Review Article

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An overview of methods for production and detection of silver nanoparticles, with emphasis on their fate and toxicological effects on human, soil, and aquatic environment

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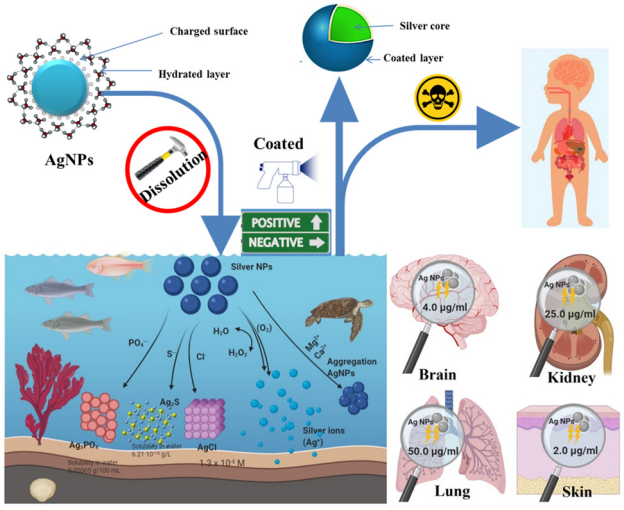
Abstract: Silver nanoparticles (AgNPs) have been extensively used in various industries; however, this is accompanied by several implications to humans and the environment. This review focuses on different aspects of AgNPs including the production and detection techniques, their fate, and dynamics in response to different environmental factors. In addition, this review illustrates the toxicity mechanism and the interaction of AgNPs with different matrices, such as



Graphical abstract: Practically, AgNPs are converted to the positively charged Ag^+ ions by dissolution process and will react with the negatively charged oxygen and nitrogen atoms in the vital organelles like DNA, mitochondrion, and the thiol group presented in protein structures and enzymes, which in terms interrupts the normal cell reproduction, and finally, the death of cell will occur according to the toxicity limit of (Ag^+) silver ions level of each organ.

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aquatic environment, soil, crops, and humans. Reduction measures and future research are discussed.

Keywords: silver ions, toxicity mechanism, AgNPs, human health, aquatic environment, soil, crops

1 Introduction

Silver nanoparticles (AgNPs) are one of the fastest-growing products in the nanotechnology industry, due to their distinctive physicochemical properties and antimicrobial activity [1–4]. Accordingly, the use of AgNPs has become extensive with an estimated global production of approximately 500 tons per year [5]. AgNPs have been widely used in medical applications, including wound dressings, contraceptive devices, surgical instruments, and bone prostheses [6–8], in addition to water purifications and indoor air quality management [9,10]. Moreover, AgNPs are used in the aquaculture industry for rapid disease detection, vaccines, hormones, nutrients, and nanosensors [11,12]. Eventually, AgNPs enter the soil and aquatic environment mainly through wastewater effluents, accidental spillages, industrial runoffs, and agricultural drainage water, where they exhibited substantial toxic effects on different organisms and humans.

However, to date, there have not been conclusive statements about their toxicity due to the lack of studies on the fate of AgNPs under laboratory conditions [13]. Three main mechanisms that explain AgNPs toxicity have been suggested: (1) AgNPs can directly damage cell membranes due to the nano-size (physical impact), (2) AgNPs and silver ions generate reactive oxygen species (ROS), and (3) AgNPs can release Ag ions. The latter mechanism was suggested by many studies [14–17]. Some researchers suggest that AgNPs could serve as a "Trojan horse," avoiding common barriers, releasing Ag^+ ions, and causing damage to the cells [18,19]. AgNPs are converted from Ago form to dissolution or ionization (Ag^+) form [20]. Some researches indicate that cysteine is vital to remove Ag^+ ion toxicity which is a free chelating agent for (Ag^+) ions [21]. While other results are somewhat conflicting, all evidence suggests that both silver ions and AgNPs cause toxicity in human cells [22,23]. Several research papers evaluated the antimicrobial and antifungal activity of AgNPs [24,25] which was attributed to the release of Ag^+ to the medium [26,27]. Several studies used AgNPs for many applications, but they did not study their side effect on the environment. There remain wide information gaps concerning the potential risks of exposure to AgNPs, considering the increasingly rising proportion of AgNPs in our societies. Although some reviews dealt with the toxicity of AgNPs, there was a lack of information about the mechanism of the ecotoxicology in addition to the lack of reduction measures. This review aims to depict how the manufacturing techniques of AgNPs and receiving environment affect the fate and impact of AgNPs on the aquatic environment and humans; in addition, reduction measures are suggested.

2 Overview of the different applications used for the synthesis of AgNPs

AgNPs have been used in various applications since ancient times, for instance, they were used for the conservation of mummies in Ancient Egypt [28] (Figure 1). Nowadays, silver is used in smart nano-systems by developing AgNPs for various functions, *e.g.*, imaging contrast, drug delivery, cell targeting, *etc.* [29]. By searching the Scopus for the words "AgNPs synthesis," one can find 42,100 publications covering the period between 2160 BC and 2020. Varied preparation methodologies of AgNPs have been reported, including, chemical, physical, biosynthesis, and photochemical methods. Forty two percent of the published researches used chemical methods, while physical, biological, and photochemical syntheses represented 33, 18, and 7%, respectively, of the scholarly output (Figure 2).

2.1 Chemical synthesis

Chemical synthesis is mainly used for the preparation of AgNPs since it allows for the preparation of stabilizing monodisperse AgNPs with various nanostructure shapes. Usually, the AgNPs were synthesized chemically based on the following three major compounds: (i) silver nitrate ($AgNO_3$) as silver precursors, (ii) an appropriate reducing agent, and (iii) a capping agent [30,31]. The production of colloidal silver solutions from silver ions reduction involves two steps: nucleation and grain growth. It has been shown that the shape and size of the synthesized AgNPs depend largely on these stages. The nucleation and grain growth of the first nuclei can be regulated by changing the parameters of the reaction, like ion precursors, temperature, pH, and types of both stabilizing and reducing agents. In several studies, stabilizing and reducing agents are the same. For example, AgNPs can be

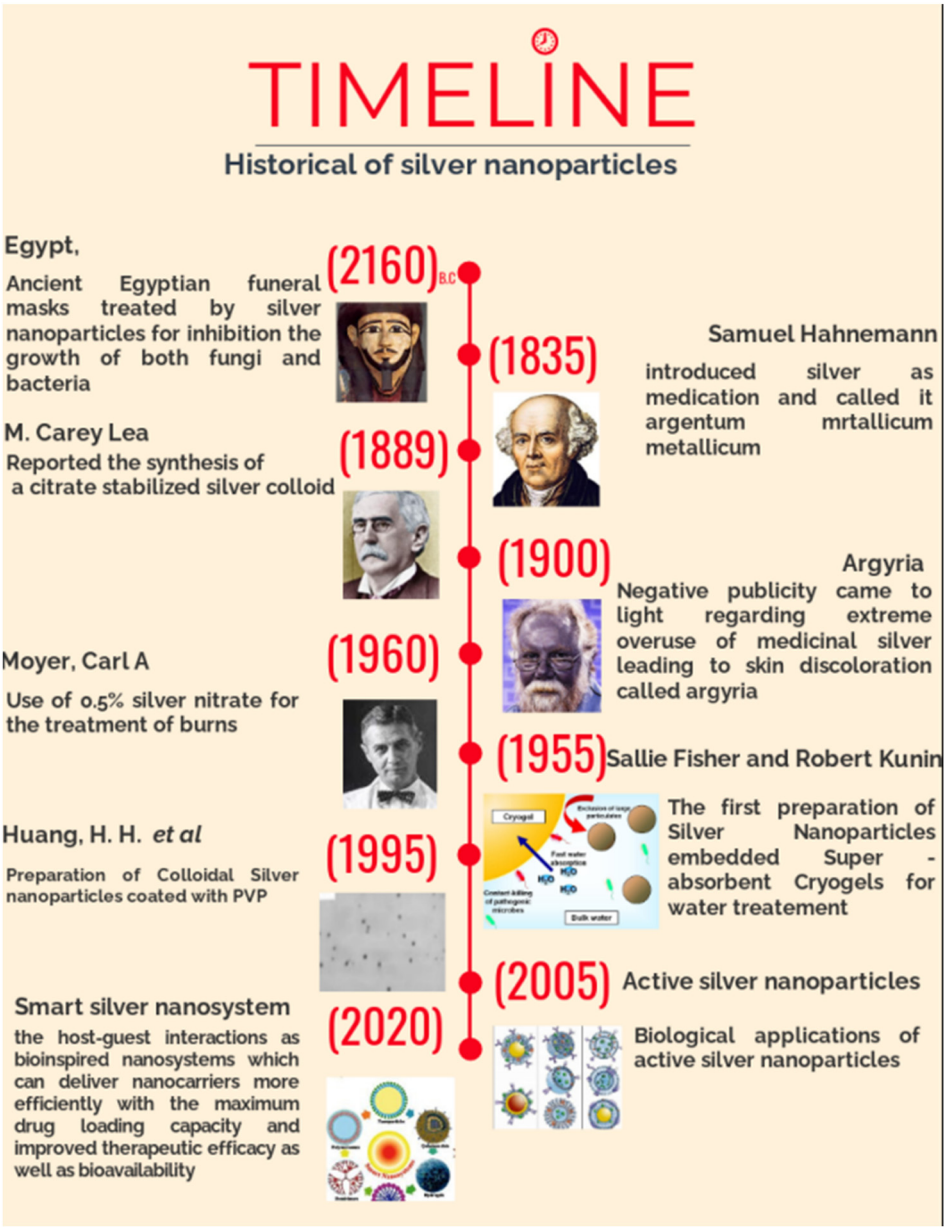

Figure 1: Historical timeline of AgNPs.

