International Journal of Molecular and Clinical Microbiology 12 (1) (2022) 1664-1683

International Journal of
Molecular and Clinical Microbiology

Silver nanoparticles: synthesis, bio-applications, and their effects on human health

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ARTICLE INFO

Article history:
Received 27 January 2022
Accepted 12 March 2022
Available online 1 June 2022

Keywords:
AgNPs, UV-Vis, XRD, FTIR, TEM, SEM

ABSTRACT

Recently, the applications of a high number of available products containing nanoparticles, especially metallic silver nanoparticles (AgNPs), have significantly increased worldwide. In this review, an attempt is made to critically explain methods of AgNPs production, including chemical, physical, microemulsion, UV-initiated photoreduction, photoinduced reduction, electrochemical, microwave-assisted, irradiation, and green synthetic methods. Different methods are used for the detection of synthetized Ag NPs. The most common methods are UV-visible spectroscopy (UV-Vis), X-ray diffraction (XRD), Fourier transform infra-red spectroscopy (FTIR), transmission electron microscopy (TEM), scanning electron microscopy (SEM), and X-ray energy dispersive spectrophotometer (EDAX). Also, the applications of AgNPs in different fields of medicine, including the treatment of infections caused by bacteria, fungi, and viruses, as well as fatal human diseases such as cancer and nervous diseases, are discussed. In addition to the studies that are discussed in this review, it is necessary to conduct further studies on the toxicity of AgNPs in relation to vital organisms.

1. Introduction

Nanotechnology refers to the technique of obtaining and using materials with dimensions ranging from 1 nm to 100 nm. Because of their particular properties, nanomaterials are distinct, superior, and necessary, making them distinct from macroscopic materials and attracting the attention of many researchers. One of the most important aspects of nanomaterials is their high surface-to-volume ratio and the large number of atoms present in their broad boundaries. Nanotechnology, like the aspects mentioned above, is an essential element of emerging sciences that may be employed in a variety of sectors such as medical, biology, physics, biomedicine, pharmacy, cosmetics, and numerous industries. (Annamalai and Nallamuthu, 2016).

Among very small-dimension nanomaterials, silver nanoparticles (AgNPs) are one of the most explored and promising candidates for unconventional and efficient applications in the contemporary world, with impressive results reported in different sciences. Physicochemical properties, mechanical and optical properties, and specific biological behavior (such as nontoxicity, antimicrobial efficiency, and biofunctionality) show that silver nanoparticles (AgNPs) are ideal for developing new and practical biomedical applications.

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For such a specific use, researchers have a significant problem in correctly balancing biocompatibility and antibacterial activity in order to achieve the intended therapeutic benefits. Nanosilver-based biomaterials and biosystems are promising candidates for traditional disinfection treatment, specific and selective platforms for detection and diagnosis, targeted and controlled drug delivery, gene therapy, soft and tissue engineering, and resuscitation medicine due to their remarkable diversity (Gherasim et al., 2020).

1. Nanoparticles types

Nanoparticles (NPs) are generally divided into different categories depending on their morphology, size, and chemical properties (Figure 1). Based on physical and chemical properties, some of the most famous NP classes are Carbon-based NPs, Ceramic NPs, Semiconductor NPs, Semiconductor NPs, Polymeric NPs, Lipid-based NPs, and Metal NPs (Mabena et al., 2011; Thomas et al., 2015; Sun, 2000; Abd Ellah and Abouelmagd, 2016; Shanmuganathan et al., 2019; Pothipor et al., 2019; Naghsh et al., 2012a). Fullerenes and carbon nanotubes (CNTs) illustrate the two major classes of carbon-based NPs. Fullerenes are nanomaterials made of the globular hollow cage-like allotropic forms of carbon. They have generated significant commercial interest because of their electrical conductivity, high strength, structure, electron affinity, and versatility (Astefanei et al., 2015). These materials have pentagonal and hexagonal carbon components. They have recently been synthesized by the chemical vapor deposition (CVD) method (Elliott et al., 2015). Because of their distinctive physical, chemical, and mechanical characteristics, these materials are used not only in virgin form but also in nanocomposites for numerous commercial applications, such as fillers (Saeed and Khan, 2014; Saeed and Khan, 2016), adsorbents efficient gas for environmental modification (Ngoy et al., 2014), and as a support medium for various inorganic and organic catalysts (Mabena et al., 2011). Ceramic NPs are nonmetallic inorganic solids that are synthesized by continuous heating and cooling. It is possible to find them in amorphous, polycrystalline, dense, porous, or hollow forms (Sigmund et al., 2006). Therefore, these NPs are of interest to researchers because of their applications like catalysis, photocatalysis, photodegradation of dyes, and imaging applications (Sun, 2000). Semiconductor materials possess properties between metals and nonmetals and have found different applications because of this susceptibility (Khan et al., 2017). In addition, semiconductor NPs have broadband gaps and have demonstrated considerable changes in their properties via band gap tuning. So, they are very significant materials in photocatalysis, photo optics, and electronic devices (Abd Ellah and Abouelmagd, 2016). These are usually organic-based NPs called polymer nanoparticles (PNP). They are mainly nanospheres or nanocapsules in shape (Mansha et al., 2016). Formers are matrix particles whose total mass is usually solid, and the other molecules are adsorbed on the outer boundary of the spherical surface. The solid mass is wholly enclosed within the particle (Rao and Geckeler, 2011). The PNPs are easily functional and therefore suitable for a set of applications (Shanmuganathan et al., 2019). These NPs comprise lipid moieties and are used efficiently in many biomedical applications. In general, a lipid NP is distinctly spherical and has a diameter ranging from 10 to 1000 nm. Like polymeric NPs, lipid NPs have a solid core produced by lipid and a matrix containing soluble lipophilic molecules. Surfactants or emulsifiers stabilized the outer core of these NPs (Rawat et al., 2011). Lipid nanotechnology (Mashaghi et al., 2013) is a specific field that focuses on the design and synthesis of lipid NPs for different applications like drug delivery (Puri et al., 2009) and antisense RNA in the treatment of many diseases such as cancer (Pothipor et al., 2019).

