Volume 9, Issue 1, 2020, 824 - 829 ISSN 2284-6808
Letters in Applied NanoBioScience
https://nanobioletters.com/
https://doi.org/10.33263/LIANBS91.824829
Original Review Article Open Access Journal
Received: 10.01.2020 / Revised: 15.02.2020 / Accepted: 17.02.2020 / Published on-line: 19.02.2020

Toxicity and application of nano-silver in multi-drug resistant therapy

Geetanjali [1], Pramod Kumar Sharma [1], Rishabha Malviya [1, *]
[1]Department of Pharmacy, School of Medical and Allied Sciences, Galgotias University, Plot No. 02, Sector 17-A, Greater Noida, Gautam Buddha Nagar, Uttar Pradesh, India
*corresponding author e-mail address: ***rishabhamalviya19@email.com*** | Scopus ID 36542724200

ABSTRACT
Nano-silver toxicity is a major challenge in the field of nanotechnology and nanoscience. Silver nanoparticles have antibacterial activity against *gram-negative* and *gram-positive* bacteria. The level of nanotoxicity varies according to the size, shape, surface charge and cellular uptake. The size of nanoparticles influences their interaction and reactivity with cell membranes. Silver nanoparticles were investigated for the broad-spectrum antibacterial activities, especially against antibiotic-resistant bacteria. In the present scenario, pharmaceutical and biomedical sectors are facing the challenges of the continuous increase in multidrug-resistant human pathogenic microbes. The development of multidrug resistance has become a global issue with serious consequences in the management of infectious diseases caused by pathogenic bacteria. For the multi-drug resistant therapy, various combinations of antibiotics were used with silver nanoparticles. This review discusses the nanotoxicity and bactericidal potential of silver nanoparticles against the multi-drug resistant bacteria.
Keywords:*silver nanoparticles; toxicity; multi-drug resistant; bacteria; oxidative stress; gram-positive; gram negative; antibiotic; DNA damage; Applications.*

1. INTRODUCTION
In antibacterial applications, nonmaterial's can play a significant role mainly due to their wide surface area and physicochemical characteristics dependent on size/shape [1]. Nano-silver is the most promising antibacterial nonmaterial's, which has much wider antibacterial potential then bulk silver products.

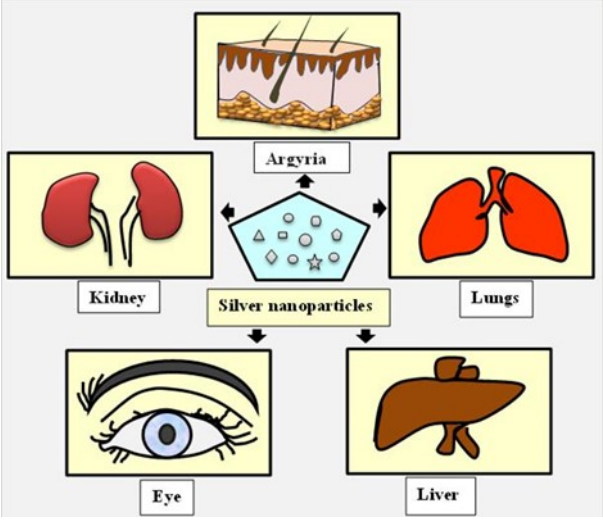

Figure 1. A schematic diagram silver nanotoxicity on various human organs.

In the study, Cameron *et al* focused the effects of nano-silver on the biological and cellular function of the cell. It could report the effects of nano-silver toxicity on cell or organism. The effects of nano-silver caused due to cellular uptake were oxidative stress, endoplasmic reticulum stress, hypoxic response, inflammation and mitochondrial endoplasmic reticulum. The suitable dose of nano-silver has effective for several applications like anti-bacterial, anti-fungal, anticancer and wound healing. Therefore, nano-silver *in vivo* studies against anti-cancer treatment can show that no adverse effect but the higher doses induce *in vitro* toxicity [2].

Silver nanoparticles suspension used for antibacterial activity against the drug-resistant pathogens (multi drug-resistant *P. aeruginosa*, ampicillin-resistant *E. coli* and erythromycin-resistant *S. aureus*). Silver nanoparticles bind to the surface of the cell membrane interface, penetrate and release silver ions. Further its inhibition of cell wall synthesis, protein synthesis and nucleic acid synthesis of the cell/organism. So, the bactericidal action of silver nanoparticles was determined against the multi-drug resistant bacteria [3].

