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REVIEW

Properties, synthesis and toxicity of silver nanoparticles

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Abstract Silver nanoparticles are actually used in several industrial sectors and end up in the environment, thus inducing a possible toxicity for living organisms. This article reviews the properties, synthesis and toxicology of silver nanoparticles, with focus on the toxicity for insects such as *Bombyx mori.*

Keywords Insect · Silk worm · *Bombyx mori* · National Nanotechnology Initiative · Silver · Nanotoxicology · Larva · Pupa · Adult moth nanotoxicity

Introduction

Silver nanomaterials are fine particles of metallic silver that have at least one dimension less than 100 nm. Nanosilver or suspensions of nanosilver refers to colloidal silver. To produce colloidal silver, a positive electrical current is applied through pure silver bars suspended in water, resulting in colloidal silver particles with the size range of 15–500 nm. Before the invention of penicillin in 1928, colloidal silver was used to treat many infections and illnesses. Unique properties of nanosilver are mainly attributed to the high surface area to volume ratio, leading many industrial sectors to incorporate silver nanomaterial into their products. A variety of chemical and physical procedures could be used for synthesis of metallic nanoparticles.

Silver is widely used as a catalyst for the oxidation of methanol to formaldehyde and ethylene to ethylene oxide (Nagy and Mestl 1999). Colloidal silver is of particular interest because of its distinctive properties, such as good conductivity, chemical stability, catalytic and antibacterial activity (Frattini et al. 2005). For example, silver colloids are useful substrates for surface-enhanced spectroscopy, since it partly requires an electrically conducting surface (Tessier et al. 2000; Rosi and Mirkin 2005). This article is an abridged version of the chapter published by Pandiarajan et al. (2016a) in the series Sustainable Agriculture Reviews (http://www.springer.com/series/8380).

Properties of silver nanoparticles

The principle parameters of nanoparticles are their shape (including appropriate aspect ratios), size and morphological substructure of the substrate. Silver nanoparticles have diverse properties like catalysis, magnetic and optical polarizability, electrical conductivity, microbial activity and enhanced Raman scattering. They possess unique optical properties because they support surface plasmons. At specific wavelengths of light, the surface plasmons are driven into resonance and the silver nanoparticles have a distinct color that is a function of their size, shape and environment (Noguez 2007). The plasmon resonance of silver nanoparticles is responsible for the yellow color in solution. Any visible change to the nanoparticles in solution typically indicates the aggregation of the nanoparticles

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(Pietrobon and Kitaev 2008). Silver nanoparticles are extraordinarily efficient in absorbing and scattering light. Many dyes and pigments have a color that depends upon the size and shape of the particles. An unique property of spherical silver nanoparticles is surface plasmon resonance peak wavelength that can be tuned from 400 nm (violet length) to 530 nm (green length) by changing the particle size and the local refractive index near the particle (Shipway et al. 2000).

Synthesis of silver nanoparticles

There are three major processes involved in the synthesis of nanoparticles. They are physical, chemical and biological method. The biological synthesis of metal nanoparticles, especially gold and silver nanoparticles, using inactivated plant tissue, plant extracts and living plant, has received more attention as a suitable alternative to chemical and physical methods. Synthesis of metal nanoparticles using plant extracts is very cost-effective and therefore can be used as an economic and valuable alternative for the large-scale production of metal nanoparticles. Extracts from plants may act both as reducing and capping agents in the synthesis of nanoparticles. The bioreduction in metal nanoparticles by the combinations of biomolecules found in plant extracts is environmentally benign (Thakkar et al. 2010).

Material Scientists are conducting research to develop novel materials with better properties, more functionality and lower cost than the existing ones. Several physical, chemical and biological synthesis methods have been developed to enhance the performance of nanoparticles with the aim to have a better control over the particle size, distribution and morphology (Shankar et al. 2003). Synthesis of nanoparticles to have a better control over particles size, distribution, morphology, purity, quantity and quality, by employing environment friendly economical processes has always been a challenge for the researchers.

Physical synthesis

Several methods including the commonly used attrition and pyrolysis can be used for physical synthesis of metallic nanoparticles. In addition, macroscale or microscale particles are ground by a size-reducing mechanism. The production rate of these aforementioned "physical" procedures for achieving synthesis of metallic nanoparticles is quite low and, importantly, the expense is very high. Disadvantage of physical method is the enormous consumption of energy to maintain the high pressure and temperature that is used in the synthesis procedures. In contrast, most of the bioprocesses occur under normal air pressure and temperature, resulting in vast energy savings (Thakkar et al. 2010).

