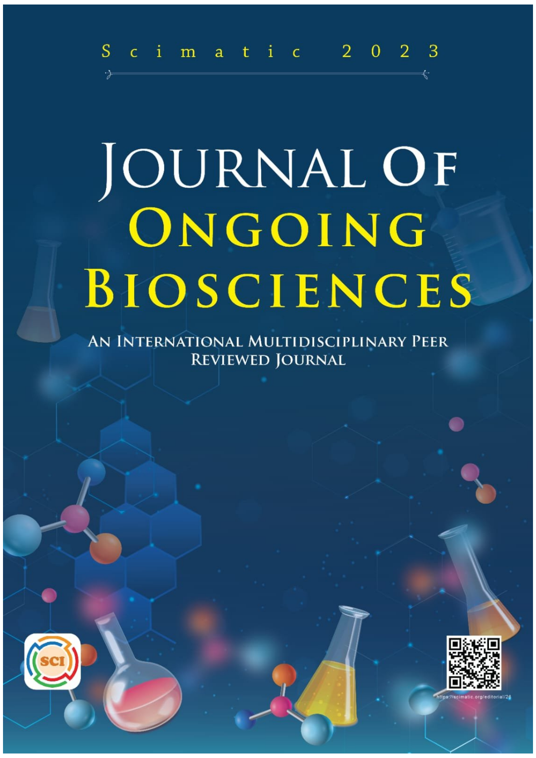
SILVER NANOPARTICLES: SYNTHESIS, APPLICATION HISTORY AND POSSIBLE TOXICITY IN BIOLOGICAL SYSTEM



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Review

Silver Nanoparticles: Synthesis, Application History and Possible Toxicity in Biological System

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Abstract

Silver nanoparticles (AgNPs) have been extensively studied by researchers due to their unique properties such as size, shape, optical, antimicrobial and electrical properties. A variety of preparation methods have been reported for the synthesis of silver nanoparticles, including laser ablation, gamma irradiation, chemical reduction, electron irradiation, microwave processing, photosynthetic methods and biological synthetic methods. AgNPs have widespread application in wastewater treatment, disease treatment, animal husbandry, fisheries and as antibacterial and antifungal agents but the toxicity of chemically synthesized AgNPs in biological system remains the concern which depends on the morphology of AgNPs. This review provides a comprehensive insight to the various techniques notably, physical, chemical and biological methods used to synthesize silver NPs. The aim of this review article is therefore to reflect the benefits of the biological techniques used for the synthesis of silver NPs and also describes some fundamental issues about non-biological techniques.

Keywords: Toxicity, Silver Nanoparticles, Chemical Synthesis, Biological Synthesis, Nanoparticle Synthesis, Physical Synthesis

Nanotechnology is a branch of science, which deals the matter at Nano scale. It is a rapidly growing technology and has gained interest in the last decade due to the history of its wide applications. It is a multi-disciplinary field and was first revealed by Richard Feynman in 1959 [1]. In 1974 Norio Tanaguchi defined nanotechnology as "being able to manipulate a single nanoscale object" [2]. "Nano" is a word, which means one-billionth of physical unit (I-e 1nm). Till now there is no agreement on the definition of nanotechnology [3]. A nanometer (nm) is a unit of measurement that is equal to one billionth of a meter. Therefore, nanotechnology deals with the study of nanomaterials, which have a size between 1 to 100 nm [4]. Nanotechnology may be defined as "the synthesis and application of materials by scientific knowledge to manipulate in the nanoscale (1-100 nm)" [1], by the United States National Nanotechnology Initiative [5]. However, some slight changes are existing in this definition such as the International Organization for Standardization (ISO), has claimed that the nanomaterials can also be found in large size and sometimes maybe 1000 nm [6]. The unique initial chemical, biological, and physical properties of nanoparticles enable them to act as a suitable agent to perform many functions at the cellular and subcellular levels [7]. Paul Ehlirch, for the first time, introduced the concept of targeted therapy or so-called "magic bullets" which means to intended cellular level target with damaging healthy cells [5]. The idea of "magic bullets" was further fused into the concept of nanoparticles [8].

Nanoparticles (NPs) are said to be raw materials used in nanotechnology [9]. These raw materials (NPs) are found in different types e.g. gold, copper, iron, nickel, and silver nanoparticles (AgNPs) [10]. In the past, gold was only known as metal, but later on, with the advancement of nanotechnology, it was realized that the physiochemical properties of gold could make it an ideal material for the synthesis of gold nanoparticles [11]. Gold nanoparticles have gained an attraction due to their chemical and biological properties [12]. Nickel and copper have been investigated for different applications [9]. However, concerns have been stated that nickel nanoparticles might play a key role in biological activities [13]. Iron nanoparticles (FeNPs) are a class of nanomaterials that are being broadly used in the therapeutic and environmental applications (Beheshtkhoo et al., 2018), while silver is a transition, lustrous, and white element in the periodic table, that has been extensively known for therapeutically, environmental, and medical benefits [16]. Medically, silver has been using for over 2000 years and silver-based compounds have been used as antibacterial since the 19th century [17]. The uniqueness of AgNPs is that it has been explored in different areas of human life e.g. washing machines, food, medicine, and fabrics on a large scale (McGillicuddy et al., 2017).

