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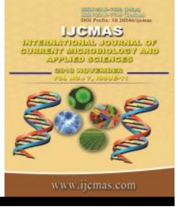

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Biological Synthesis of Silver Nanoparticles and their Antimicrobial Properties: A Review

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ABSTRACT

Nanotechnology is an important field of modern research dealing with design, synthesis, and manipulation of particles structure ranging from approximately 1-100 nm in one dimension. It includes the synthesis of nanoscale materials and exploration or utilization of their exotic physicochemical, Biological and optoelectronic properties. Silver has long been known to have strong inhibitory and bactericidal effects as well as broad spectrum of antimicrobial activities even at low concentrations. Silver has recognized importance in chemistry, physics and biology due to its unique properties. Conventional methods to synthesize silver nanoparticles are mainly by different chemical, physical and biological approaches. Biological synthesis provides advancement over chemical and physical method as it is cost effective, environment friendly, easily scaled up for large scale synthesis and in this method there is no need to use high pressure, energy, temperature and toxic chemicals. The biologically synthesized silver nanoparticles act as an antimicrobial agent and also used in pharmaceuticals, medicine and dental divisions.

Keywords

Antimicrobial, Biological Synthesis, Nanoparticles, Silver nanomaterial

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Introduction

The development of the concepts and experimental work is the broad category of nanotechnology. Recently nanotechnology is a development in scientific research, the development of its central concepts happened over a longer period of time. Since, people have been preparing the glass windows with tiny colored metal particles especially silver which provide glassy yellow color (Solomon *et al.*, 2007).

The history of nanomaterials is quite long and major developments within nano-science have taken place during the last two decades. The idea of Nanotechnology was first highlighted by Noble laureate Richard Feynman, in his famous lecture at the California Institute of Technology, 29th December, 1959. In one of his articles published in 1960 titled, “There is plenty of room at the bottom” discussed the idea of nanomaterials. He pointed out that if a bit of information required only 100 atoms, then all the books ever written could be stored in a cube with sides 0.02 inch long. Norio Taniguchi first defined the term Nanotechnology, in 1970. Nanoparticles are being used in several fields including electrical, biological textile and chemistry.

Depending up on shape and size of colloidal metal particles play crucial role in different application including preparation of magnetic, electronic devices wound healing, antimicrobial gene expression and in the preparation of bio composites and noble metal colloids have the optical, catalytical electromagnetic properties.

Nanoparticles fall into two categories: mainly organic and inorganic nanoparticles. Organic nanoparticles may include carbon nanoparticles (fullerenes) in other hand, inorganic nanoparticles may include magnetic nanoparticles, noble metal nanoparticles (like gold and silver) and semiconductor nanoparticles (like titanium dioxide and zinc oxide). There is a growing interest in inorganic nanoparticles as they provide superior material properties with functional versatility, have been examined as potential tools for medical imaging as well as for treating diseases due to their size features and advantages over available in chemical imaging drugs agents and drugs. When mesoporous silica combined with molecular machines prove to be excellent imaging and drug releasing systems. Gold nanoparticles have been used extensively in imaging, as drug carriers and in thermo therapy of biological targets (Cheon and Horace, 2009). Inorganic nanoparticles (metallic and semiconductor nanoparticles) exhibit intrinsic optical properties which may enhance the transparency of polymer- particle composites. For that reasons, inorganic nanoparticles have found special interest in studies devoted to optical properties in composites. Size dependent color of gold nanoparticles has been used to color glass for centuries (Caseri, 2009).

Nanotechnology is an important field of modern research dealing with design, synthesis, and manipulation of particles structure ranging from approximately 1-100 nm in one dimension. Remarkable growth in this upcoming technology has opened novel fundamental and applied frontiers, including the synthesis of nanoscale materials and exploration or utilization of their exotic physicochemical and optoelectronic properties. Nanotechnology is rapidly gaining importance in a number of areas such as healthcare, cosmetics, food and feed, environmental health, mechanics, optics, biomedical sciences, chemical industries, electronics, space industries, drug-gene delivery, energy science, optoelectronics, catalysis, reorography, single electron transistors, light emitters, nonlinear optical devices, and photo-electro-chemical applications (Colvin *et al.*, 1994, Wang 1991). Nanomaterials are seen as solution to many technological and environmental challenges in the field of solar energy conversion, catalysis, medicine, and water treatment. In the context of global efforts to reduce hazardous waste, the continuously increasing demand of nanomaterials must be accompanied by green synthesis methods. Nanotechnology is fundamentally changing the way in which materials are synthesized and devices are fabricated. Incorporation of nanoscale building blocks into functional assemblies and further into multifunctional devices can be achieved through a "bottom-up approach". Research on the synthesis of nanosized material is of great interest because of their unique properties like optoelectronic, magnetic, and mechanical, which differs from bulk (Atul *et al.*, 2010).

