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Review Article

Silver nanoparticles: A review of the production techniques to reduce toxicological risk in ecosystems and in human health

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Abstract

Silver nanoparticles (AgNPs) are being proposed as a new pharmaceutical product because of their antimicrobial properties and eco-toxicological profile. AgNPs can be synthesized by physical or chemical methods. However, green synthesis, the so-called biosynthesis in which organic or biological materials are used, is becoming even more popular as it is economically sustainable and non-toxic. The latter plays a significant role in loading important bioactives during the synthesis. This review discusses the state of the art of using AgNPs as antimicrobial agents and their green synthesis and environmental impact. It focuses on works published since 2019 using new molecules, e.g., plant extracts, acids, bacteria and fungi, as innovative pharmaceuticals against antimicrobial resistance. A bibliometric map of works published since 2022 indexed to the Scopus core collection is also discussed, highlighting the main research areas of this innovative topic. Their physicochemical properties strongly influence the use of AgNPs and impact ecosystems and human health. Several approaches are described for their synthesis, highlighting that the toxicological risk can be mitigated by adopting green-based methodologies.

Keywords: Silver nanoparticles; green synthesis; antimicrobial resistance; plant extracts; bibliometric map

Introduction

Nobel metals (e.g., gold and silver) are known for their resistance against corrosive and oxidative processes. They have also been proposed as materials for the synthesis of metal nanoparticles using either top-down processes (e.g., milling, lithography, laser) or bottom-up processes (e.g., chemical synthesis), which usually require the use of organic solvents [1]. The use of metal nanoparticles is extensive in diverse industrial sectors, including the pharmaceutical industry, especially in developing drug delivery systems [2].

Among commonly available metals with antimicrobial properties, silver has been known since ancient times to control infections [3]. It can be obtained by different methods. Figure 1 summarizes the commonly available processes used to produce AgNPs.

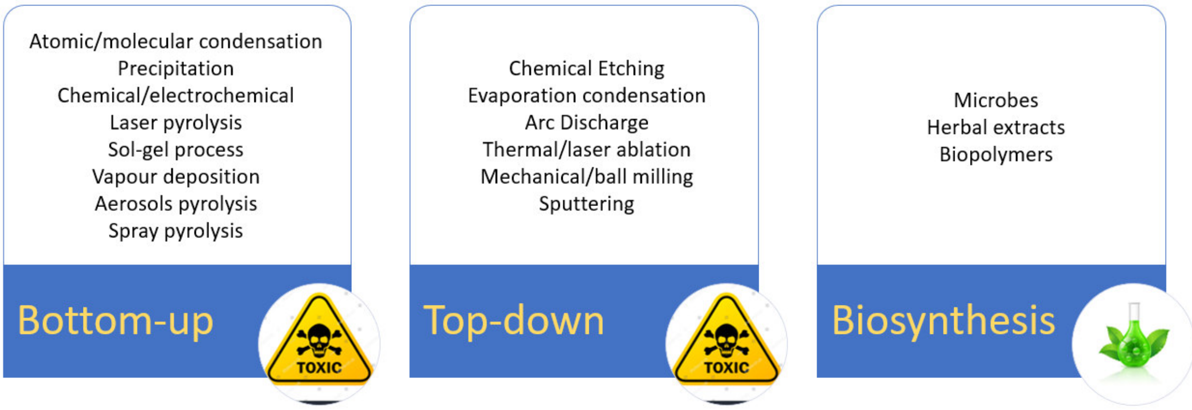

Figure 1. Commonly available methods used in the production of silver nanoparticles.

Bottom-up methods are based on molecular recognition or self-assembly, which means the combination of atoms or molecules, often needing an organic solvent, which could be environmentally friendlier. The results are influenced by temperature, pH, concentration, and covalent and ionic bonds. With the bottom-up approach, it is possible to obtain nanoparticles with better surface structure and smaller particle size compared to top-down approaches. The main techniques are colloidal precipitation, sol-gel synthesis and atomic condensation [4-6].

Top-down methods are more expensive and mainly based on grinding materials, which means that macroscopic structures are reduced to nanoparticles. This approach uses many thermal, chemical, and physical techniques to produce the energy needed to form nanoparticles. Mechanical milling can be used, including vibratory, planetary, and friction mills. Laser ablation, nanolithography, and sputtering can also downsize microparticles and turn them into nanoparticles. However, the top-down method is more used on laboratory scales [6-8].

In recent years, the use of biological methods in producing AgNPs has increased, mainly because it is an eco-friendlier method, not requiring expensive, toxic, or harmful materials, resulting in nanoparticles with good physicochemical characteristics, shapes, and sizes. Bacteria, fungi, algae, plants, and yeast are used in the green method.

To document the interest and relevance of "AgNPs" in scientific research, a quick search in the Scopus database on the 23rd of February 2024, combining "AgNPs" and "ecotoxicology" or "ecotoxicity" as keywords, resulting in a total of 25,002 documents indexed in the Scopus database since ever, out of which 3173 are published in the subject area of Pharmacology, Toxicology and Pharmaceutics. Refining our search to published works only in 2023 and 2024, a total of 288 manuscripts were retrieved. VOSviewer software was used for data analysis of these 288 papers, generating the bibliometric map shown in Figure 2 [9]. The outputs were six clusters, covering plant extracts and bioactivities, drug delivery, personalized medicine, antibacterial activity, animal experimentation and in vitro cell line studies as the major topics.