Nanotechnology is one of the most progressive field in many industrial areas at the atomic and molecular levels. The resulting materials have probably novel characteristics regarding their function with small size. [20]. Nanoscience is being developed as a multidisciplinary field based on the key properties of Nano-size materials [21]. NPs recollect amazing marantic, optical, catalytic, biological, and electronic properties, and these properties are because of their higher surface area to the volume ratio [22]. There are certain kinds of nanoparticles but the AgNPs have gained more attention due to of their chemical, biological and physical properties [23]. The size of chemical synthesized AgNPs was 10-100 nm, which defines its good activity to remove certain kinds of micro-fauna [24]. For these biological activities, nanomaterials can be existed as nanotubes, nanorods, dendrimers, fullerenes, nanowires, quantum dots, and nanoparticles [25].

1.1 Silver Nanoparticles

The present era has witnessed momentous headway in the vivid domain of nanotechnology. It is because of this revolutionizing Nano-dimensional arena that several unmet challenges have been comprehensively dealt with [26]. AgNPs have unique optical properties resulting from the collective oscillations of free electrons in response to incident light [27]. Silver illustrates the potential problem of environmental contamination by anthropogenic nanoparticles. It is a naturally occurring rare metal that is 63rd in the order of abundance of chemical elements in Earth's crust [28]. AgNPs are unique because it has been used for centuries due to their best antimicrobial activity with subjective evidence of the use of colloidal silver in the ancient Rome and Egypt [29]. Though, AgNPs are principally known for the antimicrobial activity, only 10% are fabricated for antimicrobial influences while other applications have included optics, electronics, catalysts, and bio sensing [30]. Different types of silver nanoparticles in size and shape are being fabricated. Many have a core-shell structure comprising a metallic silver core of varying size and shape and a coating that usually helps to control the size of the AgNPs during synthesis and provides a surface charge to stabilize the AgNPs in solution [31]. At the beginning of the 20th century, wounds and infections were mostly treated with colloidal silver (including AgNPs), but the development/discovery of modern antibiotics in the 1940s greatly reduced this practice [29]. With the increasing resistance of bacteria to antibiotics, Ag has again become popular in the medical field as a disinfectant [28].

Table 1. The use of silver nanoparticles in different fields of life

Source	Use	Output	Reference
Amino terminated hyper branched polymer	Cotton fabric	Best antibacterial activity	[32]
Green synthesis	Dental cement	Best result and performance	[33]
Plant induced	Target drug delivery	Promising application in drug delivery	[34]
Green synthesized	Purification of drinking water	Promising results	[35]
Green synthesized	Small ruminant disease	AgNPs be an alternative source for small ruminant disease e.g., wound healing effects	[36]
Green synthesized AgNPs	Used against certain types of bacteria and fungi isolated from archaeological manuscripts	Excellent inhibitory growth of bacterial and fungal species	[37]

1.2 Applications of silver nanoparticles

Nanotechnology is a multidisciplinary scientific field that has drawn worldwide attention from various researchers in science and industry. Nanotechnology offers the facile synthesis of metal-based biocompatible nanomaterials that can be applied to a wide range of potential applications in medical and biological sciences, including medical diagnosis, medicine, bio sensing, health care, drug delivery, coating, medical devices, wound healing, the food industry, cosmetics and environmental remediation (water purification). **Fig. 1** shows the applications of AgNPs.

AgNPs are very small particles that have been playing a vital role in the applied sciences. The application of silver nanomaterials is very diverse because of their unique properties. The AgNPs can be applied from the micro level to the macro level. The biosynthesized nanoparticles have been used in a variety of applications including drug carriers for targeted delivery, cancer treatment, gene therapy, and DNA analysis, antibacterial agents, biosensors, enhancing reaction rates, separation science, and magnetic resonance imaging (MRI).

Figure 1. A short presentation of the application of AgNPs in different fields, AgNPs is a noble material

that can be applied in many fields of science and daily life [38].

1.2.1 Wastewater treatment

Contamination of drinking water is a worldwide concern as it causes irreversible damage to plants, humans, and animals. It also spreads numerous epidemics and chronic diseases [39]. Wastewater contains a high concentration of metals, herbicides, pesticides, and toxic industrial effluents that can disrupt various biochemical processes in animals and human beings and lead to change in enzymatic activities/pathways which could cause various diseases and even genetic disorders.

Over a billion people having a lack of access to drinking pure and clean water. Many death ratios have been noticed due to waterborne disease [40]. For these issues, silver nanomaterials has potential applications in purification of wastewater treatment [41]. A laboratory-scale study concluded that 1 mg AgNPs in 1 L water could inhibit the growth of microbes by 80% [42]. Due to their specific properties, the wastewater can be reduced [43].

1.2.2 Disease treatment

The research community is in the continuous search of novel opportunities for improving disease diagnosis, drug design, and drug delivery therefore, Nano biotechnology is an important field with many novel applications [44]. Since ancient times, metals and especially silver were known for their antibacterial effects, but these days available methodologies allow the further exploitation of metal in the form of nanoscale materials. The antiphrastic approach of AgNPs is given in **Table 2**.