prepared by thermally reducing silver ions in the existence of polymer. This process is called *in situ* AgNPs formation [32]. Spherical AgNPs were synthesized *in situ* with controllable size and high monodispersity by heating a mixture of polyvinylpyrrolidone and silver nitrate [PVP]/[$AgNO_3$] with weight ratios of 5:1, 10:1, and 1:20 at a temperature of 70°C [33]. In this case, PVP severed both as a stabilizing and reducing agent. It has been shown that the shape and size of the obtained AgNPs are strongly affected by the PVP weight fraction in the mixture of [PVP]/[$AgNO_3$]. Significant amounts of monodisperse triangular silver nanoplates were synthesized *in situ* by heating a mixture of PVP and $AgNO_3$ dissolved in *N*-methylpyrrolidone (NMP) at a temperature of 100°C [34]. Another nanostructure form of silver nanocubes was produced in the existence of PVP as a stabilizer and ethylene glycol (EG) as a reducing agent of $AgNO_3$ [35]. This process is known as the "Polyol" methodology; in that case, EG acted as both a reducer and solvent, while PVP served as a stabilizer. [35] showed that PVP and its molar ratio, compared to $AgNO_3$, played important roles in determining the amount, size, and geometric form of the product. According to [36], the

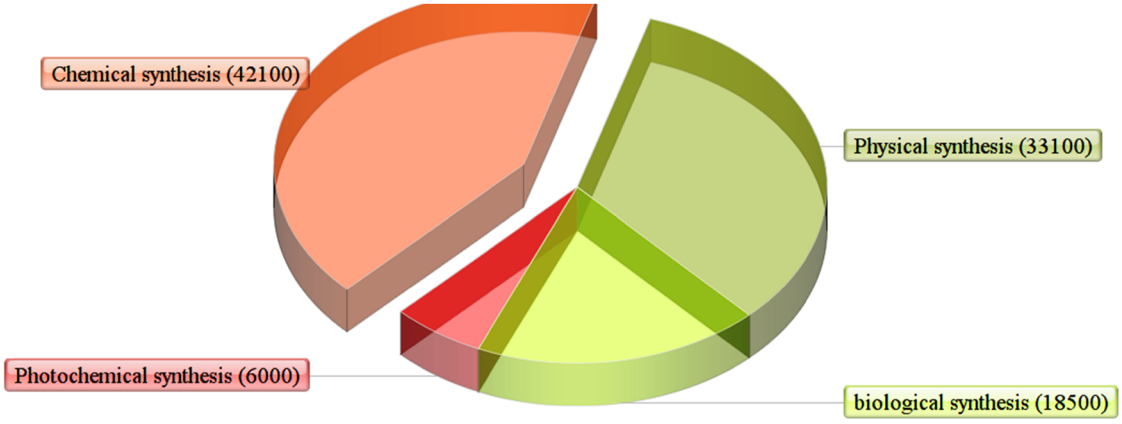

Figure 2: The published research articles on the topic of synthesis of AgNPs. The databases were collected from "Scopus" using the keyword "AgNPs," up to 30 May, 2021.

experimental conditions, such as different temperatures ranges of the mixture (PEG, PVP, and $AgNO_3$), affected the size and shape of the obtained AgNPs, where at heating rates of 1 and 7.5°C min^{-1}, the mean sizes of AgNPs were 42 and 18 nm, respectively. They were inclined to be more mono-dispersive, which means that rapid nucleation with temperature occurred in a short time. The *in situ* colloidal AgNPs formation from the reduction of their salts depends on the nucleation and grain growth. It was also revealed that the shape and the size of synthesized AgNPs are mainly dependent on experimental parameters like reactants ratio [37], the temperature of reaction [38], and pH [39].

A microwave irradiation method is another fast method, known also as one-pot, which is used to synthesize colloidal AgNPs from the reduction of $AgNO_3$ solution at a temperature within 80–128°C [40–42]. The reducing agent in the microwave irradiation method may be natural such as cuminum cyminum [43] and glucose [44]. Cai *et al.* [45] used the microwave irradiation method to synthesize a uniform size (20 nm) of AgNPs coated by polyacrylic acid. The source of the silver ions was $AgNO_3$ and monoethanolamine (MEA) was used as a reducing reagent. Liu *et al.* demonstrated that the microwave irradiation approach assisted the synthesis of a uniform structure of colloidal silver nano-rods in the absence of a polymer or surfactant [46]. In contrast, the synthesis of the AgNPs using the one-pot method was characterized by different levels of aggregation and a variety of particle shapes by adjusting the time of microwave irradiation [47]. In conjunction, AgNPs can be synthesized using the emulsions method, where the reactants of the metal precursor and reduction agents were put in two immiscible phases [6,48].

2.2 Physical synthesis

In brief, the physical synthesis method of AgNPs typically uses physical energies such as arc discharge and electric and thermal powers to generate narrow-sized AgNPs in powder form [49]. Generally, AgNPs may be synthesized *via* evaporation/condensation through a tube furnace at ambient conditions. Lee and Kang formed silver nanocrystallites 9.5 nm by the thermal decomposition of a complex of Ag-oleate at a temperature of 290°C [50].

2.3 Biological and green synthesis

The biosynthesis of AgNPs has been explored by utilizing various biological agents; bacteria have received great interest through both the extracellular and intracellular synthesis pathways due to the ease of bacterial evolution, short generation period, and light culture procedures [51]. Fast biosynthesis of AgNPs can occur with a non-pathogenic bacterium, Thiosphaera pantotropha, seeded with a solution of 2 mM $AgNO_3$ [52]. This bacterium has an unusual ability to use nitrogen oxide or nitrate as an electron acceptor and was able to perform heterotrophic nitrification exhibiting the activity of both nitrate-reductase enzymes (NaR) and nitrite-reductase enzymes (NiR). In another study, the use of Penicillium oxalicum fungal metabolites for the extracellular biosynthesis of AgNPs from $AgNO_3$ solution was reported [53]. Morphology of the obtained AgNPs yielded an irregular spherical shape with high variability in a particle diameter ranging from

60 to 80 nm. Green synthesis is a new alternative AgNPs synthesis eco-friendly approach. This eco-friendly technique used biological agents, plants agents, or microbial agents which can act as capping and reducing agents at the same time. AgNPs synthesized by green chemistry offers a novel and potential alternative to chemically synthesized nanoparticles. In the green process of AgNPs synthesis, the biological agents not only reduce the silver salts, but also can form a protected layer on the surface of AgNPs; beside, they can act as reducing agents. This protected layer has several advantages such as it (i) prevents the agglomeration of the nanoparticles, (ii) reduces AgNPs dissolution and their toxicity, and (iii) improves their antimicrobial property [54].

2.4 Photochemical synthesis

Another one-step *in situ* AgNPs formation is carried out by the irradiation technique. The γ-irradiation method at a dose of 30 kGy provided a convenient and uniform reduction process in the existence of PVP as a stabilizer [55]. The effect of γ-irradiation stems from the water radiolysis that releases six species ($^{\cdot}OH$, $^{\cdot}H$, H_2O_2, e_{hy}, H_2, and O_2) where three of them are powerful reducing agents such as $^{\cdot}H$, e_{hy}, and H_2. Furthermore, UV-initiated photoreduction has been reported by Huang and Yang for the synthesis of AgNPs *via* $AgNO_3$ photoreduction in the existence of collagen, PVP, citrate, and polyacrylic acid, which served as stabilizing agents [56].

3 Physicochemical properties of AgNPs

AgNPs can be obtained in different sizes, shapes, and surface charges (positive, neutral, and negative) depending on the method of synthesis. The stabilizers and capping agents are usually used to modify the AgNPs' surface charges, beside influencing their physicochemical properties [57]. The shape of AgNPs can be of isotropic structure (0D) or anisotropic structure, such as 1D, 2D, and 3D. The morphologies of anisotropic AgNPs exhibit new physicochemical properties due to the high surface area when compared to isotropic AgNPs of inorganic NPs. Additionally, several significant parameters control the anisotropic morphology of AgNPs during seed processes such as the concentration of precursors, reaction temperature, pH, and reaction time. Almost all silver particles have a small size, high surface area, and, therefore, great toxic potential [58].

Localized surface Plasmon resonance (SPR) of AgNPs depends on the shape, size, and mutual interactions between particles of silver in close proximity [59]. The shape and size of AgNPs can tune the AgNPs Plasmon peak in the range of 393–738 nm [60].

4 Toxicity and fate of AgNPs in aquatic systems

For Drinking Water Quality (DWQ), the World Health Organization (WHO) noted that there are insufficient data to deduce a health benefit for silver in drinking water. These guidelines state that "amounts of up to 0.1 mg L^{-1} of silver can be accepted without health hazard." Silver usage is governed by the National Secondary Drinking Water Regulations of the US Environmental Protection Agency (EPA). In sources discussing drinking water, the permissible silver contaminant level is 0.1 mg L^{-1}, a non-enforceable standard due to potential health effects, such as skin discoloration. In aquatic environments, the stability, and therefore toxicity, of AgNPs is inseparable from the chemistry of water, including parameters like dissolved organic matter (DOM), pH, ionic strength, and composition [61]. High ionic strength encourages the agglomeration of nanoparticles by screening double-layer electrostatic repulsion among similar particles, thereby reducing dissolution, toxicity, and ROS production of (Ag^+) ions [62].

