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Characterization and potential applications of silver nanoparticles: an insight on different mechanisms

Anton N. Kodintcev *

Institute of High Temperature Electrochemistry of the Ural Branch of the Russian Academy of Sciences, Ekaterinburg 620066, Russia

* Corresponding author: antonkodintsev@mail.ru

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Abstract

In the 21st century, a great interest is devoted to biomedical application of various nanoparticles, particularly, as a means of improving the effectiveness of therapy for different diseases. Silver nanoparticles (AgNPs) are among the most studied types of nanoparticles. Due to the wide spectrum of their action, silver nanoparticles may be used both to influence pathogenic microorganisms and to improve the treatment of cancer. The basic physicochemical characteristics and stabilizing agents play an important modifying role in the pharmacokinetics and pharmacodynamics of nanoparticles, determining the severity of the caused effect and their potential toxicity. This review summarizes the main physicochemical properties of AgNPs and their impact on the biological effects. Additionally, biochemical and pathophysiological mechanisms of silver nanoparticles activity against various microorganisms and tumor cells are considered. Finally, we address the problems associated with determining the optimal characteristics of nanoparticles in order to increase their efficiency and reduce their toxicity for the macroorganism.

Keywords

silver nanoparticles
physicochemical properties
biological effects
toxicity

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1. Introduction

Currently, the research on biomedical properties of various nanoparticles, synthesized from gold or silver, attracts a considerable interest. Despite the lack of data on the mechanisms of silver toxicity *in vivo*, the nanoparticles obtained from it are widely used as antibacterial substances in medical, cosmetic, food and textile industries. Silver nanoparticles (AgNPs) have unique binding properties, including internal antimicrobial activity and potentially low toxicity. Silver, and, in particular, its ions have the strongest antibacterial effect among metals; AgNPs may be used in wound dressings, local drug delivery systems, orthopedic and orthodontic materials, antiseptic solutions, catheters, bandages, tissue scaffolds and protective clothing [1–3]. Thus, AgNPs can be an effective alternative to local antibacterial drugs because of special physicochemical properties and wide spectrum of action against various Gram-negative (Escherichia coli, Neisseria gonorrhea, P. aeruginosa) and Gram-positive (S. aureus, including MRSA) bacteria, as well as intracellular microorganisms (Chlamydia trachomatis) and different viruses [3–5]. AgNPs may be considered as a means to modernize the treatment regimens for Mycobacteria, such as tuberculosis [6]. The systematic review of Fakhruddin et al. demonstrates the existence of the evidence of antimicrobial properties of silver nanoparticles against cariogenic flora *in vitro* and prevention of the dentin destruction [7].

Moreover, there is evidence of synergistic action of nanoparticles and various antibiotics. Combining AgNPs with these class of drugs could increase the antibacterial activity of imipenem, tetracycline, aminopenicillins, metronidazole, gentamicin, kanamycin, streptomycin, and vancomycin [8–14].

Silver nanoparticles may interact with bacterial membranes and penetrate into the cell with the subsequent initiation of vital malfunction and structural changes leading to destruction and death of pathogenic microorganisms [15]. The key factor is the activation of oxidative stress processes leading to dysfunction of cellular structures such as DNA (genotoxic effect). Disturbance of protein structure occurs due to the formation of Ag–S complexes, which leads to malfunction of membrane pumps and respiratory chain. Activation of lipid peroxidation processes is another important factor of cellular dysfunction [16].

A comparative analysis of the antibacterial effectiveness of silver ions and silver nanoparticles elucidated that they boost the development of many pores in the cell membrane and, consequently, cause the outside leakage of the cytoplasm and macromolecules. Besides, there is a significant damage of the flagella, which impairs the mobility of bacteria [19, 20, 21].

AgNPs have an antifungal effect (Candida albicans, Aspergillus niger) when adding material to silicone-containing linings and resins. In addition, there are data on their effectiveness against Penicillium citrinum and Trichophyton mentagrophytes [20–22]. Beyond antibacterial and antifungal activity, AgNPs demonstrate anti-inflammatory and antitumor properties [2, 3, 21, 22]. It is assumed that AgNPs are able to enhance the immunogenicity of vaccines, have an antidiabetic effect and also contribute to bone regeneration and wound healing [3].

Despite the large number of studies indicating antibacterial properties of silver, there is evidence of the possible phenotypic resistance of bacteria to AgNPs. During repeated applying of nanoparticles, the increasing aggregation under the influence of flagellin protein was detected. This process leads to subsequent loss of beneficial antibacterial effect. Inhibition of flagellin, for example, with pomegranate peel extract, helps to overcome this resistance mechanism [23, 24].

It should be noted that the bactericidal and bacteriostatic functions of AgNPs could be changed in the bacterial environment. For example, oxidation processes can induce the changes of nanoparticles in oxygen-containing liquids, which distinguishes AgNPs from the potentially stable gold nanoparticles. However, the synthesis of AgNPs is much cheaper and more affordable, so it is very important to find new ways to prevent any loss of basic silver characteristics in solutions. For example, the potential instability of AgNPs could be improved by stabilization with organic, inorganic, synthetic, natural, biotic, and abiotic substrates [15].

Silver nanoparticles are zero-dimensional materials with particle sizes ranging from 1 to 100 nm. Currently, special synthetic methods have been developed to obtain particles with certain shapes and sizes. For example, chemical (reduction of ions to atoms), physical (mechanical and pear-shaped) and biological (extracts of microorganisms and plants) methods of production are actively used (Figure 1). The most common approach is chemical synthesis; however, this method is characterized by high toxicity and pollution. Biological methods are cheaper and more ecologically friendly. Moreover, the substrates obtained during biological synthesis can be used as stabilizers for the nanoparticles [3].

2. Materials and methods

2.1. Data sources

A literature review on the properties of silver nanoparticles was performed using the following databases: MEDLINE (PubMed interface), SCOPUS, Cochrane Library, Google Scholar. The published data on the *in vitro* and *in vivo* studies were accessed between January 1990 and December 2021. Backward and forward reference searching was applied to find the most relevant articles.

2.2. Inclusion and exclusion criteria

The current review includes predominantly full-text articles presented in English language and focused on silver nanoparticles chemical/physical/biological properties. The selected articles were original studies (observational and experimental), systematic reviews, narrative reviews and meta-analyses. The studies were excluded if they were not consistent with the research objectives and the actual purposes of the current review. All studies were carried out *in vitro* (cell lines) or on mice/rats due to ethic issues.

2.3. Search strategy

Search terms included the following: silver nanoparticles, AgNP, physical, chemical, biological, biocidal, properties, effects, toxicity, microorganism, virus, bacteria, fungi, protozoa, parasites, cancer and tumor. The main search structures consisted of keywords according to each objective of the review: ((silver nanoparticle*) OR AgNP*) AND synth*; ((silver nanoparticle*) OR AgNP*) AND (chemic* OR physic* OR bio*); ((silver nanoparticle*) OR AgNP*) AND microorg*; ((silver nanoparticle*) OR AgNP*) AND propert*; ((silver nanoparticle*) OR AgNP*) AND (antibacter* OR bacter*); ((silver nanoparticle*) OR AgNP*) AND antivirus*; ((silver nanoparticle*) OR AgNP*) AND (protoz* OR parasite*); ((silver nanoparticle*) OR AgNP*) AND (anticancer* OR tumor*); ((silver nanoparticle*) OR AgNP*) AND toxic*. Grey literature and unpublished information were neither considered nor used. After reference screening the duplicates were excluded.

The key research objectives were:

1. Studying different chemical and physical properties of AgNPs, which can change biological effects.

2. Uncovering some important biological and biochemical mechanisms of AgNPs effects and toxicity against bacteria, viruses, fungi, protozoa, and cancer.

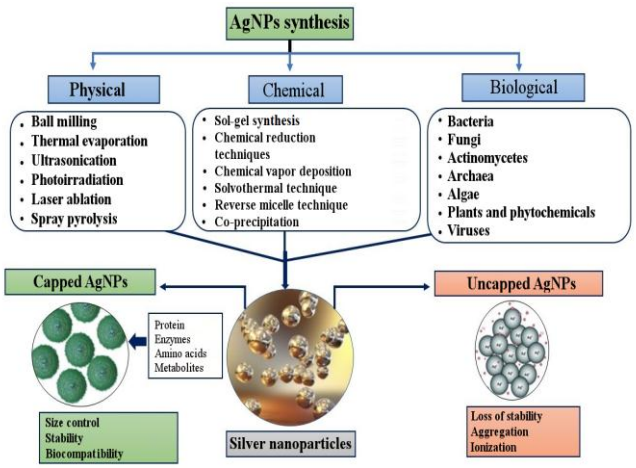

Figure 1 Characteristics of silver nanoparticles. Different ways of AgNPs synthesis. Adapted from refs [17, 18].

3. Elucidating potential harm and toxicity of AgNPs for a macroorganism and a host.

The current review was prepared according to a scale for the quality assessment of narrative review articles – SANRA [25].