Table 2. The antiparasitic approach of biological and chemical fabricated AgNPs

Parasite/ Species	Metal NP size	Synthesis	Reference
Plasmodium falciparum	AgNPs 22-44 nm Triangular shape	Biological	[45]
Leishmania tropica	AgNPs 90 nm spherical shape	Chemical	[46]
Leishmania donovani	12.82 nm spherical shape	Biological	[46]
Trypanosoma brucei	9 nm spherical shape	Chemical	[47]
T. brucei	17 nm spherical shape	Biological	[48]
Schistosoma mansoni	AgNPs 10-15 nm spherical shape	Chemical	[49]

AgNPs are a very important inhibitory material for different diseases even known as a good antimicrobial agent against pathogenic bacterial species [50]. Silver nanoparticles can react with the thiol group of proteins, which leads to the inactivation of the bacterial cell. It also can stop oxidative phosphorylation and DNA replication [51]. The inhibitory process takes place by DNA replication, reactive oxygen species, and direct damage of the microbial cell [52]. A researcher [29] has revealed that the nanoparticles first stick to the cell wall, secondly, the nanoparticles penetrate the parasite cell, and third it starts DNA damage by damaging the thiol group of protein [50]. For this reason, AgNPs are being used to treat a wide range of diseases, for instance, malaria [53].

A new era of antimalarial approach is being emerged by using nanoparticles alone or in combination with commonly used drugs and maybe an innovative therapeutic approach for malaria treatment [54]. A study was conducted for the biological synthesis of AgNPs and applied for the anti-plasmodial activity. The results were highly encouraging since growth inhibition was obtained with LC_{50} values of 3.75 µg/ml (amylase product AgNPs) and 8 µg/ml (Ashoka produced AgNPs),and 30 µg/ml (Neem produced AgNPs), whereas plant extract or amylase alone did not show any activity even up to 40 µg/ml [45].

The mechanism of antiphrastic metal AgNPs is not well known, but catalytic oxidation, binding to parasite's proteins and cellular constituents, and ion release are the principal proposed modes of action. Photocatalytic production of ROS damages parasitic components and disturbs the energy transduction pathway in the parasite that causes diseases in animals and household cattle [55].

1.2.3 Animal husbandry

The health of animals, especially household cattle and small ruminants play a significant role in food consumption and economic growth in developing countries. Fungal and bacterial infection in animal husbandry is a global concern. Bacterial and fungal species secret many chemicals that contaminate the environment, and this contamination continues to animal feed. Feed contamination causes major diseases in animals and poultry (Atef et al., 2017). Therefore, nanotechnology has the potential to solve many mysteries related to animal health [57]. In African countries, rabbit industries are at their peak regarding their production, housing management, economic growth, and nutrition [58]. For this concern, nanotechnology is being used, and nanomaterials are being given as a food supplement in the diet instead of salt and other minerals. These nanoparticles have been found with many novel properties, for instance, growth, maintaining health, and disease [59]. The more details of diagnostic and therapeutic properties of AgNPs are shown in **Table 3**.

Table 3. The table represents some examples of benefits achieved by the application of nanotechnology in animal husbandry [38]

Diagnostic purposes of nanoparticles	1. The coupling of nanoparticles specific to the tumor antibodies with better survival rates and scanning the whole body for metastatic lesions. 2. Nano-biotics can be used in surgeries and nano-cameras can be carried for real-time assistant. 3. Nanoparticles can provide rapid diagnostic tools for example nano-chips enable us to detect thousands of proteins, antigens, genes, or disease biomarkers simultaneously.
Therapeutic purposes of nanoparticles	1. High surface area to volume ratio, enable loading of high amounts of payloads. 2. The nanoparticles are very small, therefore, due to their small size, they can easily different kinds of barriers for instance blood-brain barrier. 3. Nanoparticles can treat multi antibiotics resistance pathogenic species, for instance, brucella, toxoplasma, and leishmania infections, and even chronic non-infectious diseases in animals. 4. New generations therapeutic nanoparticles are highly specific for different targets, AgNPs are developed to treat the genotype and phenotype of cancer cells. 5. An open new horizon for tissue engineering and grafting provides concepts for gene therapy, delivery of DNA, RNA, proteins, and peptides inside the animal cells.

Concerning their medicinal value, the nanoparticles are being used as a source of drug delivery in animal husbandry [60]. Foodborne disease in animals is one of the important among all animal diseases. Nanomaterials are widely used in animal feed to treat the disease due to their physicochemical properties [61]. Fungal species play an essential role in the contamination of animal feed. Many mycotoxins have been identified that contaminate the animal feed. AgNPs are a promising tactic to inhibit this contamination [62]. A study conducted by [63] regarding the nanoparticles and their use in broiler feed. Nanoparticles were supplemented in the feed. The results have concluded that the dose of the nanoparticle supplementation improved the dietary product with no toxicity. Some studies have revealed their results and concluded that nanomaterials could improve reproduction in poultry, livestock, and fisheries [64].

