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GREEN NANOTECHNOLOGY A BOON IN SILVER NANOPARTICLE (AgNPs) SYNTHESIS- CERTAIN ASPECTS OF AgNPs BIOMEDICAL APPLICATIONS AND AN OUTLINE OF ITS TOXICOLOGICAL IMPACTS - A MINIREVIEW

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ABSTRACT

Silver nanoparticles due to its vast applications in medical and physiochemical field have received global attention. Earlier they were synthesized by chemical and physical methods which due to their shortcoming are replaced by green synthesis using microorganisms and plants. Green nanotechnology has made the synthesis of nanoparticles cost effective, hazard free, faster and eco-friendly. Silver is used as an antimicrobial agent since long back; with the advent of antibiotics there use was decreased. Due to the rise in drug resistance, the scientists are focusing on the use of silver due to its oligodynamic action with antibiotics/drugs to enhance their efficacy. Apart from this due to its antimicrobial activity it is used in stents, catheters, orthodontic and orthodontic implants, water purification systems, cosmetics, agriculture, paints etc. It is expected that the use of silver nanoparticles will escalate in future due to its various antimicrobial properties which indicate huge production and usage of silver nanoparticles. This large scale production and usage will lead to toxicological impacts on the humans, animals and environment; the area that still needs exhaustive research. In this review paper we are exploring the potential of different biological sources for green synthesis of silver nanoparticle, their applications and outline the toxicological effects of excessive use of silver nanoparticles in future.

KEYWORDS: nanotechnology, nanoparticles, silver, microorganisms, green synthesis, toxicity.

BACKGROUND

Nanotechnology has become one of the most important technologies in the area of science, which deals with the manufacture, manipulation, and application of structures by controlling shape and size at nanoscale.[1] Nanomaterials have been used unknowingly for thousands of years and Silver has been known, for more than 4000 B.C.E. for its antimicrobial applications. Persian kings insisted on drinking water only out of silver vessels, for their ability to preserve fresh water. In 1800s Silver nitrate was used for the treatment of ulcerations and infected wounds and to prevent gonococcal ophthalmic infections in newborns and was ingested for the treatment of stomach ulcers. Doctors used silver sutures and wire, silver wire was used to close vesicovaginal fistulae in post-partum women when closure with silk sutures had failed.[2] Prior the discovery of antibiotics silver leaf were used to treat infections during world war I, colloidal silver was used in hospitals as an bactericidal agent for at least 1200 years.[3]

The silver in its ionic form is noxious for the micro-organisms and therefore having multiple applications in medical field.[4] Silver in its nitrate form induces strong antimicrobial effect but when silver nanoparticles (AgNPs) are used the surface area exposed to different types of microbes increases substantially.[5] The attractive and unique physiochemical properties of nano silver makes them more effective and highly in demand for infinite use in various fields. The distinctive feature of AgNPs is that they do not induce modification on living cells and, so, are unable to cause microbial resistance. Literature review give an insight of applications of silver nanoparticles in medicine, agriculture, biosensors, cosmetics, food preservation, water purification, energy generation, antimicrobial activities, targeted drug delivery, etc.

Usually silver nanoparticles that are used are of 1–100 nm size which was synthesized by two approaches “Top-down” and “Bottom-up”. In “Top-down” approach bulk material breaks down into fine particles by size reduction method using various techniques like Pulse laser ablation, evaporation–condensation, ball milling, sputtering, pulse wire discharge method etc. In “Bottom-up” approach atoms combines and grow into particle of nanoscale by chemical & biological method. Various chemical methods are used for the fabrication of nanostructure materials such as controlled precipitation, sol–gel synthesis, hydrothermal reactions, sonochemical reactions, reverse micelles and micro-emulsion technology, hydrolysis and thermolysis of precursors. The physical and chemical approach demands lot of energy, high temperature, pressure, uses harmful chemicals, time consuming, less productive and non eco-friendly process so scientists focused on Biological synthesis of nanoparticles which entail less energy, lesser time, cost effective and eco-friendly process.[6] The biological synthesis or green synthesis of silver nanoparticles using plants, microorganisms like bacteria, fungi is an alternative to physical and chemical synthesis of nanoparticles in an ecofriendly way. Hence this review focuses on the green synthesis of silver nanoparticles its applications and what all will be the harmful impact of use of these nano particles on large scale when they will enter the environment.