Synthesis routes of nanoparticles

Silver nano-crystalline particles can be synthesized by various physical, chemical and biological methods and each synthesized particles show different characteristics in terms of shape and size (Table 1). From past few years, various chemical methods of synthesizing nanoparticles have been replaced by green synthesis to reduce toxicity while synthesizing nanoparticles and to increase quality and stability (Kruis and Rellinghaus, 2000).

Approaches for nanoparticle synthesis

Basically there are two main approaches for nanoparticle synthesis i.e. the Bottom up approach and the Top down approach.

Top down approach

In the Top down approach, production of nano-silver involves mechanical grinding of a bulk piece of the material into nano-crystalline particles.

Bottom up approach

The Bottom up approach basically involves chemical and biological methods to synthesize nanoparticles. This process requires controlled growth/condensation of solute molecules formed during a chemical reaction. Desired shape and size of the nanoparticles can be achieved by the controlled condensation of nanoparticles. Biosynthesis of nanoparticles is either scale down or bottom up approach where the main reaction occurring is reduction/oxidation. The microbial enzymes or the phyto-chemicals with antioxidant or reducing properties are usually responsible for reduction of metal compounds into their respective nanoparticles (Kruis and Rellinghaus, 2000).

Silver Nanoparticles (AgNPs)

The optical properties of silver nanoparticles were used by glass founders as far back as in the time of the Roman Empire. That evidenced, so-called Lycurgus cup (4th century AD) now exposed in the British Museum. A detailed study of the composition of its bronze-mounted insets of stained glass, carried out in the late 20th century, revealed the presence of metal nanoparticles (with the average diameter of 40 nm) that consists of silver (70 %) and gold (30 %) alloy (Barber, 1990). It explained the remarkable feature in bowl to change its color from red in transmitted light to grayish green in reflected light. Before the 1980s, the scientific and practical interest in silver nanoparticles was exclusively caused by the possibility of their use as highly dispersed supports for enhancing the signals from organic molecules in the Raman spectroscopy (Creighton, *et al.,* 1979; Lee *et al.,* 1982). Fundamental studies carried out in the last three decade shows that silver nanoparticles exhibit a rare combination of valuable properties including, unique optical properties associated with the surface Plasmon resonance (SPR), well-developed surfaces, catalytic activity, high electrical double layer capacitance, etc. (Henglein, 1989). For that reason silver nanoparticles serve as a material in the development of new-generation electronic, optical and sensor devices. In the past 20 years, the trend miniaturization and the necessity of modernization of technological processes led to the substantial increase in the number of scientific publication devoted to the synthesis and properties of silver nanoparticles. Silver is used as a catalyst for the oxidation of methanol to formaldehyde and ethylene to ethylene oxide (Nagy *et al.,* 1999). This band is attributed to collective excitation of the electron gas in the particles, with a periodic change in electron density at the surface (Henglein, 1989; Ershov *et al.,* 1993). Some studies showed that use of a strong reductant such as borohydride, resulted in small particles that were somewhat monodisperse, but the generation of larger particles was difficult to control (Creighton *et al.,* 1994; Schneider *et al.,* 1979). Use of a weaker reductant such as citrate, resulted in a slower reduction rate, but the size distribution was far from narrow (Shirtcliffe *et al.,* 1999; Emory *et al.,* 1997). Synthesis of Ag NPs is based on a two steps reduction process (Schneider *et al.,* 1979). In this technique a strong reducing agent is used to produce small Ag particles, which are enlarged in a secondary step by further reduction with a weaker reducing agent (Lee *et al.,* 1982). Different studies reported the enlargement of particles in the secondary step from about 20–45 nm to 120–170 nm (Schneider *et al.,* 1994; Schirtcliffe *et al.,* 1999; Rivas *et al.,* 2001).