With the advance of antibiotic-resistant strains, silver has been proposed in different formulations for antibacterial treatments, thanks to its low trend of developing resistance [10]. This bactericidal activity is related to the size of the silver particles, with higher activity at smaller diameters, as the nanometric size allows them to cross the microbial membrane and cause intracellular damage.

AgNPs have been receiving attention for their diverse characteristics, which, in addition to antimicrobial properties [11-13], these particles promote wound healing [14,15]. More than half of the products available for wound healing are AgNP-based products using biomaterials (e.g., cotton, gauze, cellulose, alginate) in which these particles are incorporated [16]. Silver has been recognized for its active role in wound healing, particularly in preventing infection. When formulated as nanoparticles, AgNPs have the ability to promote the transformation of fibroblasts into myofibroblasts [17,18], and in this way, the particles promote proliferation and mobilization of keratinocytes [19,20].

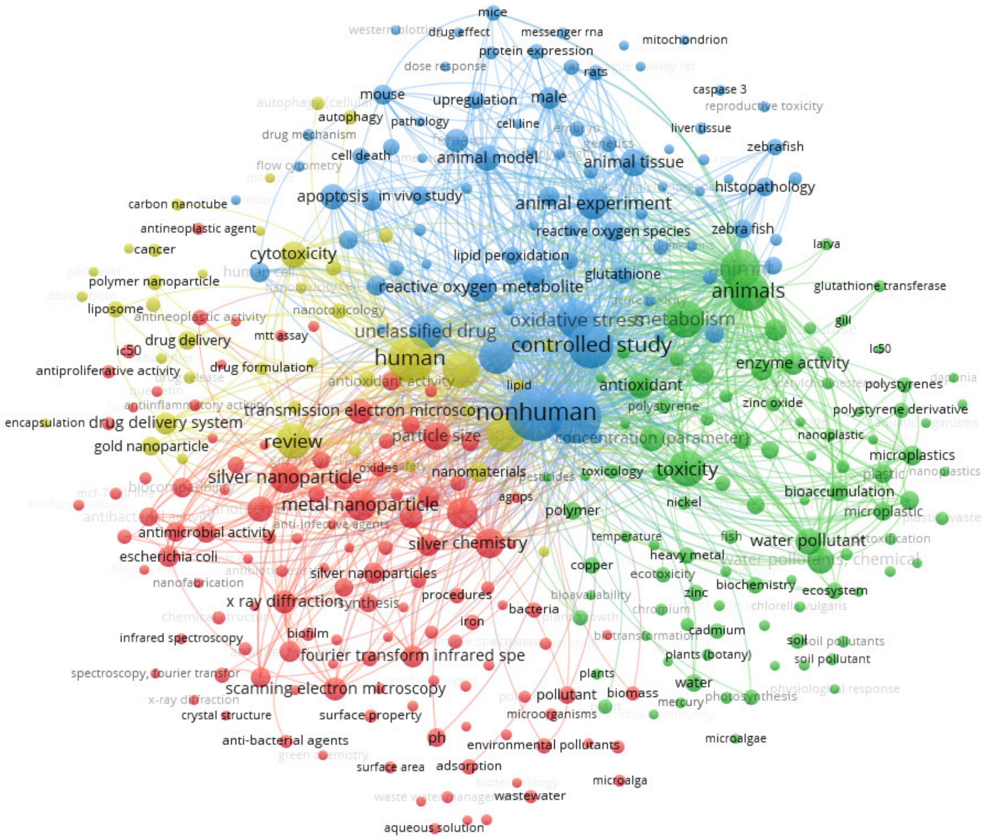

Figure 2. Bibliometric map obtained by VOSviewer software version 1.6.16 (https://www.vosviewer.com) [9], using "AgNPs" AND "ecotoxicology" OR "eco-toxicity" as keywords, recorded from Scopus database, limiting the search for publications in 2023 and 2024 in the subject area of Pharmacology, Toxicology and Pharmaceutics (search on 23rd February 2024).

The mechanism behind AgNPs' antibacterial action still needs to be fully disclosed. Various modes of action have been proposed, including the generation of reactive oxygen species (ROS), direct link to the cell membrane, and disrupting the membrane integrity, which increases cell permeability, interaction with proteins and disruption of their function, besides interfering with DNA replication causing DNA damage [21].

ROS are naturally produced by cells during normal oxygen metabolism and are typically eliminated by the cell's antioxidant defenses. However, when the production of ROS exceeds the cell's capacity to scavenge them, oxidative stress can occur due to the accumulation of excess ROS. These free radicals can attack cell membranes, react with lipids, proteins, and nucleic acids, and disrupt normal cellular processes [22].