The effect of inorganic aquatic chemistry on the stability of AgNPs (precipitation, dissolution, and aggregation) and their bacterial viability was elucidated by [63]. Little is known about both the mobility and ultimate fate of AgNPs in freshwater ecosystems. Jin and coauthors prepared various mixtures of anions and cations dissolved in water at a fixed ionic strength. The results indicated that the AgNPs seemed to be in a highly dispersed form in the ions with the absence of Mg^{2+} and Ca^{2+}. With Mg^{2+} and Ca^{2+} ions' presence, AgNPs' aggregation was enhanced regardless of the other ions' presence due to the divalent ions such as Mg^{2+} and Ca^{2+} reducing the electrostatic repulsion among AgNPs that have negative zeta potentials in aqueous media. The negative charge of AgNPs is due to the adsorption of anions on the silver surface, like sulfate hydroxide and chloride. Usually, AgNPs in water systems are not only found in metallic form, but also in a salt form such as silver sulfide (Ag_2S) and silver chloride (AgCl) (Figure 3) [64].

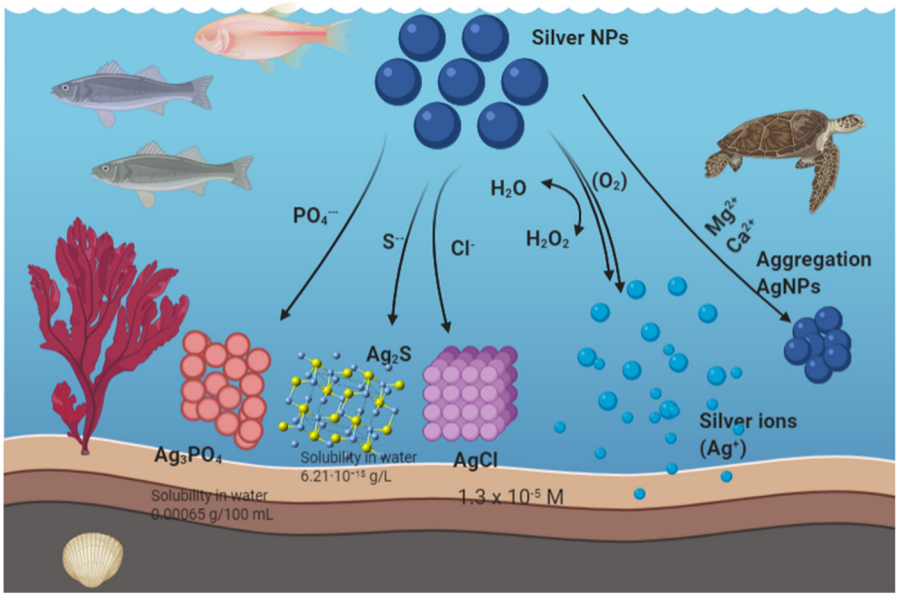

Figure 3: Behavior of AgNPs in freshwater ecosystem.

The dissolution of AgNPs by the oxidation process has been reported in several studies. Kittler *et al.* [65] prepared AgNPs stabilized with poly(vinylpyrrolidone) (PVP) and citrate to gain the silver particles' different surface fictionalization and studied the dissolution of coated silver particles in water at three temperatures of 5, 25, and 37°C for several days. The results obtained suggested that depending on their surface fictionalization (if citrate or PVP) and reaction temperature, the degree of silver dissolution was higher for nanoparticles of PVP-stabilized silver than nanoparticles of citrate-stabilized silver. This could be due to the citrate layer which serves as a chemical shield to reduce the outgoing silver ions. Liu and Hurt [66] measured the rate of silver ions' dissolution from citrate-stabilized AgNPs in different temperatures and pH values. The results indicated that the rate of silver ions' dissolution increased with temperature and decreased with the reduction of pH or with the addition of fulvic acid or humic acid. The results confirmed that organic compounds such as fulvic or humic acids in natural waters do not dissolve silver. Gao *et al.* also observed lower toxicity of AgNPs in water samples as the concentration of DOM increased [67,68]. The effects of different environmental parameters, such as the salinity dissolved oxygen (DO), temperature, and pH, on the dissolution rate of citrate-stabilized AgNPs have been studied. High salinity promotes silver particle aggregation and hinders silver dissolution [66]. In addition, the increase of DO and temperature and lower pH values enhanced the rate of silver dissolution.

Li *et al.* [69] evaluated the stability of AgNPs citrate coated in natural freshwater from six separate sites. The results showed that citrate-coated AgNPs remained stable in low-salinity waters due to the impacts of DOM which promoted the stability of NPs (Figure 4). Free ions concentrations of sulfide S_2^{2-}, chlorine Cl^-, and sulfate SO^{4-} in waters of high salinity cause rapid dissolution and sedimentation of citrate-coated AgNPs. Also, the results revealed that AgNPs remain stable for a long period in waters of low salinity. AgNPs can cause serious implications on the environment and organisms in freshwater ecosystems than in estuarine or seawater systems. Zou *et al.* [70] investigated the effect of natural organic matter (NOM) and DO in natural and synthetic freshwaters on the stability and dissolution of AgNPs for seven days; aggregations of AgNPs in synthetic freshwater were observed, where they resulted from the contraction of the electric

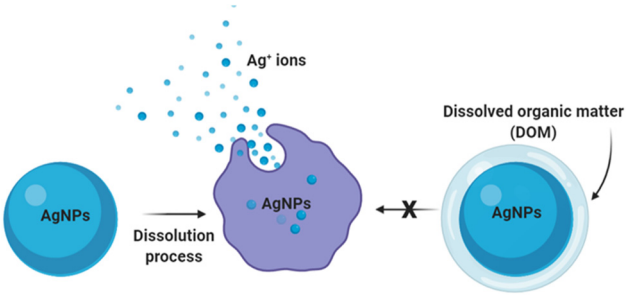

Figure 4: The effect of DOM on AgNPs' dissolutions.

double layers, followed by the dissolution of silver NPs. Nevertheless, the maximum concentration of dissolved silver (Ag_{dis}) significantly decreased from 356.5 to 272.1 mg L^{-1} under anoxic conditions. The addition of NOM mitigated the aggregation, prevented the oxidative dissolution effect, and enhanced the AgNPs' transformation into Ag_2S due to the adsorbed layers' formation of NOM. Similarly, the inhibition of oxidative dissolution occurred in oxygen-deficient natural freshwaters compared with oxygenated freshwaters, resulting in a decrease in the concentration of Ag_{dis} from 137.6 and 57.0 mg L^{-1} to 83.3 and 42.4 mg L^{-1}, respectively, in two natural freshwater locations. This indicates that AgNPs pose more serious environmental risks in freshwaters. As silver ions are found to be one of the main causes of the toxicity of AgNPs, the toxicity of Ag ions is strongly linked to the viability of nanoparticles [71]. The exposure of the freshwater alga *Microcystis aeruginosa* to AgNPs led to toxic repercussions and reduction of α chlorophyll and membrane damages [72]. The toxicity was due to the dissolved Ag ions, which emerged from the internalized AgNPs that directly targeted the photosynthetic system of the alga. AgNPs can readily transform once in water depending on many environmental factors, which included complexation with organic and inorganic species, agglomeration, and oxidizing changes which all contribute to the fate of AgNPs in water bodies.

5 Toxicity of AgNPs in aquatic organisms

Silver ions (Ag^+) have high reactivity with anionic and sweater species as well as with negative ligands found either on DOM or living cell surfaces [73]. Organic matter (OM) and sulfide may dominate silver speciation in freshwater systems and could reduce its bioavailability [74]. Neutral chemical complexes like AgCl (aq.) and AgHS (aq.) are formed at lower salt concentrations, and AgNPs dissolution occurs slowly [73]. With the increase of salinity in oceans, the supply of silver ions changes while AgCl becomes dominant [73].

Aquatic organisms exposed to AgNPs causing cytotoxic and genotoxic impacts can reach humans *via* the food chain [75]. The general mechanism of animal toxicity relies on its phase of transformation in environmental and biological products. Silver ions release the oxidative force of the surface and they interact with biomolecules like lipids, proteins, nucleic acids, *etc.* [76,77]. Silver NPs can produce toxins by triggering signaling pathways by interacting with protein molecules, entering the cell directly through endocytosis or diffusion to damage the mitochondria and generate ROS that damages DNA and causes necrosis and apoptosis [78,79]. Many studies have measured silver ions toxicity in freshwater fish [80,81]. LC_{10} was reported at concentrations of 0.8 μg L^{-1} for several fish species [82]. However, physiological changes like blood acidosis causing circulatory collapse and death were recorded in fathead minnows and trout at higher concentrations [83,84]. The effects and fate of AgNPs in rainbow trout juveniles (*Oncorhynchus mykiss*) were investigated (Figure 5), where they were exposed to 50 μg L^{-1} AgNPs (20 nm) and dissolved 1 μg L^{-1} of silver ions [85]. The results showed that water with a high organic carbon level (7 mg L^{-1}) encouraged the production of bioaccumulated AgNPs in the livers and gills of fish. AgNPs of 10–80 nm influence the development of early life stage negative effects that involve deformities of the spinal cord, cardiac arrhythmia, and zebrafish death [86,87]. AgNPs often accumulate in the tissues of the liver and gills, which impairs fish's ability to cope with low oxygen value and causes oxidative stress [88]. The exposure of the African catfish, *Clarias gariepinus*, to AgNPs' (40 nm) quantity of 10 and 100 μg L^{-1} caused serious hepatotoxic effects after being exposed for 15 days [89]. Rajkumar *et al.* [90] exposed rohu (*Labeo rohita*) to 5–100 mg kg^{-1} of AgNPs for seven days. The results showed a substantial reduction in hematological parameters compared to control samples.