Why Silver?

Silver is one of the basic element that makes up our planet. It is a rare, but naturally occurring element, slightly harder than gold and very ductile and malleable. Pure silver has the highest electrical and thermal conductivity of all metals and has the lowest contact resistance. Silver can be present in four different oxidation states: Ag0, Ag2+, Ag3+. The former two are the most abundant ones, the latter are unstable in the aquatic environment (Ramya 2012). Metallic silver itself is insoluble in water, but metallic salts such as AgNO3 and Silver chloride are soluble in water (WHO, 2002). Metallic silver is used for the surgical prosthesis and splints, fungicides and coinage. Soluble silver compounds such as silver slats, have been used in treating mental illness, epilepsy, nicotine addition, gastroenteritis and infectious diseases including syphilis and gonorrhea (Ramya 2012). Although acute toxicity of silver in the environment is dependent on the availability of free silver ions, investigations have shown that these concentrations of Ag+ ions are too low to lead toxicity (WHO, 2002). Metallic silver appears to pose minimal risk to health, whereas soluble silver compounds are more readily absorbed and have the potential to produce adverse effects. The wide variety of uses of silver allows exposure through various routes of entry into the body. Ingestion is the primary route for entry for silver compounds and colloidal silver proteins. Dietary intake of silver is estimated at 70-90µg/day. Since silver in any form is not thought to be toxic to the immune, cardiovascular, nervous or reproductive system as it is not considered to be carcinogenic (C, F.A.a.S.M, 1978), therefore silver is relatively non-toxic (Chen, 2008). Silver demand will likely to rise as silver find new uses, particularly in textiles, plastics and medical industries, changing the pattern of silver emission as these technologies and products diffuse through the global economy (Ramya, 2012).

Biological synthesis of nanoparticles

Biosynthesis of nanoparticles is a kind of bottom up approach where the main reaction occurring is reduction/oxidation. The need for biosynthesis of nanoparticles rose as the physical and chemical processes were costly. Often, chemical synthesis method leads to presence of some of the toxic chemical absorbed on the surface that may have adverse effect in the medical applications (Parasharu, 2009). This is not an issue when it comes to biosynthesized nanoparticles via green synthesis route (Begum, 2009). So, in the search of cheaper pathways for nanoparticles synthesis, scientist used microbial enzymes and plant extracts (phytochemicals). With their antioxidant or reducing properties they are usually responsible for the reduction of metal compounds into their respective nanoparticles. Green synthesis provides advancement over chemical and physical method as it is cost effective, environment friendly, easily scaled up for large scale synthesis and in this method there is no need to use high pressure, energy, temperature and toxic chemicals (Fig. 1).

Bacteria mediated silver nanoparticles

The first evidence of bacteria synthesizing silver nanoparticles was established using the

Pseudomonas stutzeri AG259 strain that was isolated from silver mine (Haefeli *et al.,* 1984). There are some microorganisms that can survive metal ion concentrations and can also grow under those conditions, and this phenomenon is due to their resistance to that metal. The mechanisms involved in the resistance are efflux systems, alteration of solubility and toxicity via reduction or oxidation, biosorption, bioaccumulation, extracellular complex formation or precipitation of metals, and lack of specific metal transport systems (Husseiny *et al.,* 2006). There is also another aspect that though these organisms can grow at lower concentrations, their exposure to higher concentrations of metal ions can induce toxicity. The most widely accepted mechanism of silver biosynthesis is the presence of the nitrate reductase enzyme. The enzyme converts nitrate into nitrite. In in vitro synthesis of silver using bacteria, the presence of alpha-nicotinamide adenine dinucleotide phosphate reduced form (NADPH) - dependent nitrate reductase would remove the downstream processing step that is required in other cases (Vaidyanathan *et al.,* 2010).

