

SILVER NANOPARTICLES, THEIR SYNTHESIS AND POSSIBLE HEALTH BENEFITS

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REVIEW

Abstract

Nanomaterials, especially nanoparticles (NPs), represent some of the most intensively studied pharmaceutical formulations in recent decades, due to their physicochemical properties and therapeutic versatility. Compared to conventional pharmaceutical forms, nanoparticles offer multiple advantages: simple synthesis methods, possibility of transposition on an industrial scale, protection of active substances against enzymatic and chemical degradation, increased stability and easy drying by freeze-drying. These colloidal systems also allow to obtain optimized pharmacokinetic profiles, with controlled and targeted release of the active substance (cytostatics, antibiotics, antivirals, peptides or proteins), reduction of adverse reactions and increase bioavailability. In this context, silver nanoparticles (AgNPs) have attracted particular interest, being obtained by ecological methods using secondary metabolites from plant extracts.

The future applicability of AgNPs is aimed at the development of nonsystems for the targeted administration of antineoplastic, antimicrobial and antiviral agents, as well as their implementation in personalized therapies with a superior safety profile. By integrating green pharmacy principles and optimizing surface characteristics, AgNPs have the potential to become essential therapeutic platforms in the nanomedicine of the future.

Keywords: nanoparticles, silver nanoparticles, secondary metabolites, green pharmacy
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INTRODUCTION

Throughout history, silver ions and colloids have proven their effectiveness in water conservation, in the treatment of wounds, gum and ophthalmic diseases, but also in the treatment of burns (Popovici & Lupuleasa, 2009)

With the development of nanotechnology and taking into account the unique properties of silver ions and colloids, silver nanoparticles (AgNPs) have been developed, which have proven to be extremely promising for the food and pharmaceutical industries. They offer multiple advantages, such as high antimicrobial and antiviral activity, chemical and colloidal stability, increased biocompatibility, the

possibility of controlled release of active substances and reduction of adverse effects associated with conventional therapy.

The synthesis of AgNPs using plant extracts is an environmentally friendly and sustainable method, avoiding toxic chemical reagents and the generation of dangerous reaction products. Secondary metabolites present in plants have the ability to act simultaneously as both reducing agents and stabilizers, conferring morphological uniformity, colloidal stability, and enhanced biocompatibility of AgNPs (Ijeoma et al., 2024; Popovici & Lupuleasa, 2009) Natural functional groups on the surface of AgNPs can contribute to the stabilization of the particles, covering the

surface of the particles with chemical groups which can ensure their controlled delivery in therapeutic systems, with minimal risk of toxicity and reduced production costs (Edwards-Jones, 2009)

AgNPs have good antibacterial activity, which is why they have become very important for some branches of industry (food, pharmaceutical). AgNPs are used in health products, in women's hygiene products, in paints, cosmetics, medical devices, sunscreens, biosensors, clothing, and electronics (Singhal et al., 2011). However, due to their strong antioxidant activity, AgNPs release silver ions, which can give more negative effects on biological systems by inducing cytotoxicity, genotoxicity, immunological responses, and even cell death (Beer et al., 2012; Chen & Schluesener, 2008; Chernousova & Epple, 2013) After exposure they can easily cross the brain barrier through the transcytosis of capillary endothelial cells or reach other critical areas or tissues (Cho et al., 2013) The use of products containing colloidal silver may have toxic potential to human health (Tang et al., 2010) Increased exposure to AgNPs can cause the accumulation of silver ions in the environment, with reported values of 22.7 ppm in soil and 0.76 ppm in water (Aueviriyavit et al., 2014)

Despite the potential adverse effects, AgNPs in the food and pharmaceutical industry show limited use, and each application requires safety assessments and regulatory compliance (Ze et al., 2013)

Recent studies suggest that the toxicity of AgNPs depends on factors such as particle size, shape, surface charge, and concentration of silver ions released, which underscores the importance of controlled nanosystem design for safe and effective pharmacological applications (Jaswal & Gupta, 2023)

I. METHODS FOR OBTAINING SILVER NANOPARTICLES

1.1. CHEMICAL METHODS

The process occurs when a complex of silver ions (AgNO_3 or AgClO_4) is converted into colloidal silver in the presence of a reducing agent. When the dissolved silver metal ions reach a sufficiently high concentration, they aggregate, forming a stable surface. When the ion group becomes energetically stable, it remains in the system and grows, fixing atomic silver in the solution. Finally, the concentration of atomic silver in

the solution decreases enough to prevent the formation of other atomic aggregates. The metallic silver remaining in the solution is absorbed by diffusion by the growing nanoparticles. In the solution there are molecules that diffuse and attach to the surface of the formed nanoparticles, stabilizing their surface energy and thus blocking the attachment of other silver ions. Finally, these molecules stop the growth of particulate matter, the most commonly used being trisodium citrate and polyvinylpyrrolidone (ANMDM, 2020)

1.2. BIOLOGICAL METHODS

Biological methods of synthesis of AgNPs do not use synthesis reducing agents, but microorganisms or plants, being considered ecological methods. Fungi and bacteria are easy to manipulate and can be genetically modified relatively easily.

