

Toxicity and Molecular Mechanisms of Actions of Silver Nanoparticles

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Abstract

Silver nanoparticles (AgNPs) have gained popularity due to their antibacterial properties, and are therefore widely used in several applications such as wound dressings, food packaging, and water purification. However, the toxicity of AgNPs to humans and the environment is a growing concern. This review aims to summarize the current knowledge on the toxicity and molecular mechanisms of action of AgNPs. The toxicity of AgNPs can be attributed to their small size, which allows them to enter cells and interact with cellular components. Reports suggest that AgNPs can induce cell death, DNA damage, and oxidative stress in various cell types. The toxic effects of AgNPs differ based on their size, shape, surface charge, and coating. The molecular mechanisms behind the toxicity of AgNPs involve the production of reactive oxygen species, disruption of cellular membranes, and activation of proinflammatory cytokines. Overall, the toxicity of AgNPs is dependent on various factors, and more research is needed to fully understand the mechanisms behind their toxicity. This review highlights the need for proper risk assessments and regulations to minimize the adverse effects of AgNPs on human health and the environment.

Keywords

Toxicity, Silver Nanoparticles, Molecular Mechanisms

1. Introduction

Silver Nanoparticles (AgNPs) have numerous prospective and existing applications because of their specific qualities, such as antimicrobial activity, electrical conductivity, and optical properties. Among the many applications for AgNPs

are: Research has been conducted on AgNPs' potential medical applications because of their unique physical and chemical properties. Examples of the application of AgNPs in medicine include: Strong antibacterial activity of AgNPs against a wide range of bacteria, including those that are antibiotic-resistant, has been demonstrated [1]. In addition to being utilized in wound dressings and medical device coatings, they can be found in topical creams used to treat infections. AgNPs have also been demonstrated to exhibit anti-inflammatory properties, suggesting that they may be useful in the treatment of conditions including osteoarthritis and inflammation brought on by autoimmune disorders [2] [3]. They have been used in diagnostic processes, including the detection of infectious and malignant illnesses. AgNPs can be used to deliver drugs, improving their efficacy and reducing any side effects [4]. However, a more in-depth study is necessary to fully appreciate the safety and effectiveness of AgNPs in medical applications.

In addition to medical activity AgNPs are being increasingly used in textiles due to their unique properties such as antimicrobial effects, water and stain resistance, UV protection, and thermal regulation [5]. AgNPs have been shown to effectively kill bacteria and fungi, making them useful for producing antimicrobial textiles [6]. These textiles can be used in healthcare settings, sports clothing, and other applications where hygiene is important. AgNPs have been used to develop textiles that can control odors. These textiles are particularly useful in sportswear, workwear, and other textiles that can become smelly due to prolonged use. It can be used to develop textiles that are resistant to stains. This is particularly useful in-home textiles such as carpets, curtains, and upholstery. AgNPs can absorb UV radiation, making them useful in producing textiles that offer protection against harmful UV rays from the sun [7]. AgNPs can help regulate body temperature by reflecting heat back to the body in cold weather and dispersing heat away from the body in hot weather [8]. This makes them useful in producing textiles for outdoor activities. Overall, the use of AgNPs in textiles has the potential to improve the functionality and longevity of textiles, making them more durable and suited to a range of applications.

AgNPs are increasingly being used in food packaging because of their antimicrobial properties [9]. These particles have been found to inhibit the growth of bacteria, viruses, and fungi, which can spoil food and cause foodborne illnesses. A "smart" package that can keep food fresh for a longer time can be made by adding AgNPs into the materials used to package food. Foods that need to be transported over great distances or kept in storage for a long time may find this to be especially crucial. Research has shown that AgNPs in food packaging are generally safe for food contact materials, although some studies have raised concerns about their potential toxicity [10]. Therefore, it is important to properly assess the risks and benefits of using AgNPs in food packaging before widespread adoption.