Biological synthesis of nanoparticles

Microorganism as nanofactories holds enormous potential as cost-effective, ecofriendly, non-toxic, chemical free and peripheral energy free method of nanoparticles synthesis giving rise to an era of "Green Nanotechnology".

Microbes have the capability to accumulate and detoxify heavy metals with the help of diverse Reductase enzymes produced by the microorganisms against heavy metal toxicity which are able to reduce metal salts to metal nanoparticles with narrow size distribution and less polydisperity (Fig: 1). In last few years various bacteria, fungi, yeasts and plants are exploited for the extra- and intracellular synthesis of silver nanoparticles.

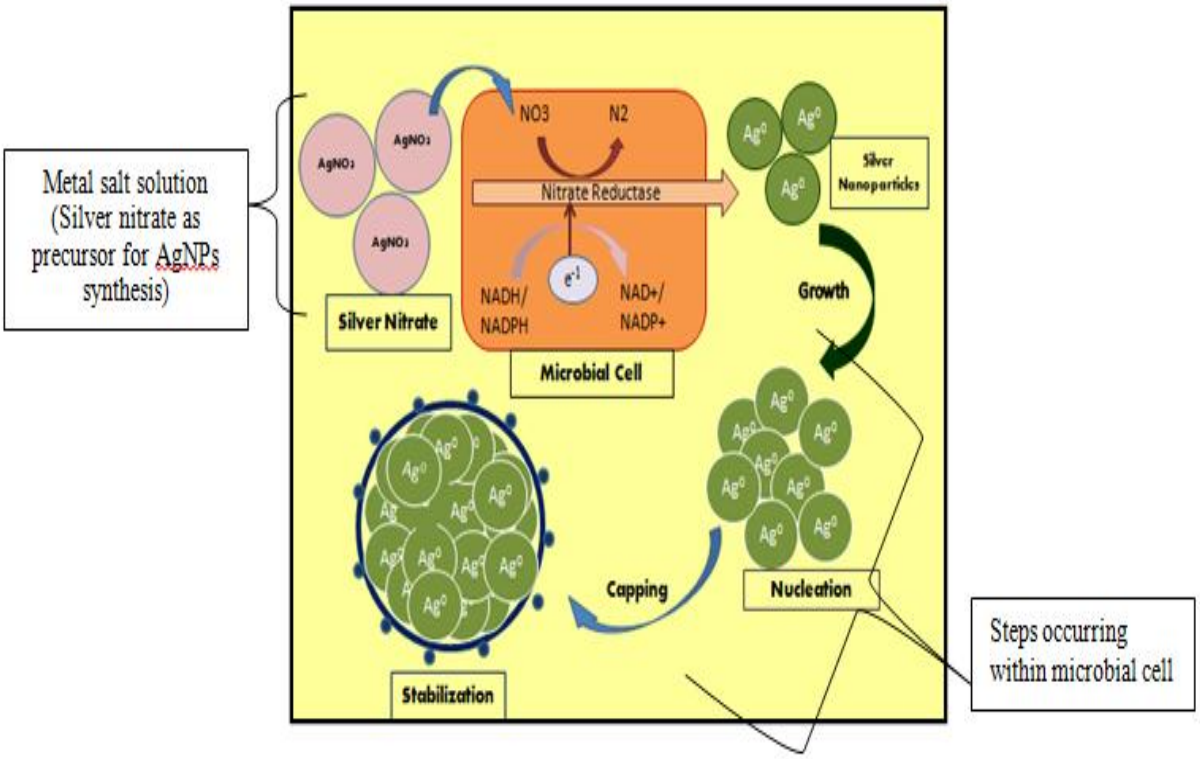


Fig: 1 Proposed Intracellular mechanism of the bioreduction and stabilization of nanoscale particles by nitrate reductase enzyme.

Extracellular synthesis is preferred over intracellular as it eliminates the downstream processing steps required for the recovery of nanoparticles. The mechanistic steps involved in the extracellular and intracellular synthesis of nanoparticles is demonstrated in Fig: 2 where intracellular synthesis requires extra steps in breakage of microbial cell wall to release the nanoparticles. The shape and the size of the nanoparticles can be controlled by optimizing the temperature and pH of the medium of microbial growth. Furthermore metal-resistant genes, proteins, peptides, enzymes, reducing cofactors, and organic materials have noteworthy role by acting as reducing agents. This biological synthesis endow natural capping to the nanoparticles preventing there agglomeration, helping them to remain stable for long time.[7]