While the mode of action of AgNPs is commonly described as governed by both Ag+ and AgNP-dependent mechanisms, van der Zende et al. (2016) [23] aimed to evaluate whether epithelial cells derived from different tissues would depict similar outcomes. The authors described distinct responses of Caco-2 and MCF-7 cell lines, with the former showing size-independent responses but a higher sensitivity and slower gene expression kinetics.

Męczyńska-Wielgosz et al. (2020) [24] evaluated the susceptibility of HepG2 cell lines to AgNPs when combined with other types of metallic nanoparticles (i.e., with AuNPs, CdTe quantum dot (QD) NPs, TiO_2NPs, or SiO_2NPs). The authors concluded that the type and ratio of nanoparticles influence the toxicity of the tested binary mixtures. The toxicity of binary mixtures was lower than the sum of toxicities determined for each tested nanoparticle type alone. It has already been documented that AgNPs produced through green synthesis may exhibit less toxicity and have a lower environmental impact [25,26].

For the green synthesis of AgNPs, bacteria, fungi, plant extracts, and even propolis have been used [11-13], as these are environmentally friendly, easy to handle, cost-effective and show greater efficiency compared to chemical synthesis [27]. To optimize this biogenic synthesis, some aspects need to be considered, namely, (i) the alkaline pH, because it promotes the ionization of hydroxyls and carboxyls of the biomaterials' molecules more efficiently, reducing Ag^+ ions in AgNPs and stabilizing the particles formed [28,29]; (ii) the concentration of $AgNO_3$, because the relationship is inversely proportional, i.e. the higher the concentration of silver nitrate, the smaller the nanoparticles will be because of the formation of more generated nuclei [29,30]; (iii) the relatively high temperature, ranging from 25°C to 50°C, because increasing temperature provides the increase of silver reduction process [30-32]; and finally, (iv) the stirring speed of 200 rpm, as studies have proven that this rotation speed applied for one hour is sufficient to obtain smaller nanoparticles without the presence of aggregations [32].

Environmentally friendly synthesis of AgNPs

Plant extracts-based green synthesis

The synthesis of AgNPs through natural extracts has been commonly used thanks to their secondary metabolites, such as flavonoids, amides, phenols, amino acids and carbohydrates, capable of acting as stabilizers and reducing agents. Thus, this form of production is cost-effective due to its simplified methodology. In the literature, AgNPs in spherical shapes are frequently synthesized, with size dimensions occurring from 5-10 nm, 48-165 nm, 9-50 nm, 10-30 nm, 10-15 nm, 72-83 nm using *Selaginella bryopteris, Phyllanthus acidus, Corylus avellana, Senna alata* and *Nardostachys jatamansi, Trigonella foenum-graecum* extracts, respectively [33-37].

Some variations were observed according to the type of plant extraction, as observed u*sing Achillea millefolium* from aqueous, ethanol and methanol extracts were shown spherical, rectangular and cubical shapes, with an average diameter of 20.77, 18.53 and 14.27 nm, respectively. According to FTIR analysis, the formation of AgNPs is related to polyphenols, proteins, carboxylic acid, and alcohol. The antibacterial activity was observed against *Staphylococcus aureus*, *Bacillus subtilis*, *Salmonella enterica*, *Escherichia coli*, and *Pseudomonas aeruginosa* [38].

Spherical silver nanoparticle morphology was observed using *Mussaenda frondosa* leaf extract, with a 10 to 30 nm diameter and a crystalline nature. Increasing $AgNO_3$ concentrations also increase the inhibition of pathogens such as *E. coli* and *S. mutans* [39]. Through FTIR analysis, we can recognize the chemical composition of the extracts through the spectra so that this analysis can tell us the reducing and stabilizing agents of the AgNPs. The absorption bands belonging to polyphenolic chemical groups from *Petroselinum crispum* showed AgNPs in a spherical shape with sizes ranging from 25 to 90 nm, besides showing great activity against Gram-positive and Gram-negative bacteria [10].

Spherical AgNPs have also been synthesized using *Azadirachta indica*. Extract of this Neem tree has been associated with large amounts of bioactive compounds like alkaloids, leucoanthocyanins, coumarins, saponins, tannins, and terpenoids [40]. Acemannan participates as a reducing and stabilizing agent for AgNPs. This bioactive compound is Aloe vera's main polysaccharide and was effective against *Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa* and *Enterobacter* [41] and also, *Acinetobacter baumannii* [42] and *Candida albicans* [43].

Syzygium cumini was used to develop AgNPs of nearly spherical shape and of 47 nm in size. The secondary metabolites of *Syzygium cumini* were confirmed by FTIR spectroscopy [44]. AgNPs synthesized using *Withania coagulans* as reducing agent were spherical and with a size of 14 nm, in which flavonoids act as reducing agents and protein acts as a stabilizer during AgNP fabrication [45]. The phytochemical frankincense present in *Boswellia carterii* produced AgNPs of mean size of 14-85 nm. These compounds are capping and surface-attached components in the NPs, showing high antibacterial action against oral pathogens. This finding may promote the development of commercial products incorporating these NPs with antimicrobial activity, such as toothpaste and mouthwash [46].