AgNPs are commonly used in water treatment because of their antimicrobial properties. When added to water, AgNPs can destroy or inhibit the growth of

bacteria, viruses, and other pathogens that can be harmful to human health [11]. To use AgNPs for water treatment, various methods can be employed. One common approach is to add AgNPs directly to the water. This can be done through a process called electrochemical deposition or by mixing the NPs with water. Another approach is to use filters that contain silver NPs, which can remove contaminants and harmful substances from the water. The AgNPs in these filters can also help prevent the growth of bacteria and viruses. It is important to note that while using AgNPs for water treatment is effective, it can also raise some environmental concerns. When AgNPs are released into the environment, they can accumulate and potentially have harmful effects on wildlife and ecosystems [12]. Therefore, it is important to use AgNPs for water treatment responsibly and to take appropriate measures to prevent their release into the environment.

Despite all of those uses, there are growing concerns about the potential toxicity of AgNPs due to their widespread use in consumer items like clothing, cosmetics, and food packaging. Some studies suggest that these NPs may have toxic effects on various organs of the body, including the liver and lungs, and may also cause DNA damage [13]. In addition, AgNPs have also been found to have antimicrobial properties, which may contribute to their toxicity [14]. While more research is needed to fully understand the potential health risks associated with exposure to these NPs, it is advisable to limit unnecessary exposure to them until their safety can be established.

2. Toxicological Effects of AgNPs

AgNPs have a wide range of applications in both consumer and industrial products because of their distinct physical and chemical characteristics. However, studies have demonstrated that exposure to AgNPs might have toxicological consequences for both the environment and human health [15] [16] [17]. For instance, AgNPs can build up in a variety of organs and tissues, including the liver and kidneys, where they can contribute to oxidative stress, DNA damage, and inflammation, all of which can result in a number of diseases, including cancer, neurological disorders, and respiratory illnesses. Additionally, AgNPs may harm aquatic animals and lead to ecological imbalances in aquatic habitats [18]. AgNPs, for example, can build up in fish tissues, alter their motility, and lower their capacity for reproduction, endangering the survival of aquatic species.

The use of AgNPs could pose a number of health risks. Some of these include: AgNPs are known to have toxic effects on various organs and tissues in the body [19]. This is because they have a tendency to accumulate in organs such as the liver, lungs, and kidneys, where they can cause damage to cells and tissues. There is concern that the use of AgNPs as an antibacterial agent could lead to the development of antibiotic-resistant bacteria. Also, it can have a negative impact on the environment if they are released into waterways or soil. Some people may be

allergic to AgNPs, which could cause skin irritation, rashes, and other symptoms. AgNPs have a tendency to form aggregates, which can increase their potential for toxicity [20].

Bioaccumulation of AgNPs refers to the gradual buildup of these particles in the tissues of living organisms, such as fish, algae, or bacteria, as they absorb them from the surrounding environment. Once AgNPs enters an organism, it can accumulate and persist for long periods of time in various tissues, including liver, kidney, and brain [21]. This can lead to toxic effects on the organism and potential health risks for humans who consume contaminated organisms. The extent of bioaccumulation depends on various factors, such as the size and concentration of AgNPs, the exposure time, and the biological pathways involved [22]. Thus, it is important to regulate the use and disposal of AgNPs to prevent or minimize its potential impact on the environment and human health. **Figure 1** indicates wide range of effects of AgNPs on different organs and tissues in the body.

Additionally, there are several potential health hazards associated with AgNPs. Some of these include: Toxicity, AgNPs are known to have toxic effects on various organs and tissues in the body. This is because they have a tendency to accumulate in organs such as the liver, lungs, and kidneys, where they can cause damage to cells and tissues [29]. There is also concern that the use of AgNPs as an antibacterial agent could lead to the development of antibiotic-resistant bacteria [30]. AgNPs can have a negative impact on the environment if they are released into waterways or soil [31]. Some people may also be allergic to AgNPs, which could cause skin irritation, rashes, and other symptoms [32]. It has a tendency to form aggregates, which can increase their potential for toxicity [33]. Overall, the effects of AgNPs on different organs and tissues are still being studied, and caution should be taken in their use and exposure. Therefore,