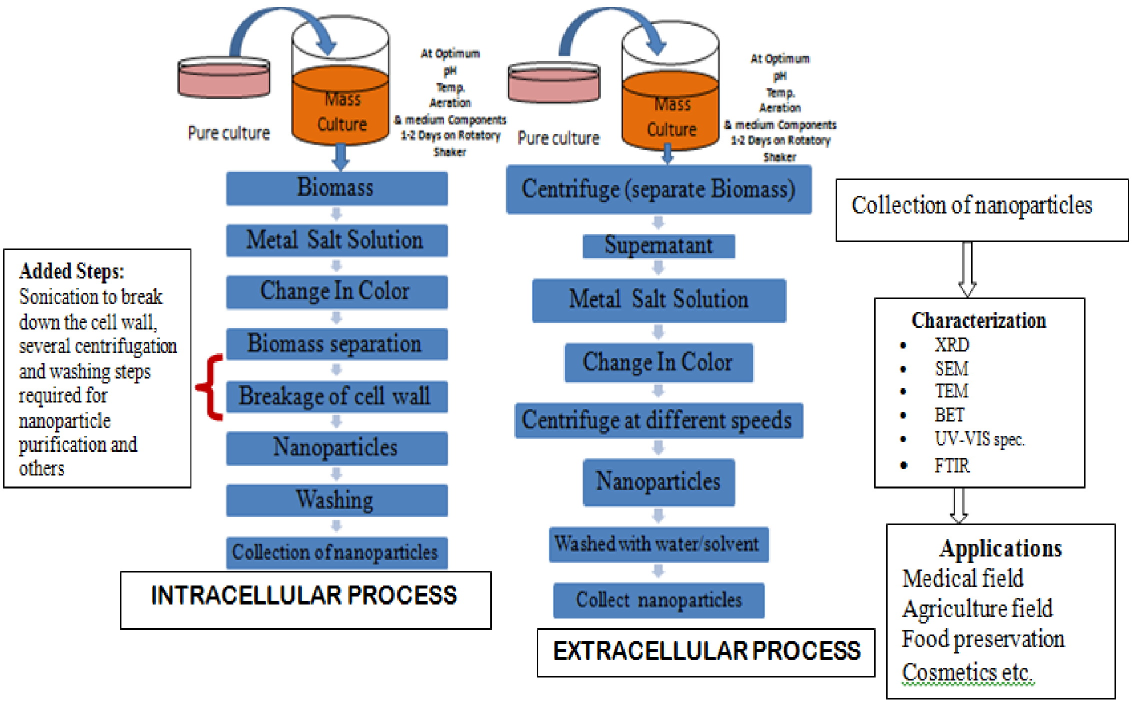


Fig 2: ***Mechanistic steps of Intracellular and extracellular silver nanoparticle synthesis using microorganisms.***

Bacterial Synthesis of AgNPs

Number of bacteria are identified which are used to prepare nanoparticles of industrial importance. Klaus et al. (1999) [8] reported the synthesis of AgNPs which were 200 nm in diameter having well defined composition and shape using silver resistant bacterial strains *Pseudomonas stutzeri AG259*. Shivaji et al. (2011)[9] used culture supernatants of *psychrophilic* bacteria whereas Kalimuthu et al. (2008)[10] showed the synthesis of AgNPs by *Bacillus licheniformis*. AgNPs were synthesized by Nanda and Saravanan (2009)[11] using culture supernatants of *Staphylococcus aureus*. To synthesize AgNPs quickly the culture supernatants of various gram negative bacteria from *Enterobacteriaceae* family can be used. Malarkod et al. (2013)[12] showed the rapid and high fabrication of silver nanoparticles by the optimizing culture of *Bacillus sp*.

Researchers are focusing on the use of bacteria for the green synthesis of nanoparticles due to their profusion and adaptation to extreme conditions, cost effectiveness and suitability for large scale synthesis.[13] The drawback is pathogenecity of few bacteria in use, slow synthesis rate and the limited number of sizes and shapes obtain as compare to conventional methods.[14]

In such condition fungi can be a suitable alternative for nanoparticle production as they secrete higher amount of protein that amplify the production of nanoparticle and fungi, also the scale up and downstream processes are very easy that makes it cost-effective and it has larger mycelia surface area than bacteria have.[15]