2.1. Metal NPs

Metal NPs (Figure 2) are fully composed of metal raw elements. Cu, Ag, and Au NPs of alkali and noble metals exhibit an exterior absorption band in the visible area of the solar electromagnetic spectrum. Controlling the aspect, size, and shape of nanoparticles is essential in today's sophisticated materials. The gold NP coating is widely used for SEM sampling to enhance the electrical current, resulting in high-quality SEM pictures, (Dreaden et al., 2012).

Metal NPs have a wide range of different uses. The importance of these materials in biomedicine is widely understood. We were interested in the potential antibacterial effects of metal oxide nanoparticles such as Ag2O, FeO, MnO2, CuO, Bi2O3, ZnO, MgO, TiO2, CaO, and Al2O3 and were also interested in the potential antibacterial effects of metal oxide nanoparticles such as Ag2O, FeO, MnO2, CuO, Bi2O3, ZnO, MgO, TiO2, CaO, and Al2O3. Other reported metal oxide applications include magnetic imaging, environmental pollution remediation, drug delivery, gene therapy, tissue development, use in surgical devices, use in the production of thermal and electric insulators, gene transfer, use as catalysts, drug carriers, use in filler materials, skin protection, coating materials, sterilization, cellular labeling, and anticancer drugs. (Thomas et al., 2015; Khan et al., 2019; Naghsh et al., 2012a).

3.1. Silver NPs

Silver nanoparticles (AgNPs) demonstrate various physical and chemical attributes contrasted to their large-scale analogs. This is primarily because of their small size and, accordingly, the exceptional surface area of these materials (Iravani et al., 2014). At present, advances in the synthesis, stabilization, and making of AgNPs have strengthened a new filiation of specific materials and intensified scientific verification in the field of nanobiotechnology. The increasing the use of AgNPs in biomedical products and its effects on human health are widely strange. (Jimenez et al., 2007).

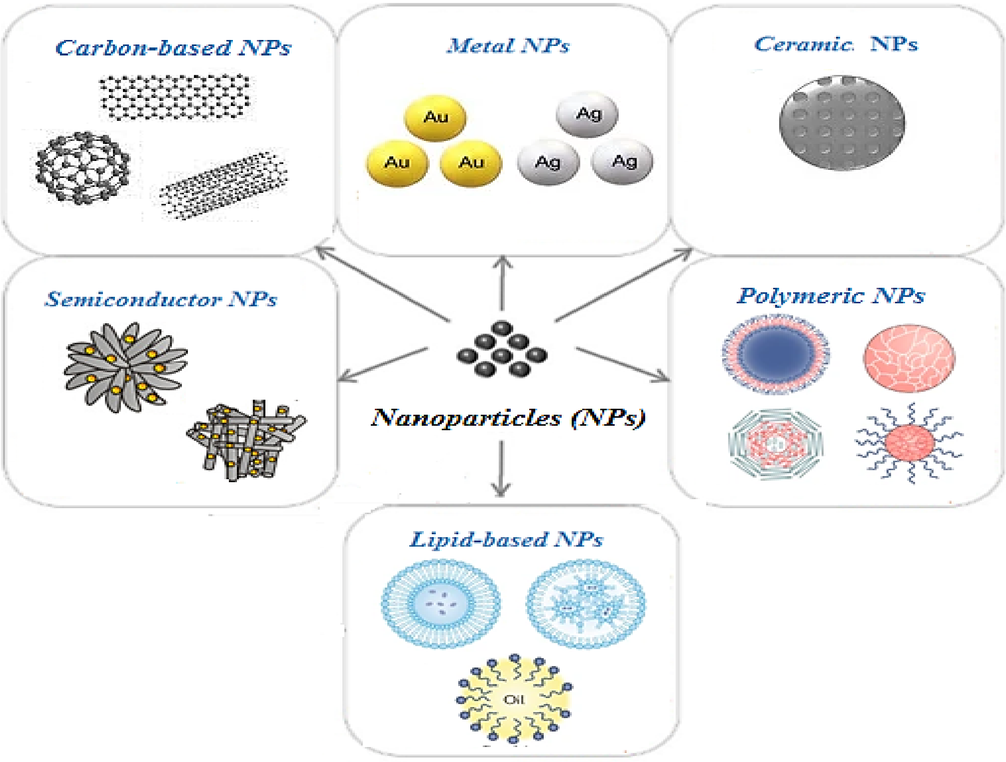

Figure 1. Different types of nanoparticles

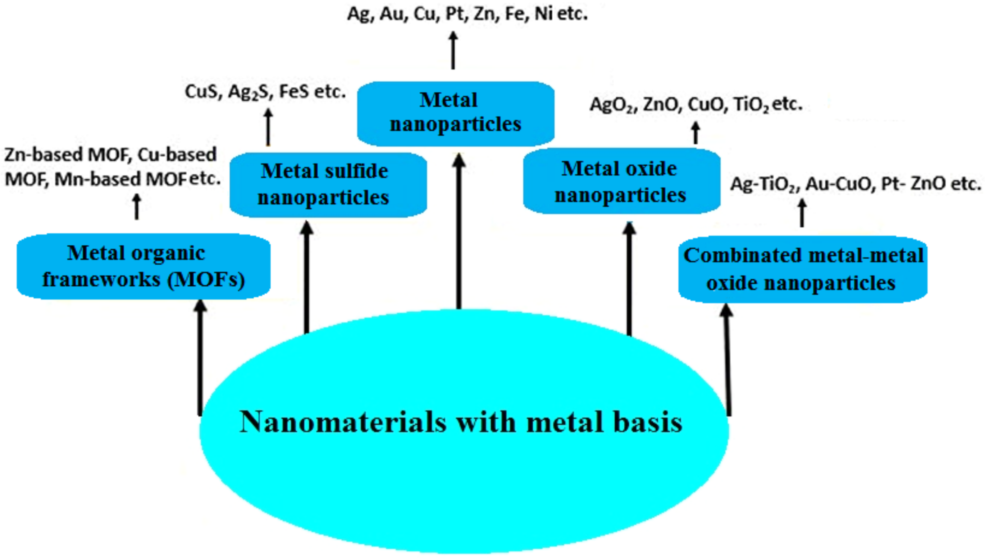

Figure 2. Different types of common nanomaterials with metal basis

3.1.1. Synthesis of Ag NPs

The different methods that have been proposed for manufacturing silver nanoparticles are as follows.

