

# Toxicity Of Silver Nanoparticles; A Mini-Review

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## Abstract

Nanotechnology is an advanced and one of the fastest-growing fields that have extensive potential for development. In recent years it has gained a lot of interest in the field of research due to its unique characteristics. Their higher surface-to-volume ratio is responsible for their distinctive properties and variable applicability. Due to their emerging clinical significance, research has revealed that in addition to their industrial and commercial uses, they are also essential from a medical standpoint. Along with their pharmacological effects, various adverse effects have also been reported, and this is the reason why they have not yet completely reached clinical trials. In the current review, we will first discuss the toxicity of biogenic and chemically synthesized silver nanoparticles (AgNPs) then we will also focus on comparing the toxicity of both types of AgNPs. Finally, we will offer some recommendations for improving the toxicity analysis in the future to clear the way for their entry into clinical trials.

## Introduction

Nano-technology is one of the cutting-edge technologies that are known because of its particle size that is ranging from 1-100nm offering a larger surface area (1). According to the research metallic nanoparticles have a wide range of pharmacological effects (2). In recent years numerous types of metallic nanoparticles (NPs) including iron, gold, silver, aluminum oxide, copper oxide, zinc oxide, and titanium oxide along with non-metallic NPs like silica, carbon-based NPs, and NPs of polymeric materials have been synthesized using different chemical, physical and biogenic approaches (2). The therapeutic significance of these NPs has been highlighted in various studies. Our topic of interest for the current article is silver nanoparticles (AgNPs).

## Silver

Silver metal has been revered as a significant therapeutic agent since ancient times. The discovery of its multiple pharmacological effects has made it an agent of immense relevance in the field of medicine. It's been used as a powerful antibacterial agent for at least six millennia. Additionally, it has improved wound healing and contributed to the development of radiology. Furthermore, silver was prescribed for a number of conditions where its efficacy was questioned, including diabetes, psoriasis, allergies, colds, etc. (3).

## Silver Nanoparticles

In recent years a large number of AgNPs have been synthesized biogenically and chemically using fungi, algae, bacteria, plant extracts, and chemical reducing agents etc. A crucial aspect is that the process for synthesizing NPs and the chemicals employed during manufacture have a significant impact on how their physical and biological properties are altered, which, in turn, causes variances in their pharmacological responses. Studies have shown tremendous therapeutic activities of AgNPs synthesized by different methods as observed by various in vitro and in vivo approaches (4-6). Anticancer (7), anti-inflammatory, antinociceptive (8), and antibiofilm (9) activities etc. of AgNPs have been discovered in various researches as shown in Table 1.

**(Table: 1)**

Type of AgNP	Source	Biological response	Reference
Biogenically synthesized AgNP	Plant extract	Antimicrobial Anticancer Anti-diabetic Anti-inflammatory Antioxidant	(10-12) (13-15) (12, 16) (12, 17) (11, 12)
	Fungi	Anti-inflammatory Antioxidant Anti-biofilm Anti-proliferative Antimicrobial	(18) (18-20) (18) (18, 21, 22) (19, 20)
	Bacteria	Antimicrobial Anticancer Antioxidant	(23-25) (23, 24) (25)
	Algae	Antimicrobial Antioxidant Anticancer	(26) (26) (26-28)
	Cyanobacteria	Anti-inflammatory Wound healing Antimicrobial Anticancer	(29) (29) (29-31) (31)
Chemically synthesized AgNPs		Anti-inflammatory Anticancer Antimicrobial Antioxidant	(32, 33) (34, 35) (35-37) (35, 38)

### Biogenically synthesized AgNPs:

Biogenic synthesis of AgNPs is achieved by using naturally occurring plant extracts or microbes like algae, fungi, bacteria, and cyanobacteria for the reduction of silver metal to its ionic form (39).

### Chemically synthesized AgNPs:

AgNPs are chemically synthesized by using different reducing agents for the chemical reduction of metal salts like silver nitrate, silver ammonia, silver sulfate, silver chlorate etc. Different capping agents are also used which also play an important role in altering their therapeutic responses.

### Toxicity of AgNPs:

Currently, various researchers have reported the toxic effects associated with the use of these AgNPs (40, 41). It has been proposed that the toxicity of nanoparticles is inversely proportional to size. The smaller size particles are more toxic than the bulk agents of the same chemical. In this review we will summarize and discuss the toxicity of different types of AgNPs synthesized using variable chemical and biogenic approaches.