Mycosynthesis of AgNPs

Bioaccumulation ability, tolerance, high binding capacity, high rate of reaction, high yield production and intracellular uptake makes fungi potential organisms for the synthesis of metallic nanoparticles.[16] Fungi secrete enormous enzymes which are utilized to reduce metal salt solution to prepare silver nanoparticles.[17] Species like *F. oxysporum*, *Aspergillus flavus*, *Cladosporium cladosporioides*, *Penicillium fellutanum*, *Aspergillus fumigates*, *Aspergillus terreus* are identified as potent AgNPs producers along with others.[14] Fungi based green synthesis was intracellular until Ahmad et al. (2003)[18] studied extracellular formulation of AgNPs, he also demonstrated that secreted enzymes are responsible for the reduction of silver nitrate and its conversion into silver nanoparticles. Extracellular synthesis is valuable as formulated nanoparticles would not bind to biomass eliminates the downstream processing steps like sonication to break down the cell wall, several centrifugation and washing steps required for nanoparticle purification, and others.[14] Mycosynthesis of nanoparticles occurs by three possible mechanisms: nitrate reductase action; electron shuttle quinones; or both.[19]

Some researchers have investigated the use of yeasts for the biogenic synthesis of the nanoparticles as it possesses the inherent capability to absorb and accumulate high concentrations of toxic metal ions from their surroundings. Yeast uses various detoxification mechanisms viz. bio-precipitation, chelation, and intracellular sequestration to tolerate metal toxicity. Yeasts have been widely investigated for the extracellular synthesis of the nanoparticles on a large scale, with straightforward downstream processing.[15]

The Table: 1 demonstrates the microorganisms used to produce silver nanoparticles.

Table: 1 Green Synthesis of AgNPs using Microorganisms – *Precursor: Silver nitrate ($AgNO_3$)

S.No.	Microrganism	Average size (nm)	Reference
Bacteria			
1.	*Cyanobacteria Spirulina platensis and actinobacteria Streptomyces spp. 211A*	7–15	[71]
2.	*Aeromonas sp. THG-FG1.2*	8–16	[72]
3.	*Serratia nematodiphila*	10–31	[73]
4.	*Pseudomonas putida NCIM 2650*	70	[74]
5.	*Escherichia coli DH5a*	10–100	[75]
6.	*Lactobacillus casei subsp. Casei*	25–50	[76]
7.	*Actinobacteria*	5–50	[77]
8.	*Bacillus sp.*	5–15	[78]
9.	*Vibrio alginolyticus*	50–100	[79]
10.	*Marine Ochrobactrum sp*	38–85	[80]
11.	*Exiguobacterium mexicanum*	5–40	[81]
12.	*Endosymbiotic Bacterium*	10–60	[82]
13.	*Bacillus subtilis (MTCC441)*	10–100	[83]
14.	*Rhodococcus spp.*	5–50	[84]
15.	*Pseudomonas Antarctic*	12.2 ±5.7	[9]
Fungi			
16.	*Humicola sp*	5–25	[85]
17.	*Penicillium citrinum*	109	[86]
18.	*Endophytic bryophilous*	25–50	[87]
19.	*Aspergillus niger, Fusarium oxysporum and Alternaria solani*	20	[88]
20.	*Schizophyllum commune*	51–93	[89]
21.	*Trichoderma harzianum*	34.77	[90]
22.	*Fusarium acuminatum*	13	[91]
23.	*Pestalotia sp*	12.40	[92]
Yeast			
24.	*Yarrowia lipolytica NCYC789*	15	[93]
25.	*Candida utilis NCIM 3469*	20–80	[94]
26.	*Saccharomyces cerevisiae*	2–20	[95]
27.	*Pichia pastoris*	70–180	[96]
28.	*Cryptococcus laurentii; Rhodotorula glutinis*	15–35	[97]

Phytonanotechnology for AgNPs synthesis

The use of plants and plant extract in green synthesis of AgNPs has stimulated as it is locally available, eco-friendly, cost effective, easily accessible, non-pathogenic, single step and safe to handle method and have a large range of metabolites that can advance the reduction of Ag ion. It is studied that green synthesis using plant and plant extracts appears to be faster than other microorganisms, such as bacteria and fungi and synthesize nanoparticles using universal solvent, water, as reducing medium.[20] The plant parts like roots, latex, stem, seeds, fruits, leaves and their extracts are being used for nanoparticle synthesis.[21] The active agent presents in these parts and the plant extracts, which makes the stabilization and reduction possible incorporate biomolecules which act both as reducing and stabilizing agent that produce stable and shape-controlled nanoparticles. Metabolites which influence the reduction and capping of the nanoparticles are terpenoids, polysaccharides, phenolics, alkaloids, flavones, amino acids, alcoholic compounds enzymes, and proteins. Similarly, chlorophyll pigments and quinal, methyl.