The *in vitro* study of silver nanoparticles toxicity was carried out on rat liver and neuronal cells. The cytotoxic effect of silver nanoparticles toxicity mechanism includes reactive oxidative species generation, DNA toxicity and cytokine induction. In a few *in vivo* studies the adverse affect on the organism level, circulatory vulnerabilities, respiratory, central nervous, hepatic and dermal system. The mechanisms have investigated the uptake and fate of silver nanoparticles on living organisms [4].

Various studies and reports suggested that nano-silver may cause ill impacts on both the individual and the environment. Free silver ions have a damaging effect on all living beings including humans. Silver ions caused bluish-grey discoloration of the skin (argyria) or eyes (argyrosis), and exposure to soluble silver compounds may result in toxic consequences for liver and kidneys; irritation of the eyes, skin, respiratory and intestinal tract; and unfavourable changes in blood cells. Sharma *et al* used cubosomes and hexasomesnanocarries formulation for the controlled release of drug delivery system. The cellular uptake of nanoparticles could be an effect due to their size and shape. It concluded that the size and shape of nanocarries have a significant

effect on pharmaceutical and biomedical application [5, 6]. Figure 1shows nano-silver toxicity on various human organs.

2. NANO-SILVER TOXICITY RELATED TO SHAPE

Silver nanoparticles have been synthesized in many shapes including spherical, hexagonal, triangular and rod-shaped. According to the shape of nanoparticles, bactericidal activity is got influenced.

In the study, silver nanoparticles were used to resolve the problem of poor delivery and drug resistance. The development of anti-angiogenesis molecules to treat angiogenic diseases like rheumatoid arthritis, atherosclerosis, diabetic retinopathy etc. and also used for the cancer treatment. The results showed to develop effective cancer and angiogenic agents containing silver nanoparticles [7]. Rai *et al* was reported bacterial growth inhibition of silver nanoparticles over the different shapes. It could use the spherical, rod and triangular shape nanoparticles that synthesized against *E. coli* at different concentrations. It reported that the antibacterial activity of silver nanoparticles higher in triangular than the spherical and less active in rod shape particles [8]. In other studies also it was found that the shape of silver nanoparticles could affect the antibacterial activity. During a study, Pal *et al* were used liquid and agar plate systems on different shaped silver nanoparticles against *gram-negative* bacteria *E. coli*. The result demonstrates that the interaction of nanoparticles with cell causes structural changes and membrane damage leads the cell death [12]. In the study, Mcshan *et al* analyzed the molecular toxicity mechanism in the biological environment using nano-silver. The anti-proliferative activity of silver nanoparticles and presented a mechanism of toxicity. It reported the inhibition of cell proliferation, mitochondrial dysfunction and generates reactive oxidative stress [10]. Silver nanoparticles were synthesized in three different shapes like quasi-spherical, cubic and star-shaped. Silver nanoparticles with cubic and star-shaped induce the cytotoxicity and the quasi-spherical were not toxic. The quasi-spherical shaped nanoparticles show the anti-biofilm activity against *S. aureus*, Methicillin-resistant SA and *Pseudomonas aeruginosa.* It concluded that cubic and star-shaped silver nanoparticles have limited stability and toxicity. The suspension of quasi-spherical nanoparticles shows better stability and no loss in anti-biofilm activity. Quasi-spherical nanoparticles show ideal shape due to their rapid synthesized with no toxic effect and used for topical treatment for biofilm-related infections [11]

From the literature survey, it can be concluded that the shape of silver nanoparticles have different toxicity levels. The non-spherical shape shows more bactericidal activity than the spherical-shaped nanoparticles.

3. NANO-SILVER TOXICITY RELATED TO SIZE

Size can also play a significant role in silver toxicity and influences their interaction and reactivity with cell membranes. Silver nanoparticles have a wide size range of 5 nm to 50 nm but having size 25 nm possessed maximum antibacterial activity.

