patients with deep burns and wounds using silver NPs since they have antibacterial activity against *S. aureus* and *E. coli*, as well as good blood clotting ability .

Silver nanoparticles (AgNPs) possesses a broad spectrum of antimicrobial activity. They provide a safer alternative to conventional antimicrobial agents in the form of a topical antimicrobial formulation. Antimicrobial activity depends on the surface area and size of silver nanoparticles. AgNPs with larger surface area–to–volume

https://journals.researchparks.org/index.php/IJOT e-ISSN: 2615-8140 | p-ISSN: 2615-7071
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ratios exhibit greater antibacterial efficiency. Nanosilver has shown antinflammatory and healing properties and can repair skin tissue.

Tiny gold and silver nanoparticles are used in certain day and night creams to give the skin a fresher appearance.[11,12] Nanosilver is used in toothpastes, soaps, deodorants, wet wipes, lip products, as well as face and body foams. Skin cleanser soap containing nanosilver exhibit antibacterial and antifungal properties and was found effective in treating acne and sun-damaged skin. AgNPs can also be used to kill yeasts such as *Candida glabrata* and *Candida albicans*, which cause infections in the mouth. Therefore, silver nanoparticles are being used in veterinary, pharmaceutical, and biological products. The nanosilver skin gel, which contains 30 times less silver than silver sulfadiazine, is a better choice for the skin of burn patients to treat infections.

Nanotechnology is a rapidly growing field due to its unique functionality and a wide range of applications. Nanomedicine explores the possibilities of applying the knowledge and tools of nanotechnology for the prevention, treatment, diagnosis and control of disease. In this regard, silver nanoparticles with diameters ranging from 1 to 100 nm are considered most important due to their unique properties, ability to form diverse nanostructures, their extraordinary range of bactericidal and anticancer properties, wound healing and other therapeutic abilities and their cost-effectiveness in production. The current paper reviews various types of physical, chemical and biological methods used in the production of silver nanoparticles. It also describes approaches employing silver nanoparticles as antimicrobial and antibiofilm agents, as antitumour agents, in dentistry and dental implants, as promoters of bone healing, in cardiovascular implants and as promoters of wound healing. The paper also explores the mechanism of action, synthesis methods and morphological characterisation of silver nanoparticles to examine their role in medical treatments and disease management.[13,14]

Results

Silver nanoparticles (AgNPs) include amphiphilic hyperbranched macromolecules, making them an effective antimicrobial surface coating agent. These nanoparticles can even be modified to increase efficiency, enabling their use in various fields, particularly healthcare. Nanoparticles synthesized through green nanotechnology, however, are an area attracting growing interest. Green nanotechnology aims to eliminate or reduce the pollution caused by conventional methods used for their synthesis. [15,16] Furthermore, environmental impacts in the product chain are estimated and mitigated, resulting in this approach becoming highly favorable for a wide range of biomedical and biotechnological applications. The production of AgNPs through green nanotechnology is a simple, cost-effective, high-yield synthesis and an eco-friendly procedure. It was introduced to the synthesis of nanoparticles without using toxic chemicals and avoids the production of undesirable toxic products. A recent study illustrates the production of AgNPs through green technology and its coating by a quaternary ammonium salt, benzalkonium chloride (BAC), with synthesized AgNPs characterized by TEM and Dynamic Light Scattering (DLS). Antimicrobial screening of AgNPs and BAC-coated AgNPs was performed against a range of gram-positive (gm+) bacteria and gram-negative (gm−) bacteria by colony-forming units, β-glucosidase activity, and a zone of inhibition.

AgNPs were synthesized with slight modifications. Firstly, fresh neem leaves were washed using double-distilled water and then air-dried at room temperature. Secondly, 50 gm neem leaves were soaked in 250 mL double-distilled water and boiled for 1 hour. The obtained extract was cooled down and filtered using Whatman filter paper No. 1.[17,18]

Then, *Azadirachta indica* leaf extract and 1 mM $AgNO_3$ were mixed in a 1:10 ratio. The solution was placed on a magnetic stirrer in an ice bath for 30 minutes at room temperature in a dark chamber to inhibit the photo-activation of silver nitrate. Ag^+ reduced to Ag^0 with the solution turning brown, implying the formation of AgNPs. Benzalkonium chloride (0.1% w/v) was coated on the surface of the resulting AgNPs in an Erlenmeyer glass at room temperature in a dark chamber on a magnetic stirrer. The morphology, dimensions, and size of AgNPs were obtained. TEM analysis samples were prepared through drop-coating of diluted NP solution on carbon-coated copper grids at standard atmospheric conditions before characterizing AgNPs. The bactericidal effect of AgNPs against four different clinical pathogenic bacteria—*Escherichia coli*, *Pseudomonas aeruginosa*, *Bacillus subtilis*, and *Streptococcus pneumoniae*—was analyzed. Through ultrasonication, AgNPs were dispersed in pre-sterilized millipore water. Desired concentrations (0.0625, 0.1250, 0.250, 0.500, and 1.0 mM) for bacterial effects analysis were formulated with the aqueous dispersions of AgNPs[19,20]

Figure 1 displays the TEM image of AgNPs, representing the fineness of the particles with a mean diameter of 30 nm. Dynamic light scattering was employed to identify the size distribution profile of AgNPs. From Figure 2, it can be seen that the average mean size of AgNPs was 30 nm.