Filter feeders tend to accumulate AgNPs with other food. A toxicity study of AgNPs on embryonic development of the oyster, *Crassostrea virginica*, revealed adverse impacts on embryonic development [91]. Multiple cellular mechanisms linked to silver ions and AgNPs were observed at concentrations of 100 mg L^{-1} in juvenile sea urchin, with series of cellular responses like *spherocyte* and *amebocyte* cell coagulation, oxidative stress, and expression of 70 kDa chaperone [92].

Phytoplankton is the primary producer in the food chain of aquatic ecosystems. Accordingly, studying the effect of AgNPs on their vitality and dynamics is a priority, where they are the first target for most pollutants in seawater. The toxic effect of AgNPs on marine phytoplankton has been extensively reported [93]. Interestingly, the exposure of phytoplankton to AgNPs not only caused toxic effects, but also showed taxa-specific effects, where the composition of the community changed in response: negatively diminishing cyanobacterial functions at concentrations of Ag ions ≥200 ng L^{-1} and altering the domains of dinoflagellate and their composition concentration of Ag ions at a 2,000 ng L^{-1}; either decrease or increase of diatom (Climacosphenia and Nitzschia, Navicula) and

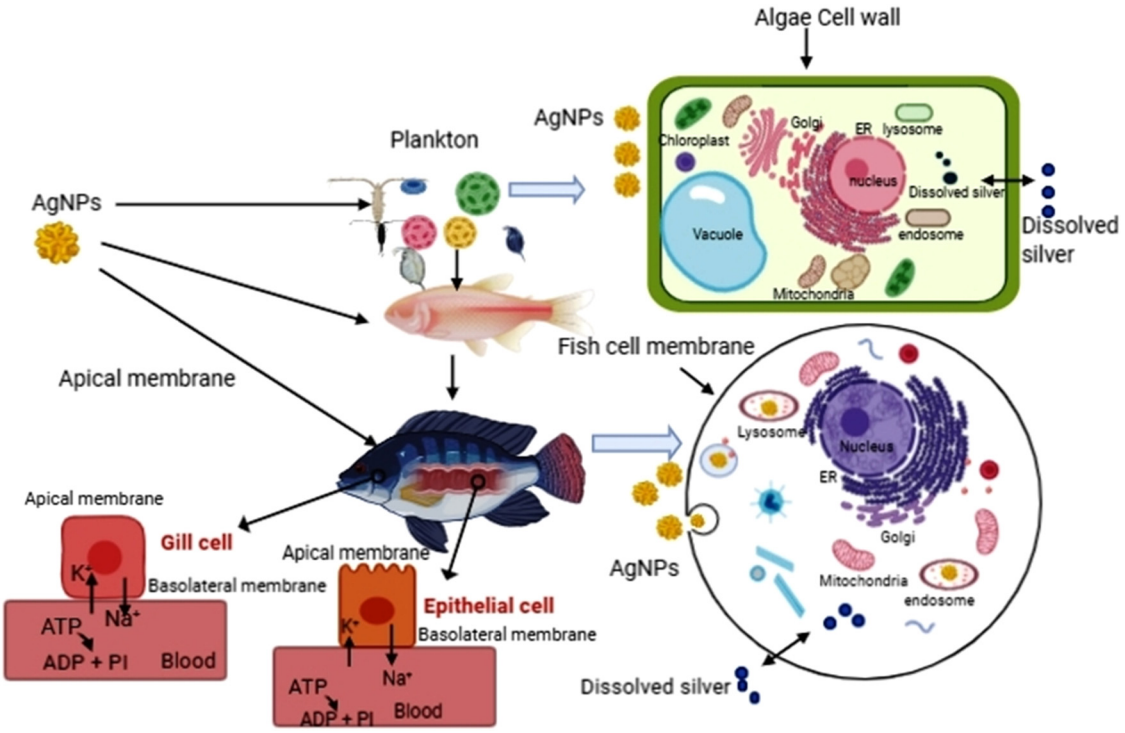

Figure 5: The effect of AgNPs' dissolutions on aquatic organisms.

Dinoflagellate (Prorocentrumand Gyrodinium and Gymnodinium) [94]. Other research showed that the particle size of AgNPs was important in determining the hazardous impact of AgNPs in the gills and intestines of adult zebrafish [95]. Zebrafish have a similar genetic composition to human cells, and their larvae and embryos are transparent which allows for easier observations. A prominent Ag^+ deposition in the basolateral membranes for 20 nm Ag silver particles disrupted the Na^+/K^+ ion channel, as Ag^+ can compete for Na^+ and disrupt the function and integrity of the channel; this was confirmed by a reduction in ATPase activity, the 20 nm particles caused significantly higher inhibition and disruption than the larger size particles.

6 The fate-life cycle of AgNPs in soil

It is known that AgNPs can reach soil from the discharge of waste liquid effluents or sludges during their synthesis or industrial production (either intentionally or unintentionally) and/or the disposal and recycling of goods containing AgNPs (Figure 6) [96,97]. Industrially, once AgNPs are discharged in waste streams, they accumulate in sewage sludge in advanced waste treatment plants. A large portion of sewage sludge is utilized in agricultural soil as fertilizers in various countries, *e.g.*, UK, USA, and Egypt. In some other European countries, these sewages are incinerated. Naturally formed AgNPs have also been documented in soil and aquatic environments through the reduction of geogenic (Ag^+) traces in the existence of (S^{2-}) ions, as a reducing agent, under some atmospheric conditions, *e.g.*, dark/light, temperature, and anoxic/aerobic conditions [98].

When AgNPs reach natural soil systems, they are exposed to many transformation mechanisms like dissolution, oxidative stress, aggregation, agglomeration, destabilization, chlorination, and sulfidation reactions. The soil environmental conditions (soil texture, moisture, ionic strength, pH, inorganic/organic matter, microbial diversity, *etc.*) can significantly affect the surface properties and fate-life cycle of AgNPs, in terms of their surface charge, size, shape, agglomeration, uptake, migration, and dissolution processes [99]. For example, the sulfur-rich soil contaminated with AgNPs can initiate a sulfidation reaction to form Ag^0/Ag_2S core–shell particles with low biological toxicity relative to AgNPs [100,101]. This is because the solubility of Ag_2S particles is lower than the AgNPs themselves; hence, the dissolution process and release of toxic silver ions into the environment are limited.

It was also demonstrated that sedimentary humic acids (SHAs, especially aliphatic-based SHAs) accelerated

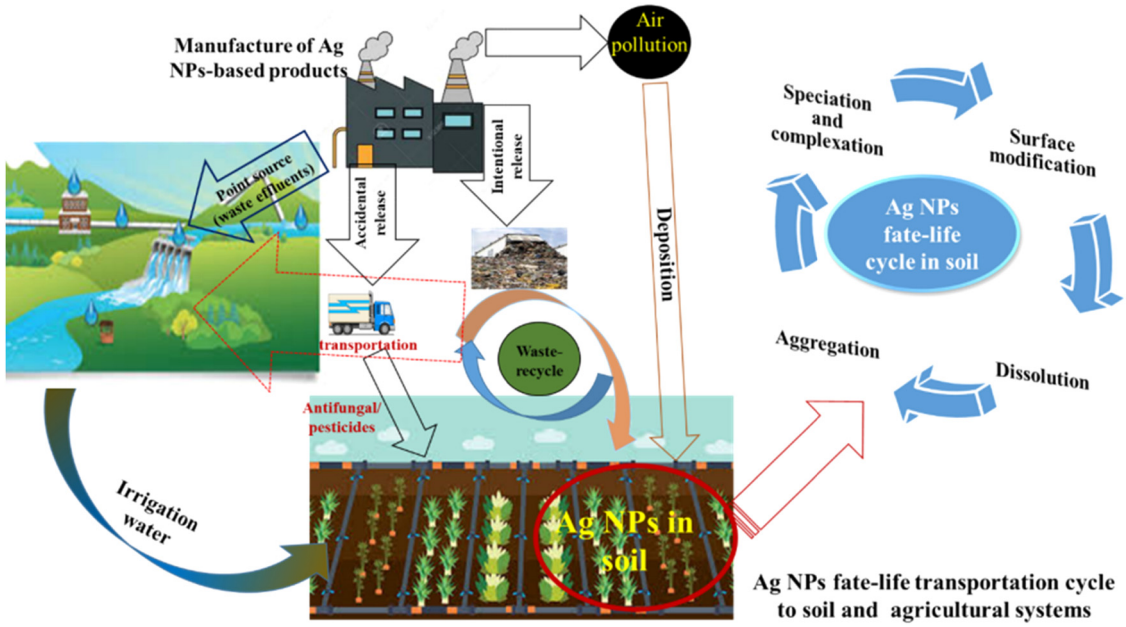

Figure 6: The fate-life cycle of nanoparticles (*e.g.*, silver nanoparticles; AgNPs) from industrialization to soil and agriculture systems.