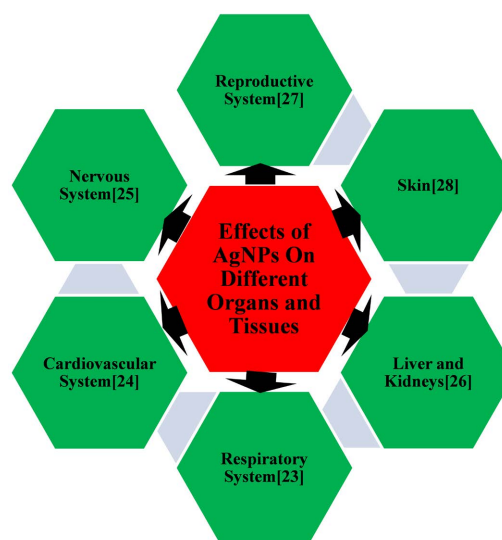


Figure 1. Effects of AgNPs on different organs and tissues [23]-[28].

the use of AgNPs should be carefully regulated to minimize their adverse effects on human health and the environment.

3. Physicochemical Properties of AgNP

AgNPs have unique physicochemical properties that make them useful in many applications, including medicine, electronics, and environmental remediation [34]. Some of the physicochemical properties of AgNP include: Size and shape, Surface area, Surface charge and Optical properties. AgNP can have various sizes and shapes depending on how they are synthesized. The size can range from 1 nm to 100 nm, and the shape can be spherical, rod-shaped, triangular, or even more complex shapes [35]. These variations in size and shape can affect the physical and chemical properties of AgNP, such as their stability, solubility, and reactivity with biological or environmental media.

Among the Physicochemical Characteristics of AgNPs are, surface area: when compared to bulk silver, AgNPs has a larger surface area to volume ratio. As a result, they become more catalytically active and highly reactive [36]. Due to the ligands that are surface-bound, AgNP often has a negatively charged surface. Their stability in solution and interactions with other molecules may be impacted by this charge. AgNP has unusual optical characteristics, including significant light absorption and scattering. They are helpful in plasmonics and sensing applications because of these characteristics. In general, AgNP's physicochemical characteristics make them a viable material for a variety of applications [37] [38]. However, it is also important to carefully research and take into account their potential toxicity and effects on the environment.

4. Biocompatibility of AgNPs

Due to their distinctive physicochemical features, AgNPs have demonstrated promising results as antibacterial agents for a variety of medicinal applications; nonetheless, their biocompatibility is a cause for worry. A number of variables, including AgNP's size, shape, surface area, surface charge, concentration, exposure period, and interactions with biological molecules, affect how biocompatible AgNP is. Both at the cellular and systemic levels, AgNP can cause toxicity in cells [39].

Numerous cellular processes, including cell growth, proliferation, differentiation, and apoptosis, have been reported to be impacted by AgNPs. AgNP exposure causes cytotoxicity, oxidative stress, DNA damage, and inflammation in cells, according to a number of studies [40]. Additionally, it has been demonstrated that AgNPs interact with different proteins and lipids to disrupt the cellular membrane, which can change cellular signaling and responses [41]. Furthermore, it has been discovered that AgNPs modulate gene expression and change the expression of a number of proteins involved in cellular processes [42]. AgNP exposure could have harmful impacts on biological systems because of their capacity to enter cells, tissues, and organs. Through repeated exposure, AgNPs can also build up in the body and cause chronic toxicity [43]. AgNP ex-

posure has been shown to cause tissue damage, fibrosis, and inflammation in a number of organs, including the brain, liver, and kidney [44]. It has also been demonstrated that AgNPs have a negative impact on the reproductive system, resulting in decreased fertility and altered reproduction [45] [46] [47]. Although AgNPs have several unique properties that make them useful in a wide range of applications, it is impossible to ignore their impact on cellular functions and potential risks when interacting with biological systems. Further investigation is required to determine the safe exposure limits for AgNPs and their long-term effects on human health and the environment.

5. Environmental Impactsof AgNP

It has been found that AgNPs may harm the ecosystem. Studies have shown that AgNPs can reduce the number of pesticides needed, but they can also be harmful to the environment. AgNPs may have several harmful environmental impacts, including ecosystem disturbance, toxicity to aquatic life, harm to soil microbial communities, and bioaccumulation [48].