3. Results and discussion

3.1. Physical and chemical properties of silver nanoparticles

3.1.1. Size

The antibacterial activity of silver nanoparticles is closely related to their size. Agnihotri et al. have investigated antibacterial activity of silver nanoparticles of different size (5, 7, 10, 15, 20, 30, 50, 63, 85, and 100 nm) against Escherichia coli MTCC 443 (E. coli) and Staphylococcus aureus NCIM 5201. Antibacterial activity of AgNPs was enhanced with decreasing size. The smallest nanoparticles of 5 nm demonstrated the best results and the highest bactericidal activity against all tested strains [26]. Baker et al. studied the antibacterial activity of nanoparticles with different sizes ranging from 5 to 70 nm (average size 15 nm) and from 50 nm to more than 100 nm (average size 75 nm), respectively. The results showed that smaller AgNPs (15 nm) were more effective against E. coli [27]. Consequently, the smaller size results in the higher antibacterial activity. This rule is explained by the fact that small AgNPs have larger specific surface area and more surface-acting centers, resulting in the increase in Ag^+ release rate and, therefore, toxicity [28, 29]. Dobias et al. demonstrated that in natural ponds, the dissolution of 5 nm AgNPS occurred faster than that of 10 nm silver nanoparticles. Smaller nanoparticles released more silver ions than 50 nm AgNPs [30]. Morones et al. showed that only nanoparticles with a diameter of 10 nm or less could penetrate through the bacterial cell membrane [31]. In addition, applying the nanoparticles with the size of 8.3±1.9 nm increases the damage of cellular DNA by influencing the nucleotide excision repair [32]. Conversely, Bélteky et al. noticed that in spite of the fact that nanoparticles with the smallest diameter have the greatest toxicity, an increase in the size of the nanoparticles promotes colloidal stability and also provides greater resistance to environmental conditions and aggregation [33].

3.1.2. Shape

Another property that determines the antibacterial activity of silver nanoparticles is their shape. There are quasi-spheres, nanotubes, rods, disks, cubes, prisms, octahedral, and triangular nanoplates [34–37] (Figure 2). Pal et al. investigated the antibacterial activity of spherical, rod-shaped, and triangular silver nanoparticles against E. coli. Truncated triangular nanoplates demonstrated the highest bactericidal activity compared to nanospheres and nanorods. The result could be explained by the presence of special active faces that determine their high reactivity. This triangular structure of nanoplates promotes more effective interaction with the bacterial cell, leading to its lysis [38]. On the contrary, in one of the latest studies, triangular nanoplates showed a smaller antibacterial effect compared to nanospheres against E. coli, S. aureus, P. aeruginosa. This can be put down to the fact that the surface area of the nanospheres (1.307±5 cm^2) exceeded the surface area of triangular nanoplates (1.028±35 cm^2) [39]. In the other studies, the greatest bactericidal activity was also demonstrated by nanoparticles with the largest surface area, which caused the accelerated formation of ions on the nanoparticle surface during their dissolution, therefore, increasing the antibacterial effect [40, 41].

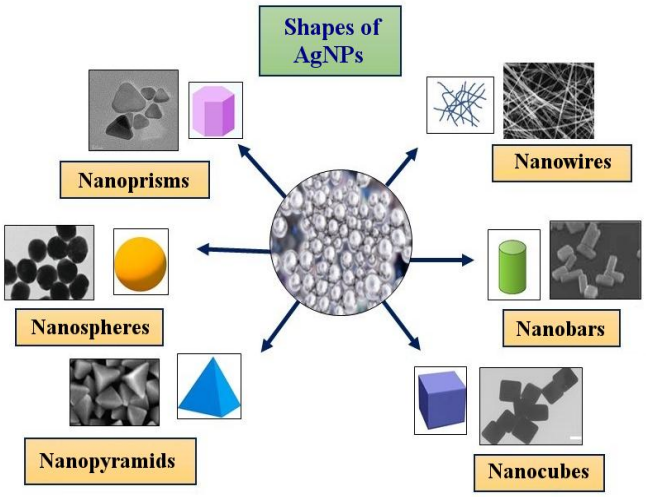

Figure 2 Different shapes of silver nanoparticles. Adapted from ref [42].

3.1.3. Concentration of nanoparticles

The dissolution of silver nanoparticles depends on their initial concentration. If this concentration is lower than the solubility of AgNPs (which depends on the size of the nanoparticles, the presence of ligands forming a complex with silver (I) and the physicochemical properties of the solution), all nanoparticles will eventually dissolve. Aggregation also explains why the initial concentration of AgNPs affects the release kinetics of silver ions. For example, if other parameters are fixed, the higher initial concentration of nanoparticles results in the slower initial release of silver ions. [43]. This is explained by the fact that at the high initial concentration AgNPs tend to aggregate more rapidly, which decreases the soluble AgNPs surface area [44]. The initial concentration of AgNPs ranging from 300 to 600 μg/L increases the aggregation rate for all three sizes of AgNPs (20, 40 and 80 nm) [45]. The antibacterial activity of AgNPs is also determined by the concentration of nanoparticles. Panáček et al. found that AgNPs are able to exhibit antibacterial activity at a very low concentration of 1.69 μg/ml [46]. Shu et al. demonstrated that the antibacterial activity of AgNPs of 13.8 nm against E. coli depended on their concentration. The growth inhibition analysis illustrated a complete suppression of the E. coli growth at AgNPs concentrations above

20.0 μg/ml [47]. Ugwoke et al. found that bactericidal activity enhanced as the dose of silver nanoparticles increased from 2 to 8 μg/ml. The smallest AgNPs (3.4±1.2 nm) demonstrated high sensitivity to bacterial strains (Coliform) at lower concentrations (8 μg/ml), compared with 30 μg of gentamicin [48]. In addition, the minimal concentration of AgNPs for antibacterial properties is mainly determined by their shape. Thus, truncated triangular silver nanoparticles showed the inhibition of bacterial growth at the 1 μg concentration, while nanospheres and nanorods induce an inhibiting effect at concentrations of 12.5 μg and 50-100 μg, respectively [31, 38]. But, the shape cannot be considered as a single factor that affects antibacterial activity, because the particle size varies with the form, which influences the overall rate of particles dissolving [34].

3.1.4. Stabilizing agents

As a rule, stabilizing agents are used during AgNPs synthesis to provide an electrostatic repulsion between individual particles and to prevent their aggregation [43]. As opposed to other silver forms, nanoparticles exhibit high surface energy values due to their small size and, therefore, they are more likely to clump and to form agglomerates. Choosing a suitable stabilizing agent is an important requirement for the nanoparticles stabilization, because coating agent affects the structural properties of the nanoparticle, including its size, shape, surface charge, and interaction with environment [49]. It is worth noting that coatings probably detach from the surface after interacting with environment [50]. Among stabilizing mechanisms of coating agents, there are electrostatic stabilization, steric stabilization, and stabilization by hydration forces, depletion stabilization and stabilization by the Van der Waals forces [51]. Organic coating agents are widely used as stabilizers for silver nanoparticles. In some cases, the stabilizing agent acts simultaneously as a reducing agent of Ag^{+} ion to Ag^{0} [52]. Also, organic molecules contribute to the complexation of silver ions, thereby accelerating their dissolution [53].

The most common coating agents for silver nanoparticles are citrate, polyvinyl alcohol (PVA), sodium dodecyl sulfate (SDS), polyvinylpyrrolidone (PVP), Tween 80 [54–58]. Citrate is one of the most commonly used stabilizers and reducing agents used for the AgNPs synthesis. Citrate-coated particles are electrostatically stabilized by negatively charged anions. However, as the pH value decreases, the citrate-anion protonates, which causes the loss of stabilization [59]. *In vivo* AgNPs capped by citrate or PVP demonstrate the greater antibacterial activity against Salmonella, compared to uncapped AgNPs, which could be explained by minimal interaction with serum proteins. Uncapped AgNPs, by contrast, lose their antibacterial activity due to interaction with bovine serum albumin (BSA) [58]. Kvítek et al. proved that any of three mentioned stabilizing agents (Twin-80, sodium dodecyl sulfate (SDS) or polyvinylpyrrolidone (PVP)) increased the antibacterial activity and excellent stabilization of silver nanoparticles dispersion against aggregation. Among all AgNPs ligands, SDS-modified AgNPs proved to be the most stable due to the electrostatic repulsion and steric effect. SDS-modified AgNPs demonstrated the highest antibacterial activity associated with good silver nanoparticles dispersibility and effective interaction with the cell membrane [60]. Ajitha et al. found that PVA-coated AgNPs had the smallest size and demonstrated high stability and antibacterial activity, compared to nanoparticles stabilized by other coatings [49].

