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Original Article

Toxicity of Silver Nanoparticles: Impacts on Human Health and Environmental Safety, and the Role of Green Synthesis as an Eco-Friendly Approach

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Abstract:

Nanotechnology involves the manipulation of materials at the nanoscale, enabling the development of innovative applications across various fields, including medicine, electronics, and environmental science. Silver nanoparticles (AgNPs), renowned for their unique physical and chemical properties, are widely used due to their strong antimicrobial effects, particularly in biomedical applications such as wound care, drug delivery, and medical device coatings. However, concerns about their potential toxicity to human health and the environment have raised alarms. In response, researchers are turning to safer, eco-friendly green synthesis methods, such as Aloe vera extracts, which enhance the stability and functionality of the nanoparticles and provide a sustainable alternative to traditional chemical processes. Despite the benefits, AgNPs have been linked to oxidative stress, inflammation, and damage to vital organs like the liver, kidneys, spleen, and reproductive tissues. These findings underscore the need for further investigation into the safety of AgNPs, along with the continued exploration of green synthesis techniques that could mitigate their toxic effects while retaining their desirable properties.

Key words: Silver nanoparticles; Oxidative stress; cellular damage; Silver nanoparticles of *Aloe vera*

Introduction:
Nanotechnology involves manipulating matter at the nanoscale (1 to 100 nanometers) to create materials and devices with unique properties. It spans various fields, including medicine (targeted drug delivery and diagnostics), electronics (smaller, more efficient components), materials science (stronger, lighter materials), and energy (improved solar cells and batteries) **(Thirumalai et al., 2010; Sack et al., 2019).**

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There is growing interest in utilizing nanoparticles (NPs) like nanotubes, nanowires, fullerene derivatives, and quantum dots in life sciences and biotechnology due to their unique properties and versatility. These nanoparticles are a key in engineering and electronics, enabling the creation of more efficient and miniaturized devices. Additionally, in environmental research, NPs are being explored for their potential to detect pollutants, enhance water treatment processes, and develop sustainable materials **(Sahu et al., 2019; Kumari et al., 2020).**

One of the most prevalent types of nanoparticles is silver nanoparticles (AgNPs). There is a growing interest in AgNPs in different fields of science, such as biomedical science, including antibacterial, antiviral, anti-inflammatory, and anticancer therapies **(Chen and Schluesener, 2008).**

Several physical, chemical, and biological techniques are available for the synthesis of various types of NPs. There are various methods for chemically synthesizing AgNPs, such as chemical reduction, which is the most commonly utilized method due to its simplicity **(Suriati et al., 2014).** Despite AgNPs' benefits, there is growing worry about the potential toxicity of AgNPs to human health and the environment. Previous studies indicate that AgNPs can cause cytotoxicity, DNA damage, oxidative stress, and inflammation in human cells **(Rosário et al., 2018).** Researchers are increasingly focusing on green synthesis methods to produce silver nanoparticles (AgNPs) using microorganisms or plant extracts. This approach helps avoid the toxicity associated with chemical synthesis, offering a safer, cost-effective, and environmentally friendly alternative that yields high results **(Tippayawat et al., 2016).**

Aloe vera (AV) is a popular therapeutic plant rich in amino acids, sugars, enzymes, vitamins, minerals, and other beneficial compounds. Its leaves contain various organic acids and phenolic compounds, contributing to its widespread use **(Abd El-kader et al., 2019).**

Nanoparticles synthesis methods:

1- Chemical methods:

Numerous techniques are available for synthesizing nanoparticles, with chemical methods being the most commonly used. Key chemical synthesis techniques include the sol-gel process, chemical precipitation, hydrothermal methods, microwave synthesis, chemical vapor deposition, electrochemical techniques, physicochemical reduction, radiolysis, and chemical reduction. These methods employ various organic and inorganic reducing agents to achieve specific particle characteristics **(Iravani et al., 2014; Gudikandula and Maringanti, 2016).**