Fungi mediated silver nanoparticles

When in comparison with bacteria, fungi can produce larger amounts of nanoparticles because they can secrete larger amounts of proteins which directly translate to higher productivity of nanoparticles (Mohanpuria *et al.,* 2008). The mechanism of silver nanoparticle production by fungi is said to follow the following steps: trapping of Ag+ ions at the surface of the fungal cells and the subsequent reduction of the silver ions by the enzymes present in the fungal system (Mukherjee *et al.,* 2001). The extracellular enzymes like naphthoquinones and anthraquinones are said to facilitate the reduction. Considering the example of *F. oxysporum*, it is believed that the NADPH-dependent nitrate reductase and a shuttle quinine extracellular process are responsible for nanoparticle formation (Ahmad *et al.,* 2003). Though the exact mechanism involved in silver nanoparticle production by fungi is not fully deciphered, it is believed that the abovementioned phenomenon is responsible for the process. A major drawback of using microbes to synthesize silver nanoparticles is that it is a very slow process when in comparison with plant extracts. Hence, the use of plant extracts to synthesize silver nanoparticles becomes an option that is feasible.

Silver nanoparticles synthesized by solar irradiation from *Bacillus amyloliquefaciens*

Silver nanoparticles (AgNPs) were obtained by using AgNO3 solar irradiation of cell-free extracts of *Bacillus amyloliquefaciens*. Many factors like light intensity, extract concentration, and NaCl addition influenced the synthesis of AgNPs. TEM (Transmission electron microscopy) and XRD (X-ray diffraction) analysis confirmed that circular and triangular crystalline AgNPs were synthesized. The potential value of the AgNPs, possibly caused by interaction with proteins likely explains the high stability of AgNPs suspensions. AgNPs showed antimicrobial activity against *Bacillus subtilis* and *Escherichia coli* in liquid and solid medium.

Antimicrobial activity of silver nanoparticles

Due to the non-toxic, safe inorganic antibacterial agent of silver nanoparticles being used for centuries and is capable of killing about 650 microorganisms that cause diseases (Jeong *et al.,* 2005). Silver has been described as being ‘oligodynamic’, that is, its ions are capable of causing a bacteriostatic (growth inhibition) or even a bactericidal (antibacterial) impact. Therefore, it has the ability to exert a bactericidal effect at minute concentration (Percivala *et al.,* 2005). It has a significant potential for a wide range of biological application such as antibacterial agents for antibiotic resistant bacteria, preventing infections, healing wounds and anti-inflammatory (Taylor *et al.,* 2005). Silver ions (Ag+) and its compounds are highly toxic to microorganism exhibiting strong biocidal effect on many species of bacteria but have a low toxicity towards animal cells. Bactericidal behavior of nanoparticles is attributed to the presence of electronic effects that are brought about as a result of change in local electronic structure of the surface due to smaller sizes. The effects are considered to be contributing towards enhancement of reactivity of silver nanoparticles surface. Silver in ionic form strongly interacts with thiol groups of vital enzymes and inactivates them. That lead DNA loses its replication ability once the bacteria are treated with silver ions (Morones *et al.,* 2005). Silver nanoparticles destabilize plasma membrane potential and depletion of levels of intracellular adenosine tri-phosphate (ATP) by targeting bacterial membrane resulting in bacterial cell death. Compounds of silver such as silver nitrate and silver sulfadiazine are used to prevent bacterial growth in drinking water, sterilization and burn care.

Action of silver nanoparticles on microbes

The exact mechanism which silver nanoparticles employ to cause antimicrobial effect is not clearly known and is a debated topic. There are however various theories on the action of silver nanoparticles on microbes to cause the microbicidal effect. Silver nanoparticles have the ability to anchor to the bacterial cell wall and subsequently penetrate it, thereby causing structural changes in the cell membrane like the permeability of the cell membrane and death of the cell. There is formation of „pits‟ on the cell surface, and there is accumulation of the nanoparticles on the cell surface (Sondi and Salopek, 2004), the formation of free radicals by the silver nanoparticles may be considered to be another mechanism by which the cells die. There have been electron spin resonance spectroscopy studies that suggested that there is formation of free radicals by the silver nanoparticles when in contact with the bacteria, and these free radicals have the ability to damage the cell membrane and make it porous which can ultimately lead to cell death (Danilcauk *et al.,* 2006, Kim *et al.,* 2007). It has also been proposed that there can be release of silver ions by the nanoparticles (Feng *et al.,* 2008), and these ions can interact with the thiol groups of many vital enzymes and inactivate them (Matsumura *et al.,* 2003). The bacterial cells in contact with silver take in silver ions, which inhibit several functions in the cell and damage the cells. Then, there is the generation of reactive oxygen species, which are produced possibly through the inhibition of a respiratory enzyme by silver ions and attack the cell itself. Silver is a soft acid, and there is a natural tendency of an acid to react with a base, in this case, a soft acid to react with a soft base. The cells are majorly made up of sulfur and phosphorus which are soft bases. The action of these nanoparticles on the cell can cause the reaction to take place and subsequently lead to cell death. Another fact is that the DNA has sulfur and phosphorus as its major components; the nanoparticles can act on these soft bases and destroy the DNA which would definitely lead to cell death (Morones *et al.,* 2005). The interaction of the silver nanoparticles with the sulfur and phosphorus of the DNA can lead to problems in the DNA replication of the bacteria and thus terminate the microbes. It has also been found that the nanoparticles can modulate the signal transduction in bacteria. It is a well-established fact that phosphorylation of protein substrates in bacteria influences bacterial signal transduction.