Rai*et al* used silver to over the resistance to drug/antibiotics in human pathogens. The bactericidal effect of silver nanoparticles against both *gram-positive* and *gram-negative* bacteria had strong activity. The effects of silver nanoparticles size produced the electronic effect that could show interact with the bacterial surface. The analysis reported the smaller than 10 nm and 25nm nanoparticles showed higher antibacterial activity [8]. In the study Choi *et al* reported smaller size silver nanoparticles with a high surface area that could be easily entered into the cell due to the cell membrane interaction. Further, the results of 5 nm silver nanoparticles were more toxic to bacteria than the other particle size ranges (e.g. 10, 15 nm). Small size particles transport inside the membranes and cause of cellular damage and constituents and metabolism [13]. H2-silver nanoparticles (18 nm) were reported to be least toxic among the silver nanoparticles investigated on the basis of particle size, as the prior study showed a reduction in toxicity with a rise in silver nanoparticles particle size [14]. Silver nanoparticles have the protein/ membrane toxicity and oxidative damage but do not cause DNA damage. Hwang *et al* demonstrated that that silver nanoparticles led to silver ions and consequently superoxide radicals being created. Therefore, it concluded the synergistic toxic effect on the cells due to the disruption of the cell membrane [15].

Size is also responsible for the penetration of silver nanoparticles in *gram-positive* bacteria the smaller sized which can inhibit the non-resistant and drug-resistant bacteria. Lower concentration of silver nanoparticles should completely inhibit *E. coli* and *S. aureus* In case of size, it has been concluded that smaller the sized nanoparticles provide a greater percentage of interaction as compared that the range of silver nanoparticles toxicity is inversely proportional to size.

4. NANO-SILVER TOXICITY RELATED TO SURFACE CHARGE

Surface charge of silver nanoparticles can affect the interaction with the cell membrane. Several studies were reported that silver ions caused toxicity on both humans and the environment.

Toxicity impact in cells could be determined by the surface charges of silver nanoparticles. For example, Zhang *et al* had studied that positive surface charge of these nanoparticles makes them more suitable, allowing them to stay in the bloodstream for a longer time compared to negatively charged nanoparticles, which is a major route for anticancer drug administration [7]. In another study, Choi *et al* had reported nanoparticles that have a size less than 5nm carried no charge could easily enter inside the cell membrane as compared to silver ions [13]. The surface charge has been analyzed by E.L. Badawy *et al* that the BPEI- silver nanoparticles having more toxic effects [14]. The mode of action of silver was assumed to depend on silver ions, which heavily inhibit bacterial growth by eliminating respiratory enzymes and elements of electron transport and interfering with DNA functions [16]. Silver ions were highly reactive, binding to molecules of sulphur and phosphate. Inflammatory cytokines such as (interleukin) IL-1, IL6, IL-12, TGF-β (transforming growth factor-

β) and others were influenced by high- dose (1 mg/kg) oral administration of silver nanoparticles [17].

5. NANO-SILVER TOXICITY RELATED TO CELLULAR BEHAVIOUR

The shape of nanoparticles influences how easily they are taken into cells, the rod-shaped nanoparticles having a lower cellular uptake than spherical ones.

In a certain study, Mcshan *et al* analyzed that the ingestion of silver nanoparticles can be better in the body. It absorbed from the stomach duct and enters into the portal vein. Further, they reach the liver cells and cause toxicity [10]. The various mammalian cell structures were evaluated by Nunez *et al* including rat liver cells, human keratinocytes and cultures of fibroblasts, and human spermatogonial stem cells and the toxicity of silver nanoparticles has been explored. A high dose of nano-silver induced oxidative stress (reactive oxygen species liberation) as a cytotoxicity mechanism in vitro [16]. Figure 2 shows the schematic diagram of the toxicity mechanism of nano-silver.

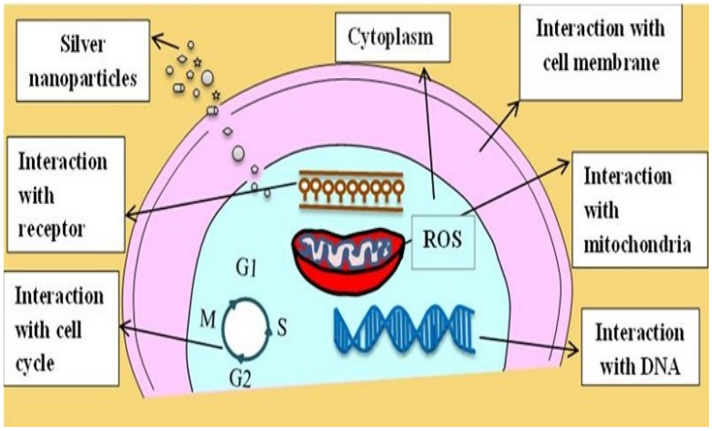

Figure 2. A schematic diagram of the toxicity mechanism of nano-silver.