In the search for new drugs using compounds of natural origin to decrease toxic side effects for the treatment of cancers, AgNPs are also being increasingly used, especially biosynthesized AgNPs [47].

With average sizes of 8-68 nm diameter, the green synthesis of nanoparticles showed activity against testicular, liver and ovarian cancer cells using extracts from *Camellia sinensis, corn silk*, and *Acacia nilotica*, respectively [48,49].

AgNPs synthesized from *Sophora pachycarpa* extract showed enhanced antibacterial, antifungal, antioxidant and antimicrobial properties, and cytotoxicity against tumor cell lines. They showed either spherical or oval-like morphology with sizes ranging from 30 to 40 nm [50].

The development of AgNPs using the methanolic extract of *Aegle marmelos* as a reducing agent generated average sizes of 15-37 nm in diameter, with spherical and hexagonal shapes. In addition to antitumor activity against cervical cancer, healing activity was evaluated [51]. The green production of AgNPs using *Piper longum* extract at a concentration of 1 mM $AgNO_3$ also acted as a strong larvicide against *Anopheles stephensi, Aedes aegypti* and *Culex quinquefasciatus* [52]. A mass remaining after extraction of the oils is called oil cake. The formation of spherical AgNPs by sesame oil cake resulted in diameters ranging from 6.6 nm to 14.8 nm. It was also observed to show antitumor activity against human breast cancer cells and antimicrobial activity against *P. aeruginosa, K. pneumoniae,* and *E. coli* [53]. The activity against breast cancer cells was also observed by AgNPs biosynthesized using *Heracleum persicum* extract [54].

In another study, the anticancer action of AgNPs biosynthesized using *Teucrium polium* was observed against human gastric cancer cell line. These studies may promote advancements in the production of effective anticancer drugs [47]. *Gloriosa superba* AgNPs showed a spherical morphology with an average size of 7 -14 nm and potent anticancer activity against a human lung cancer cell line [55].

Even using green synthesis, Ranoszek-Soliwoda et al. (2019) [56] observed that using the natural extracts of cocoa beans and grape seeds resulted in a colloidal suspension of unstable, polydisperse AgNPs. Then, it was proposed to add sodium citrate to the synthesis, resulting in stable and spherical monomodal particles [56].

Applying the best conditions to synthesize AgNPs using *Citrus limon* zest extract, 1 mM of $AgNO_3$ concentration, and a 4 h incubation period showed crystalline spherical AgNPs. In addition, these AgNPs showed excellent antipathogenic activity against *Escherichia coli, Staphylococcus aureus,* and *Candida albicans* [57]. Using the same concentration as in the previous study, AgNPs were biosynthesized using *Brassica oleracea* leaf extract. Different morphologies were found, rod-shaped and triangular, with sizes ranging from 20 nm to 40 nm [58].

For a long-term colloidal stability, the zeta potential of AgNPs should ideally be greater than +30 mV or lower than -30 mV. The zeta potential of AgNPs coated with curly kale leaf extract was determined to be -26.6 mV. This proves the particles were coated with various phytochemical compounds, leading to a highly negative zeta potential [59].

In another study, AgNPs biosynthesized with *Annona muricata* extract exhibited a crystalline nature with face-centred cubic phase particles, a mean size of approximately 87 nm, and a PDI of 0.329. The high negative charge of -27.2 mV may be related to the free amide and hydroxyl groups' [60].

Plant extracts' remarkable capability to create various silver nanostructures has led to their application in synthesizing antibacterial agents with diverse geometries, such as triangles, spheres, and cubes. AgNPs exhibit antimicrobial activity against *Escherichia coli, Staphylococcus aureus, Aspergillus flavus, Candida albicans, and Streptococcus mutans* using *Peganum harmala, Camellia sinensis, Pimpinella anisum, Rosa canina, Eucalyptus critriodora* [61-65]. AgNPs were also synthesized by *Ulva armoricana*, green algae, and showed antimicrobial activity toward both Gram-positive and Gram-negative bacteria [66].

Quercus coccifera extract was firstly analyzed for its content, and was used to synthesize AgNPs. The obtained AgNPs were spherical in shape, depicted a mean size range between 50-70 nm and were found active against several pathogens (*Escherichia coli, Staphylococcus aureus, Enterococcus faecium,* *Staphylococcus epidermidis, Salmonella enteritidis, Salmonella typhimurium, Listeria monocytogenes, Candida albicans*) [67].

The polyphenols from the commercial green tea extract (Camellia sinensis) functioned as both reducing and stabilizing agents for the produced AgNPs. To improve the dispersion and biocompatibility of the obtained biogenic AgNPs, polyethylene glycol (PEG) was applied onto their surface. The results showed the formation of spherically shaped AgNPs coated with tea polyphenols yet with moderate polydispersity. Nevertheless, the produced AgNPs did not exhibit significant toxicity against human keratinocyte (HaCaT) cells. The antimicrobial efficacy of the biogenic nanoparticles was confirmed against *Staphylococcus*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Escherichia coli* and *Salmonella enterica* bacterial strains [68].