Currently, the biosynthesis of metals and metal oxide nanoparticles, using biological agents such as bacteria, fungi, yeast, plant and algae extracts, has gained popularity in the field of nanotechnology [61]. Thus, AgNPs, which are synthesized by various microorganisms, provide high stability due to the fact that microbes produce large amounts of protein [62]. AgNPs, which are synthesized using cyanobacterial extract of Oscillatoria limnetic, have high antibacterial activity against multidrug-resistant bacteria (Escherichia coli and Bacillus cereus) as well as cytotoxicity against breast cancer and colon cancer cells at low concentrations of 6.147 μg/ ml and 5.369 μg/ml, respectively [63]. Plants contain carbohydrates, fats, proteins, nucleic acids, pigments and several types of secondary metabolites that act as stabilizers and reducing agents in the biosynthesis of silver nanoparticles [64]. Caffeine and theophylline are widely used as stabilizing agents and could be found in water-alcohol extracts of Coffea arabica and Camellia sinensis as well as in extracts of black tea [65, 66]. Utilization of fungi as reducing and stabilizing agents in the biogenic synthesis of silver nanoparticles is also attractive because they produce large amounts of protein. During biological synthesis, nanoparticles are coated with biomolecules derived from the fungus, which leads to improved stability and increased biological activity [17, 67]. Konappa et al. capped silver nanoparticles with secondary metabolites secreted by the T. Harzianum fungus. The obtained AgNPs had high stability as well as a wide range of antibacterial activity against two gram-positive bacteria (S. aureus and B. subtilis) and two gram-negative bacteria (E. coli and R. solanacearum) [68].

Silver nanoparticles also could be stabilized with polymeric carbohydrates such as starch, sodium alginate and chitosan [69–71]. Muhammad et al. used sericin (a protein that is a part of silk) as a stabilizing agent. Sericin-coated nanoparticles proved to be highly effective against bacteria and maintained stability over a wide range of temperatures and pH concentrations. The authors suggested wide use of sericin in the future because of low cost and high stability [72]. Hydroxyl groups of sericin form complexes with silver ions, thus preventing their aggregation and deposition [71]. Azócar et al. used diclofenac (d) and ketorolac (k) as stabilizing agents, which are widely used as anti-inflammatory drugs in medicine. The results demon-

strated that AgNPs-k were more stable than the uncoated nanoparticles. Under the influence of UV light (wavelength of 365 nm), capped nanoparticles generated anion radicals. This effect is probably associated with capping agents, because bare nanoparticles do not promote the formation of superoxide anion [73].

3.1.5. Surface charge of the nanoparticles

Gao et al. found that dispersion and stability of AgNPs are related to their surface charge. The negative surface charge contributes to the electrostatic stabilization of the nanoparticles against aggregation. However, the dispersion charge of particle can change depending on the pH value. The surface charge of AgNPs becomes more negative at higher pH, as confirmed by the high zeta potential value equal to –32.5 mV, which promotes the stability of the suspension. Conversely, lower pH values of 5 and 3 are characterized by a decrease in zeta potential to –22.5 and –18.2 mV, which, therefore, reduces the repulsive forces and stability [59]. Moreover, small AgNPs have lower zeta potentials than large AgNPs; thus, small particles have less electrostatic repulsion and more rapid aggregation. Surface charge is one of the most important factors of AgNPs toxicity. Recently, the antibacterial activity of positively and negatively charged AgNPs has been studied. Some studies demonstrated that positively charged AgNPs have a higher bactericidal activity against all microorganisms compared with negatively or neutral charged AgNPs [74, 75]. El Badawy et al. found out that positively charged BPEI-AgNP were more toxic against bacteria, compared with negatively charged citrate-AgNP. It could be explained by negative membrane charge of both gram-positive and gram-negative bacteria. Consequently, there is an electrostatic barrier between negatively charged citrate-AgNP and bacterial membranes that limits interaction between the cell and nanoparticles, thus reducing toxicity [76, 77]. Qiao et al. synthesized zwitterion-modified AgNPs, which could change the charge depending on the environmental pH. These AgNPs demonstrated a pH-dependent transformation of negative charge into positive charge. Therefore AgNPs were innocuous for healthy tissue cells (pH=7.4), while interacted effectively with negatively charged bacterial surfaces in foci of infection (pH=5.5) [78].

3.2. Influence of biological conditions on the nanoparticles properties

Such factors as pH, presence of dissolved oxygen, electrolytes and organic substances, in particular, proteins affect significantly the physicochemical properties and antibacterial activity of silver nanoparticles [79, 80].

3.2.1. Oxygen availability

The dissolution of the nanoparticles occurs in the presence of dissolved oxygen. The surface of AgNPs is easily oxidized by O_2 and other molecules in ecological and biological systems, resulting in the release of Ag^+ and defining their toxicity [81]. However, silver nanoparticles do not dissolve completely in the presence of molecular oxygen. A complete dissolution requires a stronger oxidizer such as H_2O_2. The AgNPs aggregation in oxygenated water is 3–8 times faster than under anaerobic conditions, indicating that dissolved molecular oxygen can also significantly affect this process [45].

3.2.2. Interaction with proteins

It is well known that nanomaterials can interact with various biomolecules of living organisms, primarily with proteins that are able to adsorb on the nanoparticles surface, forming the biomolecular corona [82]. About 300–500 human plasma proteins could be bound to different nanoparticles. Nanomaterials are rapidly coated by proteins in physiological fluids. The formation of the protein corona leads to the change in the physicochemical properties of nanoparticles, including hydrodynamic size, surface charge, and aggregation [84]. The structure of protein corona depends primarily on the nanoparticle material, size and surface properties, as well as on the composition of protein environment and experimental/physiological conditions [84–86]. Tai et al. and Alarcon et al. demonstrated that the protein corona serves as a kind of biological identity of the nanoparticle. In addition, it contributes to the colloidal stability of the particle, that presents the aggregation of the nanoparticles and protective from aggressive environmental conditions [87, 88]. Functionalization of silver nanoparticles surface significantly affects the formation dynamics of protein corona. The presence of a protein coating on the surface of the nanoparticles strongly reduces the binding degree to the protein. On the contrary, the formation of the corona on the uncoated nanoparticles improved significantly their stability in biological environment. The *in vitro* experiments showed that the physiological stability of AgNps caused by the corona formation may be directly associated with their binding to the cell, capture and toxicity [89]. The interaction between nanoparticles and different cells is determined by the composition of protein corona [90].

3.2.3. pH

The solution pH affects significantly the surface charge and oxidative dissolution of AgNPs. The behavior of nanoparticles differs under acidic and alkaline conditions. AgNPs are found to destabilize in acid and neutral pH, which results in higher aggregation rate. Under alkaline conditions, negatively charged hydroxyl ions promote the stabilization of nanoparticles [91]. Bélteky et al. found that AgNPs are more stable at alkaline and neutral values of pH than under acid conditions. An increase in the pH level leads to higher deprotonation degree of free organic functional groups and increasing negative charge on the nanoparticles surface. It facilitates the increasing electrostatic repulsion between particles and reduces the degree of aggregation [82]. Sivera et al. showed that gelatin-

stabilized AgNPs have robust resistance to aggregation in a wide range of pH (2 to 13). Moreover, these AgNPs demonstrated long-term stability against aggregation and maintained high antibacterial activity under environmental conditions for several months [92].

3.2.4. Electrolyte concentration

An increase in the electrolyte concentration leads to an increase in the AgNPs aggregation rate [43]. Stebounova et al. concluded that AgNPs aggregate in solutions with high ionic strength regardless of stabilization [79]. Bélteky et al. found that in solutions containing 50 mm of NaCl, the aggregation is slow and the size of AgNPs agglomerates does not change significantly. However, the addition of 150 mm of NaCl induces the rapid aggregation of AgNPs up to micrometer size range. Sudden changes in aggregation occur due to an increase in the concentration of Na^+, because in large quantities these ions can shield negatively charged surface groups, which provide electrostatic stabilization. With reduced repulsion, the particles form larger aggregates during collisions [82]. The presence of chloride ions in solution causes silver chloride deposition [53]. However, sulfide ligands significantly reduce the toxicity of AgNPs caused by generation of insoluble silver compounds [93]. The nanoparticle aggregation is very prominent in solutions with high concentration of divalent cations, such as Mg^{2+} and Ca^{2+}, due to the stronger neutralization of the surface charge. On the other hand, monovalent cations (K^+ and Na^+) can also enhance the aggregation of AgNPs, but they are much less effective in the shielding of surface charge than divalent ones [43]. Finally, the effect of the ionic strength on the AgNPs aggregation is more significant for smaller particles [93].

3.3. Mechanisms of AgNPs biological activity

3.3.1. The main mechanisms of antibacterial activity

The main antibacterial properties of silver nanoparticles are provided directly by silver ions; in other words, nanoparticles are a kind of transporters of the main active substance [97]. Moreover, AgNPs obtained by the "green" synthesis are more toxic than AgNPs obtained by non-biological approaches [64].

AgNPs release silver ions that interact with sulfa groups of membrane proteins, which disturb the membrane integrity and thereby increase its permeability. AgNPs interact with the cytoskeletal protein MREB, which plays an important role in the survival and formation of the bacterial cell [98]. Active adhesion of silver ions to the cell membrane leads to the change in its charge (depolarization and desensitization), lysis of cellular components and rupture of organelles. Moreover, silver ions participate in transduction processes by dephosphorylation of tyrosine residues, initiating the launch of the bacterial cell apoptosis program [13, 99].

Once in the cell, free silver ions interact with respiratory chain enzymes (dehydrogenases) and bind to functional electron donor groups (thiols, phosphates, imidazole, indoles, and hydroxyl groups), disrupting the ATP synthesis and K^+ transport [14, 98, 100].