3.1.2. Physical methods

Evaporation-condensation and laser ablation are the two most significant physical processes. When compared to chemical techniques, the benefits of physical synthesis methods include the absence of solvent contamination in accumulated thin films and the uniform distribution of NPs. However, there are several drawbacks to employing a tube furnace at atmospheric pressure for the physical synthesis of silver NPs. For example, the tube furnace uses a lot of energy and takes a long time to reach thermal stability while taking up a lot of space and raising the ambient temperature near the source material. Furthermore, a traditional tube furnace requires several kilowatts of electricity and a preheating period of several tens of minutes to attain a steady working temperature (Kruis et al., 2000).

3.1.3. Chemical methods

The most common method for synthesizing silver NPs is chemical detraction via organic and inorganic reducing factors. Generally, various increasing agents like sodium citrate, ascorbate, sodium borohydride ($NaBH_4$), Tollens reagent, N, N-dimethylformamide (DMF), elemental hydrogen, polyol process, and poly (ethylene glycol)-block copolymers are used to reduce silver ions (Ag^+) in aqueous or non-aqueous environments. These reducing factors decrease Ag^+ and lead to metallic silver (Ag^0) accumulating in oligomer clusters. These clusters finally lead to formation of metallic colloidal silver particles. (Wiley et al., 2004; Evanoff and Chumanov, 2004; Merga et al., 2007).

3.1.4. Microemulsion techniques

Microemulsion technologies can be used to create homogenous and size-controllable silver NPs. The creation of NPs in two-phase aqueous organic systems is based on the basic spatial separation of the reactants (metal precursor and reducing agent) into two immiscible phases. The pace of the interaction between metal precursors and decreasing factors is affected by the junction between the reaction liquids and the intensity of inter-phase transfer between the two phases, which is mediated by a quaternary alkyl-ammonium salt. Metal clusters generated at the common surface are stabilized by surface coating with stabilizer molecules found in the non-polar aqueous medium and carried to the organic medium through the inter-phase transporter (Krutyakov et al., 2008). One of the main drawbacks of using organic solvents is that they are very harmful (Zhang et al., 2007).

3.1.5. UV-initiated photoreduction

The reduction of UV-initiated photoreduction for the synthesis of silver NPs in the presence of citrate, polyvinylpyrrolidone, poly (acrylic acid), and collagen has been reported to be a simple and effective technique. The properties of produced NPs were studied as a function of the time of UV irradiation. The bimodal size distribution and comparatively large silver NPs were obtained when irradiated under UV for 3 h. Most irradiation decomposed silver NPs into smaller sizes with a single propagation mode until comparative stability, and a distributed size were obtained (Huang and Yang, 2008). Silver NPs (nanosphere, nanowire, and dendrite) have been prepared via the UV irradiation photoreduction method at room temperature using poly (vinyl alcohol) (as a protecting and stabilizing agent). Concentration of both poly (vinyl alcohol) and silver nitrate played an essential role in developing the nanorods and dendrites (Zhou et al., 1999).

3.1.6. Photoinduced reduction

Silver NPs can be synthesized using different photoinduced or photocatalytic diminution methods. Photochemical synthesis is a clean process with high spatial resolution, ease of use, and great versatility. Plus, photochemical synthesis enables individuals to make NPs in different mediums containing cells, emulsions, polymer films, surfactant micelles, glasses, etc. Nano-sized silver particles with an average size of 8 nm were accumulated via reducing photoinduced using poly (styrene sulfonate)/poly (allylamine hydrochloride) polyelectrolyte capsules as microreactors (Shchukin et al., 2003). In addition, it was shown that the photoinduced method could be used to convert silver nanospheres into triangular silver nanocrystals (nanoprisms) with favorable edge lengths in the 30-120 nm range (Jin et al., 2003).

3.1.7. Electrochemical synthetic method

A synthetic electrochemical method can be used to synthesize silver NPs. Particle size control is possible by adjusting electrolysis parameters and improving the uniformity of silver NPs by changing the composition of the electrolytic solutions. Silver nanospheroids were synthesized by polyphenylpyrrole coating (320 nm) by electrochemical reduction at the liquid/liquid level. This nano-compound was made by transmitting silver metal ions from the aqueous phase to the organic phase, where they reacted with pyrrole monomer (Johans et al., 2002). In another study, monodisperse silver nanospheroids (1–18 nm) were synthesized by electrochemical reduction inside or outside zeolite crystals according to the silver interchange degree of adjusted zeolite film modified electrodes (Zhang et al., 2002).

3.1.8. Irradiation methods

Silver NPs can be utilized to synthesize silver nanoparticles. Silver NPs have been produced with Laser irradiation of an aqueous solution of silver salt and surfactant with a specific shape and size distribution (Abid et al., 2002).

3.1.9. Microwave-assisted synthesis

A promising technique for the synthesis of silver NPs is microwave-assisted synthesis. Microwave heating is more reliable than conventional oil bath when it comes to consistently producing nanostructures with smaller sizes, a narrower size distribution, and a higher degree of crystallization. Microwave heating has shorter reaction times, decreased energy consumption, and better product efficacy that protects against the accumulation of particles (Nadagouda et al., 2011). In addition to removing the oil bath, microwave-assisted synthesis, combined with a benign reaction medium, can drastically diminish chemical waste and reaction times in several organic syntheses and chemical conversions (Polshettiwar et al., 2009).