5.1. Ecosystem Disturbance of AgNPs

AgNPs are increasingly being used in various industrial, agricultural, medical, and consumer products. However, AgNPs can enter the environment through various pathways, causing potential ecosystem disturbance if they are not properly managed [49]. One of the primary pathways for AgNPs into the environment is through the discharge of wastewater and sewage from industries that use them. AgNPs can also enter the environment through agricultural runoff and accidental spills during manufacturing or transportation [50]. Once released into the environment, AgNPs can interact with various components of the ecosystem, such as soil, water, and biota, causing different types of disturbances. It can affect the soil ecosystem by altering the microbial community structure, which plays a crucial role in nutrient cycling and plant health. AgNPs can also cause toxicity to nitrifying bacteria, which are essential for nitrogen cycle [51]. Additionally, it may inhibit seed germination and plant growth, potentially affecting crop yields.

In aquatic ecosystems, AgNPs can accumulate in the sediment and disrupt the food web by affecting the growth and reproduction of different biota. It can also be toxic to aquatic invertebrates and fish, causing mortality and reduced growth rates. Moreover, the migration of AgNPs from water to the atmosphere can also contribute to air pollution. The use of AgNPs can potentially cause disturbances in the ecosystem through their release into the environment [52]. The negative impact of AgNPs on the ecosystem needs to be mitigated by responsible manufacturing and disposal practices, as well as by following established environmental regulations.

5.2. Toxicity of AgNPs to Aquatic Life

The toxicity of AgNPs to aquatic life is a well-documented issue in scientific stu-

dies. When AgNPs are released into aquatic environments, they can enter the food chain as they are easily absorbed by microorganisms and can accumulate in aquatic organisms such as fish, plankton, and even invertebrates [53] [54]. Studies have shown that AgNPs can cause a range of toxic effects to aquatic life. These toxic effects can occur due to direct exposure to AgNPs, or due to indirect exposure to AgNPs through the food chain [55] [56]. Direct exposures to AgNPs can cause damage to the gills, liver, and other organs in fish and other aquatic organisms. It can also affect the growth and development of these organisms, impairing their ability to survive and reproduce [57]. Indirect exposures to AgNPs through the food chain can also have toxic effects. When smaller organisms consume AgNPs, they accumulate in their tissues and are passed up the food chain to larger organisms [16] [58]. This can result in bioaccumulation of AgNPs in the tissues of larger organisms at higher levels, which can lead to toxicity and ultimately death.

In addition, AgNPs can also affect the balance of the ecosystem. They can negatively impact the microbial communities in aquatic environments, which can have ripple effects throughout the entire ecosystem [59]. Overall, the toxicity of AgNPs to aquatic life is a major concern, and it is important to limit the release of AgNPs into aquatic environments. This can be achieved by implementing stricter regulations on the use and disposal of AgNPs in various industries.

5.3. The Effect of AgNPs on Soil Microbial Communities

The use of AgNPs in various industrial and consumer products has increased in recent years due to their unique antimicrobial properties. However, the release of these NPs into the environment can cause various adverse effects, including harm to soil microbial communities. AgNPs can interfere with the microbial processes that are essential for soil health and fertility. Studies have shown that exposure to AgNPs can reduce the microbial biomass of soil, which can affect nutrient cycling and soil structure [60] [61] [62]. The toxicity of AgNPs also varies based on their size, shape, and concentration, which can further amplify their adverse effects on soil microbial communities.

Moreover, AgNPs can disrupt the mutualistic relationships between soil microorganisms and higher organisms, such as plants. They can change the composition of soil microbial communities and reduce the population of beneficial microorganisms that promote plant growth and health [63]. In conclusion, the use of AgNPs in various industrial and consumer products should be regulated to prevent their release into the environment. Long-term studies are needed to evaluate the risks these NPs pose to soil microbial communities and the ecosystems they support.

5.4. Bioaccumulation of AgNPs

Bioaccumulation of AgNPs occurs when these particles are taken up and stored within living organisms over time. AgNPs have been found to accumulate in a

variety of organisms, including aquatic and terrestrial animals and plants [64]. The bioaccumulation of AgNPs can occur through various routes, including ingestion, inhalation, and dermal exposure. Once inside the organism, AgNPs can interact with biological molecules and cause toxicity and adverse effects [65] [66] [67].