In addition, the pathological effect of silver nanoparticles is induced by the formation of reactive oxygen species (ROS): superoxide anion radical ($O_2•^-$), peroxide ($O_2•^{-2}$), hydroxyl radical (•OH), hydrogen peroxide (H_2O2), hydroxyl ions (OH^-). Different ROS have various pathological effects, for instance: OH^-, H_2O_2 and $O_2•^-$ have the greatest antibacterial activity. OH^- interacts with positively charged cell membranes, while H_2O_2 has the greatest penetrating effect. High concentration of ROS leads to a decrease in the concentration of glutathione, an increase in lactate dehydrogenase, dysregulation of calcium channels, matrix metalloproteases and intracellular redox homeostasis [101]. Actually, ROS interacts with the thioredoxin system of S. aureus, which is one of the most important disulfide reductase systems that counteract the processes of oxidative stress. Oligomerization and dysregulation of thiol-redox homeostasis due to the depletion of intracellular thiol leads to disruption of the protective components and to activation of the oxidative stress [102].

Moreover, ROS interact with DNA, thereby triggering the processes of its modification. In addition to the indirect effect through oxidative stress, silver ions interact with sulfur and phosphorus groups of DNAs, which leads to the rupture of hydrogen bonds between the chains; the processes of replication and reproduction are disrupted (i.e., genome splitting is observed) [103]. Unipolar charge of DNA and AgNPs leads to additional destabilization of the chains. Damage to DNA molecules occurs due to oxidation and alkylation of its bases, which leads to the formation of various compounds: 8-oxoguanine, 7,8-dihydro-8-oxoguanine, 8-oxoadenine, unsubstituted and substituted with an imidazole ring of purines. These compounds are integrated into DNA under the influence of hydroxyl radicals [103, 104].

In addition to DNA, silver ions also interact with RNA and block the subunits of ribosomes (30S), which are necessary for binding tRNA [105, 106]. Being in cytoplasm AgNPs induce the processes of ribosome denaturation, inhibition of translation, protein synthesis and carbohydrate metabolism [102, 107].

The disturbance of the signal transduction processes is equally important because suppressing the phosphorylation of tyrosine residues results in blocking the cell cycle, the synthesis of exopolysaccharides and capsular polysaccharides, which ultimately leads to the interruption of the bacterial cell division [103].

Thus, the antibacterial activity of silver has a complex effect on the microorganism, disrupting various aspects of its vital activity.

Gram-negative bacteria are more sensitive to the effects of silver ions than Gram-positive bacteria, which is due to a thinner layer of peptidoglycans in the cell wall [108]. For example, S. aureus, a Gram-positive coccus with a cell wall width of 30 nm, can effectively prevent the inward penetration of nanoparticles due to the high affinity of the peptidoglycan layer [109, 110].

The antibacterial effect may depend not only on the size of the nanoparticles (nanoparticles smaller than 10 nm have high penetrating power), but also on the physicochemical properties, in particular, surface characteristics. So, positively charged nanoparticles have a greater binding ability with a negatively charged cell membrane due to the electrostatic interaction, in contrast to the negatively charged AgNPs. The higher positive charge of the ions results in the lower severity of the electrostatic barrier [97, 108, 109, 111].

Despite the fact that silver ions play a crucial role in disrupting the basic processes of microorganisms' activity, nanoparticles also have an antibacterial effect due to the mechanism of the "contact destruction".

The antibacterial properties of silver nanoparticles also depend on their shape. For example, spherical and triangular AgNPs have greater activity against E. coli and S. aureus is than AgNPs of irregular shape, which may be due to a larger surface and increased release of silver ions [5, 13]. However, Pal et al. elucidated that the triangular shape's AgNPs have a greater antibacterial effectiveness against E. coli, compared to spherical and rod-shaped particles [38]. Moreover E.coli is more sensitive to AgNP exposure than *S.* aureus regardless of AgNP size and surface properties [112].

There are published data indicating the ability of silver nanoparticles to suppress the formation of bacterial films on medical instruments without significant accumulation of silver ions in surrounding organs and tissues. The most promising direction is the approbation of this coating for catheters, drains and medical masks [5].

Moreover, numerous studies pinpoint the anti-inflammatory properties of AgNPs, which are associated with a decrease in the pro-inflammatory cytokines synthesis (TNF, IL-12, IL-1, NF-kb) and the induction of apoptosis. In addition, the modulation role of silver in the process of wound and periodontal healing has been discovered [104].

Thus, the main antibacterial mechanisms of AgNPs (Figure 3) are as follows:

1. Interaction with the membrane, impairment of its permeability and change in charge.

2. Disturbance of intracellular processes and organelles dysfunction.

3. Inhibition of mitochondrial processes (respiratory chain malfunction), activation of oxidative stress, synthesis of reactive oxygen species and lipid peroxidation.

4. Interaction with DNA and RNA, blocking the replication, transcription, and translation.

5. Inhibition of transduction of signals due to dephosphorylation of tyrosine residues.

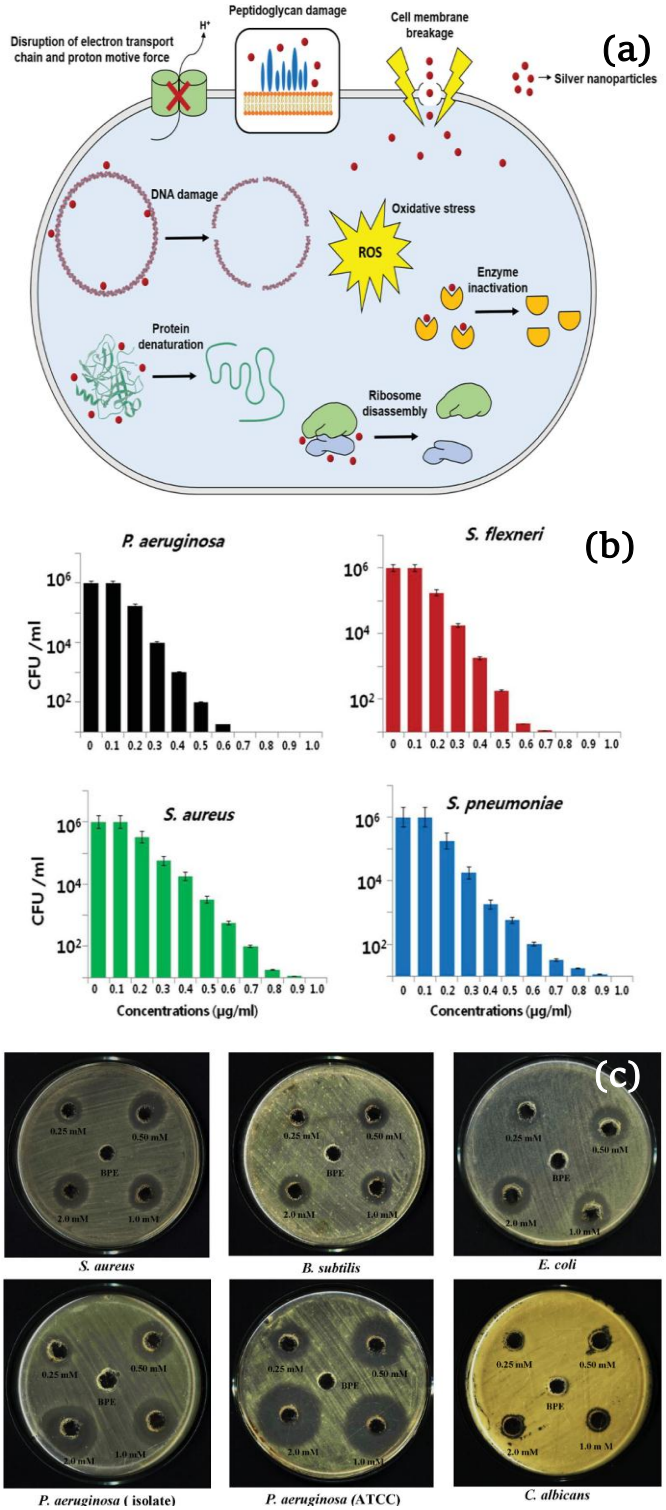

Figure 3 Antibacterial properties of AgNPs. General mechanisms of antimicrobial mode of action of silver nanoparticles (a); Bactericidal effect of green synthesized AgNPs on different bacterial strains. Dose-dependent activity of AgNPs synthesized using Allophylus cobbe leaves. The bacterial strains were incubated at various AgNPs concentrations ranging from 0.1 to 1.0 mg/ml and bacterial rate survival was estimated by colony forming unit (CFU) assay at 4 h (b); Zone of inhibition of silver nanoparticles against various pathogenic microorganisms compared to banana peel extract (BPE) (c). Presented from refs [61, 113].

3.3.2. The main mechanisms of antiviral activity

In vitro AgNPs could adhere to the virus surface, bind the viral ligand and therefore prevent its spreading in cell cultures (Figure 4a, 4b). Lv et al. indicate the property of silver nanoparticles to inhibit TGEV (transmissible gastroenteritis virus in pigs) induced apoptosis by binding to S glycoprotein. The suppression of the proapoptotic pathway is one of the possible mechanisms because TGEV causes an increase in concentration of protein BAX [114]. Based on the published data, there is assumption that the nanoparticles can also be effective against the novel coronavirus infection (COVID-19) because they have a possibility to interact with the spike glycoprotein and to decrease pH of respiratory epithelium, which would effectively prevent intracellular invasion of the virus (Figure 4c) [98, 115]. There is a description of AgNPs possibility to bind the G-protein of the respiratory syncytial virus in the hep-2 cell culture. AgNPs coated with polyvinylpyrrolidone inhibited the reproduction of RSC virus by 44%, while silver nanoparticles coated with biomolecules and RF-112 did not have a visible effect on the pathogen's life cycle [104, 116].

