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REVIEW

A scientific review on the correlation of the silver nanoparticle synthesis methods with host cytotoxicity

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Abstract – Silver nanoparticles have been extensively researched and have several applications such as antimicrobial and anticancer, and can be used in the agricultural, biomedical, pharmaceutical, textile area, among others, but its toxicity is still little understood. Nanoparticles can measure between 1 – 100 nm and the most currently studied is the silver nanoparticle (AgNP). The main methods of synthesis are the chemical and the biogenic pathway, or green, which is less environmentally polluting, more environmentally friendly, and simpler, although standardization is more complex. Morphological and physical-chemical characteristics differ according to the synthesis method and, consequently, present different degrees of toxicity. Nanotoxicology studies the toxicity of nanoparticles on living organisms and scientists seek to know about the physical-chemical properties and their influence on interaction with the environment. It is known that there are several parameters that influence toxicity, such as dose, particle size, shape, morphology, surface chemistry, agglomeration/aggregation state, synthesis method, cell type and organism in which it is tested. Therefore, this article aims to address the main ways of synthesis of AgNPs, discuss the advantages and disadvantages of each method, the parameters that influence toxicity and examples of studies.

Keywords: Nanotoxicology. Green synthesis. Nanotechnology. Antimicrobial activity. Environment.

Uma revisão científica sobre a correlação dos métodos de síntese da nanopartícula de prata com a citotoxicidade ao hospedeiro

Resumo – As nanopartículas de prata têm sido extensivamente pesquisadas e possuem diversas aplicações, como antimicrobiano e anticâncer, podem ser usadas nas áreas: agropecuária, biomédica, farmacêutica, têxtil, entre outras. Contudo, sua toxicidade ainda é pouco entendida. As nanopartículas podem apresentar tamanhos entre 1 – 100 nm, e a mais estudada atualmente é a de prata (AgNP). Os principais métodos de síntese são: químico e biogênico, ou "verde", a qual é menos poluente ao meio ambiente, sustentável e simples, apesar da padronização ser mais complexa. As características morfológicas e físico-químicas se diferenciam de acordo com o método de síntese e, consequentemente, apresentam diferentes graus de toxicidade. A nanotoxicologia estuda a toxicidade das nanopartículas sobre os organismos vivos e os cientistas buscam saber a respeito das propriedades físico-químicas e sua influência na interação com o meio ambiente. Sabe-se que há diversos parâmetros que influenciam na toxicidade, como, concentração, tamanho da partícula, forma, morfologia, química da superfície, estado de aglomeração/agregação, método de síntese e o tipo de célula que é utilizada. Portanto, esta revisão visa abordar as principais vias de síntese das AgNPs, discutir as vantagens e desvantagens de cada método, os parâmetros que influenciam na toxicidade e exemplos de estudos.

Palavras-chave: Nanotoxicologia. Síntese verde. Nanotecnologia. Atividade antimicrobiana. Meio ambiente.

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Introduction

The concept of nanotechnology was established by Professor Nori Taniguchi in 1974 and refers to the process of separation, consolidation, and deformation of materials made by atoms or molecules, and since then, this field has become extremely important and much studied (TANIGUCHI, 1974; FOX, 1974). This field has become indispensable to modern science since it solves many problems related as pharmacological and therapeutic properties of drugs (DILNAWAZ, 2018), and it is an advanced field that deals with the fabrication of different types of nanomaterials with biomedical applications (GURUNATHAN *et al.*, 2014).

Nanoparticles can have various definitions, however, in 2011 the European Union defined a nanomaterial as a material of natural, synthesized, or incidental origin containing particles, in an unbound or aggregated state, and where 50 % or more of the particles are in the size range of 1 – 100 nm (EUROPEAN COMMISSION, 2011).

Silver nanoparticles (AgNP) are the most used in industry and commerce due to their properties, such as chemical stability, malleability, flexibility, high electrical and thermal conductivity, catalytic activity, low production cost, and potent antimicrobial action against bacteria, fungi, viruses, and protozoa. Therefore, silver nanoparticles are widely used in the pharmaceutical, textile, food industries, agriculture, hygiene, perfumery, cleaning products, and paints, among others (DURÁN; SEABRA, 2018).