6. APPLICATION IN MULTI-DRUG RESISTANT THERAPY

A Multi-drug resistant bacterium is remaining a great challenge. The infections of resistant strains are increased globally day by day. Nanotechnology seems to be a better solution due to its flexible antimicrobial properties. The combination of antibiotics and natural antimicrobial compound provide a great path to counter multi-drug resistant bacteria. The toxicity issue could be overcome by the combined use of plant-based antimicrobials and nanoparticles. The basic mechanism of action in bacteria includes the inhibition of film formation and other processes [18]. Infections caused by drug-resistant microorganisms show a significant increase in mortality, morbidity and cost-related prolonged treatments [3].

The bonding reaction response between antibiotics and silver nanoparticles can cause the synergistic effect was reported by Fayaz *et al* They tested a number of antibiotics against all test strains; the largest proportion of fold was achieved by ampicillin. They analyzed that the fold increase of percentage in ampicillin along with against *gram-positive* and *gram-negative* bacteria were almost analogous. If silver nanoparticles have been taken alone, inhibition of bacteria was difficult in *gram-positive* [19]. In another study, Franci *et al* demonstrated the individual and combined effects with silver nanoparticles against seven classes of antibiotics on seven pathogenic bacteria. They show increment according to the class of antibiotics used such as aminoglycosides showed a small increment as compare to gentamicin against *Acinetobacter baumannii* and kanamycin against *P. aeruginosa.* Amoxicillin against *P. aeruginosa* enhancement of anti-bacterial effect and penicillin showed a 3-fold increase of efficiency against Streptococcus mutans. Vancomycin has been reported to have the largest overall synergistic activity combined with silver nanoparticles relative to all other antibiotics, with a 3.8-fold rise in activity against *Enterobacter aerogenes* [20]. The silver nanoparticles existing in these scaffolds are responsible for the toxicity. While in another study Madhumathi *et al* have been found that the impact on wound healing was doubtful, as prior batch have nano-silver containing wound dressings was cytotoxic *in vitro* and *in vivo* studied [21].

Silver nanoparticles with broad-spectrum antibiotics have been used against the antimicrobial activity. They have used *Pseudomonas aeruginosa* and *Staphylococcus aureus* two multi-drug resistance strains which can be isolated from the mastitis-infected goat's milk samples. The effect of silver nanoparticles on different bacterial strains is induced loss of cell viability, inactivates the respiratory chain dehydrogenases and also inhibits respiration and growth of cells. The multidrug resistance bacteria treated by the use of synthesized silver nanoparticles against the anti-microbial agents. [22]

The study uses a combination of different antibiotics with silver nanoparticles that reported the antimicrobial agent synergistic action. Silver nanoparticles seem to be effective against drug-resistant strains of Methicillin-resistant *staphylococcus aureus*, extended-spectrum beta-lactamases, vancomycin-resistant enterococcus, and multi-drug resistant *Pseudomonas aeruginosa*. Therefore, it provides a potential antimicrobial effect against all drug-resistant strains and has a viable therapeutics candidate [23].

The carboxyl methyl tamarind polysaccharides-capped silver nanoparticles prepared by 'green-synthesis' which has better properties than the presently available silver nanoparticles. These silver nanoparticles inhibit the growth and biofilm development of bacterial strains of *gram positive (B. subtilis)* and *gram negative (E.coli and Salmonella typhimurium*). The multi-drug resistance microbes with limited cytotoxicity towards mammalian cells and has a potential biomedical application of capped silver nanoparticles [24]. Singh *et al* used *Acinetobacter baumannii* pathogen and their mechanism of action for the demonstration of silver nanoparticles antibacterial activity. The various antibiotics such as tetracycline, doxycycline, and erythromycin have the property to disrupt the cell wall to kill bacteria and produce reactive oxidative species. The surface interaction of small-sized silver nanoparticles exhibits the greater microbicide activity compared to larger silver nanoparticles [25].