Chemical synthesis

Chemical reduction is the most frequently applied method for the preparation of silver nanoparticles as a stable, colloidal dispersion in water or organic solvents. Commonly used reductants are borohydride, citrate, ascorbate and elemental hydrogen (Ahmad et al. 2003). The reduction in silver ions (Ag^+) in aqueous solution generally yields colloidal silver with particle diameters of several nanometers. Previous studies showed that use of a strong reductant such as borohydride resulted in small particles, but the generation of larger particles was difficult to control. Use of a weaker reductant such as citrate resulted in a slower reduction rate, but the size distribution was far from narrow. Controlled synthesis of silver nanoparticles is based on a two-step reduction process. In this technique, a strong reducing agent is used to produce small particles, which are enlarged in a secondary step by further reduction with the aid of a weaker reducing agent (Lee and Meisel 1982). Different studies reported the enlargement of particles in the secondary step from about 20–45 to 120–170 nm. The synthesis of nanoparticles by chemical reduction methods is therefore often performed in the presence of stabilizers in order to prevent unwanted agglomeration of the colloidal silver in the solution of nanoparticles. To prevent the agglomeration of metallic nanoparticles, a stabilizing agent such as sodium dodecyl benzyl sulfate or polyvinyl pyrrolidone is also added to the reaction mixture. Generally, the chemical methods are low cost for high volume; however, their drawbacks include contamination due to precursor chemicals, use of toxic solvents and generation of hazardous by-products (Thakkar et al. 2010).

Biological synthesis

Chemical approaches are the most popular methods for the preparation of nanoparticles. However, some chemical methods cannot avoid the usage of toxic chemicals in the synthesis protocol. Since noble metal nanoparticles such as gold, silver and platinum nanoparticles are widely applied to human contacting areas and there is a growing need to develop environmentally friendly processes of nanoparticles synthesis that do not use toxic chemicals. Biological methods of nanoparticles synthesis using microorganism (Nair and Pradeep 2002), enzyme (Willner et al. 2006), and plant or plant extract (Shankar et al. 2004) are suggested as possible ecofriendly alternatives to chemical and physical methods. Using plant for nanoparticles synthesis can be advantageous over other biological processes by eliminating the elaborate process of maintaining cell cultures (Shankar et al. 2004). It can also be suitably scaled up for large-scale synthesis of nanoparticles.

The insect model *Bombyx mori*

The silkworm is a monophagous insect that mainly feeds on fresh mulberry leaves. Artificial diet for the silkworm is studied and applied extensively in Japan, China and some other countries as it contains essential nutrients for supporting the normal growth of the larva. Although artificial diet can obviate the serious drawbacks of mulberry leaves such as the seasonal limitation on supply of fresh leaves, possible harm from parasites or pesticides and high labor cost, the silkworms reared on artificial diet during all instars are not as good as those fed on fresh mulberry leaves, which are reflected in many aspects such as the filament quality and resistance of cocoons (Pandiarajan et al. 2011), survival rate of young larvae and resistance to bacterial and viral diseases (Zhou et al. 2008).

The fifth instar is a transition period for metamorphosis from larva to pupa, and for biosynthesizing and spinning, during which larvae take in almost the entire nutrition for the whole life process. Day 3 of the fifth instar is found to be a boundary for larval development. (Grzelak 1995). Most biological processes may be similar before this time point, but after that, silkworms begin to synthesize silk proteins in mass. Among all the body tissues of silkworm, midgut, hemolymph, fat body and posterior silk gland are the vital tissues during the growth and development of silkworm, which function in nutrient digestion and absorption, nutrient transportation and innate immunity, nutrient synthesis and storage, and fibroin synthesis, respectively (Zhou et al. 2008).

Toxicity assessment using the silk worm *Bombyx mori*

Improving the quality and quantity of silk by using mulberry leaves enriched with organic and inorganic supplements as feed for silkworm is tried by many workers (Subburathinam and Krishnan 1998). Sarker et al. (1995) reported the growth of larvae of *Bombyx mori* significantly improved when fed on mulberry leaves supplemented with different nutrients such as soya milk, milk powder, vitamins and potassium iodide salts.

Mulberry leaves soaked in cobalt solution (100 µg/ml) enhanced the body weight and increased the number of eggs laid by the adult (Chakrabarti and Medda 1978). Chamundeshwari and Radhakrishnaih (1994) reported that larvae fed with zinc- or nickel-sprayed mulberry leaves (1 mg/10 g wet weight), once in each instar up to fourth instar and in alternate days of fifth instar, increased the weight of larvae and silk gland. It also shows effects on economic parameters, i.e., the cocoon length, width, shell weight, shell ratio, filament length and weight were observed. These are very much significant in the larvae fed with zinc-sprayed leaves than nickel-sprayed leaves.

The effect of zinc treatment at different doses 1, 10, 50 and 100 ppm on silkworm fifth instar larvae was tried by Balamani et al. (1995) and reported that it enhances the silk quality by 50% compared to the control group left untreated. Saha and khan (1995) reported that leaves supplemented with nickel chloride appreciably increased the lipid content in treated silkworm, *Bombyx mori* at 0.25 and 0.50% concentrations. However, at higher concentrations (0.75%) the reverse results were obtained.