In medical fields, nanomaterials are being studied and used to fight cancer and help overcome the challenges that doctors have regarding the resistance of cancer cells to anticancer agents (ELANGOVAN *et al.*, 2015). The antimicrobial properties of silver were already recognized and regulated for use in wounds by the FDA (Food and Drug Administration) in 1920 (CHOPRA, 2007).

Well known for their broad-spectrum antimicrobial activity, as they can kill a variety of pathogens, even at low concentrations, such as bacteria: *Escherichia coli*, *Klebsiella pneumoniae* and *Staphylococcus aureus*; fungi, such as *Candida albicans* and *Aspergillus niger*; viruses, such as Hepatitis B (HBV) and human immunodeficiency virus (HIV) (OTARI *et al.*, 2015).

In the agricultural field, AgNPs are being widely used to control plant pathogens due to their antimicrobial activity (PARK *et al.*, 2006), replacing chemical pesticides, which are harmful to the environment and humans (HAMMES, 2020). Additionally, AgNPs can be incorporated into foods, provide encapsulation systems (such as micelles and liposomes), for use in food packaging serving as antimicrobials, and even as drugs for veterinary use for better control of drug dosage (MASSINI; JESUS, 2013).

There are several methods for obtaining AgNPs, however, synthesis by chemical reduction and biogenic synthesis, a technique that is less harmful to the environment, are the two most widely used routes. Both consist in reducing silver ions (Ag^{+}) to metallic silver (Ag^{0}). As they are produced by different methods, AgNPs have different physicochemical and morphological characteristics and, consequently, have different interactions with the environment and distinct levels of toxicity (DURÁN; SEABRA, 2018).

The study of the morphological characteristics and physicochemical properties of nanoparticles are essential since they influence the particle-cell interaction in biological media and impact their toxicity. Therefore, with the development of nanotechnology, there has been increasing debate and research on the

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toxicity and environmental impacts of nanoparticles exposure (BRAYNER, 2008; PANDA *et al.*, 2011). Studies have shown that nanoparticles have toxic effects on cells at biomolecular levels, such as genes and proteins (GURR *et al.*, 2005; CHI *et al.*, 2009).

The human body can be exposed to AgNPs by different routes, through direct contact, inhalation, ingestion, intraperitoneal or intravenous injection, with NPs being able to accumulate in various vital organs, such as lung, liver, kidney, brain, and spleen (FEWTRELL; MAJURU; HUNTER, 2017). In animal studies, the highest concentration of AgNPs were observed in the liver (TANG *et al.*, 2009; EBABE *et al.*, 2013; MARTINS *et al.*, 2017).

Considering the wide use of AgNPs and their importance in health, especially in biomedical and agricultural areas, the study of their toxicity in animals, especially mammals in vivo and cell lines in vitro, is extremely relevant. Therefore, this article addresses the main synthesis routes of AgNPs, the parameters that influence toxicity, examples of studies, and discusses the advantages and disadvantages of each method.

Material and Methods

The present work is bibliographic research in which the "PubMed" platform was used as an online database, which gathers scientific works in the health area. Initially, a search was performed about the types of synthesis methods for silver nanoparticles and their toxicity. The titles and abstracts of each article were considered for selecting papers of interest. The keywords used were “silver nanoparticles”, “silver nanoparticles toxicity”, “silver nanoparticles chemical”, “silver nanoparticles biological”, and “silver nanoparticles synthesis”. The selected papers were texts published from 2000, except for one paper from 1974, texts in English or Portuguese. Finally, 97 scientific articles were selected. Figure 1 shows a flowchart of the methodology and searches terms, and Table 1 shows a more detailed description of the selected articles.