3.1.10. Green synthesis

The mechanism of processing AgNP remains completely unexplored. Nevertheless, most of the publications qualify the AgNP synthesis via different organisms like bacteria, fungi, lichens, algae, and higher plants. Research on different organisms shows that AgNPs synthesis can accrue both inside and outside the cells. Enzymes in bacterial cell walls and secreted proteins that lead to the reduction of Ag+ to Ag0 perform extracellular synthesis of AgNPs. It has been demonstrated that both gram-positive and gram-negative bacteria regularly synthesize AgNPs extracellularly (Elbeshehy et al., 2015; Chauhan et al., 2013). Other organisms, such as fungi, also use the same synthesis method. (Abdel et al., 2017). On the other hand, some organisms use intracellular methods to synthesize nanoparticles. In these mechanisms, which mostly accrue in gram-negative bacteria, membrane proteins are used to transport the silver ions into the cell (Klaus et al., 1999; El-Baghdady et al., 2018). This mechanism was also detected in various bacteria of the genus *Streptomyces*. (Alani et al., 2012). In addition, some microorganisms are apt to biosynthetic AgNPs both intracellularly and extracellularly (Das et al., 2013). The principal factor in AgNPs intracellular or extracellular biosynthesis is the enzyme NADH-dependent nitrate reductase that has a fundamental role in AgNP formation by taking electrons from the nitrate molecule and transferring them to the metal ion for the formation of nanoparticles like an electron shuttle (Jeevan et al., 2012; Zomorodian et al., 2016). Figure 3 demonstrates the mechanism for this process. Furthermore, it is believed that a carboxylate group on the bacterial cell surface helps capture silver ions because it is mostly negatively charged, provides an electrostatic interaction between this group and positively charged silver ions (Wang et al., 2013). Some amino acids, like cysteine, glutamic acid, lysine, and methionine, operate as catalysts, producing a hydroxyl ion that reacts with reducing agents such as aldehyde. It is also implicated in reducing silver ions or silver nanocrystals (Nam et al., 2008). It has been demonstrated that disulfide bonds in peptides can also reduce Ag^+ to Ag^0 (Graf et al., 2009). One important point is that AgNPs also are biosynthesized intensity by light. This mechanism may involve the activation of reducing agents in the environment, which causes the release of electrons to reduce Ag^+ to Ag^0 nanoparticles (Wei et al., 2012). Based on the other hypothesis for synthesizing nanoparticles, certain bacteria produce the trans-membrane proton gradient in the extracellular area, which is done by the active symport of Na^+ ions and Ag ions. Silver ions attached to silver binding proteins in the cell membrane cause the uptake of silver ions inside the cells and initiate the synthesis of AgNPs by using the energy of ATP hydrolysis (Prakash et al., 2011).

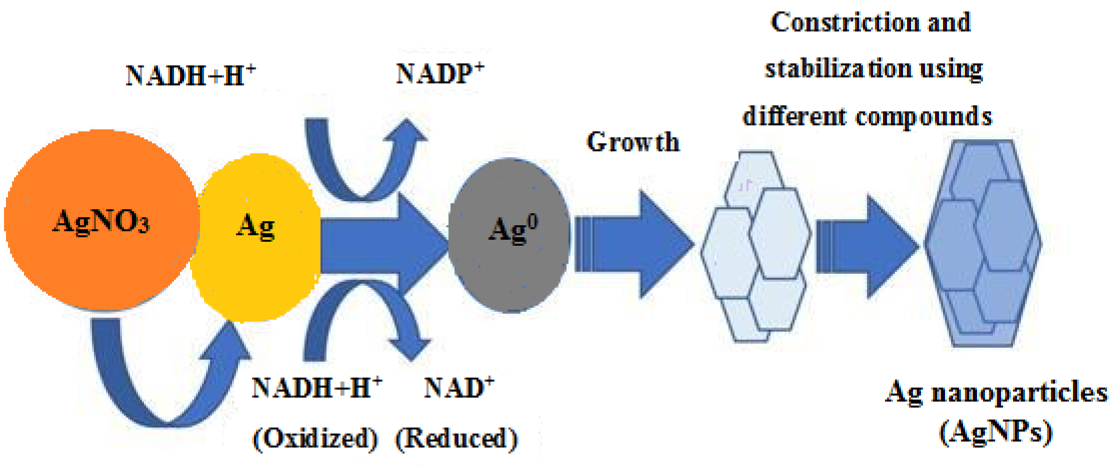

Figure 3. The mechanism which has been proposed for the biosynthesis of silver nanoparticles.

Plant extracts involve biomolecules which can enhance the bioactive properties of Ag NPs and other metal NPs resulting in the reduction of metal ion content of the NPs. The process of this biogenic production is quite rapid, can be performed at room temperature and usual pressures, and can be readily scaled up. Mediated synthesis by plant extracts is environmentally benign. Water soluble plant metabolites such as polyphenols, alkaloids, and terpenoids as well as co-enzymes induce the effect of Ag NPS and the enzymes involved in its bioactivity (Ssekatawa et al., 2021; Akintelu et al., 2020). Sadeghi et al. (2015) synthesized eco-friendly Ag NPs using an aqueous extract of *Pistacia atlantica* seeds. SEM analysis showed that the synthetized Ag NPs have antibacterial activity against most studied strains of *Staphylococcus aureus*, so that the bacterial cells were damaged and broadly disappeared by the addition of Ag NPs. Sadeghi and Gholamhoseinpoor (2015) used a single-step green process for the plant-based synthesis of Ag NPs. *Ziziphora tenuior* leaf extracts were associated with Ag NPs. The obtained Ag NPs showed high antioxidant activities. The results from TEM, SEM, FT-IR, UV–VIS and XRD analysis confirmed the right formation of Ag NPs. Hashemi et al. (2022) biosynthesized AgNPs@*SEE* using *Sambucus ebulus* extract in association with AgNPs and investigated their antibacterial, anticancer, and photo-catalysis effects. Then, the activity parameters including $AgNO_3$ concentration, contact time, and temperature, were optimized. The AgNPs@SEE showed powerful anti-proliferative effect on cancer cell lines and high antibacterial effects against Gram-positive bacteria.