X-ray diffraction (XRD) analysis is an important aspect in the study of nanoparticles. It determines not only the size but also the shape of the unit cell. The XDR analysis of the biosynthesized AgNPs with Cissus quadrangularis extract confirmed the crystalline nature of the particles, which also showed spherical shape and anticancer properties [69].

The *Passiflora subpeltata* is a valuable source of secondary metabolites with diverse applications, particularly in addressing cancer and mosquito-related issues. Through XRD analysis, the crystalline nature of the plant material was revealed, while SEM images distinctly showcased the spherical shape of the nanoparticles. Notably, the plant extract demonstrated significant anti-proliferative activity on human colon cancer cell lines and exhibited larvicidal effects against *Culex quinquefasciatus* [70].

Spherical AgNPs using *Epipremnum aureum* leaf extract might open up new studies of unusual DNA binders, which can destabilize DNA and may further be used for various biomedical applications [71]. *Moringa Oleifera* AgNPs analysis gave a spherical morphology with particle sizes ranging between 4 and 12 nm. The XRD gave a face-centred cubic phase with the crystalline structure of Ag-NPs [72].

An extract of *Eugenia jambolana* was used to encapsulate AgNPs within the matrix of the biodegradable polymer PLGA and showed antibacterial activity against *Escherichia coli* and *Pseudomonas aeruginosa* [73].

The AgNPs from *Humulus lupulus* had an average hydrodynamic size of around 92.42 and a low polydispersity index. With TEM analysis, the nanoparticles were spherical, with an average size of 17.40 nm. They were lethal to both *E. coli* and *S. aureus* and exhibited an anti-cancer effect [59].

The Medicago sativa AgNPs' analyses confirmed the formation of a face-centred cubic crystalline structure, spherical morphology, an average particle size of 15-35 nm, and highly stable antimicrobial activities against *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Escherichia coli*, *Staphylococcus epidermidis*, *Enterococcus faecalis*, *Staphylococcus aureus*, and *Candida albicans* [74].

AgNPs were synthesized using the extract of *Caulerpa scalpelliformis* to analyze the wound healing potential. The results showed spherical AgNPs and uniform distribution with diameters ranging from 16 nm to approximately 48 nm. Furthermore, the possibility of applications for antitumor activities and chronic and diabetic skin wound healing was confirmed [75].

The synthesized *Gnaphalium polycaulon* AgNPs suppressed the growth of most dreadful pathogens associated with wound infections, such as *Staphylococcus aureus*, *Escherichia coli*, and *Candida albicans*, by *in vivo* studies [76].

Cotton fabrics coated with AgNPs from *Curcuma longa* extract were tested for their antimicrobial activity and wound healing potential. The analysis showed that the AgNPs, besides having high wound healing potential from the fibroblast test, they also showed a high activity against S. *aureus, P. aeruginosa, S. pyogenes,* and *C. albicans* [77]. The incorporation of biosynthesized silver nanoparticles into dressings is of great medical importance thanks to their antimicrobial and wound healing effects.

Acids-mediated green synthesis

Tannic acid and sodium alginate as reducing and stabilizing agents respectively, and the obtained particles were found to have remarkable antibacterial and antibiofilm properties. Studies showed that optimal production resulted in spherical, stable, and monodispersed AgNPs with an average size of 18.52 nm. After exposure to the AgNPs, *S. aureus* showed irreversible cell membrane damage, changes in cellular morphology and increased cell death. In addition, the AgNPs significantly inhibited *S. aureus* biofilm formation [78]. Lignin is the most abundant, renewable and degradable biopolymer available in nature, and was used to synthesize AgNPs with face-centred cubic crystalline structure, and with a mean size between 15-20 nm. AgNPs were surface-coated with phenolic, hydroxyl and carboxylic groups of lignin. Li-AgNPs showed significant antimicrobial efficacy against several pathogens, *S. aureus* and *E. coli* and also anti-cancer effects against ovarian cancer cells [49].

These findings suggest that lignin-mediated AgNPs can find applications in different fields, including biomedical, drug delivery, biosensor, food packaging, and textile industries [79].

Algae-mediated green synthesis

In the last few years, studies on Cyanobacteria (Blue-green algae) mediated green synthesis have increased considerably, mainly due to their survival properties in acidic and basic environments, extreme temperatures, high metal content, and high salinity, besides showing antimicrobial and anticancer activity [80,81].

Oscillatoria sp. was used to form spherical AgNPs. Phosphate and amine were reported for the capping and stabilization of proteins in the AgNPs. The thermal analysis results confirmed the showed stability of the particles. The particle diameter of 558.1 nm with a polydispersity index of 0.580 had effective antibacterial activity against the tested bacterial pathogens [82].

A biomass parameter (80 µg/ml, pH 5.5, 60 °C, 60 min on UV light exposure and 1 mM $AgNO_3$ concentration) from Microchaete cell-free aqueous extract has been used to optimize the biosynthesis of spherical, polydispersed AgNPs of mean size between 60-80 nm [83].