chavicol, linalool, eugenol, ascorbic acid, theophylline, caffeine and other vitamins have also been explored.[22] According to Hussein (2014).[23] review during the plant-mediated synthesis of metal nanoparticles, all alcohol, aldehyde, phenol and flavonoids present in the plant extract are oxidized into an aldehyde, carboxylic acid, ketone, and flavones respectively, and the metal ions are reduced to metal nanoparticles. The parameters which influences metal nanoparticle formation after extract selection are the concentration of the extract, temperature, metal salt, pH, and contact time.[24]

Silver nanoparticles are synthesized using *Bunium persicum (*black cumin*)* seeds extract, *Hamamelis virginiana* leaf extract, *acinaciformis* extract, *Psychotria nilgiriensis* leaf extract, *Rubus ellipticus* (Himalayan raspberry) leaf extract, *Phyllanthus acidus L.* (gooseberry) fruit extracts, *Euphorbia heterophylla* (fireplant)leaf extract, *Carpobrotus acinaciformis extract*[13] *Ananas comosus* (pineapple juice), *Argemone mexicana* leaf extract, *Azadirachta indica* (Neem) and *Triphala* extract[14] and fruit extract of *Malus domestica* (apple).[25] The method of synthesis of nanoparticles using plants is given in the following Fig: 3.

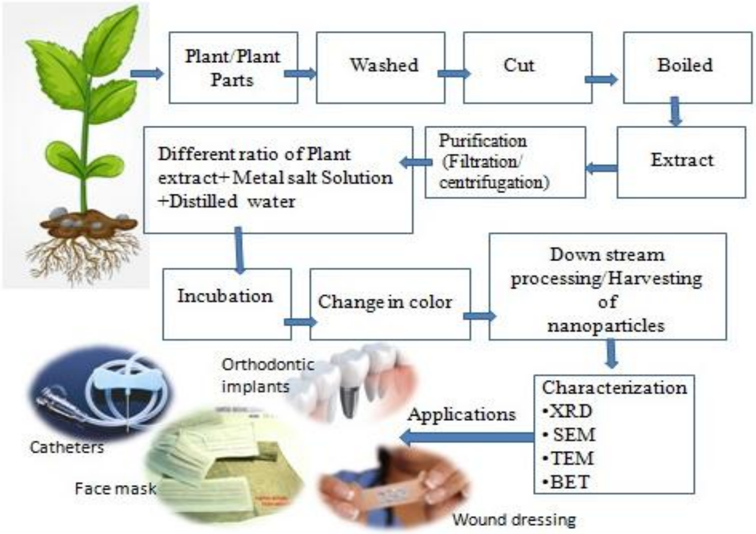


Fig: 3 Steps of synthesis of silver nanoparticles using plants.

Synthesis of Ag-NPs by using algae

Recent literature reports the use of algae like *Porphyra vietnamensis*, *Chaetomorpha linum*,*Chlorella vulgaris*, *Sargassum plagiophyllum*, *Laminaria japonica* etc. for silver nanoparticles synthesis. Researchers are exploring marine algae as nanofactories due to the presence of vast biologically active compounds and secondary metabolites that help in the conversion of metal salts into nanoparticles. The AgNPs synthesize via marine algae has antibacterial, antiplasmodial activity and methylene blue degradation ability.[15] Spirulina platensis cell extracts were used by Ahmed et al. (2016)[26] to synthesize AgNPs which were cost effective, non toxic, economically viable and environmentally benign. The Table: 2 is a list of plants used for silver nanoparticle synthesis.

Table 2: Green synthesis of silver nanoparticles by different researchers using plant extracts.