In addition to the binding to surface proteins, AgNPs interact with the viruses' nucleic acids (for instance, of the hepatitis B virus) and disrupt their replication in the host cells [103]. The inhibition of HBV RNA/DNA synthesis and creation of extracellular virions are observed in the human hepatoma HepAD38 cell line [117].

Biologically synthesized AgNPs of small size (<20 nm) have greater effectiveness against herpes simplex virus type 1/2 and human parainfluenza virus type 3 due to a more pronounced blocking effect on the interaction between the virus and a cell of the Veroline cell line. Nanoparticles are able to interact non-covalently with the thymidine kinase ligand, thereby suppressing the activity of herpesviruses. In addition to inhibition of HPV 1 and type 2, there is an inhibition of oncogenic herpesviruses, for example, Epstein-Barr virus [13, 120]. Moreover, AgNPs block the interaction of herpesviruses with heparan sulfate proteoglycans of cell membranes, preventing invasion processes. These properties could be enhanced by combining AgNPs with tannic acid [121, 122].

Particles smaller than 10 nm can prevent the spreading of influenza virus in cell culture MDCK [123]. In 2017, Lin et al. published the data about the activity of combination treatment with Zanamivir and AgNPs against the H1A1 influenza virus in MDCK cell line. This combination not only demonstrated high thermodynamic and kinetic stability, but also suppressed effectively the replication of the influenza virus by regulating neuraminidase activity [124].

There are published data about the ability of silver nanoparticles to interact with HIV and inhibit significantly its reproduction by binding to the regions of disulfide bond (sulfur-containing residues of CD4-binding domain) of gp120 [125, 126]. Moreover, silver nanoparticles could prevent infection of cervical tissue with HIV type 1 without cytotoxic effect *in vitro* [127].

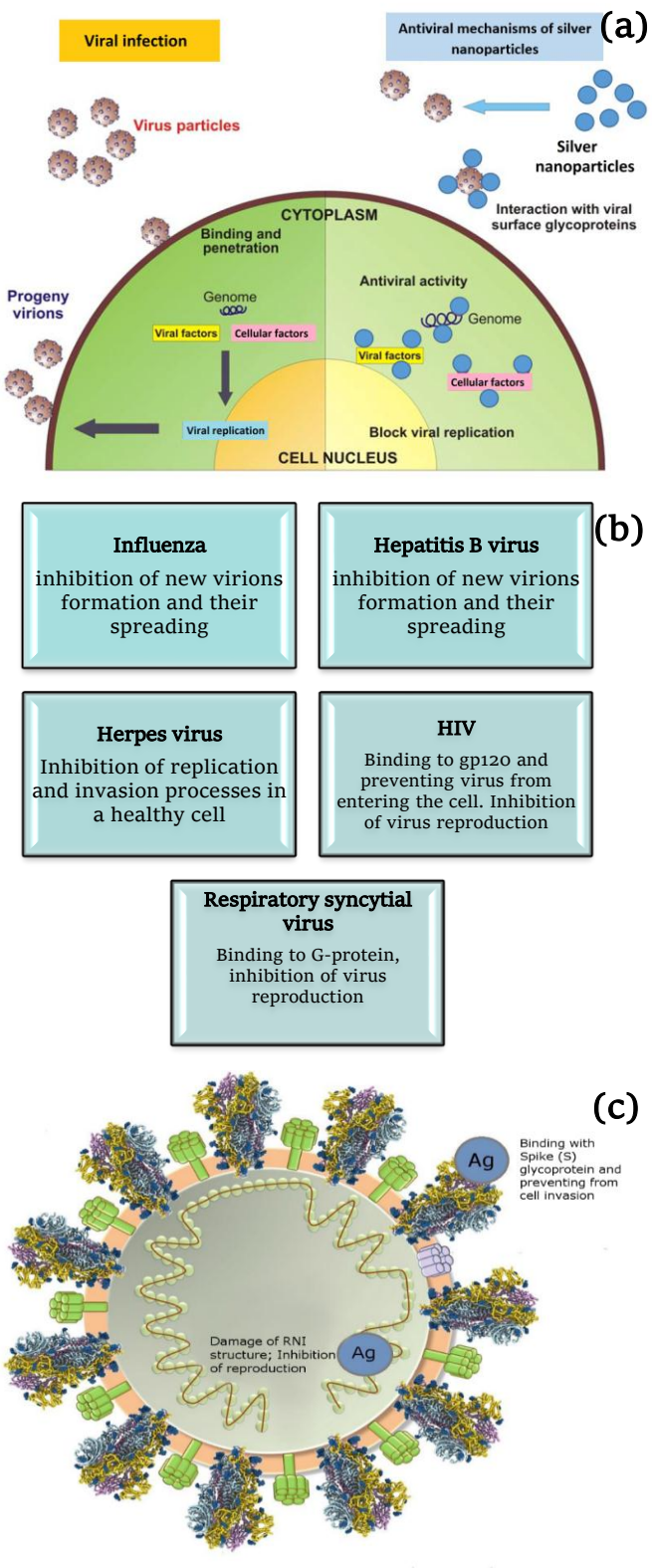

Figure 4 Antiviral properties of AgNPs. Schematic model of a virus infecting an eukaryotic cell and antiviral mechanism of metal nanoparticles. (a); The activity of silver nanoparticles against the prevalent viruses (b); Mechanisms of antiviral activity against SARS-CoV2 (c). Adapted from refs [118, 119].

Silver nanoparticles have a wide antiviral spectrum of action against different viruses that spread through mosquito bites: dengue fever, West Nile fever, Zika virus and Chikungunya virus. Both uncoated AgNPs and polysaccha-

rides- coated AgNPs have a suppressing effect on the replication of Tacaribe virus and Monkeypox virus [13, 128, 129].

3.3.3. The main mechanisms of antifungal activity

The mechanisms of AgNPs antifungal activity are not fully understood. There is a suggestion that the interaction of nanoparticles with the membrane leads to disruption of its function (the current of transmembrane ions, including protons) and division processes (especially in yeast). Also, AgNPs induce an inhibition of germ tube formation, growth of biofilm and secretion of hydrolytic enzymes [130, 131]. Beyond the membranotoxic effect, silver nanoparticles could initiate a cascade of intracellular pathological processes leading to the fungus death: oxidative stress, interaction with thiol groups and phosphorus-containing molecules, blocking protein synthesis. Thus, the fundamental antifungal mechanisms are similar to antibacterial ones (Figure 5a) [132].

The majority of the published data was acquired by studying the activity of AgNPs against plant pathogens and mold fungi [133]. However, AgNPs have antifungal properties against pathogenic fungi that cause dermatophytosis: Candida sp. (including Candida albicans) and Trichophyton mentagrophytes [134, 135]. Even amphotericin-B resistant strains of Candida glabrate were found to be sensitive to nanoparticles [136]. Silver nanoparticles also have a biocidal effect on biofilms that are formed by Candida spp. [137].

There are data on the inhibition effect of particles on fungal keratitis pathogens (Fusarium spp., Aspergillus spp., Alternaria alternate) *in vitro*. At the same time, AgNPs had a potentially greater antifungal effect than antimycotic drug – natamycin [140].

AgNPs can enhance the effect of antifungal drugs. There are data about synergy of silver nanoparticles and ketoconazole against the main cause of seborrheic dermatitis - Malassezia furfur. Combination therapy leads to a decrease in the frequency of drug use and the frequency of relapses not only of seborrheic dermatitis, but also of other malasesiosis [141]. Also, AgNPs suppress the growth of different pathogenic Aspergillus species (Aspergillus niger, Aspergillus flavus, Aspergillus fumigatus), which can cause a wide range of diseases. Due to this effect, silver nanoparticles can play an important role in the treatment of aspergillosis, especially in patients with drug-resistant strains [142]. It is worth mentioning that Aspergillus niger can be used to synthesize AgNPs (one of the directions of biological synthesis). The synthesized nanoparticles have the ability to inhibit the growth and development of Allovahlkampfia spelaea, which causes resistant keratitis [143].

Thus, silver nanoparticles can play an important role in the treatment of fungal infections, especially due to the scarcity of the antifungal drugs and increasing number of drug-resistant species (Figure 5b). The combination of nanoparticles and drugs can boost the effect of the latter and have an independent bactericidal action in the case of multiple resistance of pathogenic fungi. AgNPs can also be used to prevent the spreading of mold on different surfaces [133]. However, the inhibition of fungal growth by silver nanoparticles is less prominent than that of bacteria, which may be due to the presence of chitin in the wall of the fungus, rather than peptidoglycans [142].