Each nanoparticle synthesis technique has unique advantages and limitations based on the desired characteristics. The sol-gel process offers high purity and precise control over size and morphology. Hydrothermal methods are beneficial for producing crystalline nanoparticles under controlled conditions. Microwave synthesis allows for rapid heating and shorter reaction times, enhancing efficiency. Chemical vapor deposition is commonly used for creating thin films and coatings, known for their uniformity and strong adhesion **(Pârvulescu et al., 2010; Iravani et al., 2014).**

A- Chemical reduction:

Chemical reduction is the most common technique for producing stable colloidal dispersions of nanoparticles in water or organic solvents. In this process, nanoparticles are typically

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synthesized by reducing metal salts (e.g., silver nitrate for silver nanoparticles or gold chloride for gold nanoparticles) in the presence of reducing agents, which can be chemical reagents like sodium borohydride, citric acid, or other reducing agents. While physical and chemical methods are widely used in nanoparticle synthesis, the presence of hazardous substances in these techniques limits their biomedical applications, particularly in medical fields. Some reducing agents or stabilizers may leave residual contaminants that could be cytotoxic or provoke immune responses in living organisms **(Aashritha, 2013).**

B – Other chemical methods:

Each nanoparticle synthesis technique has distinct advantages and limitations based on the desired characteristics. For instance, the sol-gel process enables the production of high-purity nanoparticles with precise control over size, shape, and morphology, making it ideal for applications requiring homogeneity and surface functionalization, such as drug delivery or catalysis. However, it can be time-consuming and often requires high temperatures for sintering, which may limit its applicability for heat-sensitive materials.

While hydrothermal methods are an effective way to produce crystalline nanoparticles by controlling temperature and pressure in a sealed system. This technique allows precise control over particle size, shape, and crystallinity, leading to high-purity materials. It is versatile, applicable to a wide range of materials, and suitable for various applications like catalysis, energy storage, and sensors. Hydrothermal synthesis is cost-effective, scalable, and ideal for both laboratory and industrial production of nanoparticles with tailored properties **(Pârvulescu et al., 2010)**.

Microwave synthesis accelerates nanoparticle formation by providing rapid and uniform heating, which reduces reaction times and improves efficiency. This method enhances reaction kinetics, leading to higher yields, better size control, and more uniform particles. It is a versatile, energy-efficient technique applicable to a wide range of materials **(Thirumalai et al., 2010).** Meanwhile, Chemical Vapor Deposition is a widely used method for producing thin films and coatings with excellent uniformity and strong adhesion. It involves chemical reactions of gaseous reactants to deposit solid material onto a substrate, offering precise thickness control and high-quality films. It is commonly used in electronics, semiconductors, and coatings industries **(Iravani et al., 2014).**

2- Biological methods:

The limitations of traditional nanoparticle synthesis methods, particularly due to the use of toxic chemicals, have spurred interest in greener and more sustainable alternatives. Biological methods for synthesizing nanoparticles are gaining interest as eco-friendly alternatives, utilizing natural materials like plant extracts and microorganisms. These methods often yield biocompatible and environmentally safe products **(Iravani et al., 2014; Gudikandula and Maringanti, 2016).**

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A- Green synthesis of nanoparticles using *Aloe vera* extract:

Aloe vera extract (Av) has been used for the green synthesis of nanoparticles due to its rich phytochemical composition, including bioactive compounds like phenolics, flavonoids, and vitamins. These compounds act as reducing agents and enhance the stability and functionality of the nanoparticles. Additionally, *Aloe vera* possesses antioxidant properties and pharmacological effects that offer protection against infections and are beneficial in treating various clinical disorders **(Hęś et al., 2019)**.

Aloe vera-derived nanoparticles exhibit significant antibacterial properties by disrupting bacterial cell membranes, making them suitable for use in medical devices and wound dressings to control infections. Their antifungal activity suggests potential agricultural applications against crop pathogens, while their mosquitocidal properties could aid in vector control strategies to combat mosquito-borne diseases. Additionally, the antioxidant compounds in *Aloe vera* help maintain free radical balance in the body, reducing oxidative stress and its associated risks of diseases like cardiovascular disorders, cancer, and neurodegenerative conditions. The therapeutic potential of Aloe vera, rooted in its phytochemical composition and antioxidant activity, underscores its importance in both traditional and modern medicine, with ongoing research likely to reveal further health benefits **(Devanesan et al., 2020)**.