They use broad-spectrum antibiotics with silver nanoparticles against the antimicrobial activity. In the formation of silver nanoparticles, non-hazardous solvents are to be used and with the help of reduction and capping agents it can be formed. Silver nanoparticles used against the pathogenic superbugs which could be exhibited by silver combination therapy [26].

Shi *et al* use the visible light to induce the release of silver ions from silver nanoparticles and to promote the silver nanoparticles to induce reactive oxygen species in *E. coli*. The light excited the silver nanoparticles that induce the protein aggregation in *E. coli.* The indication of the bactericidal ability of silver nanoparticles relies on the light-catalyzed oxidation of cellular proteins. The fluorescence spectra bind directly to the proteins, and then it absorbs the light energy and transfers to proteins. The oxidation of proteins leads to the death of bacteria. The mechanism work to the antimicrobial application of silver nanoparticles as the efficacy of light improved. It significantly contributes to the multidrug resistance bacteria treatment [27].

Another study found that the minimum inhibitory concentration against different strains of *S. aureus*and *E. coli* is 32µg/ml and 16 to 64µg/ml respectively. The *M. koenigii* aqueous extract used in the synthesis of silver nanoparticles and due to the present growth inhibition of all strains *S. aureus* is 32 µg/ml. The activity of *gram-positive* and *gram-negative* multi-drug resistant bacteria exhibited due to *M. koenigii* silver nanoparticles. Therefore, topical applications against multi-drug resistant bacteria are to be used for antibacterial drug discovery [28].

The use of antibiotics drug combination with green approach synthesized silver nanoparticles against multidrug-resistant bacteria. In another study using an alcoholic extract of *Phyllanthus emblica* against *E. coli*, *S. aureus* and *P. aeruginosa* that exhibits the antimicrobial activity. Further, the copolymer biomaterials synthesized with high antibacterial activity against *E. coli* and *S. aureus.* These all reports concluded that the biogenic silver nanoparticles are used in combat against multidrug resistant bacterial infection [29].

Silver nanoparticles synthesized by *Ocimum gratissimum* leaf extract from bio-reduction process. The minimum inhibitory concentration and minimum bactericidal concentration against multi-drug resistant *E. coli* found 4 µg/ml and 8 µg/ml but it was higher in *S. aureus* resistant strain is 8 µgml and 16 µg/ml respectively. A similar concentration of both *E. coli* and *S. aureus* strain is inhibiting the biofilm formation. The treatment of silver nanoparticles of *E. coli* and *S. aureus* damages the cell surface and produces the reactive oxygen species and gives a potent antimicrobial activity [30].

In the study, silver nanoparticles are used against methicillin-resistant *Staphylococcus aureus* that isolated from the patients. The minimum inhibitory concentrations and minimum bactericidal concentration values were found to be low so, it indicates the very good bacteriostatic and bactericidal activity [31].

The extract of *Neurada procumbens* reducing agent is used in the synthesis of silver nanoparticles. The multi-drug resistant *gram-negative* bacteria are *Klebsiella pneumoniae*, *Acinetobacter baumannii* and *E. coli*. The three resistant bacterial strains used to determine the antimicrobial activity with silver nanoparticles. The great antibacterial activity against the multi-drug resistance has clinically isolated from the different patient samples [32].

The combination therapy of silver nanoparticles, blue light and antibiotics are used against infections caused by Methicillin-resistant *Staphylococcus aureus*. The triple combination used antibiotics such as vancomycin for providing the ineffective against Methicillin-resistant *Staphylococcus aureus*. Therefore, it used for fast-growing drug-resistance with the slow development of new antimicrobial agents. The application of triple therapy is used in patient infection ad overcome the harmful side effect and optimize the synergistic effects [33].

In the study, Chen *et al* detected the *Pseudomonas aeruginosa* in the patient lungs. The treatment options are limited in adult patients having multi-drug resistant strains. The broad-spectrum antimicrobial agent silver which effective in high doses to infections. The effective delivery of an antimicrobial agent to demonstrated the synergistic activity of the silver/minocycline combination against *P. aeruginosa* [34].