4. Methods for Ag NPs characterization

The most extensively used techniques for characterization of NPs are X-ray diffraction (XRD) and X-ray energy dispersive spectrophotometer (EDAX). Information on crystalline structure and size, phase nature, and lattice parameters may be obtained using X-ray based methods. These techniques are often used on dried forms of colloidal solutions, and they have the benefit of being statistically more representative in volume-averaged data than most other approaches. The composition of the NPs may also be determined by comparing the position and intensity of the peaks to reference patterns. The other approach is Fourier transform infrared spectroscopy (FTIR), which is based on the measurement of electromagnetic radiation absorption at wavelengths in the mid-infrared range (4000–400 cm1). The dipole moment of each molecule that absorbs the radiation is modified, and the molecule becomes IR active. The kind and strength of the bonds, as well as associated functional groups, are connected to the locations of the bands in the recorded spectrum, providing information about molecular structures and interactions. The most frequent procedures to analyzing Ag NPs size and form are scanning electron microscopy (SEM) and transmission electron microscopy (TEM), since both techniques offer direct pictures of the NPs and allow homogeneity to be assessed. UV-Vis is another widely used method for detecting optical characteristics, size, concentration, aggregation state, and metal hints, such as the form of Ag NPs (Mourdikoudis et al., 2018).

Application of AgNps in disease treatment

5.1. Bacterial infections treatment

The health care industries face challenges because of antimicrobial resistance by pathogenic bacteria. Naghsh et al. (2012a) also conducted a study on the effects of eucalyptus and nanosilver on the growth of *Escherichia coli*. The maximum inhibitory effects were obtained 1-day post-treatment, which showed that silver nanoparticles combined with eucalyptus extracts might be useful for human bacterial disease treatment. Fellahi et al. (2013) observed the antibacterial processes of silicon nano substrates associated with Ag nanoparticles or Cu nanoparticles. Their study concluded that the synthesized nanoparticles have enhanced antibacterial activities against *Escherichia coli*. The Ag-coated silicon wires were biocompatible with attention to the human lung, particularly adenocarcinoma epithelial cells, while the Cu-coated Si nanowires showed high cytotoxicity, which may lead to death. Siddiqi and Husen (2017) studied the medical applications of Pd nanoparticles and attempted to produce them more prolifically. Pd nanoparticles can act as anticancer and stabilizing agents in many pharmaceutical products.

5.2. Fungal infections treatment

Although the toxic effects of silver ions are not well known, the antifungal effect of silver NPs has only received marginal attention, and only a few studies have been performed in this field (Perween et al., 2019). Deyá and Bellotti (2017) transferred the extracts of *Aloysia triphylla* (cedrón), *Laurelia sempervirens* (laurel), and *Ruta chalepensis* (ruda) to the waterborne coating substrate to obtain silver nanoparticles for use as an antimicrobial additive. The obtained products were evaluated as opposed to fungal isolates. Conventional and molecular methods recognized the fungi as alternatives to *Chaetomium globosum* and *Alternaria*. The results showed that the coating with silver nanoparticles obtained with *L. sempervirens* extract at 60 °C with a size of 9.8 nm was the most effective in opposing the development of fungal biofilm. Naghsh et al. (2012b) investigated the inhibitory effects of AgNPs with concentrations of 100, 200, 300, 400, and 500 ppm on *Aspergillus niger* and *Escherichia coli*. The NPs with a concentration of 150 ppm inhibited the growth of the fungus after eight days of treatment, and the growth of the bacterium was inhibited with a concentration of 400 ppm after three days. In addition, Naghsh et al. (2012a), in another study, inhibited the growth of *Aspergillus niger* significantly by nano-silver -eucalyptus with a concentration of 12.5 ppm, 24 days after treatment. Rahimzadeh-Torabi et al. (2016) evaluated the antifungal effects of spherical silver and gold nanoparticles (Figure 4) on *Candida albicans* by the methods of disk diffusion and microdilution. Among the isolates, 58 samples were inhibited by both nanoparticles. The minimum inhibitory concentration (MIC) of silver and gold nanoparticles was 21.31±11.40 ppm and 32.15±25.77 ppm, respectively, and the minimum fungicidal concentration (MFC) of silver and gold nanoparticles was 16.68±9.37 ppm and 7.93±4.72 ppm, respectively. Asghari et al. (2015) investigated the effect of silver nanoparticles on *Candida* strains producing vulvovaginal candidiasis. Among the total 50 isolates, the growth of 36 isolates was inhibited by spherical silver nanoparticles. MIC was detected as 31.25-125 ppm, and MFC was between 62.5-250 ppm.

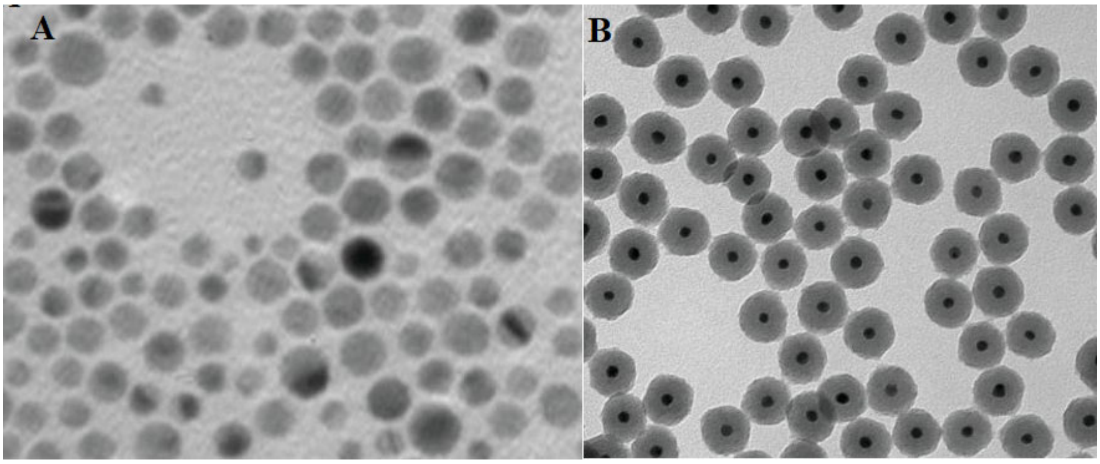

Figure 4. The TEM images of Ag NPs (A) and Au NPs (B) that used in the study of Rahimzadeh-Torabi et al. (2016)