the formation of colloidally stabilized AgNPs by the reduction of silver ions in soil when allowed to react for 25 days at 22°C or 3 h at 90°C [102]. It was noted that an increase of ionic strength leads to an increase in the aggregation of AgNPs, *i.e.*, hydrodynamic radius, and their dissolution process to Ag^+ ions with a high toxicity effect (alleviate oxidative stress) on *Escherichia coli* (*E. coli*) [103]. High chloride contents can also mediate significant changes in the toxicity and morphology of AgNPs by forming $AgCl^0_{(s)}$ bridging and species of negatively charged Ag $Cl_x^{(x-1)}$ with less toxicity on *E. coli*. Similarly, an increase of monovalent (K^+ or Na^+) cations could alter the behavior of AgNPs, *e.g.*, morphological transformation, size, dissolution, and aggregation, and their related toxicity to *Caenorhabditis elegans* (*C. elegans*) [104]. In particular, the higher concentration of K^+ or Na^+ cations (from 1–10 mM) significantly decreased the size of AgNPs (<5 nm). In this case, the smaller size of AgNPs increased their destabilization and toxicity against *C. elegans*, as determined by broad size, lifespan, and germ cell apoptosis [104]. The high contents of natural organic capping like PVP, citrate, and polyethylene glycol (PEG) could also increase the stabilization of AgNPs in the environment, causing a decrease in the production of Ag^+ ions [105,106]. When a high content of oxygen occurs, the oxidative dissolution of AgNPs will be enhanced to produce silver ions, causing high toxicity to *E. coli* [107]. Soil organic matter and redox potential (Eh) may also induce speciation of AgNPs and the release of silver (Ag^+) ions after 28 days of incubation, while other species like metallic AgCl and AgNPs emerged after two days of incubation from the initial aging of silver to soil [108]. These results indicate that the soil nature and composition significantly affected the fate of AgNPs and their associated risks to environments. However, it is noteworthy that the related toxicity of these transformed species in the *in vivo* cells is still not clear.

From the above findings, it can be concluded that the fate-life cycles (transformation, migration, dissolution, aggregations, and toxicity) of AgNPs and their intrinsic characteristics and toxicity in the soil are governed by many parameters, such as the disposal routes (liquid or sewage solids) and the surrounding environmental conditions. These parameters should be accurately considered while assessing AgNPs' toxicity on the environment and human health.

AgNPs are often used as nano-pesticide and antifungals in agriculture [109–111]. Since crops acquire their micronutrients from the irrigation water and soil, the direct contact of AgNPs in the soil/irrigated water with the plant roots could lead to their absorption and transportation to the plant organs (roots, shoots, stems, or leaves). Hence, it is crucial to identify the fate, localization, and toxicity of AgNPs in soil and their consequent physiological effects on soil biota, human health, and food safety [112]. Moreover, there are several pathways for the fate and transportation of nanomaterials, *e.g.*, AgNPs, from soil to plants' organs (Figure 7), including (1) the diffusion into seeds, then to the root and migration

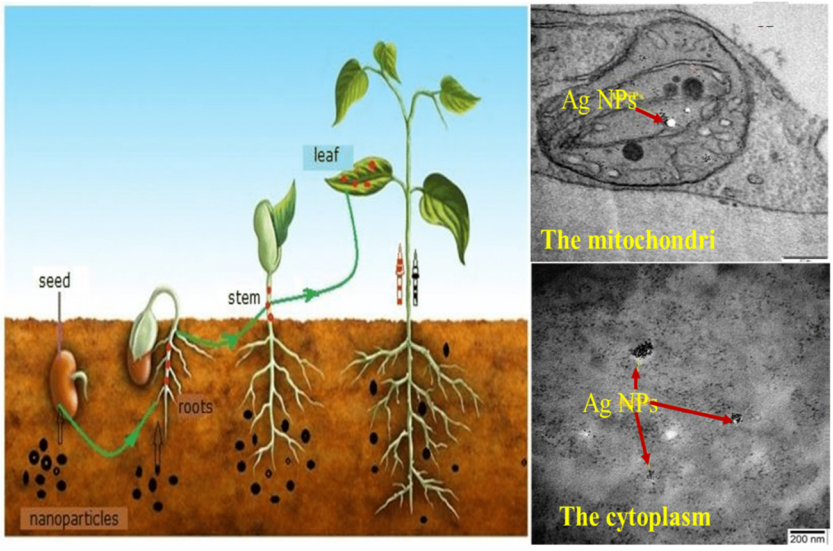

Figure 7: Migration paths of nanomaterials (*e.g.*, silver nanoparticles; AgNPs) from soil to the plant organs and the corresponding TEM images of AgNPs in the mitochondria (leaf cells) and the cytoplasm (stem cell) of wormwood (*Artemisia absinthium*) [113].

to plant organs, (2) absorption/uptake by the plant roots, then migration to other organs, and (3) the direct migration/movement to plant organs and their localization in the epidermal or xylem cells [113,114]. These distribution/migration pathways from soil/water to plant cells are known to be size-, concentration-, and AgNPs' physicochemical features-dependent, along with the nature of crops and the soil structure (composition and thickness).

Generally, the major findings in this area suggested that the toxicity effects of AgNPs in agriculture are mainly dose-dependent [98]. Also, AgNPs in irrigated water can move and penetrate soil layers up to 5 cm thickness, then migrate to seed tissues within the first 24 h of irrigation [113]. Also, AgNPs can quickly diffuse and translocate into plant cells during germination, as confirmed by TEM analysis of leaf and stem cells of wormwood grown in soil contaminated by AgNPs (Figure 7). Such observation indicates that the crops with fibrous roots are more susceptible to uptake toxic nanoparticles from contaminated soil [113].

The seedling growth in grass shoots and roots of *Lolium multiflorum* can be inhibited when exposed to a high concentration of small-sized gum arabic (GA)-coated AgNPs (6 nm) due to the cell damage resulting from the toxicity effect of Ag^+ ions released from the AgNPs' dissolution [115]. However, such toxicity effect can be decreased by sunlight irradiation that induces irreversible aggregation of AgNPs [116].

Abnormalities in the levels of antioxidant enzymes and fatty acids in peanut plants were also observed upon exposure to citrate-caped AgNPs in sandy soil (50–2,000 mg kg^{-1}) for 98 days due to the cell damage and accumulation of AgNPs in shoots and edible portions, confirming the unsafety of crops [117]. In another work, the chemical transformation (homeostasis) of commercial nanoparticles of Ag^o and Ag_2S into Ag^+ ions inside the roots/epidermis of wheat (*Triticum aestivum*) was also reported as a result of the gene defense function of plants [118].

These observations demonstrated the complexity of assessing AgNPs' toxicity in crops due to their transformation mechanisms, which depend on AgNPs' shape and concentrations and the nature of plant cells. Hence, in ecotoxicological investigations, it is important to define another monitoring system for the toxicity effect of AgNPs (or other nanomaterials) based on different biological biomarkers (enzymes, fatty acids, lipids, nutrients, *etc.*) to assess the protection of edible plants for the sake of human health.

Soils are complex matrices containing wide biodiversity of microbial communities and organic/inorganic contents, which control the fate-life cycle and toxicity of AgNPs in soil [119]. In this regard, it was demonstrated that the negative impacts of AgNPs on soil microbial communities are dependent on concentration, size, agglomeration, dissolution, the transformation of AgNPs, and their residence time in soil, as well as the chemical nature and texture properties of the soil itself [120,121].

For example, the toxicity of AgNPs significantly decreased in the microbial community in the soil in the case of (i) a sulfur-rich soil, *i.e.*, transformation to sulfurized Ag_2S from low-solubility [122] and (ii) the presence of fulvic

acid as a reducing agent, *i.e.*, dissolution decreased [123,124]. Further, it was reported that the low concentrations of AgNPs (<1 mg kg^{-1}) in the soil had no major impact on soil microbial communities after a short duration of exposure (days to a month), while, after one year, soil nitrification was greatly changed [125]. However, it should be noted that the microbial communities may protect themselves against AgNPs' toxicity by forming microbial aggregates as a defense mechanism [126].

Also, it was reported that soil microorganisms might develop other extrinsic/intrinsic defense mechanisms, *e.g.*, extrinsic like adaptive/point mutations of resistance genes or intrinsic like downregulation of porins, efflux pumps, and chromosomal resistance genes, to mitigate the toxicity of AgNPs after repeated exposure to AgNPs at low concentrations [127,128]. On the other hand, it is not expected to rule out the toxicity behavior of AgNPs against soil microorganisms using these intrinsic/extrinsic defense mechanisms, especially at high silver concentrations, because AgNPs are not naturally distributed in the soil system. These findings suggest that AgNPs may negatively affect soil fertility (biological distribution) and plant safety (crop damages), and hence, the probability of their consequence negative impacts may increase on human health and wild animals.

7 Toxicity of AgNPs against different cell lines

Several studies have shown that AgNPs would penetrate the membranes of cells [129] and the blood-brain barrier; [130] thus, AgNPs can be deposited and interact with biological processes in organs. AgNPs have been shown to induce a toxic response of various mammalian cell lines [16]. The exposure to AgNPs, therefore, led to reduced viability or lactate dehydrogenase (LDH) production in cells of rats' liver [131], stem cells in mice germline [132], in fibroblasts of humans [133], and adrenal cells in rats [134]. *In vitro* damaging caused *via* AgNPs on lung carcinoma (A-549) cells of humans was investigated by Chairuangkitti *et al.* and a direct association was identified with the production of ROS [16] as shown in Table 1.