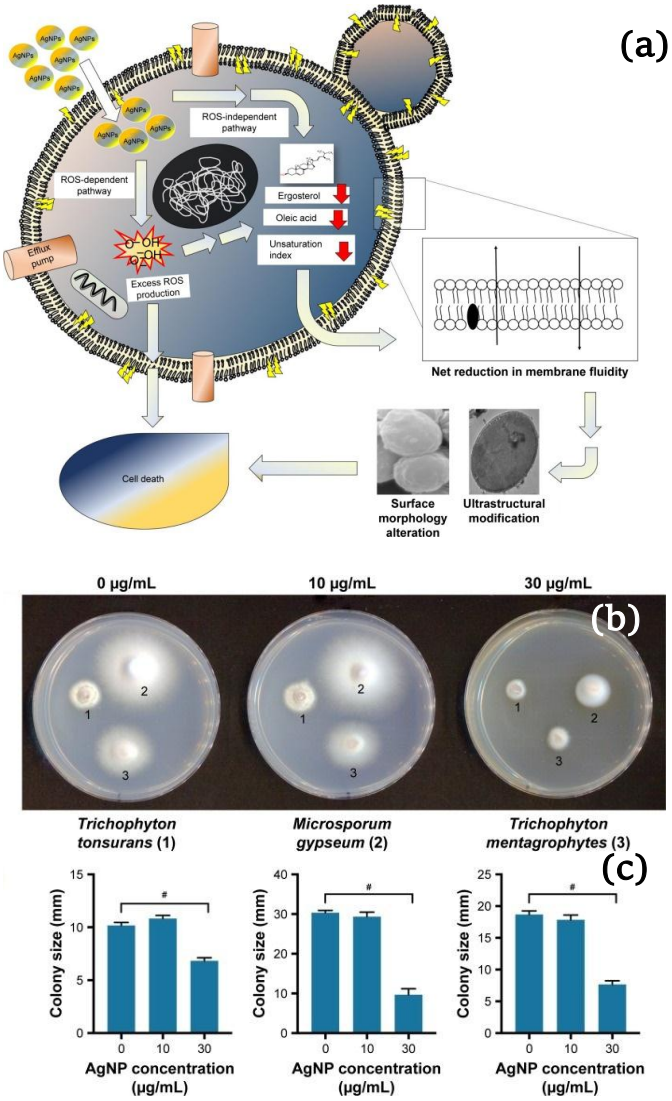

Figure 5 Antifungal activity of silver nanoparticles. Schematic representation for the proposed model for mechanism of action of AgNPs against Candida cells, depicting possible cellular targets and existence of ROS-dependent and ROS-independent pathways for fungicidal action of AgNPs (a); Antifungal activity of silver nanoparticles against: A.niger (1) and P.chrysogenum (2) at the concentrations of 200, 300, 400 and 500 μg/ml(b); Colonies of Trichophyton tonsurans (1), Microsporum gypseum (2) and Trichophyton mentagrophytes (3). On PDA and PDA supplemented with different concentrations of AgNP. The bar charts represent the diameter of the colonies in the function of AgNP concentration (b). Reproduced from [138, 139].

3.3.4. Mechanisms of antiparasitic activity

There are reliable data confirming the antiparasitic properties of silver nanoparticles, in particular, against the causative agent of cutaneous leishmaniasis (Leishmania tropica) (Figure 6a). AgNPs bind to the sulfo- and phosphorus-containing membrane and DNA proteins, blocking DNA synthesis and activation of oxidative stress. AgNPs have an anti-promastigote effect because of blocking the proliferation of promastigotes. In addition, AgNPs sup-

press the vital activity of amastigotes and reduce their survival in infected host cells. Anti-amastigote properties are boosted by additional exposure of ultraviolet light. Probably, when exposed to ultraviolet light, there is an increase in the concentration of monosulfide radicals, which are formed from complexes. These complexes are formed by interaction of silver ions and cysteine groups of parasitic proteins [144, 145].

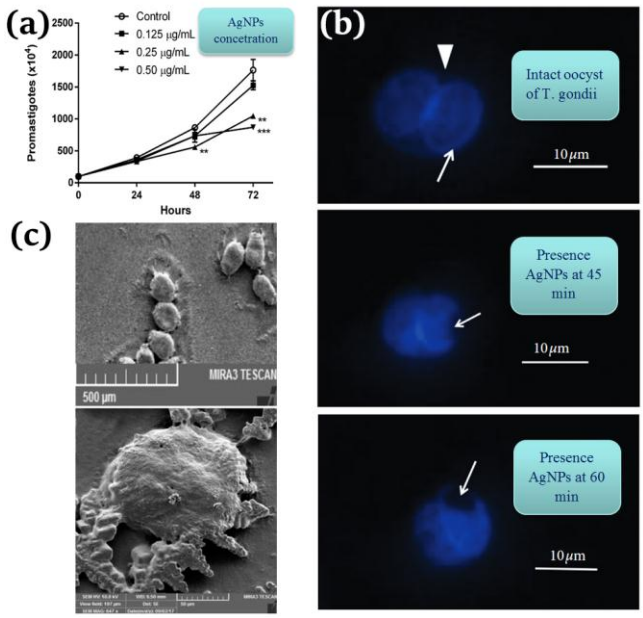

Figure 6 Antiparasitic properties of AgNP. AgNPs leishmanicidal activity. L. amazonensis promastigotes forms were subjected to different concentrations of AgNPs-bio (0.125, 0.25 and 0.50 µg/mL) and the parasite viability was assessed at 0, 24, 48 and 72 h (a); Effect of AgNPs in Toxoplasma gondii morphology as assessed by fluorescence microscopy. In the control sample, intact oocyst, in the presence AgNPs at 45 min and 60 min (b); Scanning electron microscopy (SEM) micrograph of protoscolices of E. granulosus. Protoscolices without nanoparticles and 1 mg/mL concentrations of Ag-NPs that covered protoscolex (c). Reproduced from [146–148].

Apart from Leishmania, the antibacterial activity of silver nanoparticlesis was observed against oocysts Entamoeba histolytica, Cryptosporidium parvum and several other protozoa [131, 149]. For example, in the study of Costa et al. biogenic AgNPs inhibited the replication of Toxoplasma gondi (which causes toxoplasmosis) in cell cultures, such as BeWo, HTR-8/svneo, Hela and in villous explants. Moreover, the nanoparticles induced secretion of inflammatory cytokines in cells, for example, in the BeWo line: IL-4 and IL-10; in the HTR-8/SVneo line: IL-4 and the macrophage migration inhibitory factor (MIF). Toxoplasma gondi increased the MIF concentration in the BeWo cell culture and IL-6 in HTR-8/SVneo line. In villous explants the synthesis of IL-4, IL-6 and IL-8 decreased after infesting. In Hela cell line an increase in the NO concentration, oxidative stress and reduction of pro-inflammatory cytokines, in particular, IL-8 were observed. Thus, silver nanoparticles can significantly inhibit the spread of T. Gondi without developing dysfunction of the host cells (Figure 6b) [150, 151]. In addition to the cell cultures and chorionic villi, AgNPs suppresses toxoplasma's replication in liver and spleen tissues [152]. One of the possible antiparasitic mechanisms includes the suppression of mitochondrial function, disturbing mitochondrial membrane potential, redox signaling and destruction of leucine aminopeptidase (LAP) [153].

The current data plays an important role in the development of alternative approaches to the treatment of toxoplasmosis, particularly in pregnancy, because standard drugs used for the treatment of this pathology have teratogenic and myelosuppressive properties. Moreover, toxoplasmosis is part of the TORCH complex, which includes a group of intrauterine infections that lead to impaired fetal development and even death.

The results of Younis et al. demonstrated the effectiveness of AgNPs against Blastocystis hominis, which is the causative agent of blastomycosis. The most prominent antiparasitic effect *in vitro* was observed with a combination of particles and metronidazole. The concentration of B. Hominis decreased by 71.69% in the metronidazole group, by 79.67% in the AgNPs group and by 62.65% in the combination therapy group (AgNPs + metronidazole) after 3 hours ($p<0.05$). The nanoparticles are likely to interact with and modify glycoprotein and lipophosphoglycan molecules on the parasite surface they may induce oxidative stress, and inhibit ROS synthesis and DNA replication [154].

There are data on the possible sporicidal action of nanoparticles against Echinococcus (Figure 6c). Moreover, AgNPs have a synergistic effect with albendazole and are able to prevent the development of adverse reactions in the liver associated with this drug. For example, they decrease the severity of necrosis, steatosis, and reduce the level of transaminase and IFN-γ. Combination therapy is associated with a greater degree of structural changes in echinococcal cysts (reduction of cyst size and cyst mass) [155, 156].

Additionally, silver nanoparticles are used for the development of new directions in the treatment of giardiasis (Giardia lamblia). The combination with chitosan and curcumin leads to the complete eradication of giardia in the intestine and feces of rodents without the development of adverse reactions [157]. The study of tropical malaria (Plasmodium falciparum) using AgNPs for the treatment is ongoing [158]. Moreover, silver nanoparticles could be used in ophthalmology for prevention of Acanthamoeba adhesion on contact lenses (amoebic keratitis prophylaxis) [159].