Saha and khan (1996) reported that enrichment of mulberry leaves with multivitamins and multimineral capsules at various concentrations (0.08, 0.16, 0.32 and 0.64%) reduced the larval and pupal periods and the reproductive potential was enhanced at these concentrations. Even the highest concentration, i.e., 0.64% of these capsules had deleterious effects on all parameters. Changes in the protein metabolism in the hemolymph and fat body of the fifth instar larvae were observed, following the exposure to sublethal concentration of fenitrothion and ethion (Nath et al. 1997).

The effect of administering different quantities of JHA (6,7-epoxy-3-ethyl-phenoxy)-7-methylnonane), orally to last instar larvae of *Philosamia ricini*, was studied by Singh (1990). Prolongation of the life of the larval instar followed by death, imperfect ecdysis affecting cocooning and pupation, non-viable larval–pupal intermediates with very thin cocoons are observed.

Most drug candidates obtained by in vitro screening are inappropriate as medicines due to problems of toxicity and their pharmacodynamics in humans. Preclinical tests in animal models are essential for evaluating the therapeutic effects of drug candidates for further development. Mammals, such as mouse, rat, marmot, rabbit, dog and monkey, are commonly used as drug-screening models to examine the pharmacodynamics of chemicals. The use of mammals for drug development is expensive and highly problematic with regard to ethical issues (Orlans et al. 1998; Baumans 2004). The development of invertebrate animals as drug-screening models will overcome these problems. Invertebrate animals such as *Romalea microptera* (Johny et al. 2007), *Caenorhabditis elegans* (Mahajan-Miklos et al. 1999) and *Drosophila melanogaster* (Bernal and Kimbrell 2000) are generally used in bacterial infection models. A limitation of these models is that their body sizes are too small for using in studies of pharmacodynamics. The silkworm's body size is large enough for hemolymph preparations and organ isolation, which are essential for studying the pharmacodynamics of drugs in animal bodies. Thus, we propose the use of silkworms as model animals for evaluating the therapeutic effects of drug candidates (Hamamoto and Sekimizu 2005).

Nanotoxicology

Nanotoxicology is a new field established in the current decade, which emphasizes the usage of nanomaterial in commercial goods and novel technologies, which is generating several risk factors to the human health and environment. Though the ingestion level of nanoparticles is very low in the living systems and their toxicity level is also estimated to be very less, these nanomaterial leads to the accumulation in their host, and it may explicit the adverse effect later. At one stage, the accumulation of nanoparticles may become an eco-hazard. It has been already reported that nanomaterials such as carbon nanotubes, quantum dots and metal and metal oxide nanoparticles are having the adverse toxic effects when they are dosed even in low level (Asharani et al. 2009). The earlier reports insist that biologically synthesized nanoparticles were safer materials which do not have any corrosiveness to the living host and also they do not create any potential danger. Though the biological nanoparticles are harmless, the biocompatibility of their usage can be evaluated through the in vivo and in vitro toxicity studies in the model animals. These assessments of toxicity mediated by bionanoparticles will open up several questions raised against the risk assessment in human and cattle. The experimental evidence may bring out a decline in the use of nanomaterial in several aspects such as nanomedicine, material safety, nanocoupled drug, nanocommercial goods.

Toxicity evaluation on silkworm, *Bombyx mori,* is reasonably comparable to those of other lepidopteran pest, so it is considered as a suitable model for exploring effects of any new synthetic formulations for the past two decades (Rajathi et al. 2010). Silkworm rearing is a traditional business in Tamil Nadu, and the life of many people depends on it. Increase in larval growth and cocoon quality and quantity would result better economics for this industry and meet the production needs. Consequently, the enrichment of mulberry leaves by supplementary compounds with the aim of increasing the production of cocoon is a very important aspect. Many investigations have been done on this topic, and various reports have been published (Islam et al. 2004). Copiously the earlier reports have mentioned that the silver Nanoparticles can be utilized as an ancillary complex which can boost up the growth and development of the larvae and also the quality and quantity of the cocoon.

Nutrition plays an important role in improving the growth and development of the silkworm, *Bombyx mori* L., like other organisms. Nutritional quality of mulberry leaf has greater importance on regulation over the quantum of digestibility of food among silkworms. It is direct relation with growth and silk production in silkworms. Such nutritional requirements in food consumption have direct impact on the overall physical and genetical traits such as larval and cocoon weight, quantity of silk production, pupation and reproduction. Silkworm nutrition refers the substances required by silkworm for its growth and metabolic functions and obtained from ingested food; remaining other nutritional components are being synthesized itself through various biochemical pathways including proteinous silk fiber of commercial interest. Research on silkworm, *Bombyx mori*, clearly demonstrates that nanoparticle could stimulate more production of fibroin protein which can help in producing carbon nanotube in future (Bhattacharya and Mukherjee 2008). Legay (1958) states that silk production is dependent on the larval nutrition and the nutritive value of mulberry leaves that play effective role in producing good quality cocoon.