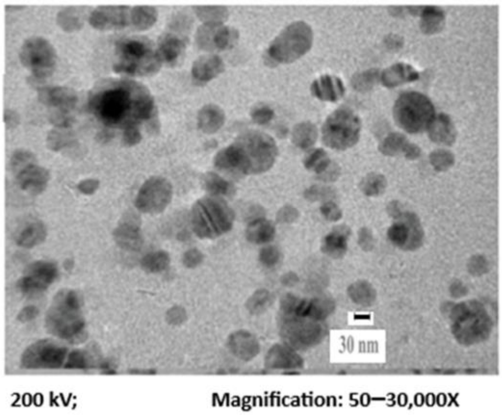

Figure 1. TEM of the synthesized AgNPs. Image Credit: Ansari & Alshanberi, 2021

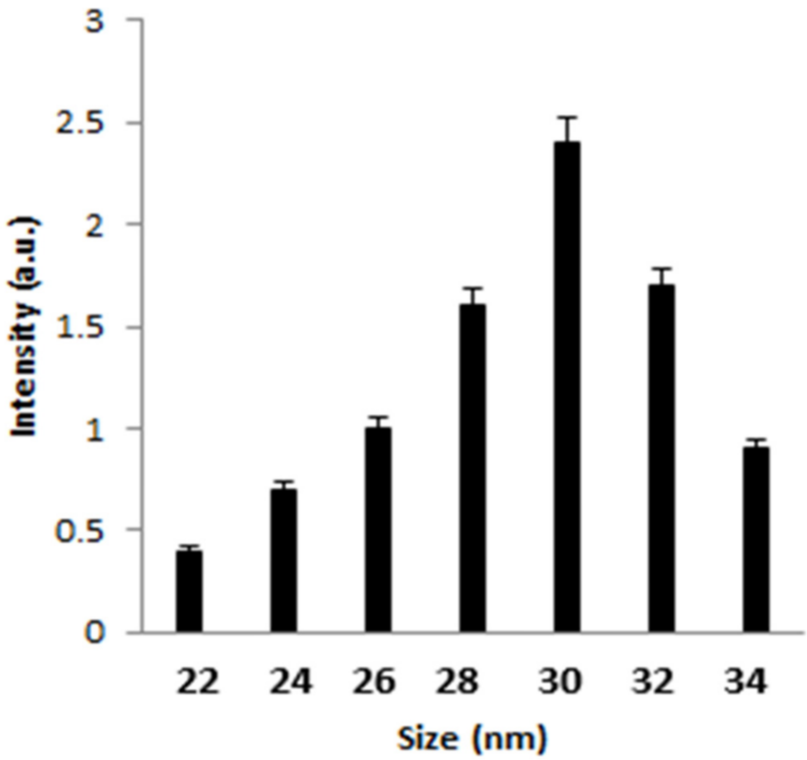

Figure 2. DLS of the synthesized AgNPs. Image Credit: Ansari & Alshanberi, 2021

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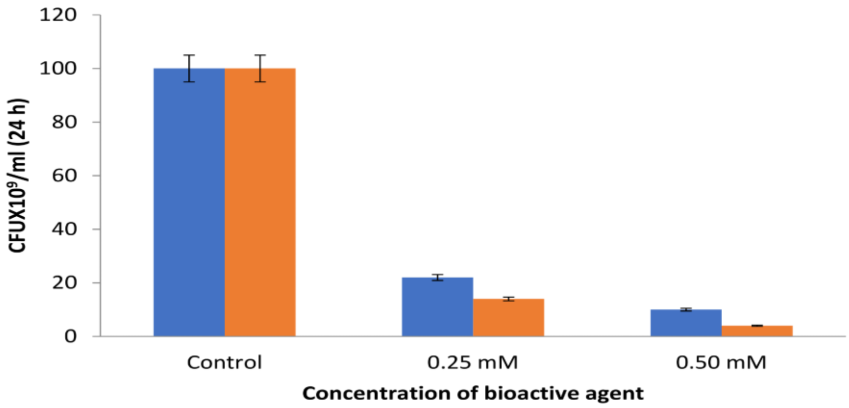
Antibacterial assays found that increased concentration of AgNPs led to a considerable reduction in CFU numbers. For instance, at 0.25 mM AgNPs, 22 × 109 CFU were formed. However, for benzalkonium chloride-coated AgNPs, this figure was reduced to 14 × 109 CFU under similar experimental conditions (see Figure 3).[21,22]



- A Green Method for Silver Nanoparticle Synthesis Using H. isora
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- Significant Insights on Optimizing Antimicrobial Ability of Silver

Figure 3. CFU by the synthesized AgNPs (blue) and BAC-coated AgNPs (orange). Image Credit: Ansari & Alshanberi, 2021