Under the optimal *Microcystis aeruginosa* extraction conditions (57 °C, pH 4.9, and 30 min), spherical AgNPs were obtained with an average size of 6.80 nm. FTIR analysis showed that the functional groups from *Microcystis aeruginosa* extract participated in the synthesis of AgNPs. In addition, these biosynthesized AgNPs showed excellent antibacterial activity against gram-positive *Staphylococcus aureus* and gram-negative *Escherichia coli* [84].

Cyanobacteria-based AgNPs were developed using *Lyngbya majuscula* under the following conditions: pH 4, 1 mM, 72 h. As a result, the AgNP presented a mean particle size between 5 and 25 nm and a spherical but also irregular shape. The green production was shown to be an effective and low-cost technique that can be widely used [85].

Fungi-mediated green synthesis

Fungi secrete attractive agents for the biogenic synthesis of AgNPs because they offer high tolerance to metals and are easy to handle. They also secrete a massive amount of proteins that contribute to reducing and capping agents of the nanoparticles [86]. Many studies have shown that fungi-based AgNPs may be used as antibacterial, antifungal, anticancer, and antioxidant agents [87-90].

In synthesis using *Letendraea* sp., the authors revealed a diameter of 33.8 nm and face-centred cubic of crystalline nature. Furthermore, the synthesized AgNPs exhibited good antioxidant and antibacterial activities against Gram-positive and Gram-negative bacteria [91].

Using *Ganoderma applanatum, a* basidiomycete species, also displayed excellent antimicrobial properties against *Staphylococcus aureus*, *Escherichia coli*, and *in vivo* antifungal activity against *Botrytis cinerea* and *Colletotrichum gloeosporioides*. The spherical shape was observed with an average size of 20-25 nm [92].

The AgNPs from *Ganoderma lucidum*, a mushroom with many medicinal properties, such as antibacterial and antifungal, were developed to demonstrate their antimicrobial activity. The nanoparticles showed a spherical shape and a particle size of 25-150 nm, with the median size of 55 nm. These AgNPs showed high antibacterial activity against *Staphylococcus aureus*, *Escherichia coli*, and

Pseudomonas aeruginosa [93]. Table 1 summarizes some relevant applications of AgNPs obtained by different green synthesis approaches.

Table 1. Summary of relevant studies reporting the production of AgNPs by green synthesis.

Type of green synthesis	Material	Particle size	Applications	References
Plant extracts	*Achillea millefolium* from aqueous, ethanol and methanol extracts	20.77, 18.53 and 14.27 nm	Antibacterial activity (*Staphylococcus aureus, Bacillus subtilis, Salmonella enterica, Escherichia coli,* and *Pseudomonas aeruginosa*)	[38]
Plant extracts	*Mussaenda frondosa* leaf extract	10-30 nm	Antibacterial activity (*E. coli and S. mutans*)	[39]
Plant extracts	*Boswellia carterii*	14–85 nm	Antibacterial activity against oral pathogens	[46]
Plant extracts	Extracts *Camellia sinensis* and corn silk.	8-68 nm	Anticancer potential	[47,48]
Plant extracts	*Sophora pachycarpa* extract	30-40 nm	Antibacterial, antifungal, antioxidant, antimicrobial, and cytotoxicity against tumor cell lines	[50]
Plant extracts	*Humulus lupulus* extract	17.40 nm	Antibacterial (*E. coli* and *S. aureus*) and anticancer effect	[59]
Algae	*Oscillatoria sp*	558.1 nm	Antibacterial activity	[82]
Algae	*Microcystis aeruginosa.*	6.8 nm	Antibacterial activity (*E. coli* and *S. aureus*)	[84]
Fungi	*Letendraea sp*	33.8 nm	Antioxidant and Antibacterial activity	[91]
Fungi	*Ganoderma applanatum*	20-25 nm	Antibacterial properties against *S. aureus, E. coli*, and *in vivo* antifungal activity against *Botrytis cinerea* and *Colletotrichum gloeosporioides.*	[92]
Fungi	*Ganoderma lucidum*	25-150 nm	Antibacterial activity (*S. aureaus*, *P. aeruginosa* and *E. coli*)	[93]

Toxicological aspects and safety assessment of AgNPs

Since AgNPs exhibit potent antibacterial, antiviral, antifungal, and antimicrobial activities, they have been widely used for various biomedical and pharmaceutical applications. Nonetheless, there is ongoing discussion on their toxicity, demanding more research.

AgNP toxicity is dependent on size, shape, and surface modification; an investigation using alveolar macrophages revealed that AgNPs with an average size of 15 nm caused the highest reduction in mitochondrial activity [26,94]. The size of nanoparticles influences the binding and activation of membrane receptors and the subsequent production of proteins in cancer cells [95].

Sun et al. (2021) [96] ran a battery of cytotoxicity and genotoxicity tests, together with the analysis of the inflammatory responses in two human cell lines (HepG2 and A549), in order to clarify the distinct hazardous effects of polyvinylpyrrolidone-capped AgNPs with varying primary particle sizes (i.e., 5, 50, and 75 nm). AgNPs-induced cytotoxicity was shown to be primarily mediated by inflammation and disturbance of mitochondrial function, as evidenced by concentration-dependent decreases in cell proliferation and mitochondrial membrane potential and increases in cytokine excretion (i.e., interleukin-6 and interleukin-8). In HepG2 cells, a gradual rise in genotoxicity was observed as the diameter of AgNPs decreased. This was linked to the accumulation of S and G2/M and the transcriptional activation of the GADD45α promoter, as indicated by luciferase activity. In A549 cells, there was additional evidence of dose-related genetic damage as demonstrated by the development of micronuclei and the Olive tail moment; however, these effects and the cytotoxicity caused by AgNPs were mainly linked to the ionic Ag release from nanoparticles.