S.No.	Plant	Plant part	Average size (nm)	Reference
1.	*Aloe vera*	Leaves	50–350	[98]
2.	*Vitis vinifera*	Fruit	30–40	[99]
3.	*Rheum palmatum*	Root	121 ± 2	[100]
4.	*Excoecaria agallocha*	Leaves	20	[101]
5.	*Tagetes erecta*	Flower	10–90	[102]
6.	*Orange*	Peel	91	[103]
7.	*Justica adhatoda*	Leaves	11–20	[104]
8.	*Eucalyptus leucoxylon*	Leaves	50	[105]
9.	*Oak*	Fruit	40	[106]
10.	*Chrysanthemum indicum L*	Flower	37.71–71.99	[107]
11.	*Ocimum tenuiforum, Azadirachta indica and Musa balbisiana*	Leaves	Up to 200	[108]
12.	*Vitex negundo*	Leaves	60	[109]
13.	*Pithophora oedogonia*	Algal extract	34.03	[110]
14.	*Sida acuta and Artemisia annua*	Leaves	-	[111]
15.	*Calotropis procera*	Latex serum extract	12.33	[112]
16.	*Datura metel*	Leaves	5–50	[113]
17.	*Allium sativum*	Leaves	4-22	[124]
18.	*Cocous nucifera*	Inflorescence	22	[115]
19.	*Tea extract*	Leaves	20-90	[123]

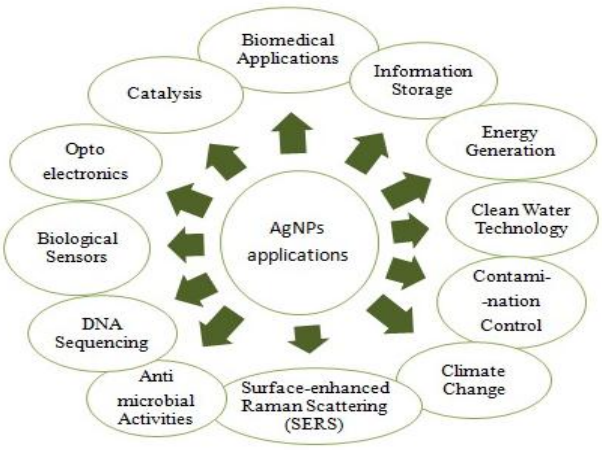
20.	*Pistacia atlantica*	Seeds	10-50	[116]
21.	*Musa paradisiacal*	Peel	20	[117]
22.	*Citrus sinensis*	Peel	10-35	[118]
23.	*Brassica rapa*	Leaves	16.4	[119]
24.	*Cymbopogan citratus*	Leaves	32	[120]
25.	*Ficus carica*	Leaves	13	[121]
26.	*Carica papaya*	Leaves	25-50	[122]

Characterization of Nanoparticles

The prepared nanoparticles are examined by numerous characterization techniques such as X-ray diffraction (XRD), scanning electron microscopy (SEM), transmission electron microscopy (TEM), Brunauer–Emmett–Teller (BET), absorbance spectroscopy, and photoluminescence spectroscopy. XRD revealed the crystalline nature of the nanoparticles. SEM and TEM images provide information about the morphology and particle size distribution, and BET disclose the surface properties of the nanoparticles. Optical properties are studied by absorbance and photoluminescence spectroscopic techniques.[27]

Applications of AgNPs

The extremely small size (1 to 100 nm) of nanoparticles enables them to access a variety of biological environments; due to smaller size its physical and chemical properties have become very different from those of the same material in bulk form. Nanotechnology has procure a great deal of public interest due to the needs and applications in many areas of human endeavors including industry, agriculture, business, energy sectors, material science, medicine and public health. Silver nanoparticles are most important of all the nanoparticles as they are used frequently in each and every field due to its enormous properties



Antimicrobial and Antiviral Applications

Silver nanoparticles are highly recommended antimicrobial agents used in several consumer products, i.e., water filters and sanitization system, deodorants, soaps, socks, cosmetics, food packaging, food preservation, paints, and room sprays.[28][29] The proposed mechanism of action is through: Disabling the respiratory chains, Cell membrane disruption and leakage of its cellular contents, blocking the replication of DNA, Denaturation of proteins and cell death through binding to functional groups of proteins and Generation of ROS (Reactive Oxygen species) in the microorganisms.[30] In similar manner silver nanoparticles had showed fungicidal activity against *Candida albicans, Candida krusei, Candida glabrata, Trichophyton mentagrophytes, and Candida tropicalis.*[31][32][33][34][28]

Conjunction of AgNPs with Antibiotics like penicillin G, amoxicillin, erythromycin, clindamycin, and vancomycin against *Staphylococcus aureus* and *Escherichia coli* was studied by disc diffusion method by Shahverdi et al. (2007).[35] They observed that antibacterial activities of all the antibiotics increased in presence of AgNPs against both bacteria. Similarly Rajawat and Qureshi (2012)[36] on *Salmonella typhi* and Fayaz and coworkers (2010)[37] on *Salmonella typhi*, *Escherichia coli*, *Staphylococcus aureus*, and *Micrococcus luteus* tested the effect of different antibiotics in combination with AgNPs and found that that antibacterial activity of all used antibiotic increased in the presence of AgNPs.