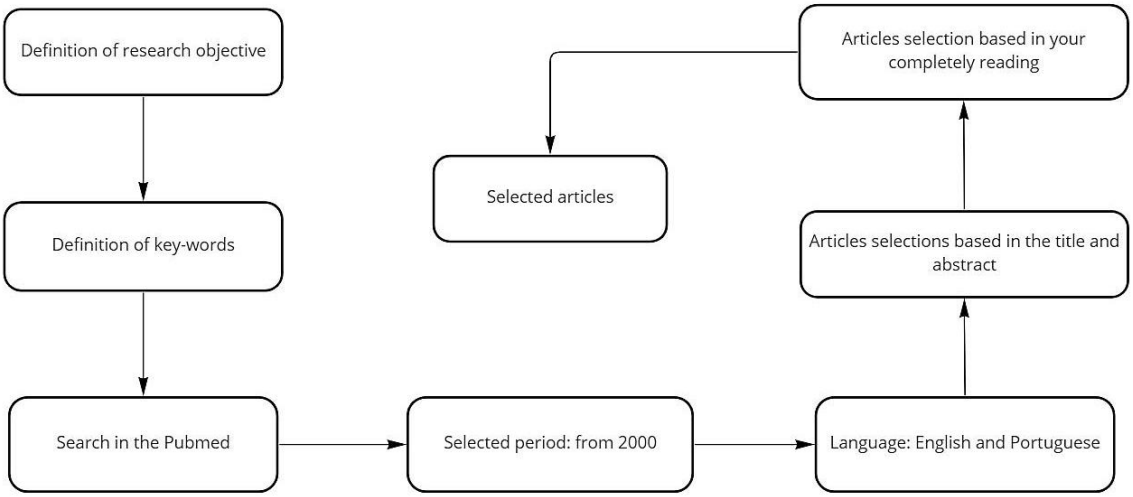

Figure 1. Methodological flowchart.

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Table 1 – Methodological description

Features of the revision	Types of references used	Criteria for article selection
Synthesis methods	Articles involving processes	Articles presenting nanoparticle characterization and results of their biological activities
Applications	Biological activities (antimicrobial, anti-inflammatory)	Articles with qualitative and quantitative results of biological activity
Toxicity	Safety studies of nanoparticles	Articles with cytotoxicity experiments with selectivity or comparative indices
Nature of nanoparticles	Papers with nanoparticle characterization (size, charge, and surface chemistry)	Articles presenting nanoparticles with different synthesis, sizes, and biological applications.
Experimental methodologies	In vitro and in vivo biological activity experiments	Articles with conventional methodologies for data comparison

Silver nanoparticles synthesis

Chemical methods

There are more studies about chemical methods in the synthesis of nanoparticles when compared to others (biological and physical) because they present interesting advantages in the applications and easier production, due to the facilities in standardization.

Silver nanoparticle can be prepared by different chemical methods: chemical reduction (ZHANG *et al.*, 2011), electrochemical technique (ROLDÁN; PELLEGRI; DE SANCTIS, 2013), chemical method assisted by irradiation (SOTIRIOU; PRATSINIS, 2010) and pyrolysis (SOTIRIOU *et al.*, 2011). Among them, the most common route to synthesize AgNP is through chemical reduction. The development of AgNP via the chemical route uses reducing agents such as sodium citrate, sodium borohydride, polyvinylalcohol (PVA) and polyethylene glycol (PEG), which also act as stabilizing agents (DÍAZ-CRUZ *et al.*, 2016; ZAHRA *et al.*, 2016). These reducing agents lead to the reduction of silver ions (Ag^{+}) to metallic silver (Ag^{0}), followed by formation of oligomeric clusters in aqueous and non-aqueous solutions (KHAN *et al.*, 2018). This route allows AgNP to be formed with certain reproducibility, which allows dispersion and size control by controlling the experimental parameters (DURÁN; SEABRA, 2018). However, some chemical synthetic routes use toxic reagents, generating byproducts that are contaminating the environment and toxic to humans. After synthesis, the surface of AgNPs must be coated to prevent oxidation and agglomeration (DURÁN; SEABRA, 2018).

The study by Faria (2016) performed an in vitro toxicity test, with Swiss mouse peritoneal cells, to verify whether the use of sodium borohydride, as a reducing agent, influences cell viability. The samples were incubated at different dilutions and the percentage of MTT ([3-(4,5-dimethylthiazol- -2yl) -2,5-diphenyl tetrazoline bromide]) salt was estimated using spectroscopy. It was found that 25 % and 50 % dilutions decreased the metabolic activity of the cells, relative to the control (99.8 %), to 42.2 % and 25.5 %, respectively. Therefore, Faria (2016) showed that the use of this reagent, depending on its concentration, can

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be cytotoxic.

Sodium borohydride discharge in the environment should be avoided as it forms a flammable hydrogen gas that upon contact can cause skin and eye irritation (FISPQ, 2014).