1.2.4 Fish and fisheries

As an important agricultural commodity, fish adds value to rural incomes, creating employment, generating revenue, and ensuring global food security. Fishery creates productive financial gain compared to any farming activity in aquaculture, even only through capture and collection. This sector is also prone to multiple challenges including overexploitation, pollution, climate change, and diseases resulting in retarded growth, and substantial financial loss. In aquaculture production, different diseases have developed into one of the major limiting factors [65]. Among the causative agents, the *Pseudomonas* and *Aeromonas* sp. are one of the important fish pathogens [66].

Among a large number of aquatic pathogens, the gram-negative "*Aeromonas hydrophila*" has been recovered from a wide variety of freshwater fishes and possesses the ability to grow in both aerobic and anaerobic conditions [67, 68]. It propels the outbreak of various fish diseases like ulcers, fin-rot, tail-rot, hemorrhagic septicemia, etc. [69]. Their infection enhances environmental pollution, the elevation of water temperature, and the addition of stressors in the aquatic medium [67]. Antimicrobials like antibiotics are generally used to prevent these diseases. However, a study on *A. hydrophila* from various fish tissues have revealed that the pathogen had developed resistance to many antibiotics like amoxicillin, ampicillin, lincomycin, novobiocin, oxacillin, penicillin, rifampicin and tetracycline [70], and thus researchers have attempted to find the alternative of these antibiotics [71]. A study conducted by [67] regarding the application of AgNPs against fish causing disease bacterial strains. In this context, the inhibitory function of biological synthesized AgNPs against *A. hydrophila* was evaluated in comparison with antibiotics. The study concluded that the bio-synthesized AgNPs can be used as an alternative source for antibiotics against *A. hydrophila* stimulated diseases in aquatic animals. Similar like another study was conducted by Fatima et al., (2020). In this study, the biological synthesized AgNPs were applied for antibacterial effect against the fish pathogens *Vibrio harveyii*, *Vibrio parahaemolyticus*, *Vibrio alginolyticus*, and *Vibrio anguillarum*. The result revealed that the highest activity was found against the pathogens *Vibrio harveyii* and *Vibrio parahaemolyticus*. Herein, the above studies have concluded that biological synthesized AgNPs might be an alternative source instead of available antibiotics and could be a promising antibacterial and antifungal agent in the fisheries.

1.2.5 Antibacterial and antifungal

Bacterial resistance is a global health concern and research on novel therapeutic agents with wide-spectrum antibacterial activity is very important. Several antibacterial agents are already available in the market, controlling bacterial and fungal contamination. However, these antibacterial agents can have several drawbacks, such as toxicity, high cost, low solubility, and side effects. Therefore, conducting studies on effective and secure anti-bacterial components is very important and of high interest.

It has been widely discussed that AgNPs have the best antimicrobial effect with the lowest Eco toxicity in the environment [73]. Comparatively the antimicrobial effect of AgNPs is different against Gram-positive and Gram-negative bacterial species [74]. It has been reported by Rafique et al., (2019) that Gram-positive bacteria are less sensitive to AgNPs as compared to Gram-negative bacteria. For instance, the results of bio-synthesized AgNPs showed that *Staphylococcus aureus* exhibit higher activity than *Escherichia coli*. Another study conducted by AlSalhi et al., (2016) evaluated the antibacterial activity of AgNPs synthesized using aqueous plant extracts of *Pimpinella anisum* seeds, against several bacterial isolates including *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Streptococcus pyogenes, Pseudomonas aeruginosa*, and *Salmonella typhi*. They also assessed the toxic influence of AgNPs on HT115 and hSSC cells using in vitro growth and proliferation assays and cell viability tests. AgNPs produced by *P. anisum* exhibited exceptional antibacterial activity on various microorganisms and demonstrated cytotoxicity on HT115□s and hSSCs.

There is a growing interest in the identification of new and novel antimicrobial agents due to the increase of the antimicrobial resistance globally threat to the public [77]. AgNPs is the best example of antimicrobial agents as the detrimental effects of silver on microbial cells can be increased by the production of smaller nanomaterials [78]. Jebril et al., (2020) reported that plant-induced AgNPs are the most promising antimicrobial sources against certain kinds of fungal isolates. The results of plant-mediated AgNPs revealed that the presence of AgNPs in a concentration of 60 ppm significantly decreased the growth of *Verticillium dahalia*. Guerra et al., (2020) reported that 55-60% of broth fungal cell growth was decreased after the application of AgNPs [80]. The AgNPs are a good antimicrobial agent and this activity involved certain mechanisms [81].

1.3 Mechanism action of silver nanoparticles

Silver nanoparticles are widely used in our daily life, but their mechanism of action is not fully understood [82]. The mechanism action of AgNPs has always been a debatable topic and the exact mechanism is not clear yet, but there are some theories on the action mechanism of AgNPs on microorganisms.

Silver nanomaterials enter the bacterial cell wall, afterward breach it and finally cause changes in the cell membrane, which leads to bacterial cell death [81]. The AgNPs create small pores on the cell surface and the cell becomes porous, therefore the accumulation of AgNPs occurs on the surface of the cell [83]. A free radical formation might be considered another mechanism of action when AgNPs formed a cluster of radicals inside the bacterial cell, which also leads to cell death [81]. A conducted study by using electron spin resonance spectroscopy showed that there is a cluster formation of radicals of AgNPs when in contact with bacterial cells, these free radicals can destruct the bacterial cells and make them permeable, hence, the cells automatically died [84].