The use of plant extracts has proven to be advantageous because it does not involve an expensive method, does not use toxic reagents and is faster compared to methods that use bacteria and fungi. Using plant extracts, AgNPs of different sizes are obtained (ANMDM, 2020)

1.3. PHYSICAL METHODS

The evaporation-condensation method and laser ablation are two of the most well-known physical methods of synthesis of AgNPs. Compared to chemical methods, nanoparticles obtained by physical methods are homogeneously distributed and there are no residual solvents. However, slow synthesis and high energy consumption are important disadvantages of these methods (ANMDM, 2020)

II. MECHANISMS OF ANTIBACTERIAL ACTIVITY OF SILVER NANOPARTICLES

AgNPs can interact with the bacterial cell and accumulate on the surface of the cell, producing structural changes in the bacterial wall, increasing its permeability. The size of AgNPs, their shape and concentration influence the adhesion process to the bacterial wall (Franci et al., 2015) According to a review published by Tikam Chand Dakal et al., the most important mechanisms by which AgNp exerts its antimicrobial action are:

- Positively charged AgNPs adhere to the surface of the negatively charged cell wall of bacteria, resulting in the morphological alteration of the bacterial cell and the rupture of the bacterial wall, followed by the loss of cytoplasm and then by cell apoptosis.

- AgNPs can also penetrate the interior of the cell and the nucleus, destabilizing the intracellular structures: mitochondrial dysfunction, destabilization and denaturation of proteins, alteration of ribosomes, interaction with DNA result.
- AgNPs produce cytotoxicity and oxidative stress. The production of reactive oxygen species (SOR) by AgNPs explains their antibacterial, antifungal and antiviral actions. SOR oxidizes proteins and lipids, as well as the nitrogenous bases of DNA.
- Modulation of cellular signaling pathways. Phosphorylation of protein substrates underlies DNA replication and bacterial metabolism. AgNPs intervene by dephosphorylating tyrosine (Tyr) residues of important bacterial peptide substrates, thereby inhibiting bacterial growth (Dakal et al., 2016)

The comparison of the stand-alone antibacterial action of synthesized AgNPs by reducing AgNO₃ using sodium carboxymethylcellulose aqueous solution, with the synergistic effect (AgNPs + broad-spectrum antibiotic) on the pathogenic bacterial species tested, reveals a more intense inhibition of bacterial growth in the case of the use of a broad-spectrum antibiotic together with the synthesized nanoparticles (Prema et al., 2017)

III. HEALTH BENEFITS OF AgNPs

III.1. ANTIOXIDANT ACTIVITY

Abdel-Aziz M.S. et al., prepared AgNPs from the leaf extract of *Chenopodium murale* L. Following the analyses it was observed that the total polyphenol content of AgNPs was higher (80.83 ± 0.15 mg GAE/g plant product) compared to that of the aqueous extract (74.9 ± 0.23 mg GAE/g plant product), the flavonoid content was lower in the case of AgNPs (12.77 ± 0.07 mg QE/g plant product) compared to that of plant extract (14.1 ± 0.12 mg QE/g plant product). For the determination of antioxidant activity by the DPPH method, for two different concentrations. An increase in the percentage of inhibition was observed from 12.63 ± 0.15% (5 mg/L) to 59.43 ± 0.15% (20 mg/L) for the aqueous extract and from 13.27 ± 0.12 % (5 mg/L) to 65.43 ± 0.18 % (20 mg/L) for AgNPs, demonstrating that AgNPs have a higher antioxidant activity than the aqueous extract itself (Abdel-Aziz et al., 2014)

III.2. ANTICANCER ACTIVITY

Kalaiarasi, K. et al., showed that AgNPs obtained from the species *Bambusa*

arundinacea (L.) Voss and *Bambusa nutans* Wall. e.g. Munro could be used as potential anticancer preparations, due to the polyphenols and anthocyanins present in the two extracts, compounds that have antitumor activity, being toxic to human prostate cancer cells, but which have no effect on normal cells. The cytotoxic effect was determined by identifying the formation of reactive oxygen species, such as superoxide radical, hydrogen peroxide and hydroxyl radical, which cause damage to cellular components (lipids, DNA, proteins) and ultimately lead to death (Kalaiarasi et al., 2015)

II.3. ANTIMICROBIAL ACTIVITY

Following a study on AgNPs obtained from the dried root extract of *Abelia grandiflora* (Rovelli ex André) Rehder (Sharma et al., 2014) their antimicrobial effect on both Gram (+) and Gram (-) bacteria was highlighted. The best action was performed by the 0.02 mmol/mL colloid solution of AgNPs against *E. coli* and *S. aureus* (27 mm), followed by *B. megaterium* (26 mm), *B. subtilis* (24 mm), and the lowest action on *K. pneumonia* and *P. vulgaris* (23 mm), which demonstrates that the biosynthesized AgNPs have a valuable antibacterial effect against Gram (+) versus Gram (-) bacteria. Sondi I. and Salopek-Sondi B. (Sondi & Salopek-Sondi, 2004) suggested that the antibacterial effects of AgNPs on Gram (-) bacteria depend on the concentration of AgNPs, which act on the cell wall of bacteria, by gathering on their surface, disrupting their permeability and respiration and thus destroying them. Mohanta Y.K. et al., showed that AgNPs synthesized from the leaves of *Cassia fistula* L. shows antimicrobial activity on *Bacillus subtilis* (16.6 ± 1.4), *Staphylococcus aureus* (18.6 ± 1.1), *Candida kruseii* (23.3 ± 1.1) and *Trichophyton mentagrophytes* (21.6 ± 1.1) (Mohanta et al., 2016)

CONCLUSIONS

According to the data presented, we believe that silver nanoparticles, obtained from plant extracts, represent an innovative and sustainable alternative to conventional chemical synthesis, offering advantages related to cost, safety and ecological compatibility. Recent studies confirm their antimicrobial, antioxidant and anticancer potential, supporting the possibility of integrating AgNPs in the pharmaceutical and cosmetic fields. However, in order to become safe and effective therapeutic solutions, it is necessary to

optimize the synthesis conditions, correlated with in-depth biocompatibility and toxicity assessments.

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