Furthermore literature reported that the silver nanoparticle show antiviral activity against viruses like human immunodeficiency virus-1, Influenza virus, (HIV-1), Herpes simplex virus, HSV-2, Monkey pox virus, hepatitis B, HSV-1, and Respiratory syncytial virus.[38] [39] [40] [41] [42] [43] [44]

Medical applications

Silver nanoparticles are used in prosthetic silicone heart valve to avoid the bacterial contamination and reduce the occurrence of endocarditis.[45] There incorporation in prosthetic valves enhances biocompatibility, resistance to calcification, and toughness of heart valves.[46] They are also used in the coatings of stents showing antithrombogenic and antibacterial properties.[47]

The polyurethane catheters are at high risk of contamination; coating with silver nanoparticles decreases the biofilm formation and reduce the risk of Catheter-Associated Ventriculitis (CAV) in patients.[48]

Silver nanoparticles used in wound dressings can enhance healing in superficial burn wounds, quicken re epithelialization.[49] It diminished injury therapeutic time by a standard of 3.35 days as compare to standard Ag Sulfadiazine and gauze dressing.[50] Also vanishes the occurrence of argyria or skin staining caused by 1% Ag sulfadiazine dressing.[51] Moreover they are also used in the preparation of surgical gloves, veils, patient dresses, antibacterial injury dressings, defensive face covers, suits against biohazards, restorative items along with others.

These nanoparticles are also used in Orthopedic and orthodontic implants and fixations. Amalgamation of silver nanoparticles into orthodontic adhesive can increase or maintain the shear bond strength of an orthodontic adhesive while expanding its resistance to bacteria.[52]

Role of silver nanoparticles in Drug delivery, as Nano Biosensors & in Industries

The nanoparticles can access the layers which normal drugs are unable to giving us an insight that binding nanoparticles to chemo therapeutic drugs will be an added horizon in targeted drug delivery in innumerable fatal diseases like cancer, brain tumor.[53]

Bioaffinity nanoparticle probes/ Bio-sensors for molecular and cellular imaging, disease diagnosis, early detection and screening of cancer and cell tracking are also developed.[54] [55] [56] [57]

Apart from this silver nanoparticle are used in optical fiber-based sensor for the detection of hydrogen peroxide in various industrial applications. They are also used in the detection of algal toxins, mycobacteria, and mercury present in drinking water and also used in water purification filters. Further they are used for the monitoring of hormonal regulation in plants and for detecting crop pests, viruses, soil nutrient levels, and stress factors in plants.[7]

Toxicological limitations of silver nanoparticles

Due to the vast usage of nanoparticles in various fields, the living organisms are coming directly or indirectly in contact with these nanoparticles raising the question about their toxicity. The toxicological effect of nanoparticles could be a major issue that ought to be addressed to avoid affecting living organisms or environment in harmful ways. So as to review toxicity of silver nanoparticles different research groups used different cell lines, culturing conditions, and incubation times. Biological models like cells in culture, aquatic organisms including embryonic zebrafish (Danio rerio) and whole-animal tests like rodents, are accustomed to determine potential toxicological effects of nanoparticles.[58]

The assorted hypotheses about the toxicological effects of silver nanoparticles are as follows:

May be cytotoxic

It is possible that AgNPs may accumulate within cells and cause intracellular changes like disruption of organelle integrity or gene alternations or even they are going to transform into more toxic form within the environment. In an *in vitro* study on cell lines it was found that they induce cytotoxicity by producing reactive oxygen species or they can increase in intracellular oxidative stress and trigger necrobiosis, causing apoptosis and necrosis.[59] In another study by Hussain et al. (2005)[60] in rat liver cells the silver nanoparticles even at low-level exposure resulted in oxidative stress and impaired mitochondrial function.