- **Toxicity of Biogenic AgNPs:**

Extensive research has been done on the toxicity of biogenically synthesized AgNPs using prokaryotes and eukaryotes like plants, fungi, bacteria, algae, animals, and lower vertebrates like zebra fish, and invertebrates like brine shrimp, etc. Similarly different in vitro methods have also been carried out for the analysis of their toxicity (42, 43). When applied to agriculture in lower concentrations they enhance the growth but higher amount results in negative effects like stunted growth (44, 45). A study conducted in 2015, analyzed four types of AgNPs on *Pseudomonas putida* and demonstrated that toxicity could be identical for NPs of similar size and properties, regardless of the source from which they were biosynthesized (46). Another research conducted in 2019 showed that biogenic AgNPs were non-toxic against *Mesocyclops thermocyclopoides* (47). Brine shrimp lethality assay showed that the toxicity of bio-AgNPs was dose and exposure dependent and a high mortality rate was observed at the exposure of 108hrs. The adult mortality rate, however, was lower than that of nauplii (48). Research in 2016 revealed 100% mortality of bio Nano silver at a concentration of 15 nM concentration (49). The antibacterial properties of bio nanosilver are predicted to increase *Artemia's* survival rate in aquatic environments (50). The immunomodulatory effect has been induced by biogenic AgNPs as observed in *Labeo rohita*, a freshwater fish (51). However, a recent study found that bio Nano silver caused oxidative stress, which changed biochemistry and histology (52). Embryonic anomalies have been reported in zebrafish from biogenic AgNPs, in similar research it was identified that the toxicity depends upon the exposure time, source, and concentration of biogenic AgNPs (53, 54). According to a recent study, the toxicity was mostly associated with the cardiovascular system, embryonic development, and apoptosis (55). An increase in oxidative stress and immune-toxicity has been recorded in some experiments (56, 57). Biogenic AgNPs are found to be non-toxic in mice in the in vivo experiments at a dose of 2000mg/kg (58). The non-toxic nature of five different types of antimicrobial biogenic AgNPs has also been reported with the least mortality and accumulation in vital organs (59). On the other hand, bio nanosilver negatively impacted spermatogenesis in newborn mice, demonstrating reproductive toxicity (60). Similarly, no prominent toxic effects were observed in Swiss albino rats when observed through the acute toxicity and histopathological experiments (61). When tested in Wistar rats no significant toxic effects were observed at a lower dose but the serum levels of a few enzymes and the blood biochemistry were deranged but returned to normal following wash-out, further demonstrating their safety (62, 63). Few studies demonstrated dysfunctional mitochondria. Hence, these findings showed that most but not all biogenic AgNPs are safe. Few of them that can enter the cell may cause cellular organelle toxicity.

- **Toxicity of chemically synthesized AgNPs:**

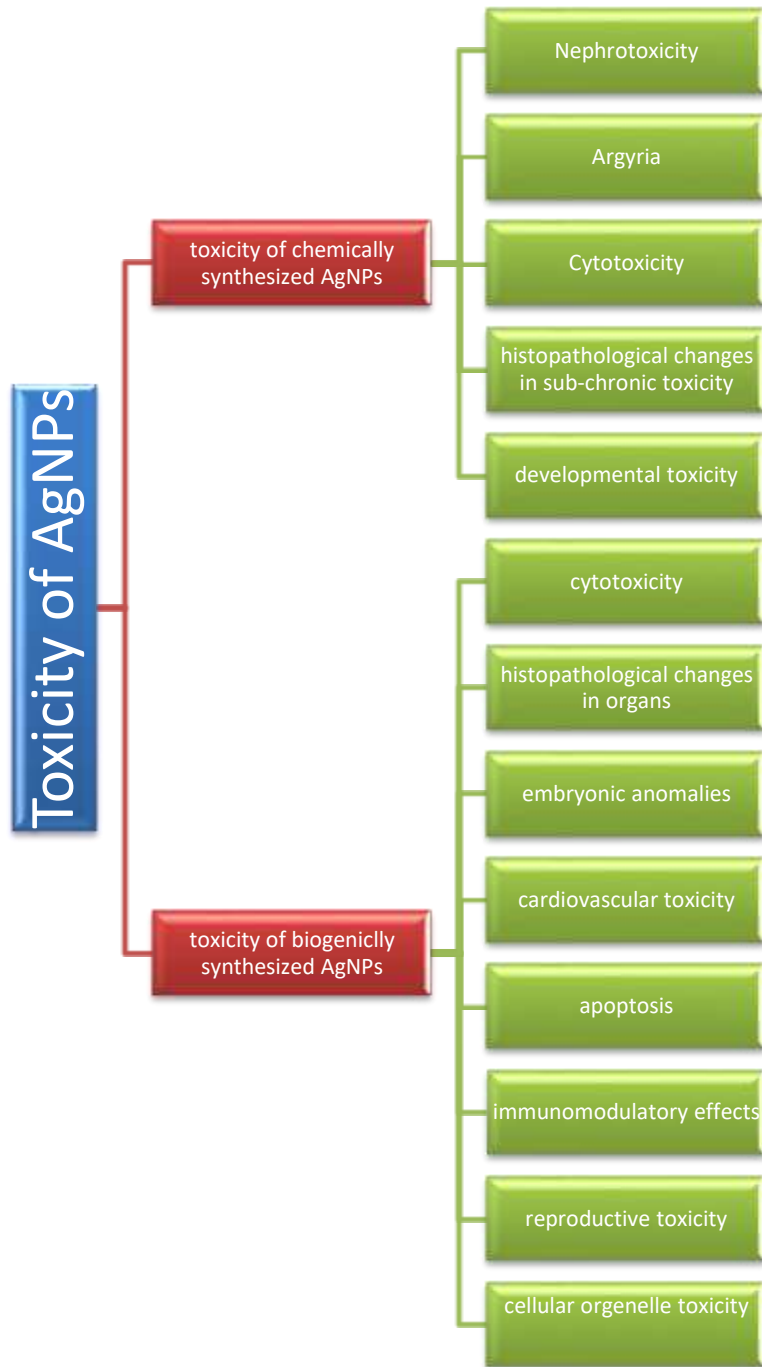
Numerous studies have highlighted the toxicity of chemically synthesized AgNPs and it has also been the subject of various review articles but the results are conflicting (64, 65). Research conducted in 2017 reported the nephrotoxicity of chemically synthesized AgNPs. For that purpose, renal mitochondria and renal epithelial cell lines were studied. Significant nephrotoxicity was observed with altered renal morphology although behavioral signs of animals were normal (66). Chronic exposure to AgNPs may cause argyria, a condition that is characterized by the presence of bluish-colored lesions over the skin (67, 68). AgNPs are found to have harmful effects on the developing fetus and embryo (69). In terms of higher oxidative stress, alteration in cell viability, and lactate dehydrogenase leakage AgNPs are considered to be more toxic than other metallic nanoparticles (70). The type of coating material used for coating during