In vitro and in vivo nanotoxicity

During the investigation, the fifth instar larvae were fed with leaves supplemented with silver nanoparticles with varying concentrations (1, 10, 100 ppm) Observations were made on the larval and cocoon characters (Tables 1, 2, 3, 4;

Table 1 Weight increase at larval stages of *Bombyx mori* during different dosage of treatment at 24-h interval (10 larvae—chosen for study)

Weight of the larvae (10) (in g)				
Contents	Day 1	Day 2 After 24 h	Day 3 After 48 h	Day 4 After 72 h
Control	21.77	26.23	27.20	26.95
1 ppm	21.77	27.19	30.88	28.44
10 ppm	21.77	25.20	28.66	27.80
100 ppm	21.77	26.73	28.31	27.80
LE	21.77	25.44	27.94	25.94

Table 2 Weight of total pupa and cocoon (shell) at pupal stage of *Bombyx mori* during different dosage of treatment at 24-h interval

Weight of the pupa + cocoon (2 insects) (in g)						
Contents	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Control	3.02	2.52	2.7	2.60	2.56	2.23
1 ppm	2.70	3.05	3.20	2.86	2.95	2.34
10 ppm	3.29	2.82	3.13	2.68	2.69	2.25
100 ppm	3.22	3.37	3.07	2.55	2.53	2.72
LE	2.97	3.14	3.11	2.33	2.60	2.14

Table 3 Weight of pupa (alone) of *Bombyx mori* at larval treatment stage with different doses at 24-h interval

Weight of the pupa (in gm)						
Contents	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
CONTROL	2.53	2.06	2.10	2.02	2.04	1.83
1 ppm	2.17	1.99	2.61	2.26	2.26	1.83
10 ppm	2.67	2.14	2.60	2.28	2.19	1.75
100 ppm	2.74	2.81	2.51	2.01	2.01	2.23
LE	2.44	2.66	2.48	1.89	2.17	1.70

Table 4 Weight of shell of pupa (alone) at different dosage of treatment during larval stage of *Bombyx mori* at 24-h interval

Weight of the cocoon shell (in g)						
Contents	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
CONTROL	0.43	0.39	0.51	0.41	0.40	0.38
1 ppm	0.45	0.63	0.53	0.53	0.52	0.49
10 ppm	0.50	0.45	0.51	0.40	0.48	0.46
100 ppm	0.46	0.51	0.51	0.50	0.49	0.38
LE	0.50	0.51	0.52	0.44	0.41	0.42

Figs. 1, 2, 3, 4). Maximum larval weight was observed in 1 ppm silver nanoparticles treatment (2.888 g) as compared to control (2.679 g). Marked increase in cocoon weight was found in silver nanoparticles (1.465 g) treatment. Minimum cocoon weight (1.319 g) was recorded in control. The results observed with respect to pupal weight were found to be maximum (1.206 g) in 100 ppm silver nanoparticles treatment with minimum pupal weight obtained in control untreated group (1.067 g). Maximum shell weight (4.97 g (20 cocoons)) was observed in treatment with 1 ppm, followed by 10 ppm (4.77 g), 100 ppm (4.76 g) treatment, respectively. Least shell weight was observed with the control (4 g). Significant increase in shell ratio was observed in treatment with 1 ppm (16.95%) as compared to control (15.92%) (Tables 1, 2, 3, 4; Figs. 1, 2, 3, 4) (Pandiarajan et al. 2016b).

Nanosilver disrupt soil microbial communities

Information on the toxicity of terrestrial and sediment organisms is limited, but is slowly being investigated. Again toxicity appears to be dependent on physicochemical soil properties and sediment properties. There is currently very little research on the effect of silver nanoparticles on soil microbial communities in situ, that is, in real soils. But in situ studies have demonstrated that silver, even in larger particle form, inhibits microbial growth below concentrations of other heavy metals (Murata et al. 2007). It is especially toxic to heterotrophic (ammonifying/nitrogen fixing) and chemolithotrophic bacteria. Chemolithotrophic bacteria belong to the lithotrophic family of microbes and consume inorganic material. These organisms liberate many crucial nutrients and are essential in the formation of soil. Ratte (1999) showed that silver ions inhibit enzymes needed for nitrifying bacteria. The toxic effect of silver on bacteria also appears to disrupt denitrification processes, with the potential to cause ecosystem-level disruption (Throback et al. 2007). Denitrification is a bacteria-driven process where nitrates are converted to nitrogen gas in some soils, wetlands and other wet environments. A denitrifying bacterium plays an important role in removing nitrate from water contaminated by the usage of excessive fertilizer. Denitrification is important because excess nitrates reduce plant productivity and can result in eutrophication (an unhealthy increase in nutrients) in rivers, lakes and marine ecosystems and are a drinking water pollutant.