5.3. Antiviral activity of AgNPs

One of the human disease pathogens identified is the virus in modern human history. Despite their apparent structural simplicity, viruses in the face of dangerous diseases like Spanish influenza, HIV, Ebola, and Marburg, and finally, the 2020 epidemic caused by COVID-19, reveal a significant threat. It proves to us that we know little about fighting viruses. The pathogenic nature of viruses involves adhesion and infiltration into the host cell. In this case, the virus uses its protein components to bind to receptors and proteins on the surface of the cell membrane. Preventing this kind of connection seems to be the best way to prevent cell infection. The mechanism of antiviral activity of AgNPs' is not yet well understood, but the data from many investigations are as follows: (1) AgNPs bind to the virus protein's protective layer and inhibit binding; and (2) AgNPs bind to virus DNA or RNA and inhibit virus replication in host cells (Salleh et al., 2020). For example, AgNPs have been demonstrated to offset the transmitted gastroenteritis virus (TGEV) infection by binding to a surface protein, S-glycoprotein. It has been suggested that silver nanoparticles can alter the structure of surface proteins and thus reduce their recognition and adhesion to host-specific receptors (Lv et al., 2014). Speshoc et al. (Speshock et al., 2010) found inhibition of the replication process in the virus genome with silver nanoparticles. There is evidence to prevent herpes simplex virus (HSV) types 1/2, human parainfluenza virus type-3 (Gaikwad et al., 2013), and influenza virus (Mori et al., 2013) infection by avoiding host cell contact.In addition, AgNPs are effective against HIV-infected human cells through adherence to the HIV envelope (Lara et al., 2011). Sharma et al. (2019) illustrated a decrease in the viability of cells infected with Chikungunya arbovirus, spread via two species of mosquito: *Aedes albopictus* and *Aedes aegypti*.

A critical study is the suppression of COVID-19 viral activity. Thus, Sarkar (2020) suggests that silver nanoparticles can connect to virus spike glycoproteins, prevent them from binding to the target cell, and also act as a weak acid that can adjust the pH of respiratory epithelium, which is the main target of the coronavirus attack, leading to its death. The size of silver nanoparticles seems to play an essential role in the antiviral effect (i.e., smaller particles are more effective (Nakamura et al., 2019). More research on the AgNPs' antiviral activity may open up new possibilities in the combat of diseases invocated by different viruses. Due to the need for an efficient factor as opposed to SARS-CoV-2, Jeremiah et al. (2020) evaluated many AgNPs in different sizes and concentrations. They observed that particles with a diameter of around 10 nm effectively resisted extracellular SARS-CoV-2 in concentrations ranging between 1 and 10 ppm, while the cytotoxic effect was perceived at concentrations of 20 ppm and above. Furthermore, the luciferase-based pseudovirus entry method showed that AgNPs strongly inhibited the viral entry step by disrupting viral integrity. These results show that AgNPs are highly potent microbicides that inhibit SARS-CoV-2 but should be utilized with caution due to their cytotoxic impacts and their potential to derange environmental ecosystems when incorrectly disposed of.

5.4. Burn treatment by AgNPs

In some investigations, a few strategies are possible for clinical wound management. For example, skin autografts and xenografts are good treatment choices for severe wounds in terms of compatibility and enhanced healing. However, except for expensive methods, these strategies have certain limitations, like limiting bioavailability immunogenicity, and increasing the likelihood of disease transmission (Atiyeh and Costagliola, 2007; Diegidio et al., 2017). Furthermore, oxygen-enriched therapy is helpful for rapid wound healing because oxygen is vital for stimulating collagen synthesis and subsequent re-epithelialization and inducing angiogenesis (Eggleton et al., 2015; Kaufman et al., 2018). However, in addition to being a costly and inconvenient procedure, it has also been reported that hyperbaric oxygen therapy has limited efficiency because negative pressure therapy is usually comfortable for minor wounds and may produce several physical effects that can disrupt the healing process (Lima et al., 2017; Sexton et al., 2020). Another treatment strategy for wound healing involves the use of a wound dressing that supports the structural and functional repair of damaged tissue and protects against external pathogens. Several critical aspects of an effective wound dressing should be considered: biocompatibility, fluid (super) absorption, partial permeability to water and oxygen, nonimmunogenicity, and easy and nontraumatic removal (Ousey et al., 2016; Han et al., 2017).

Even if a wide variety of dressings are commercially available, the current tendency in wound care management is to create unique and functional dressings that provide the appropriate compositional, structural, and biofunctional properties for the proper wound healing process (Mihai et al., 2019; Stoica et al., 2020). The opportunistic microbial contamination and wound colonization generally lead to delay and circumstantial inadequate healing process but may also lead to severe infections and acute healthcare complications (Wu et al., 2019; Milne and Penn-Barwell, 2020). Thus, considerable attention has been focused on developing anti-infective wound dressings, which can be created by embedding dressing materials with various antimicrobial factors, like synthetic antibiotics (Liu et al., 2018) and antibacterial nanoparticles (Wang et al., 2020). Silver derivatives have been used for wound care since ancient times because even Hippocrates described their effectiveness in wound healing (Yapijakis, 2009). Also, silver-based compounds have been used to decrease the risk of intraoperative wound infection since the late XIX century (Alexander, 2009) and have remained the preferred agent for the treatment of minor burns since the middle of the XX century (because they can better absorb fluids and reduce infectious processes) (Nherera et al., 2018).

In a study conducted by Naghsh et al. (2013a), the effect of a new nano-plant composition was prepared by Cucurbita pepo and nanosilver and used for skin wound repair in male mice. The results showed that ethanol extract (80%) had the highest repair effect at 28 days post-treatment. Furthermore, these findings showed the synergic effects between Cucurbita pepo alcoholic extract and nanosilver in this nanocomposite.