Figure 2. A different mechanism of cytotoxicity effects of AgNPs. 1: AgNPs adhere to the cell membrane that alters the membrane structure which leads to leakage of cellular contents. 2: AgNPs penetrate inside the cell and destabilize the DNA. 3: ROS generation leads to oxidizing proteins and lipids and makes the ribosome destabilize. 4: AgNPs cause genotoxicity that damages the DNA base which leads to inhibition of replication and transcription [85].

Another mechanism has proposed that the bacterial enzymes are inactivated probably due to ion formation by AgNPs. Furthermore, inside the bacterial cell, these ions interact with the thiol group of enzymes and inactivate them [86, 87]. AgNPs are a soft acid, consequently, there is a natural phenomenon that the acid always reacts with the base [88]. The bacterial cell is mostly made up of phosphorous and sulfur, which are soft bases. Now the silver present in AgNPs is a soft acid. The reaction between silver ions, phosphorous, and sulfur leads to bacterial cell death. Another statistic is that bacterial cell contains DNA, and DNA is itself consist of phosphorous and sulfur. Silver, as soft acid, reacts with these soft bases, which leads to the destruction of the bacterial cell [89]. This mechanism of action was further supported by another study. When *Staphylococcus aureus* was exposed to AgNPs and studied by combined X-ray microanalysis and electron microscopy. Their results have revealed that the cell wall was detached from the cytoplasm. A condensed DNA molecule was found alone. Silver and sulfur were found by visualizing X-ray microanalysis. The DNA lost its ability to be replicated. All these were found after the treating of bacterial cells with

AgNPs [86]. Due to the revealed mechanisms, silver nanoparticles are among the most studied nanomaterials are the most applicable nanomaterials for example; antimicrobial activities, animal feed, fish diseases, and provide many benefits but little is known about their toxicity [90]. Therefore, it is very important to measure the toxicity caused by AgNPs.

1.4 Toxicity of silver nanoparticles in a biological system

The toxicity of AgNPs has been reported in different studies due to their shape, size, and surface capping [91]. The long exposure time of AgNPs increases the toxicity level [92]. One of the previous studies has revealed that the BEAS-2B cells were exposed to AgNPs in different size (10-40 nm) the toxicity of AgNPs were investigated by photon cross-correlation spectroscopy which has revealed the DNA damage [93]. The harmful and dangerous properties of AgNPs on the environment and their contact with biotic and abiotic factors have been raising concerns in the last decade [94], because these NPs are continuously released into terrestrial and aquatic environments [95]. The cytotoxic effects of AgNPs have mostly been characterized in turns of oxidative stress, DNA damage, and modulation of cytokine production. The cell uptake of AgNPs can stimulate the production of ROS, resulting in oxidative stress and genotoxic effects ROS are produced owing to a disruption in the flux of ions and electron across the mitochondrial membrane; if produced in sufficient high amounts, ROS can inductive cell death by either apoptosis or necrosis in human [96]. Studies have shown AgNPs toxicity to be both size and shape dependent; for example, one study with alveolar macrophages indicated that AgNPs with a mean size 15 nm induced the greatest loss in mitochondrial activity [97]. However, contradictory data exists on the influence of AgNPs size and mitochondrial toxicity [98], suggesting that such effects could be bioaccumulation and histological alteration [99]

Figure .3. The toxicological effects of silver nanoparticles in the biotic and abiotic systems.

Nanoparticles can enter the environment by human activities and can be transferred from one place to another place with the help of water, air, and soil [100]. This transformation process of AgNPs might be accumulated in plants and can lead to AgNPs toxicity in plants [101], and fish gut bacterial dysbiosis [102].

Table 4. The toxicity of silver nanoparticles in a different biological system

Size (nm)	Model	Results	Reference:
13-15	Rat	Mucous production increased	[103]
60	Rat	Alteration in lungs, lesions formed	[104]
60	Rat liver cells	Bioaccumulation	[105]
15	Mouse germ cells	ROS, cytotoxicity	[98] [106]
15	Stem cells and germ cells	Cell death	[107]
15	Mouse embryonic cells	Apoptosis	[108]
20	Rat	Epididymal sperm cells decreased	[109]
45-59	*Cyprinus carpio*	Disturbed gut bacteria	[110]
10	*Cyprinus carpio*	Bioaccumulated in different organs	[111]
28	HeLa and HaCaT	Oxidative stress	[112]
10	Human epithelial	Disruption in signaling	
15	HepG2 cells	cytotoxicity	
15	Leaves	Inhibited growth, color change from green to yellow	[113]
15	*Arabidopsis thaliana*	Inhibit root elongation	[114]

1.4.1 The importance of AgNPs toxicity in fish

The exposure of nanoparticles in the environment has adverse effects on living organisms and public concern. The size, shape, morphology, composition, and distribution of nanoparticles are the leading cause of toxicity [115]. Not only the nature of nanoparticles, but their toxicity also depends on the opponent species and nature of species [116]. AgNPs cause toxicity in the environments by releasing silver species (Ag^{+}) [50] by promoting membrane damage, ROS generation, protein oxidation and denaturation, DNA damage, and cell denaturation and in terrestrial and aquatic organisms [117].