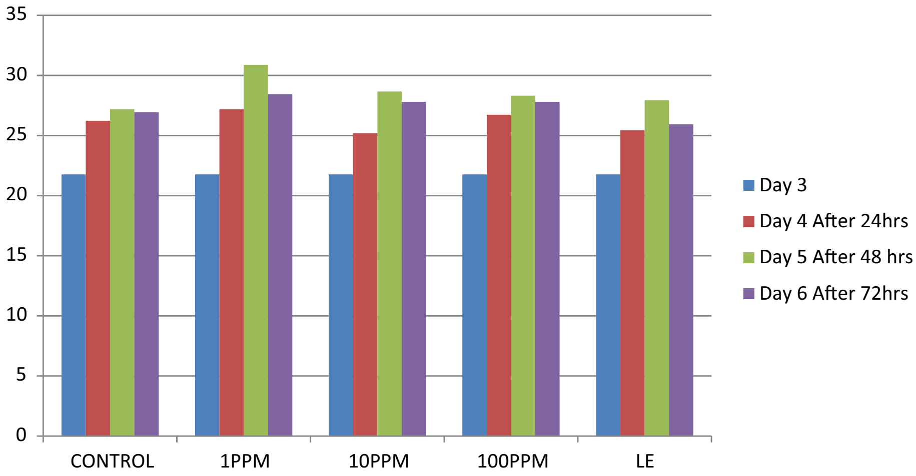


Fig. 1 Weight increase at larval stages of *Bombyx mori* during different dosage of treatment at 24-h interval

Fig. 2 Weight of total pupa and cocoon (shell) at pupal stage of *Bombyx mori* during different dosage of treatment at 24-h interval

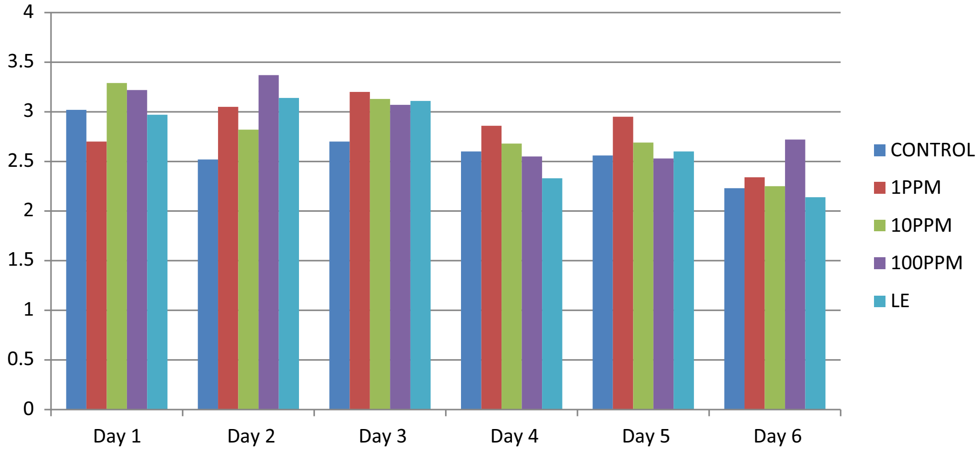


Fig. 3 Weight of pupa (alone) of *Bombyx mori* at larval treatment stage with different doses at 24-h interval

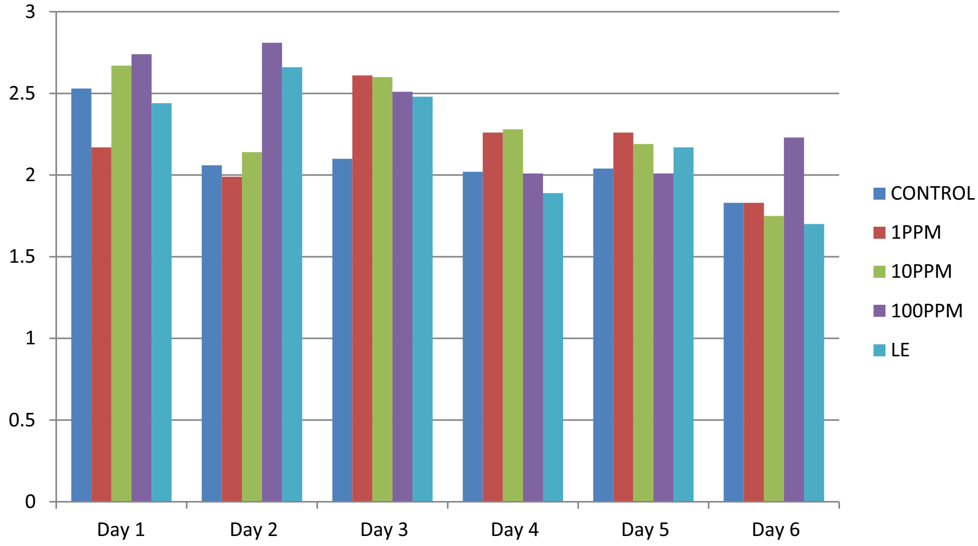
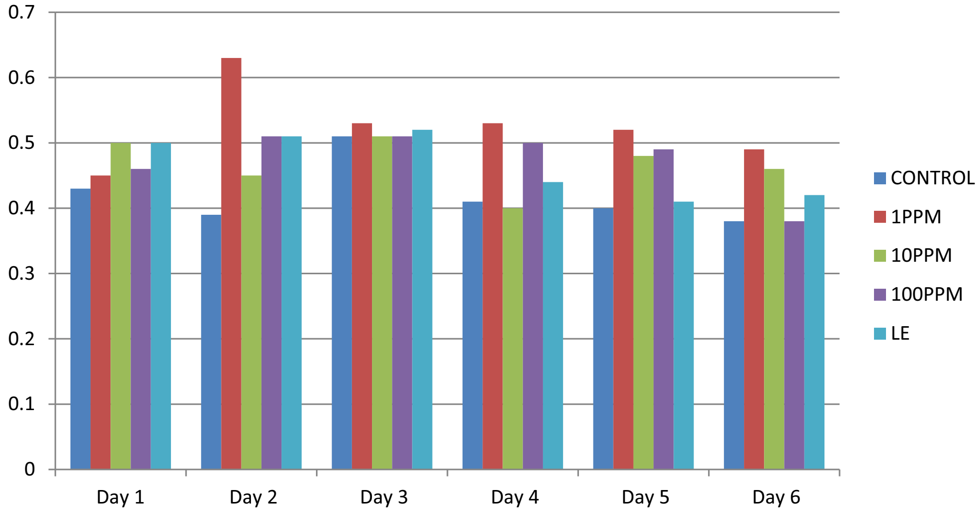