AgNPs triggered toxic effects that can be categorized into ROS-independent and ROS-dependent pathways. Several experiments have demonstrated that AgNPs can be toxic to the vital organs of humans and especially to the lung [135]. Porntipa Chairuangkitti *et al.* [16] evaluated the *in vitro* mechanism of AgNPs' (<100 nm) toxicity in relation to the generation of ROS in A549 cells. Ag NPs caused ROS formation in the cells, a reduction in their cell viability and mitochondrial membrane potential (MMP), an increase in the proportion of cells in the sub-G1 (apoptosis) population, S phase arrest, and downregulation of the cell cycle-associated proliferating cell nuclear antigen (PCNA) protein, in a concentration- and time-dependent manner. Pretreatment of the A549 cells with *N*-acetyl-cysteine (NAC), an antioxidant, decreased the effects of AgNPs on the reduced cell viability, change in the MMP, and proportion of cells in the sub-G1population, but had no effect on the AgNPs-mediated S phase arrest or downregulation of PCNA. These observations allow us to propose that the *in vitro* toxic effects of AgNPs on A549 cells are mediated *via* both ROS-dependent (cytotoxicity) and ROS-independent (cell cycle arrest) pathways [16].

Cytotoxicity of silver NPs can be controlled by many factors including the synthetic route (chemical, physical, and biological) and physicochemical properties (size, shape, concentration, and aggregation/agglomeration) [136]. AgNPs possess powerful oxidative activity that releases Ag ions. Ag ions can induce serious effects on biological macromolecules like DNA and mitochondria through some actions such as induced cytotoxicity, genotoxicity, immunological responses, and eventually, cell death [137–140].

8 The mechanisms of AgNPs' accumulation in human cells and their related diseases

Accumulation of Ag ions inside cells, through either endocytosis or diffusion, leads to mitochondrial dysfunction through glutathione (GSH) reduction, lipid peroxidation, ROS-derived DNA damage, apoptosis, and necrosis [77,148]. The mode of action begins with AgNPs' interaction with cell membrane proteins and activation of signaling pathways that produce ROS, which in turn contributes to protein and nucleic acid degradation and eventual inhibition of cell proliferation [148]. Another induced mechanism is thought to be related to oxidative stress. H_2O_2 and superoxide radical (O_2^-) can act as ROS that is important for keeping normal physiological responses. Even so, excessive ROS can harm the antioxidant defense system, resulting in protein, lipid, and DNA damage [149].

Table 1: The summary of the recent reports of the cytotoxicity of silver NPs against different cell lines

Preparation route	Particle size (nm)	Shape	Concentration ($\mu g\,mL^{-1}$)	Coating materials	Tested cell line	Cytotoxicity assay	Recorded effect	Duration of incubation (h)	References
Green synthesis using *Eucalyptus tereticornis* leaf extract	24–54	Spherical	63.257	*Eucalyptus tereticornis* leaf extract	MCF-7	MTT assay	50% inhibition of total cell number	48	[141]
Biological synthesis using chitosan as capping and reducing agent	17–50	Spherical	48	Chitosan	HepG2	– MTT assay – Trypan blue exclusion assay	50% inhibition of total cell number	24	[142]
Green synthesis using *Delonix regia* leaf extract	72.77	Nonuniform (anisotropic)	– 14.96 for A549 and – 15.96 for SiHa	*Delonix regia* leaf extract	– A459 – SiHa	MTT assay	50% inhibition of total cell number	48	[143]
Biological synthesis using Asian spider flower leaf extract	<50	Spherical	40	Asian spider flower leaf extract	MCF-7	– MTT assay – Apoptosis assay	50% inhibition of total cell number	48	[144]
Green synthesis by *Cassia roxburghii* extract	10–30	Spherical	20	*Cassia roxburghii* extract	Vero normal cells	MTT assay	50% inhibition of total cell number	24	[145]
Green synthesis by *Pistacia atlantica* leaf extract	40–60	Spherical	200	*Pistacia atlantica* leaf extract	HUVEC	MTT assay	20% inhibition of total cell number	48	[146]
Chemical reduction of $AgNO_3$ by chitosan	10–230	Spherical	—	Chitosan	L929 fibroblast cells	MTT assay	3% inhibition of total cell number	24	[147]

Apparently, after entering the cell, AgNPs usually produce ROS [150]. After increasing ROS levels, GSH level dramatically decreases, and LDH increases in the medium, which eventually leads to apoptosis [151]. Moreover, redox homeostasis can be affected by ROS generation at the intracellular level. Consequently, protein carbonylation and lipid peroxidation take place. Simultaneously, antioxidant enzyme activity and the glutathione level are decreased. Thus, protein-bound sulfhydryl group depletion, antioxidant enzyme activity, and glutathione level promote apoptosis [152]. Therefore, apoptosis-mediated cell death is the main cytotoxic impact of silver NPs [153]. Apoptotic pathways like AKT, p53, and MAPK which activate cell death are also reported [154].

8.1 Trojan horse effect

The Trojan horse effect was suggested as the toxicity mechanism of AgNPs [155]. Some metal oxide nanoparticles affect lung epithelial cells by this effect [156]. According to the Trojan horse theory, if silver NPs with very small size (≤40 nm) cross through the cell membrane, they may continuously release (Ag^+) silver ions once inside [157]. Inside the cell, the silver ions (Ag^+) can form ROS and cause lipid peroxidation [158]. Ag^+ ions attach to the host cell, consumed by the cells before reaching the vital organelles inside the normal cells [159] as shown in Figure 8a. In a defense response to the Ag^+ ions, the normal cells secrete the reductase enzyme to reduce the dangerous effect of Ag^+ ions and finally engulf silver NPs, which also carries the liberated Ag^+ ions outside their surface [160] as displayed in Figure 8b. AgNPs with the formed Ag^+ ions inside the normal cells are considered to be the beginning point of the toxic behavior and the hazardous effect starting inside the normal cell [15] as exhibited in Figure 8c. Figure 8b and c displayed the Trojan horse effect [161].

Finally, the positively charged Ag^+ ions will react with the negatively charged oxygen and nitrogen atoms in the vital organelles like DNA, mitochondrion, and the thiol group presented in protein structures and enzymes, which in turn interrupts the normal cell reproduction, and finally, the death of cell will occur [162] as presented in Figure 8d.

The evaluation of AgNPs toxicity is essentially affected by their movement inside the human body [163]. Additionally, because of the high surface area of AgNPs, pollutants may be adsorbed on the surface of AgNPs [164]. In the synthesis of nanomaterials-based compounds, a growing aggregation of AgNPs in the water and/or the atmosphere may happen [165]. Also, AgNPs can be absorbed and

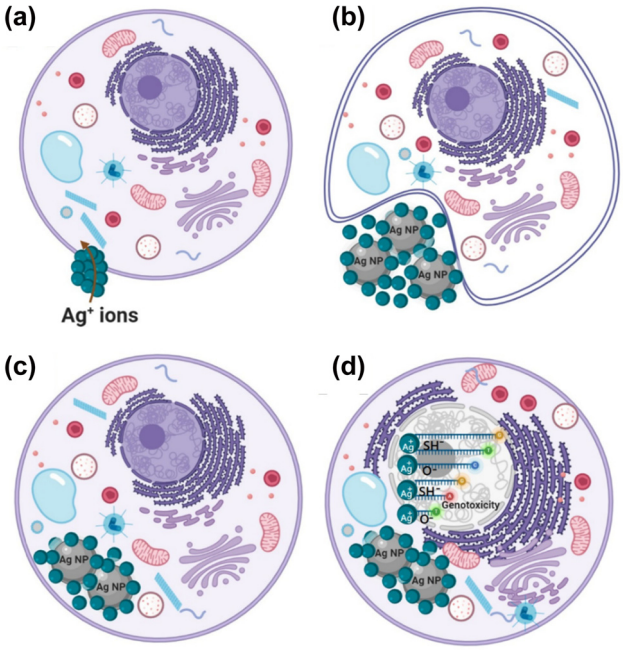

Figure 8: Toxicity of AgNPs and silver ions on the normal cells and Trojan horse effect. (a) cell defense response to Ag^+ (b) engulf AgNPs and Ag^+ ions (c) excite of Ag ions inside cell and (d) death cell occur.

utilized by some crops or different living animals; the present AgNPs can arrive at the food series [166]. Through the past ten years, it was believed that AgNPs and silver ions are nonlethal to animal and human cells, but severe argyria and blue skin coloration were observed after contact with nano silver-based materials [138].

The principal AgNPs' uptake probabilities inside the human body are by the first-line defense: skin by direct contact, or the respiratory region through inhalation, or finally through the gastrointestinal tract by AgNPs-contaminated foods [167]. Thus, AgNPs' quantity, configuration, and exterior adjustment perform an essential function in human organs [168]. AgNPs present in the respiratory region can transfer to the lymph stream, then the blood circulation [168]. Recent studies showed that AgNPs can move into the blood-brain barrier [169] and penetrate cell membranes [129 thus accumulating in vital organs and biological systems [129]. Because AgNPs were the subject of various earlier investigations, the potentially dangerous impacts of AgNPs were revealed. It is significant to examine the lethal effect more strongly. Accordingly, Figure 9 shows the toxic impact of AgNPs and Ag ions on human organs and their related diseases. The different diseases in various human organs were displayed in Figure 9, after the exposure to the toxic levels of AgNPs in drinking water, determined to be above 5.0 μg kg^{-1} body weight/day (according to the EPA) [170].