Widespread use of AgNPs has certainly led to their release and presence in natural aquatic environments [118]. Additionally, AgNPs have been used in wastewater treatment and bioremediation [119]. In the aquatic ecosystem, the main exposure route is by ingestion or contact, due to sorption to phytoplankton or zooplankton, transfer from water to sediment, and uptake in benthic organisms, which can be then directly ingested by large vertebrates such as fish [120]. For this purpose, most of the experiments are conducted by using zebrafish and common carp fish. These two fish species are used as experimental animal models [121]. Many studies have been conducted using *C. carpio* regarding AgNPs toxicity. Recently a study has revealed that the AgNPs are mostly accumulated in the liver, followed by the intestine, muscles, and gills [122]. Another study has revealed that the AgNPs stay for a long time in fish body [123]. The *C. carpio* matters and have an importance impact in human nutrition and global food supply [124]. Thus, consumption of fish by the human can lead to the shifting of nanoparticles from fish to human [125]. Therefore, measurement of the toxicity and accumulation of nanoparticles in fish is very important [126]. Experimentally, AgNPs have been detected in different organs, for instance, lungs, brain, spleen, kidney, and liver. Another study reported that the nanoparticles are mostly bio accumulated in human pancreatic cells [127] and lymphatic tissue [128]. This accumulation causes severe destruction in human cells, for instance, ingested nanoparticles pass through the gastrointestinal tract which leads to damage of the digestive gland cell membrane via oxidative stress [129]. Hence, the above studies proved that the measurement of toxicity in fish is very important. Moreover, the AgNPs show more toxicity in terms of cell viability, generation of reactive oxygen species, and lactate dehydrogenase leakage [98]. Therefore, it is a very important aspect to check the toxicity, genotoxicity, and bioaccumulation of AgNPs in *C. carpio*.

1.5 Synthesis of Nanoparticles

The synthesis of nanomaterials takes place by two main methods called as 1: Top-down approach, 2: Bottom-up approach. The top-down approach is a method in which a large piece changes into small desired nanomaterials. This method of synthesis includes etching, grinding, and cutting of materials into small particles. This method can fabricate small particles ranging between 10-100 nm [130]. The bottom-up approach is when the molecular precursors are decomposed and make metal atoms that grow into monodispersed colloids. This concept for the synthesis of nanomaterials is said to be a bottom-up approach [130]. Both approaches are shown in **Fig. 4**.

Figure 4. A modified figure of the top-down approach versus the bottom-up approaches [130].

The synthesis of AgNPs can take place easily by using a bottom-up approach. This is a good approach for fabrication because this approach provides an opportunity to fabricate AgNPs in the small range of 10-100 nm [131]. The second advantage of the bottom-up approach is that synthesized Ag nanomaterials are stable and formed in a crystalline structure [132]. The bottom-up approach includes the biologically fabrication of nanoparticles while the Top-down approach includes chemically synthesis of AgNPs [133].

1.5.1 Chemical synthesis of silver nanoparticles

Generally, certain steps are required in the chemical fabrication of AgNPs i.e., metal atoms formation by reduction process. These metal atoms then passed from an elementary nucleation process. Finally, leads to the formation of the nanoparticles (Murray et al., 2000). The nucleation process is important because saturated or supersaturated solutions are unstable thermodynamically. For the occurrence of the nucleation process, a supersaturating solution "sol gel" is must to generate quite small size particles or materials (Burda et al., 2005). After the formation of nuclei for the supersaturated solution, they grow up through soluble species over the solid surface. When the concentration falls down the critical level, the nucleation process stops, but continuously the particles growing up until the balance of species is reached [137]. Chemically nanomaterials can be synthesized by various methods such as micro-emulsion [138], polyol reduction [139], and thermal decomposing method [140]. The monodisperse colloid growth and typical synthetic apparatus are given in **Fig. 5.** Due to the high toxicity, the preference is given to the biological synthesis of AgNPs instead of the chemical approach [141].

Figure 5. The modified conceptual figure of synthesis of nanoparticles via chemical method (Khan et al., 2018 b).

1.5.2 Synthesis of silver nanoparticles using biological sources

Biological entities and inorganic materials have been in constant touch with each other ever since the inception of life on the earth. Due to this regular interaction, life could sustain on this planet with a well-organized deposit of minerals. Recently scientists have become more and more interested in the interaction between inorganic molecules and biological species. Studies have found that many microorganisms can produce inorganic nanoparticles through either intracellular or extracellular routes. This section describes the production of silver nanoparticles via biological methods.