Studies have shown that the bioaccumulation of AgNPs can vary depending on factors such as the size of the particles, the surface coating, and the exposure route. Additionally, the accumulation of AgNPs can differ between different species, with some organisms being more susceptible to accumulation than others [68] [69] [70]. Overall, the bioaccumulation of AgNPs is an area of concern due to the potential ecological and human health risks associated with their accumulation in organisms and potential transfer through food webs. Further research is needed to fully understand the mechanisms and impacts of silver nanoparticle bioaccumulation.

6. Molecular Mechanisms of Actions of AgNPs

AgNPs have intricate adverse effects that are susceptible to change when other chemicals are present. It can have negative impacts on a variety of biological systems, depending on the size, shape, and coating of the particles as well as the environment in which they are introduced. The precise chemical pathways causing these effects are still unknown. These techniques most likely also depend on the size, shape, and coating of the NPs [20] [71].

The toxicity of AgNPs is mainly due to their small size, large surface area-to-volume ratio, and ability to generate reactive oxygen species (ROS). The molecular mechanisms of toxicity of AgNPs include: Reactive Oxygen Species generation, AgNPs can generate ROS such as superoxide (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radicals (OH^-) through redox reactions [72] [73]. ROS can damage cellular components such as lipids, proteins, and DNA, leading to oxidative stress and cell death [74]. It can interact with the cell membrane and cause structural damage, thereby disrupting the normal functioning of the membrane. This can result in altered membrane permeability, loss of function, and even cell death. AgNPs can enter the mitochondria and cause dysfunction, leading to the production of ROS and impaired oxidative phosphorylation. This can result in reduced ATP production, cell death, and other harmful effects.

Additionally, AgNPs can interact with DNA and break DNA strands or form adducts, both of which result in structural damage. This may result in cell death, chromosomal abnormalities, and mutations [75]. It may cause the body to respond with inflammation, releasing inflammatory cytokines and chemokines. This may lead to inflammatory disorders, organ dysfunction, and tissue damage. AgNP toxicity is multifaceted and includes intricate, poorly understood molecular pathways overall [76]. To create safe and successful uses for AgNPs, it is crucial to have a better knowledge of these mechanisms.

Silver nanoparticles (AgNPs) work through a number of chemical pathways,

including physical interactions with biological targets including cells. Some significant molecular pathways through which AgNPs work are shown in **Figure 2**.

Here are some commonly proposed mechanisms of actions:

1) Cellular Uptake: AgNPs have multiple ways to enter cells, including endocytosis or directly penetrating the cell membrane. Once they gain entry into the cell, they have the ability to interact with different cellular structures.

2) Reactive Oxygen Species (ROS) Generation: AgNPs can induce the generation of ROS, such as superoxide radicals and hydrogen peroxide. ROS can cause oxidative stress, damaging cellular components and leading to various cellular responses.

3) Protein Interaction and Denaturation: AgNPs can interact with proteins present in cells or in the extracellular environment. These interactions can lead to protein denaturation, disrupting their normal function and affecting cellular processes.

4) DNA Binding and Damage: AgNPs can bind to DNA molecules, potentially leading to DNA damage and genomic instability. This interaction can interfere with DNA replication, transcription, and repair processes.

5) Inhibition of Enzyme Activity: AgNPs can inhibit the activity of various enzymes involved in essential cellular functions. This inhibition can disrupt metabolic pathways and affect cellular homeostasis.

6) Membrane Interaction: AgNPs can interact with cell membranes, leading to structural changes and compromising their integrity. This interaction can modulate membrane-associated processes, such as transport of molecules and signaling pathways.

It's important to note that the exact mechanisms can vary depending on factors such as nanoparticle size, surface coating, and cell type. Additionally, the biological response to AgNPs can vary depending on the specific cell type, exposure conditions, and experimental design. In addition, more research is still needed to fully understand the complete molecular mechanisms of AgNP action.

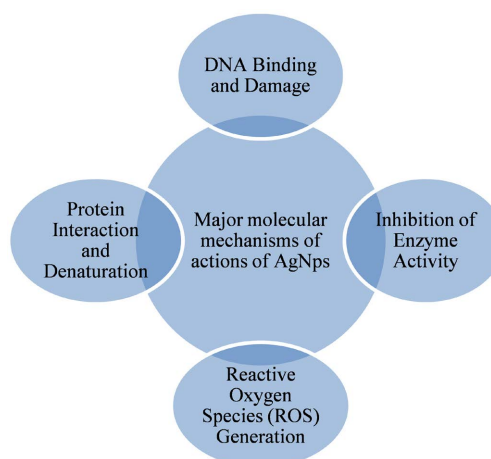


Figure 2. Some molecular mechanisms of actions of AgNPs.