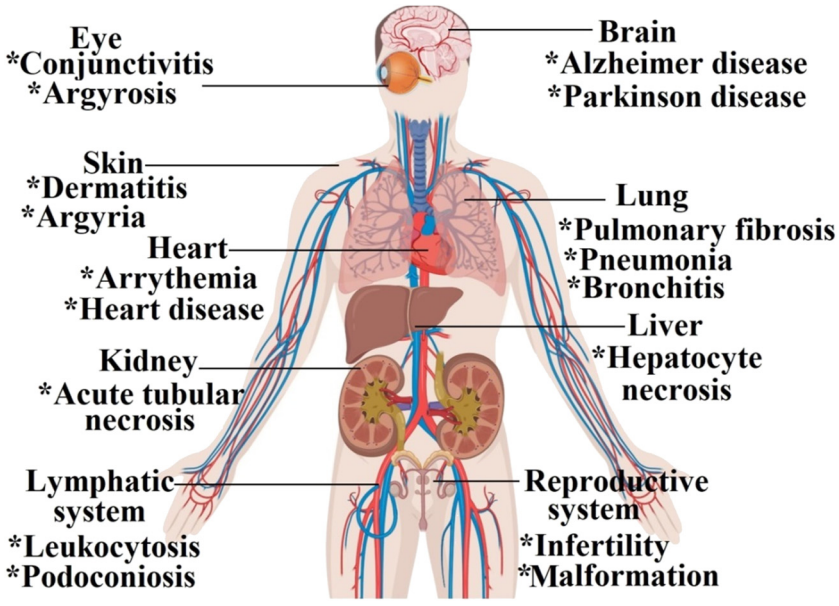

Figure 9: The related diseases after exposure to the toxic level of silver NPs.

Despite a notable uptake within the normal cells, AgNPs possessed an entirely irrelevant hazardous effect on kidney cells at concentrations more than 25.0 μg mL^{-1} [171] as displayed in Figure 10. Brain cells subjected to 2.0 μg mL^{-1} of AgNPs did not reveal any important difference in the levels of total glutathione, reduced glutathione, glutathione reductase, superoxide dismutase (SOD), catalase, and glutathione peroxidase activity. On the contrary, above 4.0 μg mL^{-1}, AgNPs revealed a notable decrease in the levels of all the brain enzymes, reduced glutathione, and total glutathione [172] as shown in Figure 10. In severe oral and dermal toxicity experiments, none of the tested models displayed any unusual symptoms or death at a dosage level less than 2.0 μg mL^{-1} [173] as exhibited in Figure 10. After examining the cytotoxicity of AgNPs (50 μg mL^{-1}) on the lung cells, the results indicate that there was no difference in the level of surfactant protein-B in the bronchoalveolar lavage. After seven days of the introduction of AgNPs (at concentration more than 50 μg mL^{-1}), an increase in bronchoalveolar lavage cell numbers and a reduction in lung function were recognized [174].

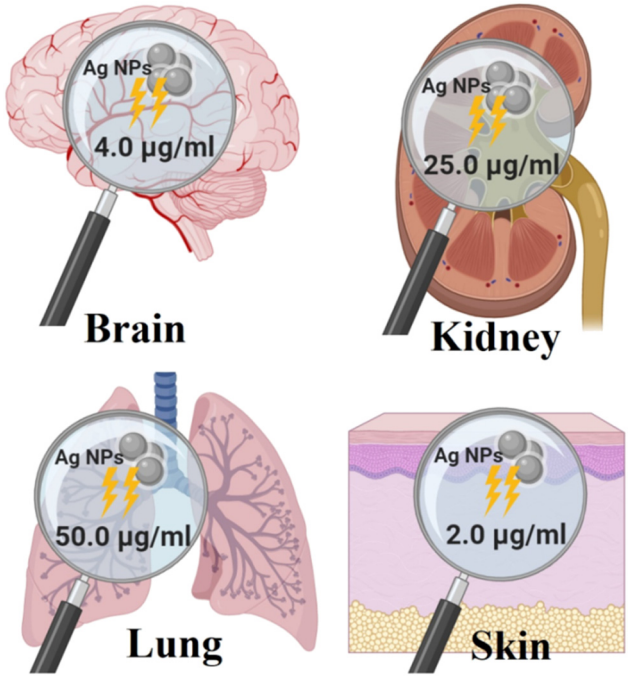

Figure 10: The toxicity levels of AgNPs in different organs.

Scientific information on the potentially harmful effects of AgNPs on human health severely lags behind their exponentially growing applications in consumer products [175]. In assessing the toxic risk of AgNP usage, the liver, as a detoxifying organ, is particularly important. Different studies [176,177] were aimed to explore the toxicity mechanisms of nano and ionic forms of silver on human cells. Their results showed that silver ions and AgNPs reduced cell viability in a dose-dependent manner. The IC50 values of silver ions and AgNPs were 0.5 and 50 mg L^{-1}, respectively. AgNPs affected the transform toxic metabolites (TTM); the LDH leakage and inhibition of albumin synthesis, along with decreased alanine transaminase (ALT) activity, indicated that treatment with either AgNP or Ag ions resulted in membrane damage and

reduced the cell function of human liver cells. Evaluation of oxidative stress markers demonstrating depletion of glutathione (GSH), increased ROS production, and increased SOD activity indicated that oxidative stress might contribute to the toxicity effects of nano and ionic forms of silver. The observed toxic effect of AgNPs on human hepatic cells was substantially weaker than that caused by ionic silver, while the uptake of nano and ionic forms of silver by HepG2 cells was nearly the same [176].

9 Different methods for silver ions detection

Different detection methods for Ag^+ ions detection were developed for the nanomolar (nM) level. There are several strategies for silver (Ag^+) ions detection that rely on the combination of metal ion analysis with enzymatic or oxidative amplifying strategies. It was recognized and developed as a powerful tool for improving the sensitivity of metal ion detection. The biosensors approach gained attention due to their high sensitivity, less time consumption, and operational convenience [178]. These methods are based on nucleic acid interaction with metal ions in very low concentrations which can be detected.

For instance, in the past few years, significant advances have been made in the analysis of nanoparticles using single-particle ICP-MS methods, and methods have also been developed for analysis in tissues. These methods were developed due to the increased production of nanoparticles which leads to increased volume of these substances in the environment, in particular in sewage and sewage sludge, and also in water, sediments, and soils. The methods must be widely available, uncomplicated, and inexpensive, as well as accurate and reliable to become commonly used by both research and control laboratories. Hence, it is necessary to develop some new methodological solutions and subsequent applications for analytical practice. It would allow researchers to obtain repeatable and reliable results which could provide the basis for adequate analytical interpretation [179]. Mitrano *et al.* [180] tracked the AgNPs' dissolution at environmentally relevant concentrations in the laboratory, natural, and processed waters using single-particle ICP-MS. The track changes in particle diameter over time for 60 and 100 nm Ag NPs coated by citrate, tannic acid, and PVP were quantitatively demonstrated using ICP-MS by direct measurement of Ag^+ (aq.). Montano *et al.* [181] used ICP-MS for fast detection time ((~500 μs)) of Ag^+ (aq.) in very low concentration (ng L^{-1}). Although an increasing number of analytical techniques and methods are becoming available for the detection, characterization, and quantification of AgNPs, their application to complex samples is still very limited and far from being incorporated into routine analysis. AgNPs can be transformed into different four complex environmental matrices during anaerobic treatment of wastewater and post-processing of sewage sludge such as Ag carbonate (Ag_2CO_3), Ag oxide (Ag_2O), Ag sulfide (Ag_2S), and "bulk" AgCl [182]. To rid silver ions complexion, additional development of standard ICP methods was needed to get information about inorganic nanoparticles, the use of ICP-MS in combination with field-flow fractionation (FFF) separations or in single-particle detection mode are finding their way in the most recent analytical approaches, because of the supplementary information that can provide [183]. In addition, there have been advances in determining the speciation of Ag and the transformation products of AgNPs using X-ray absorption spectroscopy (XAS) and X-ray absorption near edge structure (XANES) techniques: [184] used microalga *Coccomyxa actinabiotis* to take up and cope with Ag^+ that was detected using XAS; X-ray diffraction over the concentration range of 10−7 to 10−2 M. Lombi *et al.* [182] used XANES spectroscopy to investigate the behavior and transformation of AgNPs. XANES data were collected at the Materials Research Collaborative Access Team (MRCAT) beamline 10-ID, Sector 10 located at the Advanced Photon Source (APS), Argonne National Laboratory (ANL), Argonne, IL [185].

9.1 Biosensors

Ono *et al.* [186] stated that silver ions (Ag^+) could selectively connect *via* coordinating bonds with cytosine (C) molecules to form a strong C–Ag^+–C framework and transform single-stranded DNA into the double-helix structure. The C–Ag^+–C interaction is highly selective because the C–C mismatching interaction with silver ions is stronger than other metal ions. Xie *et al.* [187] used an electrochemical-based biosensors method to design a fluorescent FAM-labeled DNA for silver ions detection. The interaction of cytosine and silver ions (C–Ag^+–C) in the existence of graphene oxide results in the mismatch of C–C that leads to increasing the intensity of FAM fluorescence and a red shift of the emission wavelength (λ_{em}) of FAM fluorescence.