Dephosphorylation is noted only in the tyrosine residues of gram-negative bacteria. The phosphotyrosine profile of bacterial peptides is altered by the nanoparticles. It was found that the nanoparticles dephosphorylate the peptide substrates on tyrosine residues, which leads to signal transduction inhibition and thus the stoppage of growth. It is however necessary to understand that further research is required on the topic to thoroughly establish the claims (Hatchett and Henry, 1996).

Silver as Bactericidal agent

Nanometers size of bacteria, use enzymes to metabolize nutrients and create energy in a similar fashion as living organisms. They are unicellular with only one compartment of protein and they store all the elements of the cell. Thus, in order to stop the exponential rate of bacterial replication and disrupt the bacterial enzymes and energy metabolism.

Silver ions attack microbes in three different pathways including; respiration, replication, and cell wall synthesis. Silver nanoparticles penetrate the bacterial cell membrane and change their structural composition by interacting with the bacteria's sulfate groups, which are the active site of enzymes. Silver ions disrupt the bacterial enzymes responsible for energy metabolism and electrolyte transport.

The lack of enzyme activity ultimately suffocates the bacteria. As an additional means of attack, these powerful silver ions also detached the bacterial replication process by disrupting their DNA backbone finally creating structural imperfections within the cell's protective layers and speeding the collapse or burst of the bacteria (*Geranio et al.,* 2011). Therefore, by targeting these three areas, silver ions prevent bacteria proliferation by establishing a defense system, slowing bacterial growth, and eventually killing them.

Toxicity of silver nanoparticles

The unique physical and chemical properties of silver nanoparticles make them excellent candidates for a number of day-to-day activities, and also the antimicrobial and anti-inflammatory properties make them excellent candidates for many purposes in the medical field. However, there are studies and reports that suggest that nano-silver can allegedly cause adverse effects on humans as well as the environment. It is estimated that tonnes of silver are released into the environment from industrial wastes, and it is believed that the toxicity of silver in the environment is majorly due to free silver ions in the aqueous phase. The adverse effects of these free silver ions on humans and all living beings include permanent bluish-gray discoloration of the skin (argyria) or the eyes (argyrosis), and exposure to soluble silver compounds may produce toxic effects like liver and kidney damage; eye, skin, respiratory, and intestinal tract irritations; and untoward changes in blood cells (Panyala, *et al.*, 2008). Since the beginning of the twenty-first century, nanosilver has been gaining popularity and is now being used in almost every field, most importantly the medical field. However, there have been reports of how nanosilver cannot discriminate between different strains of bacteria and can hence destroy microbes beneficial to the ecology (Allsopp, *et al.*, 2007). There are only very few studies conducted to assess the toxicity of nano-silver. In one study, in vitro toxicity assay of silver nanoparticles in rat liver cells has shown that even low-level exposure to silver nanoparticles resulted in oxidative stress and impaired mitochondrial function (Hussain, *et al.*, 2005). Silver nanoparticles also proved to be toxic to in vitro mouse germ line stem cells as they impaired mitochondrial function and caused leakage through the cell membranes. Nanosilver aggregates are said to be more cytotoxic than asbestos (Soto, *et al.*, 2008).