Biological methods

Various chemical and physical syntheses require high energy, highly toxic reducing agents, and stabilizing agents, which can cause harmful effects in humans. Differently, the green synthesis of metal nanoparticles, is an environmentally friendly bio reduction method that requires low energy to initiate the reaction (SINGH *et al.*, 2018). The biological synthesis of AgNPs has major advantages over chemical and physical methods. This route is environmentally friendly, as no toxic reducing or stabilizing agents are used during the synthesis (SINGH *et al.*, 2018). The decrease in health risks occurs by replacing the stabilizing agents with biomolecules, such as proteins (NAIK *et al.*, 2002) and carbohydrates (GE *et al.*, 2014). These biomolecules are produced by microorganisms and other living beings, for example, bacteria (ASANITHI; CHAIYAKUN; LIMSUWAN, 2012), fungi (BALAJI *et al.*, 2009), plants (PARK, 2014), and algae (MOHANPURIA; RANA; YADAV, 2008).

This route has become more popular recently (RAJPUT *et al.*, 2017), as it is an advantageous, sustainable option, and without the use of external stabilizing agents (ZHANG *et al.*, 2016; SONG; KIM, 2009). Another important point is that the reducing agent is also responsible for coating the surface of the NP obtained, increasing its stability, and preventing its agglomeration. The disadvantages of this synthesis consist of the difficulty of production standardization, scaling up, and yield; thus, more studies are needed for its development (DURÁN; SEABRA, 2018). Fungi are useful microorganisms for the synthesis of AgNPs due to their rapid collection capacity, ability to capture metals, and the large number of enzymes produced by them allowing the reduction of AgNO3 solution (KOWSHIK *et al.*, 2002). The study by Ahmad *et al.* (2003) showed that AgNPs with sizes of 5 – 50 nm could be synthesized extracellularly using the fungus Fusarium oxysporum. Durán *et al.* (2007), reported that AgNPs produced by this fungus were reduced and stabilized by fungal proteins, such as nitrate reductase and anthraquinones.

The studies presented in this topic show a trend of increasing this type of biological method for different metal nanoparticles due to the need to use cleaner and more sustainable processes.

Nanotoxicology

Nanotoxicology studies the toxicological effects of nanomaterials on various biological systems, such as cells, tissues, and living organisms (SELVARAJ *et al.*, 2018). The interactions between nanoparticles and animals, humans and the environment are extremely complex (GERLOFF *et al.*, 2017), due to these researchers are still trying to understand how physicochemical and morphological properties can influence these interactions and determine the impact of nanoparticles on health and the environment (DURÁN; GUTERRES; ALVES, 2014).

The environmental contamination by chemically synthesized nanoparticles can be due to the

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concentration of toxic compounds on their surface, such as sodium borohydride, which can contaminate soil, water, and accumulate in the food chain, interfering in biological processes (QUINA, 2004). Moreover, AgNPs can interfere with seed germination and plant growth (FARKAS *et al.*, 2011; NAIR; CHUNG, 2014). In the studies of Lee *et al.* (2007) and Asharani *et al.* (2008) it was found through transmission electron microscopy imaging that AgNPs associated with organic compounds can be internalized by fish cells and therefore can interfere in the aquatic ecosystem.

Studies have shown that nanoparticles increase reactive oxygen species (ROS) and can damage DNA, in addition to causing apoptosis and necrosis (ARORA *et al.*, 2008; KIM *et al.*, 2009; FOLDBJERG; DANG; AUTROP, 2011). AgNP synthesized by the chemical pathway has a high affinity for cell membranes and can accumulate in tissues for a long time causing various toxic effects on eukaryotic cells (BOUDREAU *et al.*, 2016). For example, AgNPs deposited in the lungs can cause asthma and pneumonia (SEIFFERT *et al.* ,2015), it can also cross the testis barrier in animal models, reducing fertility and causing teratogenicity in progeny (NGO *et al.*, 2016). AgNPs can also, enter the human cell through endosomal uptake or by diffusion (FROLICH; FROLICH, 2016).

The American Conference of Governmental Industrial Hygienists (ACGIH) has established a threshold value for metallic silver (0.1 mg/m3) and soluble silver components (0.01 mg/m3), considering that prolonged exposure to Ag by oral or inhalation may cause Argyria or Argyrosis (CHERNOUSOVA; EPPLE, 2013; MIYAYAMA; ARAI; HIRANO, 2015).