7. Safety and Regulation

AgNPs have gained popularity in recent years due to their unique properties which make them useful in various applications such as in medicine, electronics, and textiles. However, there have been concerns about the safety of these NPs as they may have harmful effects on human health and the environment. In terms of regulations, various countries have different guidelines for the use of AgNPs [77]. For instance, the US Food and Drug Administration (FDA) has approved the use of AgNPs in medical devices such as wound dressings, catheters, and surgical instruments, but these devices must meet specific safety standards [78] [79] [80]. The European Union also has regulations in place for the use of AgNPs in products such as cosmetics and food packaging [81] [82].

Regarding safety, studies have shown that AgNPs can potentially cause damage to human cells and organs. Animal studies have also shown that exposure to AgNPs can lead to adverse effects on the liver, kidneys, and nervous system. However, more research is needed to fully understand the extent of these effects on human health [83] [84]. Overall, the use of AgNPs is still a topic of debate, and it is important to take precautionary measures when handling these NPs. It is also crucial to adhere to the regulations set by the authorities to ensure their safe use.

8. Future Perspectives

Regarding medical applications, AgNPs have been widely used as antimicrobial agents in wound dressings, medical devices, and drug delivery applications. However, there are concerns about their potential toxicity and adverse effects on human health. Some of the current research trends and needs in this area include:

- 1) Understanding the mechanisms by which AgNPs interact with biological systems and cells, including uptake, distribution, and toxicity.
- 2) Developing reliable and standardized methods for the assessment of AgNP toxicity and exposure, including in vivo and in vitro models.
- 3) Investigating the potential risks associated with long-term exposure to silver NPs, including their potential effects on the immune system and reproductive system.
- 4) Developing alternative strategies to reduce the toxicity of AgNPs while preserving their antimicrobial properties, such as surface modification and chemical functionalization.

Regarding environmental applications, AgNPs are used in various consumer products, including textiles, cosmetics, and food packaging. However, there are concerns about their potential environmental impacts and risks to aquatic organisms. Some of the current research trends and needs in this area include:

- 1) Understanding the fate and transport of AgNPs in the environment, including their interactions with soil, water, and sediment.
- 2) Investigating the potential ecological risks associated with the release of

AgNPs into the environment, including their effects on aquatic organisms, bio-accumulation, and potential toxicity.

3) Developing sustainable manufacturing practices that minimize the release of AgNPs into the environment.

4) Developing alternative strategies to reduce the environmental impact of AgNPs while preserving their beneficial properties, such as the use of biodegradable nanomaterials.

9. Concluding Remarks

AgNPs have gained significant attention in recent years due to their unique physicochemical properties and various potential applications in medicine, electronics, and environmental remediation. However, the research on the toxicity and molecular mechanisms of AgNPs has been rapidly growing due to their extensive use in various medical and environmental applications. Numerous studies have investigated the mechanisms of AgNP toxicity, and it has been shown that AgNPs can induce oxidative stress, inflammation, DNA damage, and apoptosis in cells. The toxicity of AgNPs is dependent on various factors, including their size, shape, surface charge, and concentration. The toxicity and molecular mechanisms of actions of AgNPs are complex and depend on the specific biological system under investigation. However, some general conclusions can be drawn. AgNPs are known to induce toxicity through the release of silver ions (Ag^+), which can interact with cellular components such as proteins, enzymes, and DNA. The size and shape of AgNPs can also influence their toxicity by altering their interactions with cells and tissues. Generally, the potential toxicity of AgNPs is a growing concern, and further research is needed to fully understand their molecular mechanisms of action and potential health and environmental implications. It is important to study the toxicity of AgNPs under various conditions and in different biological systems to gain a comprehensive understanding of their potential risks.

Authors' Contributions

Gemechis Waktole designed the study, retrieved the data, analyzed the data and wrote the manuscript.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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