Fig. 4 Weight of shell of pupa (alone) at different dosage of treatment during larval stage of *Bombyx mori* at 24-h interval



Nanotoxicity for aquatic life

Currently little is known about the fate of silver nanoparticles in the environment. However, depending on their surface structure and shape, silver nanoparticles may have different reactivity. Silver nanoparticles also act as a reservoir of silver ions and may release Ag^+ ions continuously. Silver is toxic to fish, crabs, algae and other water plants, as well as nitrogen fixing bacteria (Albright and Wilson 1974). Of which, special importance may be the effect of silver on lithotrophs, organisms that play an important role in the digestion of inorganic material and creation of soils.

Aquatic organisms differ significantly in their sensitivity to silver. The accumulation of silver and its toxicity depends on and varies with environmental conditions such as salinity and pH. Research into the toxicity of nanosilver to aquatic organisms is still limited and tends to focus on a small number of key species—zebra fish, invertebrates, some algae. Toxicity of silver is a result of silver ions and depends on their concentration. Silver ions react with thiol (a molecular group that includes a bonded sulfur and hydrogen atom (–SH) in biomolecules). For instance, in fish, silver ions block the active absorption of sodium and chlorine as well as causing sublethal effects (Hogstrand and Wood 1996). In water fleas, silver ions disturb ion regulation via a competitive inhibition of Na^+ (sodium) uptake.

The freshwater invertebrates, *Ceriodaphnia dubia* and *Daphnia magna* are not only standard testing organisms for aquatic toxicity testing, but they are also one of the most sensitive organisms to silver. Naddy et al. (2007) showed that chronic exposure of *D. magna* and *C. dubia* to silver resulted in decreased growth and reproduction (8.80 and 2.65 mg dissolved silver/l), and complete mortality at higher levels. It is well known that silver ions in the natural environment tend to form stable complexes both inorganic (e.g., chloride, thiosulphate and sulfide) and organic (monomeric thiols and natural organic matter). Silver thiosulphate was thought to be relatively inert. However, Hiriart-Baer et al. (2006) showed that silver thiosulphate complexes can be transported across cell membranes in *Chlamydomonas reinhardtii* and *Pseudokirchneriella subcapitata* (two freshwater algae species) and lead to increased toxicity.

Navarro et al. (2008) investigated the toxicity of silver nanoparticles versus silver ions to *C. reinhardtii*. Based on total silver concentration, the silver ions appeared to be 18 times more toxic than the nanosilver particles. However, the closer inspection revealed that when compared to a function of silver concentration, the silver nanoparticles appeared more toxic than the silver ions. The researchers reasoned that silver nanoparticles contributed to the overall toxicity of silver to the algae by providing a continuous source of silver ions.

The release of silver nanoparticles into fresh water ecosystems can lead to more biological, physical and chemical irrecoverable impacts on the ecosystems and their fishes (Kalbassi et al. 2011). Silver ions are known to be one of the most toxic metals to freshwater fish. However, their effect is often mediated by a variety of agents (e.g., chloride) present in water (Grosell et al. 2000). Silver ions are the most potent gill toxicant in freshwater fish. The toxicity of nanosilver particle appears to be independent from silver ions. Griffitt et al. (2009) found that when zebra fish was exposed to nanosilver particles, the silver level in their gills increased. Gene expression proofing suggested that the silver nanoparticles interacted with the gills in a different manner than soluble silver particles and hence the observed effects were not due to silver ions.