AgNPs can be genotoxic, causing mutations, oxidation of DNA bases, strand breaks, cross-link formation, and structural changes. In addition, they can induce DNA damage directly through binding to DNA, indirectly through binding to associated proteins of mitotic spindle components, or through the generation of ROS, which act on DNA (MAGDOLENOVA *et al.*, 2013). Important parameters influence the toxicity of AgNPs, considering that each nanoparticle is unique because of its preparation route, size, aggregation state, stability in biological media, chemical nature of the coating, surface charge, among others (DURÁN; SEABRA, 2018). Therefore, many parameters are important to define the toxicity of AgNPs (DE LIMA; SEABRA; DURÁN, 2012).

Surface chemicals

Coating agents binds to the surface of the NPs by covalent bonds or chemical interactions and stabilizes its thermodynamics, being a key factor to prevent aggregation and increase the solubility of the nano system (SING *et al.*, 2009; SEABRA; DURÁN, 2010). Some examples of coating agents are water-soluble polymers, oligosaccharides, and polysaccharides (DE LIMA; SEABRA; DURÁN, 2012).

The surface chemistry is extremely important for the action of the nanoparticle, since it will have a direct interaction with the biological agent and will directly influence toxicity (DURÁN; SEABRA, 2018). Thus, many studies suggest that modifications on the AgNP surface influence its interaction with cellular components (DE MATTEIS *et al.*, 2018).

In the study by Ahamed *et al.*, (2008) uncoated AgNPs synthesized by plasma gas and AgNPs coated

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with polysaccharides and synthesized by reducing silver ions in a polysaccharide solution (acacia gum) were analyzed. Both were found to lead to genotoxic effects in two mammalian cell lines: mouse embryonic stem cells and mouse embryonic fibroblasts. However, the coated AgNPs had the biggest genotoxic effect, due to the chemical difference in the coating.

In a cytotoxicity study using the MTT method, mammalian cells were incubated with coated and uncoated AgNP. After 24 h of incubation, the cells treated with coated and uncoated AgNPs showed 50 % survival at 50 µg/mL. After 48 h of incubation, cell survival in the presence of uncoated AgNPs was maintained at 50 %, however, cell survival decreased by 20 % for those treated with coated AgNPs. Cells incubated with coated nanoparticles suffered greater cellular damage than uncoated AgNPs. Therefore, the authors concluded that the polysaccharide-coated particles were more distributed, and the crowding of the uncoated particles limited the surface area, availability, and access to cellular organelles (AHAMED *et al.*, 2008).

Thus, we believe that surface chemistry is one of the most important characteristics when we think of biological activities and applications in health care.

Size

The size of AgNP affects the toxicity. It has been reported that smaller sized nanoparticles can penetrate more into cells and have a greater tendency to be toxic due to a larger surface area, promoting more contact and interaction area (DURÁN; SEABRA, 2018); in addition to being highly reactive and therefore more genotoxic (ORDZHONIKIDZE *et al.*, 2009; KIM *et al.*, 2011).

The study by Larese *et al.* (2015) concluded that nanoparticles smaller than 4 nm can penetrate and permeate intact skin, nanoparticles between 4 nm and 20 nm can permeate both intact and damaged skin, nanoparticles between 21 and 45 nm can penetrate and permeate only the damaged skin, and nanoparticles larger than 45 nm generally do not penetrate or permeate the skin.

For example, smaller nanoparticles are more likely to reach the lung and trigger collateral effects (OBERDORSTER., 2005). However, nanoparticle size is not the only factor that characterizes toxicity (DE LIMA; SEABRA; DURÁN, 2012; DURÁN *et al.*, 2016).

Larger AgNPs (100 nm) may not enter the cell and instead may exert indirect effects through signaling receptors, such as serine/threonine protein kinase (PAK), mitogen-activated protein kinase (MAPK), and protein phosphatase 2A (PP2A) (VERANO-BRAGA *et al.*, 2014). However, smaller AgNPs can enter the cell, release Ag+ ions, interact with biomolecules, and bind to sulfur-containing proteins and peptides such as glutathione, thioredoxin, thioredoxin peroxidase, and superoxide dismutase through their sulfhydryl groups (MCSHAN; RAY; YU, 2014; ZHANG *et al.*, 2014; MAO *et al.*, 2016; VERANO-BRAGA *et al.*, 2014).