Silver nanoparticles (AgNPs):

Silver nanoparticles (AgNPs) are among the most widely used nanomaterials due to their unique physical and chemical properties, such as strong catalytic activity, chemical stability, high thermal and electrical conductivity, and nonlinear optical behavior. These characteristics make AgNPs particularly valuable for applications in electronics, inks, and medicine **(Edwards, 2009).**

Silver nanoparticles (AgNPs) are renowned for their antimicrobial properties against a wide range of microorganisms, including viruses, fungi, and bacteria. This makes them popular in various everyday commercial products such as plastics, food packaging, soaps, paints, cosmetics, sunscreen, and textiles. Additionally, AgNPs are used in therapeutic devices, pharmacology, biotechnology, electronics, engineering, energy, and environmental remediation due to their effectiveness in both solution and solid forms **(Yin et al., 2015)**.

Routes of AgNPs penetration:

Research indicates that silver nanoparticles (AgNPs) can enter the human body through various routes, including oral ingestion, dermal contact (especially via skin lesions or abrasions), respiratory inhalation, and intravenous or intraperitoneal administration for diagnostic or therapeutic purposes. Each of these pathways enables AgNPs to penetrate biological systems, which could lead to potential adverse effects **(Lankveld et al., 2010).**

Detrimental effects of AgNPs:

As shown in figure (1), the increasing use of silver nanoparticles (AgNPs) in various products raises concerns about their potential toxicity and environmental impact. Their small size and

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high surface area facilitate the dissolution and release of silver ions, leading to increased exposure risks for humans and the environment. Once inside biological systems, AgNPs can accumulate and disrupt cellular functions, generating reactive oxygen species (ROS) that induce oxidative stress and damage critical biomolecules, potentially causing cell death **(Tortella et al., 2020).**

Silver nanoparticles (AgNPs) possess antibacterial properties but can cause cytotoxicity through mitochondrial dysfunction. Mitochondria, which resemble bacteria, are particularly vulnerable to AgNPs, especially in individuals with mitochondrial impairments. AgNPs reduce ATP production, affecting cells based on type and age, and may trigger apoptosis. They distribute throughout the body, affecting organs like the liver, lungs, and brain, with slower retention in some areas **(Maurer and Meyer, 2016).**

Additionally, AgNPs can damage the endoplasmic reticulum, causing structural changes in liver tissue that impact metabolism and organ function **(Al-Doaiss et al., 2020).** Exposure to AgNPs may also increase lysosome frequency, indicating cellular breakdown or repair processes in response to stress or damage caused by the nanoparticles **(Albadawi et al., 2024).**

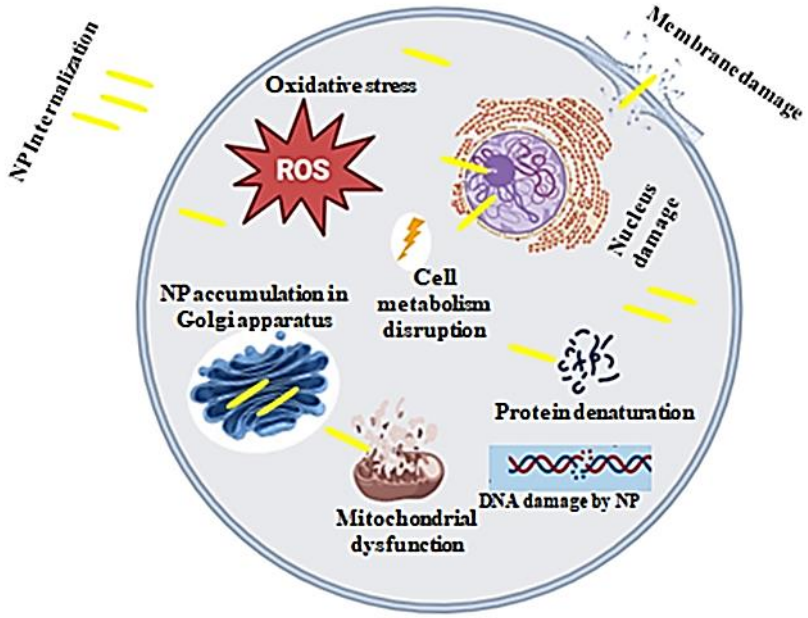

Figure 1. The mechanism of nanoparticles toxicity

Toxic effects of AgNPs on biochemical, histological and histochemical studies on some organs of mice:

Evidence indicates that the use of AgNPs could significantly harm the structure and function of various organs, likely by triggering oxidative stress and inflammatory responses within those organs **(Hassan et al., 2019)**.