Silver nanoparticles administered in vivo to zebra fish embryos increased deformation rates and, ultimately, led to death. Individual silver nanoparticles were found inside embryos at each developmental stage (Lee et al. 2007). Scown et al. (2010) evaluated the effects of silver nanoparticles in fish, rainbow trout (*Oncorhynchus mykiss*), were exposed via the water to commercial silver particles. It is reported that exposure of silver nanoparticles to rainbow trout at concentrations close to current estimations of environmental levels can result in accumulation of silver in the gills and liver of fish and can affect likely oxidative metabolism in the gills. Significant inhibitions of growth and reproduction of daphnia were observed when the daphnia exposed to silver nanoparticles (Zhao and Wang 2011).

Bioaccumulation of silver nanoparticles

Silver nanoparticles present in consumer goods are released into the environment, where they could be bioaccumulated or enter the food chain/drinking water supplies (Karn et al. 2009; Gao et al. 2009). The environmental fate of nanosilver will depend upon the nature of the nanoparticles. The bioavailability of these materials can be determined by their uptake when they are in contact with organisms. The uptake of silver nanoparticles is relatively fast and time dependent. Usually after 24 h of exposure, the vast majority of cells contain silver nanoparticles. Sometimes, uptake saturation is observed after prolonged incubation (Lu et al. 2010; Mahmood et al. 2010). Silver nanoparticles uptake can be influenced by several factors, such as morphology of nanoparticles, their size, concentration and surface properties (Mailander and Landfester 2009). Impact of silver nanoparticles depends not only on their dose but also on their size (Lankveld et al. 2010).

Sardari et al. (2012) suggested that the effect of nanosilver particles on the tissues may cause organ toxicity in rats. Accumulation silver nanoparticles showed tissue damages, bloodshed, cell necrosis and apoptosis in rats.

Skin

Silver nanoparticles are widely used in medicine, physics, material sciences and chemistry. Many medical products are coated or embedded with nanosilver, for example surgical instruments, bone prostheses and dental alloys. Being present in consumer goods, silver nanoparticles can easily penetrate the human body through different portals, for example, silver nanoparticles released from different surface coatings can readily be inhaled (Panyala et al. 2008) or can be directly from medical devices, such as catheters or dental and bone implants (Chen and Schluesener 2008). Silver nanoparticles present in dressings for burns and ointments are used for wound healing, nanosilver-based textiles and cosmetics (like antibacterial deodorants) as they can penetrate into skin (Arora et al. 2008; Samberg et al. 2010) and localize in stratum corneum and the upper layers of epidermis (Larese et al. 2009).

Digestive system

Nanoparticles can be entered into the body via oral route by water, food, cosmetics, drugs, drug delivery devices, etc. Shahare et al. (2013) assessed the oral exposure of silver nanoparticles on the mucosa of the small intestine in mice. The study revealed that significant decrease in body weight of mice in silver nanoparticles-treated mice. The main function of small intestine is absorption. Due to the loss of microvilli of enterocytes, the absorptive surface area of the intestine was markedly reduced which led to decrease in the absorption of nutrient materials resulting in a reduction in the body weight of mice.

Circulatory system

Tang et al. (2009) examined the ability of silver nanoparticles and silver microparticles to traverse the brain blood barrier. Silver nanoparticles crossed the blood brain barrier only after subcutaneous injection and they caused neuronal degeneration/necrosis. All effects were time dependent, reaching a plateau after 12 weeks.

The role of the cardiovascular system in silver nanoparticles distribution and discrimination in the body was subsequently examined. A high percentage of silver nanoparticles, but not microparticles, is translocated to the blood circulatory system after their subcutaneous administration and was deposited in all main organs (kidneys, liver, spleen, brain and lungs). Ultra structural observations confirmed silver nanoparticles accumulation in renal tubular epithelial cells, hepatocytes and neurons. Human erythrocytes when exposed to different concentration of starch coated silver nanoparticles (25–400 µg/ml) shows deleterious effects when compared to cells exposed to uncoated silver nanoparticles within 3 h of exposure (Asharani et al. 2011).

European perch (*Perca fulviatilis*) was treated with varying concentrations of silver nanoparticles and silver nitrate separately. From which it was found that silver nanoparticles-treated group did not show any adverse effect on basal metabolic rate, whereas European perch treated with silver nitrate alone resulted in significant increase in basal metabolic rate (Bilberg et al. 2010). Silver nanoparticles affect early development of zebra fish (*Danio rerio*). Developmental retardation, increased heart rates, neurodevelopmental effects, sluggish circulation, pericardial edema, tube heart and eye malformation are observed resulting from embryonic exposure to silver nanoparticles (Wu et al. 2010).

Respiratory system

Takenaka et al. (2001) observed the pulmonary and systemic distribution of inhaled ultrafine elemental silver (EAg) particles in rats. The inhaled silver nanoparticles were also observed in the liver, kidney, spleen, brain and heart in low concentrations.