Table.1 Characteristics of synthetic routes for synthesizing silver nanoparticles (refer)

Methods	Precursors	Reducing agents	Stabilizer	Particle size
Chemical	AgNO3	Trisodium Citrate	Trisodium citrate	30-60 nm
		NaBH4	Dodecenoic acid	7 nm
		Thermal Decomposition	Sodium Oleate	Nanosilver powder
Physical	AgNO3	Electric discharge	Sodium citrate	14-27 nm
	AgNO3	TX-100, UV	TX-100	30 nm
	Ag wires	Electric discharge arc	Sodium Citrate	10 nm
Biological	AgNO3	Bacteria	*Bacillus* sp.	5-15 nm
		Fungus	*Trichoderma viride*	5-40 nm
		Plant	*Azadirachta indica*	50-83 nm

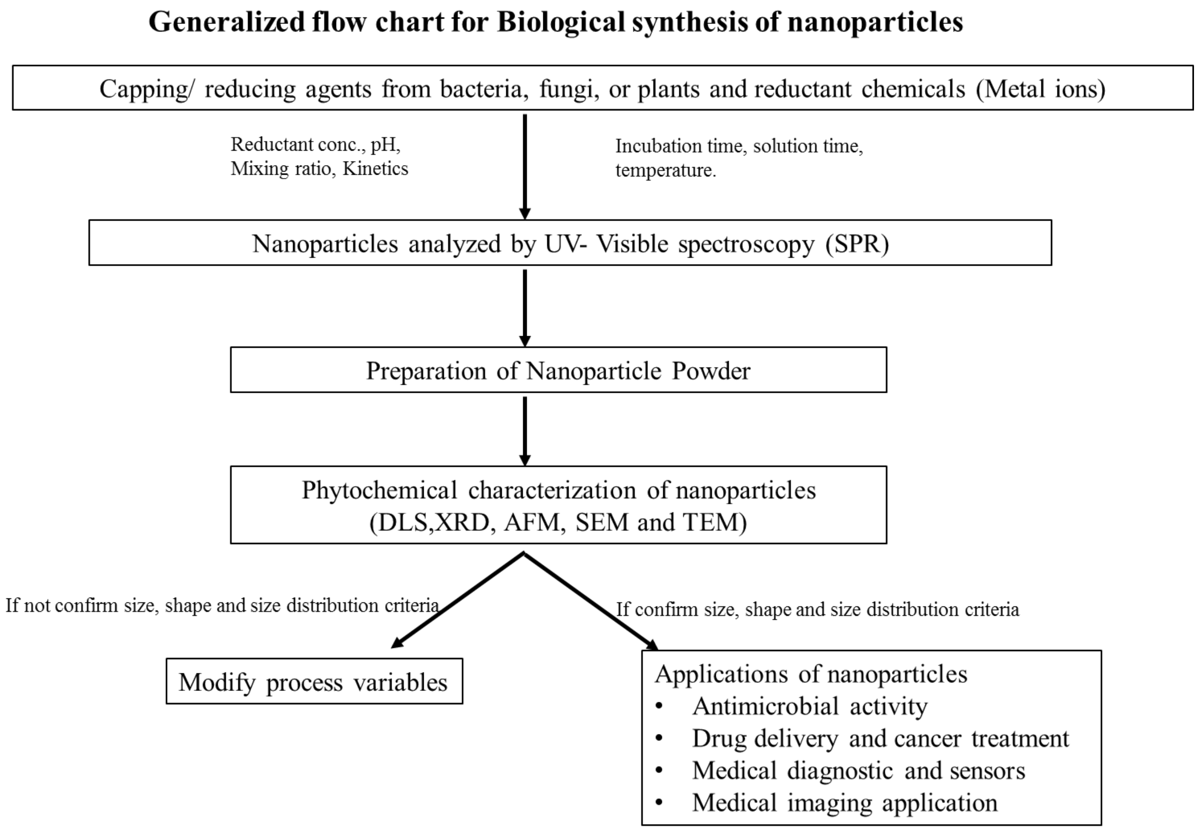
Table.2 Applications of silver nanoparticles in pharmaceutics, medicine, and dentistry

Pharmaceutics & Medicines	• **Treatment of dermatitis; inhibition of HIV-1 replication** • **Treatment of ulcerative colitis & acne** • **Antimicrobial effects against infectious organisms** • **Remote laser light-induced opening of microcapsules** • **Silver/dendrimer nanocomposite for cell labeling** • **Molecular imaging of cancer cells** • **Enhanced Raman Scattering (SERS) spectroscopy** • **Detection of viral structures (SERS & Silver nanorods)** • **Coating of hospital textile (surgical gowns, face mask)** • **Additive in bone cement** • **Implantable material using clay-layers with starch-** • **stabilized Ag NPs** • **Orthopedic stocking** • **Hydrogel for wound dressing**
Dentistry	• **Additive in polymerizable dental materials Patent** • **Silver-loaded SiO2 nanocomposite resin filler (Dental** • **resin composite)** • **Polyethylene tubes filled with fibrin sponge embedded** • **with Ag NPs dispersion**