3.3.5. Main mechanisms of anticancer activity

Silver nanoparticles are promising for developing and modifying approaches to antitumor therapy. AgNPs can have a cytotoxic effect on tumor cells with subsequent suppression of the pathological process. The decreased lymphatic outflow in malignant tumors allows nanoparticles to accumulate and act longer [160]. Moreover, tumor cells absorb AgNPs (by endocytosis) to greater than normal cells [2].

There are main mechanisms of anticancer activity: induction of oxidative stress, changing the structural-cellular morphology and activation of pro-apoptotic processes (caspase 3 and 9, regulation of p53, p38 MAPK, HIF-1α, increase in BAX concentration and decrease in Bcl-2 concentration) [161]. Apart from apoptosis, there are also necrosis and autophagy in cancer cells are activated by stimulation of autophagosomes formation through the PtdIns3K signaling pathway. Except direct pro-apoptotic effect, there is also an indirect activation of apoptosis through oxidative stress and synthesis of pro-inflammatory cytokines (IL-6). An increase in the concentration of TNF-alpha and "NF-kB" nuclear factor contributes to the activation of pro-inflammatory processes in the tumor cell [162]. The increased concentration of oxygen radicals and significant depletion of glutathione leads to the dysfunction of mitochondria and the NADP/NAD system, impaired permeability of the outer mitochondrial membrane, destruction of the respiratory chain, blocking the ATP synthesis and release of cytochrome C into cytosol, which are important activating factors of caspase 3 (through apaf-1) and caspase 9 (Figure 7) [3, 101, 163–165].

Besides inhibiting the mitochondrial activity, AgNPs affect structural and functional characteristics of DNA. AgNPs provoke the DNA methylation, increasing the number of chromosomal aberrations and malfunction of the repair system. For example, they cause the downregulation of proliferating cell nuclear antigen, i.e. the clamp of DNA polymerase, which plays an important role in the synthesis and reparation of DNA. As in bacterial cells, the released silver ions are able to disrupt the hydrogen bonds between the DNA bases, which leads to disorganization [3]. The activation of c-Jun NH_2 terminal kinase (JNK) is an additional factor in DNA fragmentation and the atopic bodies formation [162].

Moreover, the action of AgNPs is characterized by the disturbance of metabolic processes and sensitization of the tumor cell, increasing its sensitivity to antitumor drugs, in particular, to 5-fluorouracil due to the modulating effect on expression of uracil phosphoribosyl transferase, which ultimately leads to active induction of apoptosis [166]. In addition, there are data on the pharmacological synergism of AgNPs and doxorubicin [167].

In lung fibroblasts and glioblastoma cells AgNPs induce different processes, such as metallothionein up-regulation, downregulation of the actin-binding protein and filamine, cell cycle arrest in phase G (2)/M [2, 168]. Biosynthesized AgNPs can block the cell cycle in G1 phase. One possible mechanism of the cell cycle arrest is the downregulation of cyclin B and cyclin E, whose normal functioning is of the paramount importance for division processes [162].

AgNPs have antiangiogenic properties. In particular, AgNPs inhibit growth of blood vessels in tumor, limiting its progression. Probably, this effect is associated with VEGF (vascular endothelial growth factor) blocking and angiogenic FGF-2 (fibroblast growth factor 2) synthesis, as well as the inhibition of the transduction processes of the signaling pathways through the phosphorylation of KDR tyrosinekinase (VEGFR-2) and PI3K/Akt [169–171].

Another mechanism of inhibiting cancer cell proliferation, vascular growth, and tumor progression implies a disruption of signaling transduction by suppressing the effects of hypoxia-induced factor-1a (HIF-1α) and matrix metalloproteases. Active growth and progression of the tumor are accompanied by insufficiently active formation of the vascular network, which leads to the cell hypoxia and, consequently, an increase in the concentration of HIF-1α. HIF-1α regulates the expression of genes responsible for cellular activity: division, growth, and angiogenesis [172]. Matrix metalloproteases have similar functions. Resistance to the therapy is often accompanied with high activity of these signaling pathways, so their blocking plays a potentially important role in the modification of contemporary treatment approaches [3].

The antitumor effect of nanoparticles can be enhanced by coating with nano transfers, for example, with chitosan. Chitosan-coated nanoparticles have a greater inhibitory effect and cause apoptosis at a lower concentration than uncoated AgNPs [2, 173]. Smaller nanoparticles (10, 20 nm) have the strongest antineoplastic effect compared to the large AgNPs (100 nm), which may be due to the greater penetrating capacity.

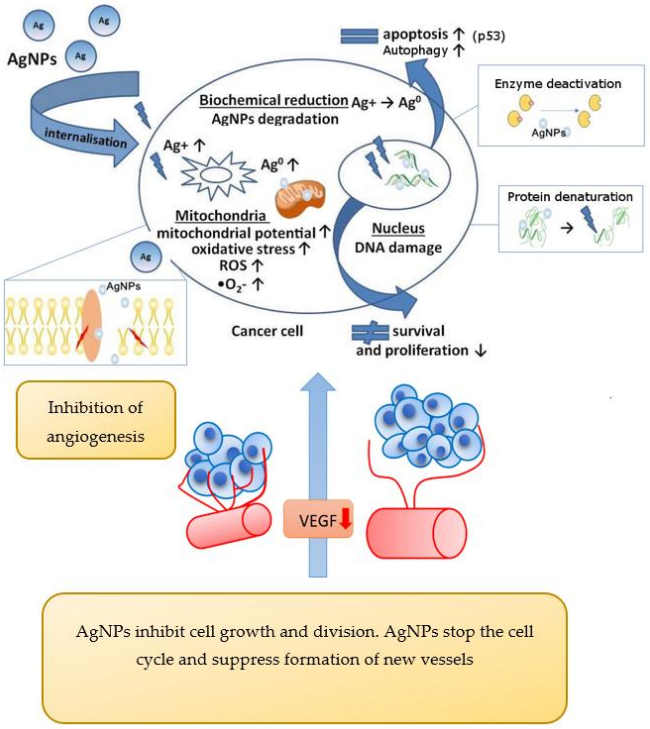

Figure 7 Anticancer properties of AgNPs. AgNPs have a cytotoxic effect, inhibit the mitochondrial functions and boost the processes of oxidative stress and damage of tumor cell membrane. AgNPs also contribute to the suppression of the vascular growth factor (VEGF), which leads to the inhibition of the new vessels formation. Moreover, processes of tumor cells division are disturbed and the phenomenon of autophagy is observed. Reproduced from refs [180, 181].

Moreover, charge and electrostatic interaction also affect internalization. For example, positively charged particles penetrate more quickly and have greater cytotoxicity than particles with a neutral or negative charge.

A positive charge allows the interaction both with a negatively charged membrane and albumin, which leads to formation of a protein shell. The "protein corona" allows AgNPs to enter cells through receptor-mediated endocytosis with further implementation of cytotoxic and genotoxic effects [75, 174, 175].

There are published data on the antitumor activity of AgNPs against a wide spectrum of oncological diseases *in vitro*: blood cancer (acute myeloid leukemia), breast cancer, hepatocellular carcinoma, osteosarcoma, lung cancer, melanoma of the skin and mucous membranes, squamous cell carcinoma of the skin, colon cancer, osteosarcoma, cervical cancer, prostate cancer, adenocarcinoma of the stomach, bladder cancer and pancreas cancer [1, 3, 13, 176–179].

3.3.6. Potential toxicity of silver nanoparticles

Despite the data indicating the broad therapeutic potential of AgNPs, it is important to assess their toxicity, since the main biochemical effects of nanoparticles do not have biological selectivity and can interact with the macroorganism cells. Studying of toxic effects allows us to determine the therapeutic properties of drugs contain AgNPs and to minimize adverse side effects. The toxic properties of AgNPs depend on their size, shape, surface feature (negatively charged particles are less toxic), stabilizing agent and coating. Moreover, local environmental factors have an equally important role in toxicity: the strength of the ion interaction, presence of ligands, macromolecules and bivalent cations, as well as pH parameters [74, 182]. Toxic effects of nanoparticles have been studied either *in vitro* on cell cultures or *in vivo* on rodents. Different methodologies and approaches make it difficult to determine common parameters and characteristics of AgNPs toxicity.

Pharmacokinetic features of AgNPs have wide distribution in organs and tissues (lungs, CNS, kidneys, heart, liver, spleen, etc.), independent of the route of administration. The clearance of nanoparticles can differ from 17 days to 4 months. In tissues containing natural physiological barriers, for example, brain, excretion of silver proceeds more slowly (up to 260 days), which creates additional conditions for its accumulation [183, 184]. Excessive accumulation of AgNPs leads to disruption of cells activity in different organs and systems: skin (argyria, contact dermatitis), respiratory system (bronchitis, alveolitis, fibrosis, provocation of bronchial asthma exacerbations) visual system (conjunctivitis, argyrias), gastrointestinal tract (hepatobiliary and intestinal dysfunction), immune system (dysregulation of cytokine synthesis and function of cells), CNS (cognitive impairment, Alzheimer's disease, epileptic seizures), urinary system (acute tubular necrosis, glomerular dysfunction), cardiovascular system (bradycardia, AV block, ventricular arrhythmias) (Figure 8) [3, 161, 185]. The possible nanoparticles accumulation in the reproductive system and damage of the germ cells structures were discovered by studying the pathological effects of AgNPs in mice. Apart from the metabolic disturbances in germ cells and reduction of female oocyte fertility, the dysfunction of Leydig and Sertoli cells in males, which leads to infertility and a decrease in testosterone synthesis, was observed [3]. An embryotoxic effect was detected in mice and zebrafish. This effect depended on the size and coating of AgNPs nanoparticles. Smaller AgNPs of 20 nm have greater toxicity than large particles of 110 nm, and polypyrimidine-coated particles are more toxic than citrate-coated AgNPs [186]. AgNPs also have a genotoxic effect due to chromosome damage, oxidative stress, and interaction with DNA [185, 187].