Rahman et al. (2009)[61] through their experimental study showed that AgNPs generate neurotoxicity by producing free radical induced oxidative stress and also by changing gene expression, generate neurotoxicity and apoptosis. Silver ions change the permeability of the plasma membrane to potassium and sodium ions at concentrations that don’t even limit sodium, potassium, ATP, or mitochondrial activity.[62] It is also proved that AgNPs can induce toxic effects on the proliferation and cytokine expression by peripheral blood mononuclear cells.[63]

Affect Male Reproductive organ

AgNPs show severe toxic effects on the male reproductive system. Research shows that AgNPs can cross the blood-testes barrier and deposit within the testes where they adversely affect the sperm cells.[64]

May escalate lung related auto immune disorders

Another research concluded that when nanoparticles are inhaled they deposit dispersedly upon the alveolar surface, resulting in scattered chemoattractant signal and leading to lower recognition and alveolar macrophage responses. The individuals suffering from asthma or chronic obstructive pulmonary diseases are more vulnerable than the healthy individuals.[66] [67]

Affect the skin/organs

Intentional long duration skin exposure to silver nanoparticles whether through the appliance of lotions, creams like sunscreen, wound dressing, detergents and socks or unintentionally coming in contact with anthropomorphic substances generated during nanomaterial manufacture or combustion may lead to skin allergies or changes in skin colour. Long term exposure of skin with AgNPs can cause argyria a blue-gray discoloration of the skin and other organs.[68] Commercially available silver-based dressings are proved to own cytotoxic effects on various experimental models.[65]

Exposure of soluble silver compounds can cause liver and kidney damage, eye, skin, respiratory and intestinal tract irritations; and untoward changes in blood cells.[69]

Will disturb the Nature

Knowingly or unknowingly manufactured nanoparticles will enter the environment from the production industries either as atmospheric emissions or as solid or liquid waste into the water streams. Apart from this the nanoparticles used in products like paint, cosmetics, fabrics, health care and personal products enter the environment proportional to their use which will ultimately deposit on land and water surfaces. Once the nanoparticles reaches the ground this will contaminate the soil, migrate into surface and ground waters. Silver is a good antimicrobial agent but when unintentionally it will enter the soil it will affect the healthy microbial flora in soil like heterotrophic (nitrogen-fixing and ammonifying bacteria) and chemolithotrophic bacteria affecting biological process. Nanoparticles in solid wastes, waste water effluents, direct discharges, or accidental spillages may be transported to aquatic systems by wind or rainwater runoff adversely affecting the health of the estuarine system.[58]

AgNPs show toxic effect on aquatic life as silver ions can interact with the gills of fish and inhibit basolateral Na^{+}-K^{+}-ATPase activity, which may successively inhibit osmoregulation within the fishes.[70]

These studies suggest that nanosilver can induce toxicity to living organisms at the same time we need to understand that nanosilver toxicity study were done in *in vitro* conditions which are drastically different from *in vivo* conditions and at quite high concentrations of nanosilver particles. Hence more studies should be carried out to assess the toxicity effect in *in vivo* conditions.

CONCLUSION

Silver and its derivatives are used as an antimicrobial agent since long ago and still the scientists are exploring their applications in different fields. Green synthesis of silver nanoparticles has opened a way for cost-effective, eco-accommodating and effectively scaled up method of large scale synthesis. Increased exploration of green chemistry and utilization of prokaryotic and eukaryotic organisms including higher complex eukaryotes for the synthesis of nanoparticles of desired shape and size has pave the way for green nanotechnology. The synthesis of nanoparticles using microorganisms is bit tricky having low synthesis rate and limited number of size and shape of nanoparticles has embark Phytonanotechnology. The use of plant parts and its extract is healthy and eco-friendly approach of synthesizing more stable nanoparticles.

Still the challenge is to explore the chemical constituents and the mechanism involved in the biological synthesis of nanoparticles, so that in future we can synthesize desired shape and size nanoparticles. We have to discover those active groups from biological sources attach to the nanoparticle surface responsible for higher efficacy of nanoparticles. Also detailed research in the area of effects of these nanoparticles released in the environment has to be carried out to find out the ill effects of these nanoparticles in future on flora and fauna. So far *in vitro* studies have showed the harmful effects of nanoparticles in appropriate concentration on animal cells, so we need to find out the exact concentration lethal for human and animal survival on earth. Silver nanoparticles has vast applications in various fields like cardiovascular implants, dentistry, medicine, therapeutics, biosensors, agriculture and many more to be discovered. The investigation into the bioavailability and biocompatibility of nanoparticles are still at early stages, and considerable research is needed in this direction.

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