β-glucosidase activity was observed under different AgNPs concentrations. Researchers found a substantial increase in the enzymatic activity of β-glucosidase beyond 0.0625 mM and up to 0.5 mM concentration of AgNPs and BAC–AgNPs (see Figure 4)[23,24]

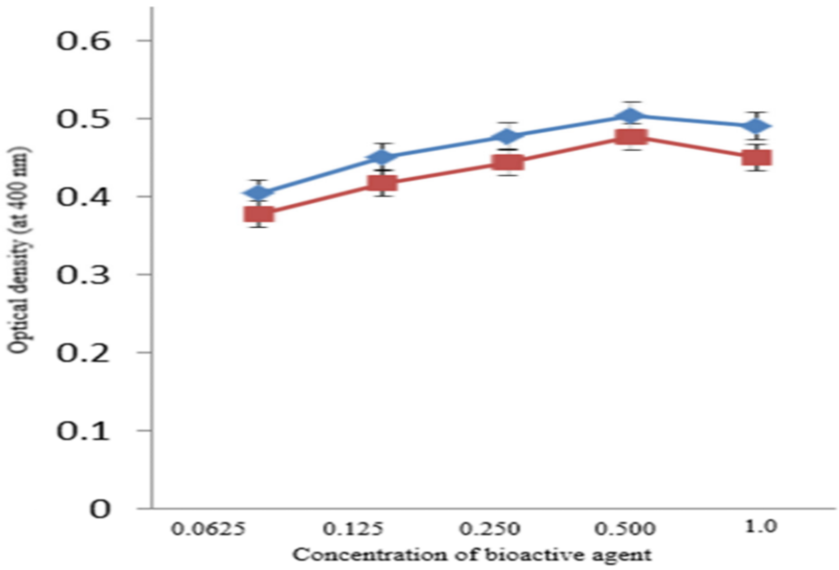

Figure 4. Activity of β-glucosidase with the synthesized AgNPs (blue) and BAC-coated AgNPs (red). Image Credit: Ansari & Alshanberi, 2021

No additional changes in activity were observed beyond this concentration. Table 1 indicates the zone of inhibition of AgNPs and BAC–AgNPs against *E. coli*, *P. aeruginosa*, *B. subtilis*, and *S. pneumoniae* at 0.25 and 0.50 mM concentration of these bioactive agents, respectively.[25,26]

Table 1. Zone of inhibition (diameter, cm) of antibacterial test of AgNPs and Benzalkonium chloride (BAC)-coated AgNPs. Source: Ansari & Alshanberi, 2021

Concentration (mM)	*E. coli*		*B. subtilis*		*P. aeruginosa*		*S. pneumonia*	
	AgNPs	BAC–AgNPs	AgNPs	BAC–AgNPs	AgNPs	BAC–AgNPs	AgNPs	BAC–AgNPs
0.25	3.45 ± 0.85	3.56 ± 0.54	4.28 ± 0.39	4.40 ± 0.58	3.36 ± 1.2	3.47 ± 1.34	3.44 ± 0.96	3.62 ± 0.68
0.50	4.28 ± 0.73	4.40 ± 0.68	4.36 ± 0.98	4.44 ± 0.77	4.28 ± 0.98	4.37 ± 1.55	3.78 ± 0.27	3.91 ± 0.37

An increase in the concentration of these bioactive agents to 0.5 mM led to a significant decrease in the ZOI for BAC–AgNPs than AgNPs. *E. coli* ZOI was found to be 4.28 and 4.40 cm, while *S. pneumoniae* ZOI was 3.78 and 3.91 cm for AgNPs and BAC–AgNPs, respectively under similar incubation conditions. In this study, the synthesis of AgNPs using neem leaf meets all the conditions of a 100% green chemical process.[27,28] This includes an environmentally friendly, fast, and green approach that is economical and does not use reducing agents or external stabilizers. Researchers found that the use of benzalkonium chloride as a quaternary ammonium compound led to major improvements in the antibacterial activity of the silver nanoparticles produced from the neem leaves. Superior antimicrobial efficacy was achieved against bacterial strains like *E. coli*, *P. aeruginosa*, *B. subtilis*, and *S. pneumoniae*. The persistent antibacterial activity of such nanoparticles against other microorganisms may be studied to extend their use to biomedical, environmental, and biotechnological sectors. This study will also have major implications for the development of other nanoparticles by clean and green technologies. [29,30]

Conclusions

The biosynthesized silver nanoparticles (b-AgNPs) exhibit multifunctional activities (4-in-1 system) such as biocompatibility, anti-cancer & anti-bacterial activity and fluorescence imaging. To the best of our knowledge, [31,32]there is not a single report of bio-synthesized silver nanoparticles (b-AgNPs) that demonstrates the versatile applications (4-in-1 system) towards various biomedical applications. Additionally, a plausible mechanistic approach has been investigated for anti-bacterial & anti-cancer activity of b-AgNPs. The results together will provide the basic foundation for the development of versatile applications of biosynthesized AgNPs towards biomedical technology in near future.[33]

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