Table.3 Mechanisms of antibacterial effects of silver nanoparticles (AgNPs)

- Cell death due to uncoupling of oxidative phosphorylation
- Cell death due to induction of free radical formation
- Interference with respiratory chain at Cyt C level
- Interference with components of microbial ETS
- Interactions with protein thiol groups & membrane bound enzymes
- Interaction with phosphorous- and sulfur-containing compounds such as DNA

Fig.1 Flowchart representing the biosynthesis of nanoparticles



There is evidence that shows that silver ions cause changes in the permeability of the cell membrane to potassium and sodium ions at concentrations that do not even limit sodium, potassium, ATP, or mitochondrial activity (Kone, *et al.*, 1998). The literature also proves that nanosilver can induce toxic effects on the proliferation and cytokine expression by peripheral blood mononuclear cells (Shin, *et al.*, 2007). Nanosilver is also known to show severe toxic effects on the male reproductive system. Research shows that nanosilver can cross the blood-testes barrier and be deposited in the testes where they adversely affect the sperm cells (McAuliffe and Perry, 2007). Even commercially available silver-based dressings have been proved to have cytotoxic effects on various experimental models (Burd, *et al.*, 2007). In vivo studies on the oral toxicity of nanosilver on rats have indicated that the target organ in mouse for the nanosilver was the liver. It was also found from histopathological studies that there was a higher incidence of bile duct hyperplasia, with or without necrosis, fibrosis, and pigmentation in the study animals (Kim, *et al.*, 2010). Studies have also suggested that there is release of silver when the nanoparticles are stored over a period of time. Hence, it has to be said that aged nanosilver is more toxic than new nanosilver (Kittler, *et al.*, 2010). Nanosilver with its antimicrobial activity can hinder the growth of many "friendly" bacteria in the soil. By showing toxic effects on denitrifying bacteria, silver can disrupt the denitrification process, which involves the conversion of nitrates into nitrogen gas which is essential for the plants. Loss of environmental denitrification through reduction of plant productivity can lead to eutrophication of rivers, lakes, and marine ecosystems and destroy the ecosystem. Nanosilver also has toxic effects on aquatic animals because silver ions can interact with the gills of fish and inhibit basolateral Na+-K+-ATPase activity, which can in turn inhibit osmoregulation in the fish (Wood, *et al.*, 1993). To understand the toxic potential nanosilver has on the freshwater environment, the Daphnia magna 48-h immobilization test was conducted, and the results showed that the silver nanoparticles have to be classified under „category acute 1" as per the Globally Harmonized System of Classification and Labelling of Chemicals, suggesting that the release of nanosilver into the environment has to be carefully considered (Asghari, *et al.*, 2012). Though these studies tend to suggest that nanosilver can induce toxicity to living beings, it has to be understood that the studies on nanosilver toxicity were done in in vitro conditions which are drastically different from in vivo conditions and at quite high concentrations of nanosilver particles. Hence, it is imperative that more studies be carried out to assess the toxicity effect nanosilver has in vivo before a conclusion on its toxicity is reached.