The mechanisms of action of AgNPs involved in their toxicological risk seem to be related to the production of reactive oxygen species (ROS) upon the uptake of particles by the cells, causing mitochondrial dysfunction [97]. ROS are known to promote cell death by mechanisms of apoptosis or necrosis [94]. Chang et al. (2021) [98] reported the cytotoxicity of AgNPs in a mouse hippocampal neuronal cell line (HT22 cells). The MTT and LDH experiment showed that AgNPs decreased cell viability and caused membrane leakage in a dose-dependent manner. AgNPs induced oxidative stress and excessive generation of ROS in HT22 cells at dosages of 25, 50, and 100 μg/ml for 24 h.

Gurunathan et al. (2018) [99] prepared AgNPs using an anti-oxidant polyphenol (myricetin) and evaluated their effects on NIH3T3 mouse embryonic. AgNPs caused dose-dependent cell viability and proliferation loss, as demonstrated by increased lactate dehydrogenase (LDH) leakage from cells. One possible source of harm was ROS. Additionally, AgNPs decreased glutathione and superoxide dismutase, raised oxidative stress and malondialdehyde levels, decreased mitochondrial membrane potential and adenosine triphosphate (ATP), and damaged DNA in NIH3T3 cells by upregulating the expressions of the p53 and p21 genes and the level of 8-hydroxy-2′-deoxyguanosine. Asharani et al. (2023) [95] described the ability of AgNPs to adsorb cytosolic proteins onto their surface, which may have an impact on the activity of intracellular factors that control genes related to DNA damage response and repair in cancer cell lines, as well as cell cycle progression. On the other hand, the mechanisms that lead AgNPs to build up ROS and hyperpolarise the membrane potential in the mitochondria are also responsible for their effects on changing cell function or phenotype in a dose-dependent way. AgNPs can be used against single-cell biophysical features of colon cancer cells HCT-116, potentially advancing AgNP-based cancer therapy [97].

Studies in experimental animals document that AgNPs are absorbed in the gastrointestinal system [100], diffuse to numerous organs and tissues, and accumulate in several organs (primarily the colon, small intestine, kidney, and heart) [101].

Environmental impact of AgNPs

The behaviour of AgNPs in the environment is influenced by various factors, including their size and surface properties and the surrounding environmental conditions (Figure 3). AgNPs can exist as individual particles in suspension and be transported over long distances in aquatic environments governed by water flow rate, sedimentation, and interactions with other particles and surfaces. AgNPs may tend to aggregate in high ionic strength environments [102]. When the concentration of ions in the solution is high, such as in the presence of salts, the electrostatic repulsion between particles decreases, leading to aggregation. Aggregation can affect the behaviour and fate of AgNPs in the environment [103].

Upon contact with oxygen and other oxidants, AgNPs can undergo partial oxidation, resulting in the dissolution of Ag^+ ions [104]. This process can occur at the nanoparticle surface, releasing silver ions into the surrounding environment. The extent of oxidation and dissolution depends on the reactivity of AgNPs and the availability of oxidants [105]. AgNPs can react with various natural substances present in the environment, such as sulphide and chloride ions [106]. These reactions can modify the original properties of AgNPs and lead to the formation of different silver-based compounds, which may influence their toxicity, stability, and bioavailability.

Capping agents, which are amphiphilic compounds used to prevent agglomeration during AgNP production, also affect their surface chemistry and, thus, their biological activity and influence nanoparticles' interaction with the environment. On the other hand, electrolyte composition, solution ionic strength, pH, and the presence of natural organic matter can all affect the stability, aggregation, and transformations of AgNPs in the environment. The pH of the suspension is another critical factor influencing the stability and aggregation of AgNPs. Nanoparticles exhibit different aggregation states across a wide pH range, with aggregate sizes increasing near the pH of the point of zero charge. The pH affects the surface potential of particles and dominates the risk of aggregation, which in turn affects the particle size [107]. Understanding these processes is crucial for assessing the potential environmental impact of AgNPs and developing appropriate strategies for green synthesis approaches to reduce toxicological concerns in ecosystems and human health.

AgNPs can escape into the air during various stages of manufacturing processes, such as drying, grinding, mixing, and packaging. Their use in disinfection and anti-odor sprays also contributes to their emission into the atmosphere.