The study by Park *et al.* (2010) demonstrated the size-dependent toxicity of AgNPs in mice, which were treated with nanoparticles at a single dose of 1 mg/kg for 14 days by oral administration. The smaller AgNP (22–71 nm) were found in various organs, such as the brain, kidneys, liver, testicles, and lung, whereas the larger nanoparticles were not found in the tissues. The levels of biochemical markers, such as TGF-β and

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B cells, were high in the serum of the animals treated with the smaller nanoparticles, however, this was not observed for the larger nanoparticles.

In another study, Liu and coauthors (2010) evaluated the cytotoxic effects of commercial AgNPs of different sizes (5, 20 and 50 nm) coated with polyvinylpyrrolidone (PVP) on human cells. The cytotoxic effect was observed with the smaller nanoparticles (5 nm) compared to the larger ones (20 and 50 nm) and there was greater internalization of the smaller nanoparticles.

In the study by Hsin *et al.* (2008), decreased viability of rat fibroblast cells, rat vascular smooth muscle and human colon cancer cells were induced only by silver nanoparticles smaller than 100 nm.

Studies report that the toxicity of AgNPs measuring 20 – 80 nm is due to the release of silver ions, whereas the mechanism of AgNPs below 10 nm is by the action of the nanoparticle itself. The mechanism of toxicity in non-cancerous cells is through the internalization of nanoparticles, which release a significant number of toxic silver ions. As such, nanoparticle size is an extremely important parameter for toxicity (HSIAO *et al.*, 2015; LIU *et al.*, 2010).

One study demonstrated size-dependent toxicity in the lungs, where smaller-sized nanoparticles showed a greater ability to induce lung inflammation and tissue injury than larger-sized nanoparticles (KAEWAMATAWONG *et al.*, 2005; KAEWAMATAWONG *et al.*, 2006).

Many researchers believe that particle size is "extremely" important in nanoparticle applications, but we must not forget that other characteristics, such as particle loading and targeting, are as relevant as their sizes, especially when they involve biological activity.

Dose

The 50 % Lethal Dose (LD50) of AgNP, according to recent literature, is between 1 – 7 µg/mL for both in vivo and in vitro studies, as has been demonstrated in cell cultures (WISE *et al.*, 2010), crustaceans (PARK; CHOI, 2010) and larvae (NAIR *et al.*, 2011).

According to some studies, silver is one of the least toxic metals for animal cells, since its concentration to kill microorganisms is 0.1 µg/L, and for humans the toxic concentration is 10 mg/L (LEVIN *et al.*, 2009; LEITE, 2003).

Foldbjerg *et al.* (2009) conducted a study with acute monocytic leukemia (THP-1) cells and flow cytometry assay, which could show how the induction of the cell to apoptosis and necrosis being dose and exposure time-dependent. Moreover, a drastic increase in ROS production was detected after 6-24 hours, showing the important role of oxidative stress in AgNP-induced cytotoxicity. The dose-dependent cellular toxicity caused by exposure to AgNPs and Ag^+ ions was confirmed in lung carcinoma cells, and a correlation between ROS levels and mitochondrial dysfunction or apoptosis was demonstrated.

The liver is responsible for the metabolization of nanoparticles when ingested, and part of them tend to be sequestered, degraded, and accumulated in the liver, being the organ that is attacked the most. The gallbladder collects, stores, and excretes the bile or biological waste into the intestine. AgNPs are exported from the liver to the intestine by this route, so hepatocytes are widely studied to analyze the toxicity caused by

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AgNPs in the liver. In the study by De Maglie *et al.* (2015) in rats it was observed that AgNPs induce severe hepatobiliary damage, such as necrosis in hepatocytes and hemorrhage in the gallbladder. As such, AgNPs showed dose- and size-dependent hepatobiliary toxicity, where smaller particles and larger doses produced more toxic effects.

In summary, the accumulation of AgNPs due to their exposure is dose and size-dependent in most tissues, such as the brain, lung, liver, dermis, blood, and testicles (XU *et al.*, 2020).