Excretory system

In fischer F344 rats, more adverse effects including loss of body weight, changes in blood biochemical parameters, bile duct hyperplasia, fibrosis and accumulation of silver nanoparticles in kidney are observed in cells treated with 30, 125 and 500 mg/kg of silver nanoparticles (Kim et al. 2010).

Reproductive system

Silver nanoparticle accumulationalso affects the reproductive system. Roh et al. (2010) reported that accumulation of silver nanoparticles induced reproductive failure in *C. elegans* and that oxidative stress. Gromadzka-Ostrowska et al. (2012) tested the effects of different sizes and doses of nanosilver (silver nanoparticles) on male rats. Sperm count, germ cell DNA damage and seminiferous tubule morphometry were measured after the intravenously administered low dose of small silver nanoparticles. Silver nanoparticles also caused changes in sperm counts and the study suggested a genotoxic effect of low-dose small-size silver nanoparticles.

Apoptosis

Studies revealed that accumulation of nanoparticles very toxic to cell. Nanoparticles enter to the cell via endocytotic routes and cause various types of cell injury through free radical reactions. Gopinath et al. (2010) reported that small-sized uncoated silver nanoparticles (18 nm) at concentration 11 µg/ml, induced P^{53}-mediated apoptosis in baby hamster kidney (BHK21) and human colon adenocarcinoma (HT29) cells. Li et al. (2010) observed and reported embryonic toxicity in mouse blastocysts when exposed to silver nanoparticles (25 and 50 µM). Samberg et al. (2010) evaluated the toxicity of silver nanoparticles in human epidermal keratinocytes both in vitro and in vivo. Here the cells are treated with different concentrations of uncoated and carbon-coated silver nanoparticles separately. Dose-dependent decrease in viability of cells is observed in cells treated with uncoated silver nanoparticles, whereas no toxic effect is observed in the cells treated with carbon-coated silver nanoparticles. Arora et al. (2008) reported the reduced cell viability, oxidative stress, DNA damage and higher CASP3 activity in HT-1080 human fibrosarcoma cells (derived from dermis) and A431 human skin carcinoma cells (derived from epidermis) when treated with silver nanoparticles.

As with many substances at the nanoscale, the toxicity of nanosilver is greater than that of silver in bulk form; silver is comparatively more toxic than other heavy metals when it is in nanoparticle form (Braydich-Stolle et al. 2005). Physical characteristics of nanomaterials, such as their size, shape and surface properties, can exert a toxic effect that goes beyond that associated with their chemical composition (Brunner et al. 2006). For instance, Hussain et al. (2005) demonstrated that nanoparticles of silver produce reactive oxygen species (ROS), which may result in oxidative stress-mediated toxicity. Production of ROS, highly reactive molecules which include free radicals, can interfere with cellular metabolism, cause inflammation and damage proteins, membranes and DNA. Reactive oxygen species production is a key mechanism for nanomaterials toxicity (Nel et al. 2006). Chae et al. (2009) evaluated the toxic impact of silver nanoparticles on Japanese medaka (*Oryzias latipes*) and reported that exposure of Ag-NPs led to cellular and DNA damage, as well as carcinogenic and oxidative stresses, genes related to metal detoxification/metabolism regulation and radical scavenging action were also induced.

Silver and nanosilver are toxic

DNA damage

In adult zebra fish, there is evidence of the uptake of silver nanoparticles through the gills that caused silver nanoparticles-specific changes in gene expression and resulted in increased mortality. Increased mortality upon treatment with silver nanoparticles was observed in adult Japanese medaka (*O. latipes*), accompanied by induction of DNA damage (Wu et al. 2010). Treatment of rainbow trout (*O. mykiss*) with silver nanoparticles caused an increase in expression of cytochrome P450 1A2 (*cyp1a20)* in the gills (Grosell et al. 2000).

Conclusion

Every person is exposed to nanometer-sized foreign particles; we inhale them with every breath and consume them with every drink. In truth, every organism on Earth continuously encounters nanometer-sized entities. Nanoparticles are defined as a small object that behaves as a whole unit in terms of its transport and properties. Nanoscience is an emerging field that deals with interaction between molecules, cells and engineered substances such as molecular fragments, atoms and molecules. In terms of size constraints, the National Nanotechnology Initiative (NNI) defines nanotechnology in dimensions of roughly 1–100 nm. But in broader range it can be extended up to 1000 nm. Nanotechnology can be defined as the design, synthesis and application of materials and devices whose size and shape have been engineered at the nanoscale. It exploits unique chemical, physical, electrical and mechanical properties that emerge when matter is structured at the nanoscale. Silver has been valued throughout history for many of its properties that are useful to humans. It is used as a precious commodity in currencies, ornaments, jewelery, electrical contacts and photography, among others. One of the most beneficial uses of silver has been as a potent antimicrobial agent that is toxic to fungi, viruses and algae. Silver has long been used as a disinfectant; for example, the metal has been used in treating wounds and burns because of its broad-spectrum toxicity to bacteria as well as because of its reputation of limited toxicity to humans.

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