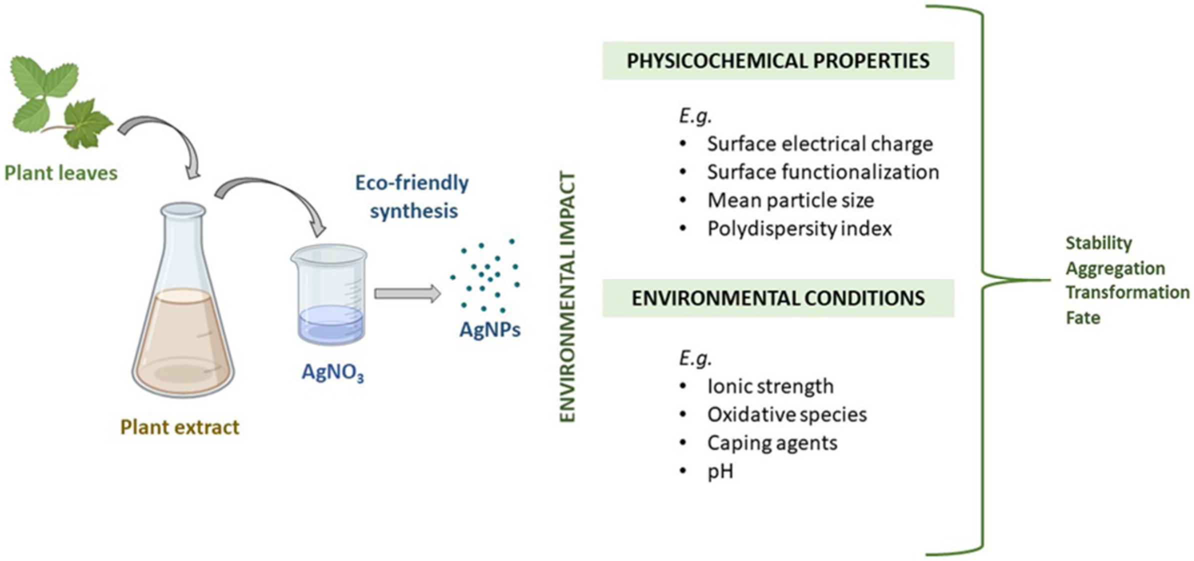

Figure 3. Schematic representation of the green synthesis process and the factors influencing the behaviour of AgNPs and their impact on the environment.

The small size of AgNPs allows for rapid diffusion in the air, potentially enabling long-distance mobility. Their large surface area makes them reactive and more toxic than larger particles. AgNPs can be deposited on surfaces and transferred through cleaning and laundering or transported through the air [108].

AgNPs can enter soils through direct disposal of AgNP products, such as their use as fertilizer in agriculture [109]. The fate and transport of AgNPs in soils depend on factors like particle size, surface charge, and soil characteristics. AgNPs may adsorb organic contaminants and serve as carriers for their transport. The interaction between AgNPs and different soil types, influenced by their surface charge, affects their mobility. AgNPs can strongly adsorb onto soils, reducing their availability in the environment.

Conclusion

In summary, the antibacterial activity of AgNPs involves complex processes, and multiple modes of action have been proposed. These include the generation of ROS, direct interaction with cell membranes, changes in membrane permeability, disruption of protein function, and interference with DNA replication. The specific mode of action may vary depending on the type of cell or organism being studied. On the other hand, the impact of AgNPs on ecosystems and human health is governed by the physicochemical properties of the obtained nanoparticles. The toxicological risk can be mitigated by adopting green synthesis approaches.

In this review, evidence is given that the synthesis of green AgNPs is expanding continuously. Nevertheless, careful considerations in the selection of green material for nanomaterial production, and more importantly, a comprehensive screening protocol for these green particles, are mandatory to predict the performance of nanoparticles on living cells and in the environment. Once the nanomaterial is produced, a thorough analysis of its structure and physicochemical properties must be conducted to determine the morphology, average size, surface chemistry, and other important parameters. This step in the development process is equally significant as the synthesis itself, as the results obtained can either suggest and recommend the use of the developed nanomaterials for further biological testing or demand additional refinements if nanoparticles with undesirable properties are produced. To enhance the biological characterisations of nanoparticle manufacturing processes, it is necessary to expand the scope by incorporating various cell types and strains and undertake *in vivo* studies.

Abbreviations

AgNO3: Silver nitrate; **AgNPs**: Silver nanoparticles; **AuNPs**: Gold nanoparticles; **CdTe**: Cadmium telluride; **DNA**: Deoxyribonucleic acid; **FTIR**: Fourier Transform Infrared; **PDI**: Polydispersity index; **PEG**: Polyethylene glycol; **ROS**: Reactive oxygen species; **TiO2NPs**: Titanium dioxide nanoparticles; **SiO2NPs**: Silicon dioxide nanoparticles.

Contributions

Conceptualization, writing—original draft preparation, ETSL, VLSS, PS and EBS; methodology, validation, formal analysis, visualization, CASV, SJ, JCC, RLCAJ, KK and AML; investigation, resources, data curation, writing—review and editing, supervision and project administration KK, PS and EBS; All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

The authors confirm that ethics approval and participation consent are not applicable to this work and that no ethics issues are raised in this manuscript.

Availability of data and material

The datasets generated during and analysed during the current study are available from the corresponding author upon reasonable request.

Declaration of interest

The authors declare no conflict of interest.

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