Li *et al.* [188] prepared a sensitive silver ions detection method based on a fluorescence biosensor using cytosine (C). Since oligo-1 implies C–C mismatches in cytosine (C) molecules, the existence of Ag^+ ions can be collected to form pairs of C–Ag^+–C that result in a blunt

terminus with a structure of double helix. The obtained double-helix shape can be destroyed by exonuclease III to release silver ions and trigger DNA. The released silver ions bind with (oligo-1) and (oligo-2) that may be produced in the digestion cycles and promote the plentiful G-quadruplex DNA generation. Hybridization *N*-methyl-mesoporphyrin IX (NMM) fluorochrome with the G-quadruplex DNA allows Ag^+ to be detected in the concentration from 5 up to 1,500 pM L^{-1}, with a limit of detection at 2 pM L^{-1}.

Xu *et al.* [189] developed a colorimetric approach for silver ions (Ag^+) detection based on the interaction among Methylene Blue (MB) and C-rich Single-Stranded DNA (ssDNA). When the MB was absorbed on the S-SDNA surface, the MB color changed from blue to purple. However, in the existence of Ag^+ ions, the specific C–Ag^+–C pair is formed and removed the interaction among S-SDNA and MB, returning to the blue color. For DNA duplexes, pairs of cytosine–cytosine (C–C) can catch Ag^+ exclusively to form base pairs C–Ag^+–C. Based on this feature, Li *et al.* [190] developed a method for silver ions' detection by adding cysteine that removed base pairs C–Ag^+–C because it binds to Ag^+ instead of cytosine. The amount of free cysteine was critical for colorimetric detection using ABTS–H_2O_2 (ABTS = 2, 2′-azinobis-(3-ethylbenzthiazoline-6-sulfonate)). Li *et al.* [191] developed a biosensor based on electro-chem-iluminescence (ECL) of Ru (bpy)2(mcbpy-O-Su-ester)(PF6)2 for a highly sensitive and selective Ag^+ detection. This process, based on deoxyribonucleic acid (DNA tetrahedron TS primer (STTS)), consists of three hybridized oligonucleotides forming three dual-stranded DNAs, close to a Y-shaped DNA structure. The formation of DNA-TS makes signal intensity change of Ru (bpy)2(mcbpy-O-Su-ester)(PF6)2 at different concentrations of Ag^+ ions.

9.2 Chemical sensors

The highly sensitive chemical colorimetric sensor approach for silver ions' detection in the Picomolar (pM) range was established by Gao *et al.* [192]. This approach uses Pt nanocubes coated by PVP as artificial peroxidases. The peroxidase substrates generate a colored signal that diminishes the existence of Ag^+ ions. This colorimetric approach will achieve an 80 pM as an ultralow detection limit and a 10–2–104 nM as a wide dynamic range.

Alizadeh *et al.* [193] described a colorimetric approach for silver ions' (Ag^+) detection that comprises measuring the changes in SPR of modified gold nanoparticles (AuNPs) with furfuryl alcohol (Fu-AuNPs). The silver ion (Ag^+) detection occurred within the limit of 12 nM.

Selva Sharma *et al.* [194] developed a colorimetric sensor based on Ascorbic Acid (AA) and AuNPs for silver ions' detection at concentrations of 2–28 μM in aqueous solutions. The mechanism of sensing depends on the Ag^+ reduction to Ag^o on the surface of AuNPs/AA. The reduction of silver ions resulted in the SPR blue shift from AuNPs at 512 nm and it is accompanied by a new peak observed at around 385 nm.

Ghobashy and Mohamed [195] prepared a nanocomposite membrane of Cu–(PAAc/PVA) by gamma radiation for Rapid Colorimetric Detection (RCD) of silver Ag^+ and mercury Hg^{2+} ions associated with significant changes of color of the Cu–(PAAc/PVA) membrane from yellow to dark green and pale gray color, respectively. A detection limit of Hg^{2+} and Ag^+ as low as 10^{-5} and 10^{-6} M, respectively, occurred.

Wang *et al.* [196] describe a simple colorimetric sensor employing cationic polymer single-stranded AuNPs and ligand of DNA (ssDNA) to detect silver ions (Ag^+). The cationic polymer is combined with ssDNA leading to AuNP aggregation, thus changing color. When the silver ions are present, they bind to cytosine (C) that prevents polymers' interaction with ssDNA. The AuNPs strategy used as a colorimetric sensor for silver ions is in several studies [197–200]. Another nonmetal ion used as a colorimetric sensor of silver ions is carbon dot. Carbon dots (CDs) have fluorescence emission properties that quench when its surface is attached to metal ions such as silver ions [201–203]. Murugesan *et al.* [204] synthesized CDs with strong fluorescent emission at 479 nm when excited over 370 nm. This fluorescent emission was quenched in the existence of silver ion (Ag^+) in an aqueous solution.

10 Recommendations for future research

The toxicity of AgNPs is caused by the release of (Ag^+) silver ions. Silver widely disperses throughout the body and in laboratory animals regardless of form or exposure and can cross both the placental and blood-brain barriers. Silver, in exposed humans, was found abundantly across the body. To limit the toxicity of (Ag^+) silver ions released from AgNPs, it is recommended to coat AgNPs to prevent their dissolution (Figure 11).

AgNPs coating is an excellent technique to improve their advantages and limit their toxicity. Of course, the

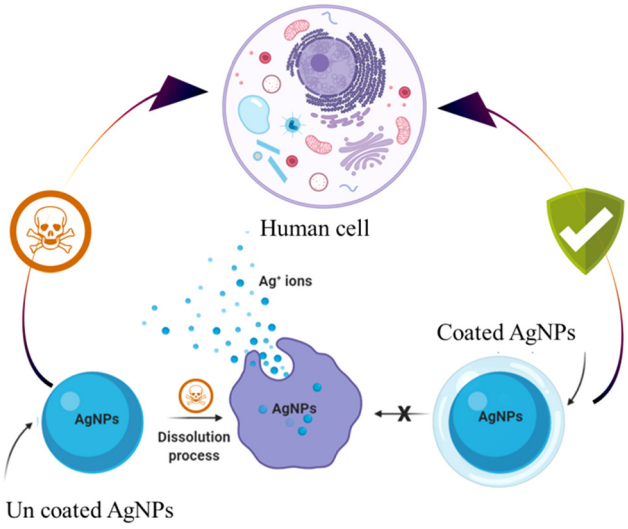

Figure 11: A scheme explaining how to limit the toxicity of silver ions.

coating technique can enhance the AgNPs' stability *via* the electrostatic stabilization between silver particles and can reduce their particles' agglomeration. One of the main functions of coating is to avoid the cytotoxic impact of AgNPs on living cells [205]. Most of the coating substances have proved successful in stabilizing AgNPs, preserving their distinctive structure, and reducing silver ions dissolution which are major contributing factors of AgNPs toxicity. The role of the coating depends heavily on the characteristics of the coating substances, including organic coating materials such as synthetic polymer and natural polymer and inorganic coating materials such as carbon dot, TiO_2, graphene, *etc.* Zook *et al.* investigated the dissolution of AgNPs in cell culture medium (DMEM) and observed a fractional dissolution of various polymer-coated AgNPs. The dissolution was increased in the biological medium in comparison to inorganic salt solutions which is presumably owing to the complexation of the liberated silver ions [206].

The behavior of polymer-coated AgNPs in two simulated biological fluids representative of the fluids present in lungs, as inhalation is regarded as an important uptake route in humans [207], was studied by Stebounova *et al.* [208]. The results showed that the initial concentration of nanoparticles has a significant impact on their stability and sedimentation. The authors use Dejaguin–Landau–Verwey–Overbeek (DLVO) theory as a basis for theoretical calculations explaining nanoparticles' behavior in solution, and their experimental results concur with the theory used. According to DLVO theory, the stability of particles is determined by the net electrostatic surface interactions of the particles and their Van der Waals forces. Polymer-coated AgNPs (with higher surface charge) were more stable than the other studied type (with unspecified coating) in both water and simulated biological fluids. The release of Ag ions into interstitial or lysosomal fluids appears to be negligible as determined by ICP analysis in these simulated fluids. Samberg *et al.* (2010) identified the toxicity of AgNPs *in vitro* and *in vivo* human epidermal *keratinocytes* [209]. The cells were subjected to different concentrations of coated and uncoated silver carbon, individually. The cells subjected to uncoated silver showed decreased viability. On the contrary, there was no toxicity observed in the cells treated with coated silver carbon [210].

11 Conclusion

Although AgNPs have been extensively used in several applications including water treatment, health, and industry, silver ions immobilized by AgNPs are harmful to humans and the environment. Various preparation methodologies and the effect of environmental factors largely affect the fate of AgNPs (precipitation, dissolution, aggregation). These observations demonstrated the complexity of assessing AgNPs' toxicity in crops due to their transformation mechanisms, which are dependent on the AgNPs' shape and concentration and the nature of plant cells. The previous research study deals with the toxicity of AgNPs and related diseases in the human body confirmed that the (Ag^+) ions can induce serious effects on biological macromolecules like DNA and mitochondria through some actions such as induced cytotoxicity, genotoxicity, immunological responses, and eventually cell death. Some researchers suggested that AgNPs could serve as a "Trojan horse," avoiding common barriers and releasing Ag^+ ions, and causing damage to the cells. In a defense response to the Ag^+ ions, the normal cells had been secreted by the reductase enzyme to reduce the dangerous effect of Ag^+ ions, and finally engulfs AgNPs which also carries outside their surface the liberated Ag^+ ions. The toxicity mechanism of AgNPs depends on the degree of silver ions' dissolution from their nanoparticles form; the AgNPs' coating alerts their cytotoxicity. The coated AgNPs stabilized with PVP and other organic compounds could decrease the dissolution of coated silver particles in water for several days than AgNPs uncoated.

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