1.5.2.1 Synthesis of silver nanoparticles by Plant

The biological synthesis of the nanoparticle is called green synthesis, and if the synthesis of nanoparticles takes place by employing any plant species is called Phyto-synthesized nanoparticles [143]. Plants are known to be a factory of bioactive compounds. Flavonoids, terpenoids, and phenols are mostly present in many plant species [144]. These biological compounds play a vital role in the synthesis of AgNPs by a bio-reduction process [145]. The interest in the phyto-nanotechnology was very enhanced in the last decade [146]. The photo—Nano synthesis technique is important for the control size and well-defined shape [145], as shown in **Fig. 6**. Biosynthesis of AgNPs by plant species has substituted the chemical synthesis method [147]. Because plant fabrication for nano-silver is more beneficial and less toxic than chemical synthesis [148]. Several studies have been reported for the fabrication of nano-silver [149]. An aqueous extract of *Ficus hispida* was used by [150] to fabricate AgNPs. A well dispersed and small size of AgNPs were fabricated. Another study was conducted for the synthesis of AgNPs using plant species *Saccharopolyspora spinosa.* The majority of spherical and small size AgNPs were confirmed via FESEM [151].

Figure 6. Plant-induced synthesis of silver nanoparticles. Any part of the plant can be used to synthesize the silver nanoparticles. Herein a complete process is given.

The word Phyto-fabrication designates to synthesize the nanomaterials with the help of plant species. Plants are known to be the factory of enzymes and biological compounds such as reductase and flavonoids. These are involved in the synthesis of nanoparticles. [152]. Plants extract contained different biological compounds and these compounds act as capping agents [153]. Plants are favorable sources for the synthesis of AgNPs because they can easily be handled as plants are not toxic as compared to other biological resources. Many plants have been used to synthesize the nanomaterials and many are being under investigation to use for the synthesize of NPs [154]. Some plants are known to synthesize a higher concentration of nanomaterials, such as *Brassica juncea* [155]. Year-wise different researchers have conducted studies for the fabrication of nanoparticles given in **Table 5.** The biological synthesis is not only done by plants, but the microorganisms also take part in the biological synthesis of AgNPs.

Table 5. Different literature studies were conducted by different researchers regarding plant synthesis of nanoparticles.

Species	Part of plant	Type of NP	Size in nm	Reference
Capsicum annuum	Leaves	Ag	15-20 nm	[156]
Gliricidia sepium	Leaves	Ag	10-50 nm	[157]
Alfaalfa	Seeds	Ag	2-4 nm	[154]
Pelargonium graveolens	Leaf	Ag	25-40 nm	[158]
Azadirachta indica	Leaf	Ag	5-35 nm	[159]
Emblica officinalis	Fruit	Ag	15-25 nm	[160]
Aloe vera	Leaves (Gel)	Ag	15.15.6 nm	[161]
Capsicum annuum	Leaves	Ag	20-30 nm	[156]

1.5.2.2 Microbial Synthesis of silver nanoparticles

As discussed above the biological fabrication of silver nanoparticle using plants, however microorganisms are also an important biological source for the fabrication of AgNPs. As we know, microorganisms are easily available everywhere. Especially environmental microorganisms are available easily and these microorganisms are not much toxic to humans. Therefore, these kinds of microorganisms might easily be used to synthesize AgNPs. The conducted literature is given in Table 6. A variety of literature is available for the synthesis of AgNPs using microbial species. The synthesis of AgNPs by microbial strains is a very simple, less costly, and friendly to environment [162]. Nanoparticles are biosynthesized when the microorganisms grab target ions from their environment and then turn the metal ions into element metal through enzymes generated by the cell activities [163]. The microorganism synthesis AgNPs into the cell is intracellular and when microorganisms synthesized AgNPs on the surface of the cell is extracellular synthesis [164]. Nanoscale silver is Nano sized particles with a high surface area to volume ratio [165]. Using microorganisms such as fungi, archaea, bacteria, etc., can easily reduce the silver salt into AgNPs and these are low-priced techniques and friendly to environments [166], as given in **Fig 8**. *Bacillus* is a common bacterial strain that are capable of synthesizing AgNPs easily [167]. *Pseudomonas stutzeri* is another bacterial species found to be capable of the synthesis of AgNPs intracellularly [168]. Bacterial species *Staphylococcus aureus, Klebsiella pneumonia,* and *E. coli.* Were used by (Ali et al., 2018) for the synthesis of AgNPs.

Table 6. A previously conducted literature studies about the role of bacterial and fungal species in the fabrication of silver nanoparticles

Bacterial species	Source	Reference
Pantoea ananatis	Soil	[169]
Agrococcus Sp.	Soil	[170]
Bacillus sp.	Heavy metals	[171]
Pseudomonas stutzeri	Soil	[168]
E. coli	Soil	[172]
Bacillus siamensis	Medicinal plant	[173]
Staphylococcus aureus	Soil	(Ali et al., 2018)
Klebsiella pneumonia	Soil	(Ali et al., 2018)
Sphingobium sp. MAH-11	Soil	[174]
Fusarium. oxysporum	Soil	[175]
Penicillium verucosum	Soil	[176]
Pleurotus florida	Soil	[177]
White rot fungi	Soil	[178]
Beauveria bassiana	Water	[179]