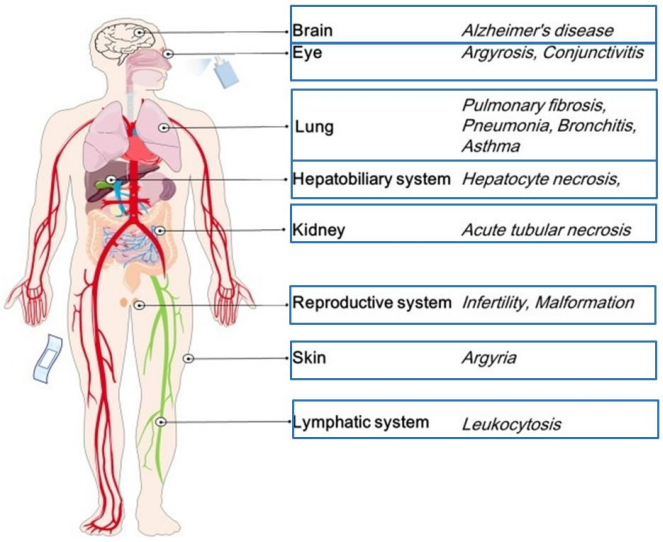

Figure 8 Main spectrum of AgNPs toxicity. AgNPs have a wide spectrum of toxicity, which has been studied in mice. The collected data made it possible to predict the different consequences of nanoparticles accumulation in various organs and systems. Reproduced rom ref. [180].

The process of the silver ions permutation and their interaction with oxygen or sulfur, which induce a pathological biochemical cascade in cell, are considered the main mechanism of potential AgNPs cytotoxicity. It is believed that formation of Ag^+ plays a key role in activation of lysosomal acid phosphatases, dysfunction of the actin cytoskelet, inhibition of Na^+/K^+-ATPase, stimulation of apoptosis (through the protein p53, ACT, TP38), induction of oxidative stress, depletion of glutathione and diffusion of cellular components [101, 185, 188]. However, according to another hypothesis, independent mechanisms of metallic ions toxicity, which can be found for various nanoparticles, cause the pathological effects [189]. Except the direct entering into cell through the membrane (diffusion, endocytosis), it is supposed that AgNPs may penetrate through ion channels ("flip-flop" mechanism) and by the "Trojan horse" approach. The latter method consists of phagocytosis and further induction of petrochemical changes in active cells by silver ionization in the cytosol [101]. It is

worth mentioning that the most prominent morphological changes are observed in the liver, lungs, and kidneys, which may be due to the greatest participation of these organs in the clearance of nanoparticles [190].

AgNPs were found to induce oxidative stress in rat liver cells due to disturbance of metabolism and mitochondrialal malfunction. These changes resulted in the focal liver necrosis, spleen edema and apoptosis in thymus cortex [185, 191]. Exposure to the most effective small nanoparticles (10 nm or less) caused much more prominent pathological shifts [192]. The excretion of silver from the body is mostly carried out by the hepatobiliary system (more than 50%), which may be associated with more severe hepatotoxicity because of the greatest accumulation in hepatocytes, Kupffer cells and sinusoidal endotheliocytes [193]. Kidneys are the second important excretion system. Silver nanoparticles accumulate in all structural components of cortex and medulla in spite of a low urinary excretion fraction (less than 0.01%) [161, 193].

Beyond hepato- and nephrotoxicity, silver particles may provokepathological changes in the intestinal wall despite a rather low level of absorption in the intestine ranging from 0.12% to 0.88%, which can be caused by the binding of nanoparticles to undigested food [193]. However, oral administration of silver nanoparticles in mice causes destruction of epithelial villi and glands. The implication of bowel dysfunction causes weight loss [194].

In addition, nanoparticles have toxic effect on hearing and retina due to the activation of oxidative stress in the mitochondria, which leads to the loss of hearing and vision [3, 190].

The accumulation of AgNPs in the central nervous system leads to disorganization of the cytoskeleton, activation of neuroinflammation and increase in the insoluble beta-amyloid concentration. These processes are important pathophysiological entity of Alzheimer's disease. Thus, it is possible to conclude that AgNPs can induce the development of neurodegenerative disorders, particularly due to low clearance and pathological accumulation [195].

Positively charged silver nanoparticles are known to have toxic effects on myocardial I_{NA} and I_{K1} channels, which leads to significantly increased risk of severe bradycardia [196]. Prolonged inhalation of AgNPs causes reduction of tidal volume and enhancing of inflammatory processes in bronchopulmonary system [131, 197].

Thus, it is necessary to study and compare different AgNPs in order to determine the possibilities to synthesize less toxic nanoparticles with the strongest therapeutic effect. The study of pharmacodynamics and pharmacokinetics properties of AgNPs to prevent pathological accumulation is equally important. Moreover, it is necessary to conduct further research, devoted to direct comparison of coating agents and to selecting the optimal coating approach, because the coating and stabilization have beenproved to have a huge modifying effect.

4. Conclusion

Given the wide range of biological, physical, and chemical properties of silver nanoparticles, a potential role of this compound in clinical medicine may be suggested. Approbation and usage of AgNPs are highly promising, especially in the era of growing antimicrobial resistance. In addition to activity against pathogenic bacteria, viruses, protozoa and fungi, silver nanoparticles are able to inhibit the activity of tumor cells or play the role of drug carriers in the structures of malignant neoplasms in order to increase the effectiveness of chemotherapy [198]. Despite the promising results of the studies, most of them are conducted mainly in cell cultures or mice. Therefore, pharmacodynamics and pharmacokinetics of silver nanoparticles in human have not been fully studied due to the reliable data on possible multisystem toxicity, which could restrict performing these kinds of studies. Moreover, silver nanoparticles are among the most toxic nanocompounds. Therefore, it is of tremendous importance to develop and evaluate potential AgNPs antidotes, such as sulfides [199]. A careful selection of the minimum toxic and at the same time the most effective dose of AgNPs is an important aspect of planning the clinical and paraclinical trials. The nanoparticles synthesized by the "green synthesis" methods are likely to have less toxicity and a wider biological spectrum against microorganisms, which makes this approach more preferable than chemical or physical synthesis [200]. Further studies of different properties of nanoparticles are needed to determine the most optimal concentration, shape, structure and enveloping substance *in vivo*. These may be achieved by evaluating the dose-response parameters via comparison of the equivalent values with the results from animal studies and extrapolated potential effects on humans [188].

Thus, it can be concluded that the integration of nanotechnologies, AgNPs in particular, for various medical purposes is highly promising due to the clear biocidal effects. However, the lack of unified methodological approaches and the inconsistencies in the data leave a wide field for further research and development of unified algorithms to prevent biases, trial heterogeneity, inaccurate data processing and compilation.

Limitations

The type of article is a narrative review. It means a more relaxed literature search strategy, and it is affected by subjective approach (in contrast with PRSIMA and multiple search strategy by two or more authors), which limits the comprehensive data extraction and strict study selection. There is a high probability of heterogeneity among studies due to the lack of strict prespecified criteria (selection bias), which leads to the impossibility of generalizing results and performing the statistical summary effect assessment. All studies are carried out *in vitro* (cell lines) or

on mice/rats which makes it difficult to extrapolate the obtained results to humans and assess a potential minimal clinical important difference. There is a high demand for systematic reviews and meta-analyses according to the PRISMA guidelines for every particular topic of the current review, including extensive analysis of the published/unpublished literature and following the evidence-based practice. Such approach could improve the accuracy and understanding of the research objective for the medical application of silver nanoparticles.

Supplementary materials

No supplementary materials are available.

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Author contributions

There is only one author.

Conflict of interest

The author declares no conflict of interest.

Additional information

Kodintcev Anton Nikolaevich – adult general neurologist at polyclinic of the Institute of High Temperature Electrochemistry of the Ural Branch of the Russian Academy of Sciences and a young scientist at the same institute.

Education: (MD) at Ural State Medical University (USMU), Faculty of General Medicine.

Postgraduate courses, 2019–2022 at Ural State Medical University (USMU), Department of Neurology, Neurosurgery and Medical Genetics

Neurology residency: 2018–2020 at Yekaterinburg Medical Research Center for Prophylaxis and Health Protection in Industrial Workers is a Research Institute of the Russian Agency for Consumers Rights Protection (Rospotrebnadzor), Department of Neurology.

Scientific interest: researching of new and cheap diagnostic methods of neurodegenerative disorders, in particular, Alzheimer's disease based on different biomarkers of biofluids.

Website:

Institute of High Temperature Electrochemistry, http://www.ihte.uran.ru/?page_id=3106.

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