Effect of Ag^+ ions

Silver nanoparticles can release Ag^+ ions when they are exposed to water and oxygen, which are present in the biological environment. Toxicity is highly related to the surface area achieved since a larger surface area can release more Ag^+ ions, which are associated with toxicity and antimicrobial action. Ag^+ ions when released inside cells can cause oxidative stress, which can lead to cell death (DE LIMA, 2012; DURÁN *et al.*, 2016). Therefore, the smaller the size of AgNP, the greater amount will be internalized by cells, which increases the possibility of cell death. Many factors can influence the number of Ag^+ ions released, such as the size of the nanoparticle, the pH of the medium, type of coating around the nanoparticle (MANSHIAN *et al.*, 2015; QIAN *et al.*, 2015; DURÁN *et al.*, 2015; MAO *et al.*, 2016).

Synthesis routes

The method of synthesis of AgNP influences their toxicity and genotoxicity, in agreement with this statement, from De Lima's (2012) literature review, it can be concluded that in general bio-AgNP is less toxic than chemically synthesized ones and smaller particles show high toxicity compared to larger nanoparticles.

Organism used

According to De Lima (2012) the organism most resistant to genotoxicity is human cell cultures. The silver nanoparticle is highly toxic to bacteria, with this, it plays an important role as an antimicrobial. The study by Kim *et al.* (2007) compared the effects of AgNPs in *E. coli* and *S. aureus*, showing that *E. coli* had higher sensitivity than *S. aureus*.

Therefore, considering the distribution of AgNPs in various tissues, studies have shown that cell types can influence the response to AgNPs (KHAN *et al.*, 2018). For example, fibroblasts and colon cancer epithelial cells had different responses when exposed to AgNPs (HSIN *et al.*, 2008). Fibroblasts increased the expression of ROS and c-Jun N-terminal kinases, which activated the mitochondrial apoptotic pathway. However, epithelial cells had a milder response, as an expression of the anti-apoptotic protein bcl-2 was activated to protect against apoptotic stimulation.

Advantages and disadvantages of the different synthesis methods

The major disadvantage of using the chemical method is the use of highly toxic organic solvents, which have low biocompatibility and limits their natural applications (PARK, 2014). In the review article by Durán

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et al. (2016) it was possible to conclude that the biogenic synthesis of silver nanoparticles has become a very attractive area for researchers because of the combination of biological, technological impacts and the use of ecological pathways compared to chemical synthesis protocols.

The advantage of using the biological, or green, method over the chemical method is that this route does not use toxic solvents and biopolymers play an important role as stabilizing and reducing agents (SAIFUDDIN; WONG; YASUMIRA, 2009). Other advantages are high stability (SAIFUDDIN; WONG; YASUMIRA, 2009), biocompatibility, more cost-effective and sustainability (KHAN *et al.*, 2018). Among the disadvantages are the difficulty of standardization of biological synthesis and higher susceptibility to bacterial contamination, which an important restriction for biomedical applications (SINTUBIN; VERSTRAETE; BOON, 2012). Thus, it is not easy to determine the best synthesis method, as this will depend on many conditions (type of application, toxicity, sustainability, and cost-effectiveness) and "field tests".

Conclusion

AgNP is a highly promising technology, mainly due to its versatility and scope in several areas. With this fact in mind, its safe use is essential to avoid subsequent ecotoxicity, toxicity due to long-term exposure, and genotoxicity. Therefore, considering the studies cited in this literature review, it is possible to conclude that numerous factors influence the toxicity of AgNP, among them, the most significant is the synthesis method, the dose, the size, the surface chemistry, and the organism used. The biological synthesis method is less toxic compared to chemical synthesis, as it does not use toxic reagents, is environmentally friendly and is also more economical. Most studies have shown that the toxicity is both concentration and size-dependent, where larger doses are more toxic and smaller AgNPs are more toxic, as they can get more into the cells, have a larger surface area of contact and interaction. The coating agents of the AgNPs have a great influence on their toxicity and genotoxicity, since they are the agents that interact directly with the biological environment in which they are inserted. Therefore, several parameters need to be analyzed to assess toxicity and use AgNPs safety.

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Conflict of interests

The authors declare that the research was conducted in the absence of any potential conflicts of interest.

Ethical statements

The authors confirm that the ethical guidelines adopted by the journal were followed by this work, and all authors agree with the submission, content and transfer of the publication rights of the article to the journal.

They also declare that the work has not been previously published nor is it being considered for publication in another journal.

The authors assume full responsibility for the originality of the article, and may incur on them any charges arising from claims, by third parties, in relation to the authorship of the article.

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