5.5. Cancer and nervous disease treatment by AgNPs

Silver nanoparticles have a special role in modern anticancer treatments and have have been used for detection and diagnosis of malignant tumors (Pothipor et al., 2019; Hasanzadeh et al., 2019), controlled and externally triggered drug delivery systems (Nigam Joshi et al., 2017, Karuppaiah et al., 2020). Similar to the antimicrobial activity of AgNPs, their efficiency opposes cancer cells' need for nanosilver cellular uptake, which can be received via diffusion, phagocytosis, pinocytosis, and receptor-mediated endocytosis (Brkic Ahmed et al., 2017, Azhar et al., 2020). Furthermore, the size, morphology, and surface characteristics of AgNPs are likable for internalization by cancer cells, leading to the local release of silver ions which are effective on free radicals of oxidative stress (Bin-Jumah et al., 2020). Such events are more likely to cause cancer cells to die, or by (i) apoptosis, which occurs due to mitochondrial changes and unbalance between antiapoptotic proteins and proapoptotic kinases, and (ii) structural and functional defects of cellular substructures, which occur for specific reasons with silver nanoparticles and ions (Azizi et al., 2017; Ishida, 2017).

Intravenous administration of nanoparticles is a promising delivery system for neurodegenerative disease treatment (Saraiva et al., 2016), e.g., in the case of Alzheimer's disease, which is a type of dementia that leads to problems in memory, cognition, and behavior (Hajipour et al., 2017), biodegradable polymeric nanoparticles consisting of polyethylene glycol or poly(lactic-co-glycolic acid) and to eliminate and prevent the formation of amyloid fibrils that lead to this disease, use with specific antibodies (Carradori et al., 2018, Loureiro et al., 2016) or oligopeptide drugs (Zheng et al., 2017). Youssif et al. (2019) successfully used the aqueous extracts of aerial parts of *Lampranthus coccineus* and *Malephora lutea* F. Aizoaceae to synthesize silver nanoparticles. Next, SNPs' neuroprotective properties were evaluated by an investigation of the inhibitory activity of antioxidants and cholinesterase. Metabolomic profiling was performed on methanolic extracts of *L. coccineus* and *M. lutea*, which led to the identification of 12 compounds. To investigate the possible interaction between the identified compounds and human acetylcholinesterase, butyrylcholinesterase, and glutathione transferase receptor, the corresponding docking connection was performed. This plant extract has promising anticholinesterase and antioxidant activity against Alzheimer's and oxidative stress.

5.6. The effects of AgNPs on immune system promoting

The immune system can fight to oppose tumors and other diseases due to multiple immune checkpoints inside the cells that regulate or dictate tumor immune surveillance monitoring within an organism; many of these checkpoints are bypassed in micro tumor environments. Therefore, targeting these changed immune checkpoints by adoptive T-cell treatment, using chimeric antigen receptors, or the induction of several inflammatory mechanisms in the tumor microenvironment are the most essential goals in cancer immunotherapy (Keenan et al., 2013).

Nanoparticles interact with immune systems or affect immune-stimulants or immunesuppressors. Nanoparticles are usually first absorbed by phagocytic immune cells (e.g., macrophages and dendritic cells); nanoparticles may enhance inflammatory or anti-inflammatory reactions via adverse interactions between nanoparticles and the immune system. In addition, immune cells may consider nanoparticles as foreign organisms, thus leading to an unwanted multilevel immune reaction against the nanoparticle (e.g., allergic response); this response may eventually lead to toxicity within the biological system. Finally, the physical properties of nanoparticles, such as size, hydrophobicity or hydrophilicity, surface charge, and the steric impacts of their coatings, can influence their immune system compatibility (Zolnik et al., 2010).

Recent research has shown that AgNPs also elicit an immunologic response within biological hosts, including immune cells (Haase et al., 2014). By suppressing TNF- and IL-12, nanocrystalline silver induces apoptosis in inflammatory cells (Bhol et al., 2005). AgNPs have been reported to interact with HIV-1 via gp120 glycoprotein knobs. In freshwater fish, AgNPs are associated with an inflammatory response. (Gagne et al., 2013). AgNPs have also been shown to inhibit molecules involved in the cholinergic system, thereby disrupting the differentiation of the zebrafish's immune system (Myrzakhanova et al., 2013). As reported in a recent proteome-based study AgNPs act as allergens in mice (Su et al., 2013). Intravenous administration of AgNPs also demonstrated immunotoxicity in murine models (de Jong et al., 2013). Respiratory tract immune toxicity is also related to AgNPs (Liu et al., 2013). AgNP treatment of peripheral blood mononuclear cells and human mesenchymal stem cells prevented the generation of cytokines like IFN-γ, IL-6, IL-8, IL-11, TNF-α, and weaker IL-5 (Greulich et al., 2009). In a recent in laboratory study, AgNP exposure indicated an induction of expression of IL-8 and stress genes in macrophages (Lim et al., 2012). Hence, it is suggested that there is a relation between AgNPs and the immune system. In accordance with the important roles of white blood cells (WBC) and hepatocytes in the immune system and body detoxification, respectively. Naghsh et al. (2012c) investigated the effects of nanosilver particles (50, 100, 200, and 400ppm intraperitoneal injection) on the count of WBC and the level of the liver enzyme' alanine aminotransferase (ALT) in male Wistar rats. Intraperitoneally injection of AgNPs in rats led to an increase in the creation of white blood cells, although it induced liver damage in rats.