Fungi is a type of microorganism that is generally found everywhere in the world. Macro fungi are used as food, and micro-fungi are used in the field of medicine [180]. Besides that, the fungi also play a vital role in the synthesis of AgNPs, because they offer high tolerance to metals and are easy to handle [181]. Many studies have confirmed and concluded that fungi synthesize AgNPs by producing extracellular secondary metabolites, and the metabolites reduce Silver nitrate into AgNPs [182]. Biosynthesis of AgNPs by fungal species enhances the stability of AgNPs, reduces toxicity, and best capping agent [183]. Due to high affinity towards the metals, fungi are more effective in the synthesis of AgNPs as compared to other biological species [21], then fungi produce more protein content as compared to bacteria; therefore, fungal species can fabricate nanomaterials in bulk [182]. A study concluded that a fungal species, *F. oxysporum* having biological power, includes extracellular enzymes. These enzymes are an excellent source of reducing agents, and this property is a very important factor for the biological synthesis of AgNPs [184]. Extracellular synthesis of nanomaterials has been reported by [185], in which the AgNPs were synthesized by *Pestalotia* sp. Different fungal species can be used and can be easily available for the synthesis of AgNPs such as *Fusarium, Penicillium, Aspergillus, Pleurotus,* and some other species [182]. Ingle et al., (2008) has used *F. acuminatum* broth to synthesize AgNPs. This study concluded that *F. acuminatum* can synthesize AgNPs easily and rapidly. Ahmad et al., (2003) reported that *F. acuminatum* was treated with $AgNO_3$ solution. Rapid synthesis took place, in which 5-15 nm small-sized AgNPs were obtained. Another researcher, [188] reported the synthesis of AgNPs by using *Penicillium* sp. isolated from the soil. [189] reported the biological synthesis of AgNPs by using *Aspergillus niger* isolated from the soil. The use of plants, bacteria, and fungi is the great achievement in synthetic biology but, there are some disadvantages such as the use of toxic chemicals, fungal contamination, and generation of waste which cause environmental pollution [181]. Therefore, it is very important to find a new biological direction for the fabrication of AgNPs.

Figure 7. Microbial synthesis of silver nanoparticles. Bacteria, fungi, algae and cyanobacteria can be used to synthesize silver nanoparticles.

1.7 Animal blood serum

Slaughterhouse blood is an inevitable part of the waste product which represents a rich in protein. The physicochemical characteristics and utilization of animal blood in many industries and applied fields have been well explored. Animal blood is a red fluid, which mainly consists of cells and plasma. Cells are further consisting of red blood cells, white blood cells, and platelets. Plasma or serum is made up of water, organic substance, inorganic substance, and many biological molecules i.e., proteins and enzymes.

Plasma or serum, the part of the blood remaining after removal of the cells from un-clotted blood contains 6 to 8% proteins, consisting primarily of albumin, globulin, and fibrinogen as shown in. These as well as more than 100 smaller proteins have been well characterized. Animal blood has been used in many industrial applications such as pet food, animal feed, aquatic feed, laboratory, medical microbiology, and research [190]. Therefore, a previous study used animal blood serum for biological synthesis of AgNPs and obtained a well dispersed and under size AgNPs [191]

1.8 Conclusion

Silver nanoparticles have gained significant interest because of their valuable properties and their proven applicability in diverse fields such as medicine, biotechnology, nanotechnology, bio-engineering science, water treatment, textile engineering and catalysis. These NPs can be used as antimicrobial and antifungal agents in a diverse range of products because of their significant antimicrobial and antifungal activities.

The flexibility in the methods of synthesis and assured incorporation silver nanoparticles into different media have inspired the researchers to further explore the mechanism behind their antimicrobial, antiviral antiinflammatory effects. The shape, size and size distribution of silver nanoparticles can be controlled by adjusting the reaction condition, such as the reducing agent, stabilizer or by employing the various synthetic methods. Hence, it is crucial to understand the impact of reaction conditions on the morphology and size of these NPs.

Several techniques have been developed to produce silver nanoparticles with different shapes and sizes, such as laser ablation, electron radiation, gamma radiation, chemical reduction, microwave processing, photochemical methods and thermal decomposition of silver oxalates in water and in ethylene glycol, as well as biological synthetic methods.

Chemical and physical methods have been used for synthesizing silver nanoparticles for several decades, but they can be expensive and often evolve the use of chemical toxic chemicals, making biological synthesis a more desirable option. In the chemical reducing method, the reducing agents are chemicals solutions such as polyol, N_2H_4, $NaBH_4$ sodium citrate and N,N-dimethylformide. In case of biological method, a collection of enzymes, predominantly, nitrate reductase plays such a role. In the case of chemical synthesis, a stabilizer (Surfactant) is added to the solution to prevent agglomeration, however, there is no need to add a stabilizing agent in biological synthesis. Biosynthetic methods of NPs offer a new and convenient way to synthesize them using natural reducing and stabilizing agent. Biosynthesis of metal and semiconductor nanoparticles using organisms has been suggested as a highly viable and sustainable alternative to traditional chemical and physical approaches. Not only it is environmentally friendly but it is also economically advantageous. Particle dimensions, size and shape are critical factors in assessment of NPs synthesis. Therefore, it is crucial to explore efficient ways to control the morphology and monodispersity of NPs. It is important to optimize the reaction conditions. By using screened organisms with high production capability and carefully controlled reaction conditions, it is possible to obtain well-characterized NPs at synthesis rates that are comparable to or faster than physical and chemical approaches. This eco-friendly method has the potential to be used in various areas, including pharmaceuticals, cosmetics, food and medical application.

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