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I-Biochemical markers:

A-Total oxidative status (TOS) and total antioxidant capacity (TAC):

Research has focused on the effects of AgNPs on total oxidative status (TOS) and total antioxidant capacity (TAC), which are vital indicators of oxidative stress and the body's ability to respond. An increase in TOS alongside a decrease in TAC signifies heightened oxidative stress, potentially causing significant cellular damage **(Kim et al., 2014)**.

Studies have shown that AgNPs exposure can elevate oxidative stress markers, particularly in liver tissues, correlating with lipid peroxidation activation. This oxidative damage can disrupt cellular membranes and lead to the release of liver enzymes, indicating hepatocellular injury. Additionally, AgNPs have been linked to increased malondialdehyde (MDA) levels in kidney cells, signaling oxidative damage and contributing to renal injury progression **(Olugbodi et al., 2023)**.

AgNPs generate ROS, leading to cellular component damage and inflammation. This oxidative stress triggers stress response pathways and can result in cell death. Elevated lipid peroxidation markers have also been observed in the spleens of animals exposed to AgNPs **(Yousef et al., 2022)**.

Moreover, AgNPs can induce apoptosis in spermatogonia and spermatocytes by increasing ROS levels, which causes oxidative damage to DNA and disrupts normal cellular functions. This oxidative stress impairs spermatogenesis, resulting in decreased sperm count and motility, thereby significantly affecting fertility **(Braydich-Stolle et al., 2010).**

B- Liver Function:

AgNPs are of significant concern due to their potential toxicity, particularly regarding liver health. They can adversely affect key liver enzymes like glutamate oxaloacetate transaminase (GOT or AST) and glutamate pyruvate transaminase (GPT or ALT), which are important indicators of liver function. AgNPs induce oxidative stress by generating ROS, leading to cellular damage and the release of these enzymes into the bloodstream, signaling liver injury **(Patlolla et al., 2015)**.

Moreover, AgNPs exposure can trigger inflammatory responses that further impair liver function and increase enzyme levels. They can disrupt hepatocyte membranes and alter metabolic pathways, contributing to the leakage of GOT and GPT. These findings highlight the risks associated with AgNPs exposure and emphasize the need for further research into their safety and toxicological mechanisms **(Chernousova and Epple, 2013).**

C- Kidney Function:

Urea and creatinine are metabolic byproducts excreted by the kidneys, and elevated levels of these substances can indicate liver and kidney dysfunction. The liver plays a crucial role in detoxifying ammonia, a harmful byproduct of protein metabolism, by converting it into urea through the urea cycle **(Olugbodi et al., 2023).** Research by **Sarhan and Hussein (2014) and Hassan et al. (2019)** revealed that treatment with AgNPs led to significantly increased serum

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levels of lipid peroxides, urea, and creatinine, while simultaneously decreasing total antioxidant capacity. These findings suggest that AgNPs may have toxic effects on liver and kidney function.

II-Histological and histochemical studies:

1. **The Liver**

The liver is a vital organ responsible for various functions, including synthesis, metabolism, excretion, and detoxification. Damage to the liver can significantly impact overall health. Research indicates that AgNPs can induce liver damage by activating Kupffer cells, which release pro-inflammatory cytokines, leading to inflammation and chronic tissue damage. Studies have shown that exposure to AgNPs results in significant histological changes, including necrosis, inflammation, and fibrosis, which correlate with elevated enzyme levels indicative of liver injury **(Cheraghi et al., 2013; Patlolla et al., 2015).**

Further investigations revealed that AgNPs cause structural damage to hepatocytes, characterized by cellular necrosis and alterations in liver architecture, including inflammatory infiltrates and fibrosis. Histopathological analysis of AgNPs-treated livers showed disrupted organ architecture, fat accumulation in cells, enlarged hepatocytes, and narrowing of sinusoids **(Sarhan and Hussein, 2014)**. Additionally, changes such as hypertrophied endothelial cells, increased inflammatory cells, and damaged mitochondria in Kupffer cells were observed, reinforcing the hepatotoxic effects of AgNPs **(Jiang et al., 2014; Hassan et al., 2019)**.