Application of silver nanoparticles

Nanoparticles are of great interest due to their extremely small size and large surface to volume ratio, which lead to both chemical and physical differences in their properties compared to bulk of the same chemical composition, such as mechanical, biological and sterical properties, catalytic activity, thermal and electrical conductivity, optical absorption and melting point (Daniel, 2004). Therefore, designing and production of materials with novel applications can be resulted by controlling shape and size at nanometer scale. Nanoparticles exhibit size and shape-dependent properties which are of interest for applications ranging from biosensing and catalysts to optics, antimicrobial activity, computer transistors, electrometers, chemical sensors, and wireless electronic logic and memory schemes. These particles also have many applications in different fields such as medical imaging, nano-composites, filters, drug delivery, and hyperthermia of tumors (Lee, *et al.*, 2008, Tan, *et al.*, 2006). Silver nanoparticles have drawn the attention of researchers because of their extensive applications in areas such as integrated circuits (Kasthuri and Rajendran, 2009) sensors (Zhang, 2003) biolabelling, filters, antimicrobial deodorant fibres (Hong, *et al.*, 2006), cell electrodes (Cho, *et al.*, 2005) low-cost paper batteries (silver nano-wires) (Duran, *et al.*, 2007) and antimicrobials (Liu, 2009). Silver nanoparticles have been used extensively as antimicrobial agents in health industry, food storage, textile coatings and a number of environmental applications. Antimicrobial properties of silver nanoparticles caused the use of these nano-metals in different fields of medicine, various industries, animal husbandry, packaging, accessories, cosmetics, health and military. For instance, it was shown that silver nanoparticles mainly in the range of 1-10 nm attached to the surface of *E. coli* cell membrane, and disturbed its proper function such as respiration and permeability.

In general, therapeutic effects of silver particles (in suspension form) depend on important aspects, including particle size (surface area and energy), particle shape (catalytic activity), particle concentration (therapeutic index) and particle charge (oligodynamic quality) (Yoon, *et al.*, 2007). Mechanisms of antimicrobial effects of silver nanoparticles are still not fully understood, but several studies have revealed that silver nanoparticles may attach to the negatively charged bacterial cell wall and rupture it, which leads to denaturation of protein and finally cell death (Table 2). Fluorescent bacteria were used to study antibacterial effects of silver nanoparticles. Green fluorescent proteins were adapted to these investigations (Sharma, *et al.*, 2007). It was found that silver nanoparticles attached to sulfur-containing proteins of bacteria, and caused death. Moreover, fluorescent measurements of cell-free supernatants showed the effect of silver nanoparticles on recombination of bacteria. The attachment of silver ions or nanoparticles to the cell wall caused accumulation of envelope protein precursors resulting in immediate dissipation of the proton motive force (Sharma, 2007).

Catalytic mechanism of silver nanoparticle composites and their damage to the cell by interaction with phosphorous- and sulfur-containing compounds such as DNA have been also investigated (Kumar, *et al.*, 2004). Furthermore, silver nanoparticles exhibited destabilization of the outer membrane and rupture of the plasma membrane, thereby causing depletion of intracellular ATP. Another mechanism involves the association of silver with oxygen and its reaction with sulfhydryl groups on the cell wall to form R-S-S-R bonds, thereby blocking respiration and causing cell death (Table 3).

Diagnostic applications

Silver nanoparticles can be used in numerous assays and biosensors where the silver nanoparticle materials can play a role as biological markers for quantitative detection.

Antibacterial applications

Their antibacterial property can be incorporated in apparel, wound dressings, footwear, paints appliances, cosmetics, and plastics.

Conductive applications

Silver nanoparticles are also used in conductive inks and integrated into composites to increase thermal and electrical conductivity.

Optical applications

Silver nanoparticles can be used to efficiently harvest light and for enhanced optical spectroscopies including metal-enhanced fluorescence (MEF) and surface-enhanced Raman scattering (SERS).

Human health applications

The production of nanoparticles has many different effects on human health relative to bulk material (Albrecht, 2006). Increase the biological activity of nanoparticles can be determined beneficial, detrimental or both. Nanoparticles are enough to access to skin, lungs, and brain (Koziara *et al.*, 2003; Oberdorster *et al.*, 2004). Exposure of metal containing nanoparticles to human lung epithelial cells generated reactive oxygen species, which lead to oxidative stress and damage of the cells (Limbach *et al.*, 2007; Xi *et al.*, 2006).A study on toxic effects of silver nanoparticles was done, that results show a deposition of particles on organs and severe developmental effects. The biocompatibility and toxicity of silver nanoparticles were exhibited at each development stage by observing single silver nanoparticle inside embryos.

Environment applications

Silver nanoparticles have a great concern to wastewater treatment utilities and to biological systems. The inhibitory effects of silver nanoparticles on microbial growth were evaluated at a treatment facility using an extant respirometry technique. The nitrifying bacteria were susceptible to inhibition by silver nanoparticles, which could have detrimental effects on the microorganisms in wastewater treatment. The environmental risk of silver nanoparticles was recently investigated by determining released silver from commercial clothing. The sock material and wash water contained silver nanoparticles of 10–500 nm diameter.

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