The biofilm formation against the multi-drug resistant *Staphylococcus aureus* is a major health concern. The great challenge is to treat the infections caused by a microorganism. New approaches have been developed, such as small molecules, enzyme treatments that weaken the biofilm structure, antibodies and vaccines that target any important stage of biofilm formation [35].

The green synthesis nanoparticles produced by *Bacillus mojavensis* having antibacterial activity against multidrug-resistant pathogens. Silver nanoparticles exhibits activity against *E. coli*, *Klebsiella Pneumonia*, *Acinetobacter sp.* and *Pseudomonas aeruginosa* [36].

The nanoparticles synthesized by *Corchorus capsularis* leaf extract and use for the treatment of drug-resistant *P. aeruginosa* and *Staphylococcus aureus*. The treatment of coagulase-negative staphylococci is isolated from post-surgical wound infections. The antibacterial efficacy of silver nanoparticles increases with the concentration and found to be highly toxic to the bacterial strains. The silver nanoparticles suspension has shown the effective treatment of wound infections [37].

In the study, *staphylococcus aureus* infectious agent develops on the skin infection that is related to antibiotic resistance such as burn wounds. Multi-drug therapy can control the use of antibiotic resistance. The *Droserabinata* extract metabolites affect the antibacterial agent's *staphylococcus aureus* and biofilm. The synergistic effects create between *Drosera binata* extract and silver nanoparticles. Therefore, no cytotoxic effect on human keratinocytes has been analyzed [38].

The bactericidal activity of silver nanoparticles against pathogenic bacteria was demonstrated and the Ag^+ is limited. The broad spectrum of antimicrobial drugs to be used against multidrug-resistant microbial pathogens such as Methicillin-resistant *S. aureus*, Staphylococcus epidermidis, Vancomycin-resistant *Enterococcus faecium* and *Klebsiella pneumoniae*. The antimicrobial properties of silver nanoparticles exhibit reactive oxygen species (ROS) including hydrogen peroxide [39].

Silver nanoparticles combinations with anticancer drugs are used against the multidrug-resistant cells. They can observe the increased drug efficacy and cytotoxicity regarding all the combinations. The silver nanoparticles are playing important tools for improving the multi-drug resistant cancer chemotherapy [40].

In a study, Liu *et al* used cell-penetrating peptide with modified silver (mean size 8 mm) for cancer treatment. The modified silver used to enhance intracellular delivery against both multi-drug resistant cells and non- resistant cells. It was based on the size exclusion effect of nanoparticles which can significantly effect the tumor cells compared with modification nanoparticles. For further

confirmation, the modified nanoparticles dose 1 nmol/kg compared with the effective dose (4.3 µmol/kg) of doxorubicin. They showed the inhibition of tumor growth and significantly reduced adverse *in vivo* toxicity. It concluded that the nanoparticles with the modification showed enhanced multi-drug resistant treatment for cancer [41].

Silver nanoparticles synthesized by the *Murraya koenigii* leaf extract against the antibacterial activity. Antibiotics with silver nanoparticles against pathogenic bacteria like *E. coli*, *S. aureus* and *P. Aeruginosa*. The effect of silver nanoparticles with various antibiotics like gentamicin and tetracycline showed different activity. The results showed the maximum activity of gentamicin against *E. coli* followed by *P. Aeruginosa* and *S. aureus.* The tetracycline show maximum activity against *S. aureus* followed by *P. Aeruginosa* and and *E. coli* [42].

7. CONCLUSION

From the literature survey, nano-silver toxicity is the major and concern field of nanoscience and technology. The silver nanoparticles synthesized by the reduction process that created non-expensive and eco-friendly environment. The study demonstrated that silver nanoparticles cause toxicity due to factors like size, shape, surface charge and cellular behavior. The effect of toxicity on cells causes oxidative stress, mitochondrial damage, reactive oxidative species, and inflammation. The applications of silver nanoparticles have found in several fields such as drug delivery, gene delivery and cancer therapy. The broad-spectrum antibiotics used with the silver nanoparticles against infectious diseases caused by pathogenic bacteria.

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9. ACKNOWLEDGEMENTS

Authors are highly thankful to Department of Pharmacy, School of Medical and Allied Sciences, Galgotias University, Greater Noida, India for providing library facilitates.