Masson's trichrome staining revealed that AgNPs cause significant fibrotic changes in liver tissues, indicating long-term health risks **(Assar et al., 2022).** AgNPs lead to hepatocyte damage, inflammation, and oxidative stress, compromising liver function and reducing glycogen storage, which disrupts energy homeostasis. Additionally, elevated ROS further impact carbohydrate content **(Assar et al., 2022; Ostaszewska et al., 2018).**

2. **The kidney**

Studies indicate that exposure to AgNPs can lead to significant histopathological changes in kidney tissues, demonstrating dose-dependent nephrotoxicity characterized by tubular damage and glomerular alterations **(Liu et al., 2020)**.

Observed changes include thicker basement membranes, enlarged epithelial cells with cytoplasmic vacuolization, and podocyte swelling. Additionally, AgNPs exposure has been linked to tubular degeneration and interstitial inflammation, disrupting the kidney's reabsorption and secretion functions. Changes in the glomeruli, such as hypercellularity and mesangial expansion, can impair filtration capacity and lead to proteinuria, indicating further renal dysfunction **(Ibrahim et al., 2018).**

Exposure to AgNPs has been shown to increase collagen deposition in the kidneys, disrupting their normal architecture and function, which can lead to renal impairment and chronic kidney disease due to fibrosis and reduced glomerular filtration rate **(Nosrati et al., 2021)**.

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Furthermore, AgNPs disrupt carbohydrate metabolism in the kidneys, affecting glucose homeostasis and overall metabolic function **(Tiwari et al., 2021).**

3. The Spleen

AgNPs adversely affect the immune system in the spleen. Studies show significant structural changes, including vascular congestion and lymphoid follicle hyperplasia, which indicate a stress response. Histological analyses revealed disrupted white pulp and increased apoptosis, leading to reduced lymphocyte counts and compromised immune function, making the spleen more vulnerable to infections **(Mazen et al., 2017).**

AgNPs can cause fibrotic changes in the spleen, characterized by increased collagen deposition due to oxidative stress and inflammation. Additionally, AgNPs disrupt carbohydrate metabolism, leading to reduced glycogen levels, which impairs energy availability and immune function. This metabolic disruption hinders the ability of splenic macrophages to respond to infections, increasing susceptibility to disease **(Eid et al., 2015; Bajilan et al., 2023)**

4. The testes

AgNPs cause significant damage to testicular tissue, including degeneration of the germinal epithelium, impaired spermatogenesis, and disruption of Sertoli and Leydig cell function. AgNPs reduce testosterone production, hinder sperm development, and induce DNA damage in testicular cells. This leads to decreased sperm count, motility, and abnormal morphology, highlighting potential fertility issues and reproductive health concerns **(Whitney and Suttie, 2018; EL-Mosallamy et al., 2023).**

AgNPs disrupt collagen homeostasis and glycogen metabolism in testicular tissues, affecting Sertoli cell function. Altered collagen levels impair Sertoli cells' ability to support developing germ cells during spermatogenesis, while fibrosis may increase pressure within the testes, compromising blood flow and nutrient delivery. Additionally, reduced glycogen content, likely due to oxidative stress and inflammation, further disrupts testicular function by impairing enzyme activity involved in glycogen synthesis and utilization **(Assar et al., 2023; Wahyuni et al., 2024)**.

Conclusion:

Silver nanoparticles (AgNPs) are widely used for their antimicrobial properties, but concerns over their toxicity to human health and the environment have emerged. Green synthesis methods, like using Aloe vera extracts, offer a safer alternative. However, AgNPs can still cause oxidative stress and organ damage, highlighting the need for further research into their safety and sustainable production methods.

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