6. The effects of AgNPs, and Ag containing materials on human health

Over the past two decades, extensive efforts have been devoted to the status of the toxicity effects of AgNPs, coating verification of environmental regions, and including a plethora of *In Vivo* and *In Vitro* research (Marambio-Jones and Hoek, 2010; Fabrega et al., 2011; Zhang et al., 2014). Numerous *In Vitro* studies have provided evidence that AgNPs not only transport and internalize cells but also target endosomes and lysosomes (120, 121), cause lung fibroblasts, damage to cell membranes, chromosome damage and genetic toxicity, DNA fragmentation, and apoptosis (Almofti et al., 2003; Jiang et al., 2004; Yang et al., 2012). Placing A549 cells (human alveolar basal epithelial cells) against AgNPs resulted in the production of reactive oxygen species and reduced cell viability and mitochondrial membrane. Conversely, exposure to AgNPs at high concentrations (up to 6.25 μg/ml) not only caused apoptosis and oxidative stress but also morphological changes in HT 1080 (human fibrosarcoma) and A431 cells (human skin/carcinoma) cells, which became less polyhedral, more fusiform, shrunken, and rounded. While AgNPs have toxic effects on bacteria, hence their primary use in the formulation of antibacterial products, considerable evidence shows the toxicity of AgNPs to other organisms (Marambio-Jones and Hoek, 2010). AgNPs have also been toxic to models like zebrafish, *Drosophila melanogaster*, and *Daphnia Magna*. It has been found that nano-silver ions penetrate the skin and blood tubes of zebrafish larvae (Yeo and Yoon, 2009), while AgNPs induce heat shock, oxidative stress, DNA damage, and apoptosis in *Drosophila melanogaster* (Ahamed et al., 2010). Plus, silver nanowires were toxic not only to Daphnia Magna but also to found that the surface coating of silver nanowires (AgNWs) changed dramatically when extracted from the organism's hemolymph (compared to pristine AgNWs) (Scanlan et al., 2013). Naghsh et al.

(2013b) investigated the effects of AgNPs on phosphocreatine kinase activity and histological changes in skeletal muscle tissue in Wistar male rats. After eight days, the mean activity of phosphocreatine kinase increased by different amounts (50-400 ppm) of AgNPs. The 400 ppm AgNPs caused histological changes in the rats' skeletal muscles. Naghsh et al. (2013c) conducted a study on the effects of AgNPs on the skin, causing blood damage according to mean corpuscular hemoglobin (MCH) and high hemoglobin (HGB) counts in male rats in an in vivo condition. Stimulated red blood cells were shown in all groups, and in the concentration of 50 ppm AgNPs, MCH was changed possibly because of releasing free radicals, which cause oxidative stress and apoptosis in red blood cells.

In cosmetology and dermatology, metal and metal oxide NPs are broadly used. NPs are utilized for dermatological treatments, skincare, and diagnostic imaging of skin diseases (Fabrega et al., 2011). Sub-dermal exposure of Ag NPs for 7 and 28 days in male rats causes changes in sperm count and motility as well as the levels of testosterone (T), luteinizing hormone (LH), and follicle-stimulating hormone (FSH) along with tissue abnormalities (Olugbodi et al., 2020). In some studies, it has been shown that NPs cannot penetrate the skin, while in others, penetration of metallic NPs, containing iron NPs, is confirmed through hair follicles (Donnelly et al., 2012). This depends on NP size, since it has been recorded that NPs with a 4 nm size can penetrate the skin with no difficulty, but NPs can only enter through perverse skin at size of 45 nm (Filon et al., 2015).

Even though the health benefits of Ag on humans have not yet been proven, colloidal silver suspensions are included in dietary supplements. Occupational health studies have demonstrated that long-term Ag exposure causes permanent disorders such as argyria, in which the skin becomes bluish as a result of Ag buildup in key organs. According to research, the liver is the primary organ for nanosilver accumulation and detoxification. Although the majority of Ag-containing consumer items are designed for topical application, the danger of silver percutaneous absorption is negligible since the human epidermis is a strongly impermeable barrier (the exception being dermal abrasions, wounds, and cuts). Although the usage of Ag in silver thread and textile fibers is rising, there is no evidence that blood silver levels rise or silver deposits build in the skin after long-term exposure, and the risks of argyria in these circumstances are considered insignificant. (Lansdown, 2006). To this end, the toxic risks related to silver ingestion are low, as most Ag-ion products for oral or gastrointestinal hygiene have been removed from pharmacopeias and permitted lists in many countries in light of the risks of argyria. Skóra et al. (2021) demonstrate that sulfur-rich combination action as a capping factor being adsorbed on the surface of AgNPs and the decreased cytotoxic impact on the mammalian somatic and tumoral cells was confirmed by the sulfur coated AgNPs.

Doudi et al. (2013) investigate the effect of AgNPs on extended-spectrum beta-lactamase (ESBL) producing isolates of *Klebsiella* pneumonia. All isolates were sensitive to the AgNPs with a concentration of 100 ppm. In vitro analysis on the cytotoxicity of AgNPs in Wistar rats showed no significant changes in the rats' mean weight before and after the injection of silver nanoparticles at 100 ppm, but three days after the treatment, the mean ALT activity was increased in the injected rats. In another study, Zamani et al. (2014) compared the effects of thioacetamide and AgNP injection on the liver enzyme levels in mice. The results showed that thioacetamide increased the activities of serum glutamic oxaloacetic transaminases (SGOT) and serum glutamic pyruvic transaminase (SGPT) enzymes. However, nanosilver injection only led to increased SGPT enzyme activity. More comprehensive studies and research are needed to help assess the risk and identify the toxic mechanisms of AgNPs and their toxicological impacts in human health-related cases. In a study, Karam Sichani et al. (2012) studied the effects of ethanol extract of *Peganum harmala* on the serum enzymes (catalase and glutathione peroxidase) activities and serum malondialdehyde levels in mice intraperitoneally injected with AgNPs. An increase in serum malondialdehyde was seen in the mice treated with AgNPs, while the levels of catalase and glutathione peroxidase activity were significantly decreased. However, by treating with *P. harmala* extract, the catalase and glutathione peroxidase activities and malondialdehyde levels were decreased. The results showed that plant drug resources such as

P. harmalawith extract may have antioxidant properties, resulting in a decrease of free radicals produced by AgNPs.

Conclusion

From the investigations discussed above, it can be concluded that AgNPs have attracted remarkable attention because of their wide range of applications in different areas of science and technology, including material science, biological fields, and nanomedical processes. AgNPs produced by different chemical, physical, and biological procedures, have been potentially applied against pathogenic microorganisms and neoplastic cells. Furthermore, the toxic effects of chemical AgNPs used for the treatment of human diseases and other higher organisms than microorganisms are another considered aspect of future studies conducted on AgNPs. More investigations on new methods for AgNPs productions such as green synthesis may lead to healthier production. Furthermore, the green synthesis of nanoparticles could be suggested as a safe method for treating many diseases.

Refereces

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