the synthesis of AgNPs also plays an important role in altering their toxicity as the peptide-coated AgNPs were found to be more cytotoxic than citrate-coated when tested in human cancer cell lines (2).

- **Comparative analysis of chemically v/s biologically synthesized AgNPs:**

When toxicity of biogenic was compared with chemically synthesized AgNPs against crustaceans, *Daphnia magna* biogenic were found to be non-toxic (71) and were lower toxic as compared to chemically synthesized AgNPs (72). In another comparative study, the mortality rate of biogenic AgNPs was 4 times lower i.e. 16.67% than the mortality of chemically derived AgNPs 66.67% when observed at the concentration of 200 µg/mL in freshwater fish, *Oreochromis niloticus*, and in similar research the non-toxic nature of biogenic AgNPs was evident from the lower expression of Heat shock protein (HSP 70) as compared to chemically synthesized AgNPs (73). Research conducted in 2015 reported that biogenic AgNPs were 5 times lower toxic than chemically synthesized AgNPs when observed in adult zebrafish (56).

Figure: 01



**Table 02**

TOXICITY OF AgNPs		
		References
Toxicity of Biogenically Synthesized AgNPs	• Cytotoxicity	(11, 49, 50)
	• Histopathological changes in organs	(52, 61-63)
	• Embryonic anomalies	(55)
	• Cardiovascular toxicity	(55)
	• Immunomodulatory effects	(51, 56, 57)
	• Apoptosis	(55)
	• Reproductive toxicity	(60)
Toxicity of Chemically synthesized AgNPs	• Cytotoxicity	(70, 74-79)
	• Nephrotoxicity	(66)
	• Argyria	(67, 68)
	• Histopathological changes in organs	(80)
	• Developmental toxicity	(69)

**Discussion:**

Due to the promising features of silver nanoparticles they are attracting the attention of many researchers, making them a modern marvel with a wide range of applications in the domains of food technology, agriculture, medicine, industry, etc. (2, 65) Along with their exclusive emerging applications their adverse effects have also been identified (Table 02) this is because of their smaller size and larger surface area that allows them to penetrate and accumulate in various cellular regions and tissues, but their toxicity is dependent on their source, dose, and duration of exposure (81). Despite the fact that AgNPs have been found to have multiple pharmacological properties (as shown in Table: 1) they haven't quite made it to clinical trials because a variety of negative consequences have also been identified (Fig: 01). Few of them have been discussed in this article but still, they are very conflicting. Numerous errors and biases in the execution of the experiment are the cause of the various disputes and contradictions in the toxicity study of AgNPs. This may involve improper characterization, lack of including suitable control groups, unable to interpret collected data, poor understanding of their biotransformation, etc. It's crucial to get through these obstacles in order to better understand their toxicity so they may enter clinical trials with ease and we can get advantages from their myriad health benefits (82).

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