REVIEW ARTICLE

INTERNATIONAL JOURNAL OF BIOASSAYS
ISSN: 2278-778X
CODEN: IJBNHY
OPEN ACCESS

Silver nanoparticles - synthesis, applications and toxic effects on humans: a review

S. Janardana Reddy
Division of Nanotechnology, Department of Fishery Science and Aquaculture, Sri Venkateswara University, Tirupathi-517502, Andhra Pradesh, India.

Received for publication: September 12, 2015; **Accepted**: October 7, 2015

Abstract: The silver nanoparticles (AgNPs) have diverted the surveillance of the scientific communities and industrialists itself due to their wide range of applications in industry for the preparation of consumer products and highly accepted application in biomedical fields (especially their efficacy against microbes, anti-inflammatory effects, and wound healing ability). The development of nanotechnology in different industries, its modernity, and also the lack of information on its negative effects on human health and the environment originate from the novel mechanisms that are also related to nanotoxicology. Some researchers are intrinsically against using nanomaterials in human medicine and in the environment while others are in favor. The important point here is that because there are many nanomaterials with many different uses, it is difficult to test all of them and estimate their effects on human health. Therefore, some scientists believe that their side effects are acceptable. Nanotechnology has wide applications in many fields, especially in the biological sciences and medicine. Nanomaterials are applied as coating materials or in treatment and diagnosis.

Key words: Silver Nanoparticles; Nanotoxicology; Synthesis; Applications; Bioconjugation; Biodistribution.

INTRODUCTION

The large and increasing use of silver nanoparticles (AgNPs) represents an emerging environmental issue. Indeed, they are extensively used in many domains, mainly in medicine and textiles from which they are released in the environment. AgNPs are employed for their antimicrobial and biocidal properties. Silver is well-known for its toxic properties to organisms. In the last decade, an increasing number of studies have focused on AgNP toxicity[1].

Nanoparticles are those having diameters of nanometer size. With the advent of modern technology, humans can make nano-sized particles that were not present in nature. Manufactured nanomaterials are materials with diameters of nanometer size, while nanotechnology is one of the fastest growing sectors of the hi-tech economy. The application of nanotechnology has recently been extended to areas in medicine, biotechnology, materials and process development, energy and the environment. The comprehensive applications of this technology is in part due to the finding that, as the size of the particles were reduced, many new properties have been realized in various scientific fields, such as pharmacology, electronic engineering, magnetic fields and semi-conductors. Nanomaterials used include nanotubes, nanowires, fullerene derivatives, and quantum dots. Nanoparticles are those having diameters of nanometer size. With the advent of modern technology, humans can make nano-sized particles that were not present in nature. The use of nanotechnology extends to medicine, biotechnology, materials, process development, energy and environments[2]. Perspecuously, interest in the potential benefits of nano materials and a greater production of these materials has naturally led to an increased concern about the potential toxic effects resulting from their usage or unintentional release into the environment[3]. A number of nanotoxicological studies so far have focused on atmospheric contamination and the respiratory effects in mammals or in vitro assays with mammalian cells[4].

Nanotoxicology

Nanotoxicology is a branch of bio-nanoscience, which deals with the study and application of the toxicity of Nanomaterials. Nanomaterials, even when made of inert elements such as gold, become highly active at nanometer dimensions. Nanotoxicological studies are used to determine whether and to what extent these properties may pose a threat to the environment and to human health. Nanoparticles play a remarkable role in toxicity, which is important for toxicologists, especially in respiratory diseases. Their size is an important factor in the occurrence of disease[5]. Some studies on the different sizes of carbon and titanium oxide showed that reduction in nanoparticle size increases its toxicity in the lungs. Also notable is that combining some metals with each other causes complex toxicity, which does not occur with single metals. In 1975, a study showed the effect of oxidative stress caused by asbestos as the main factor in asbestosis and also in disturbing cell structure[6]. In 1998, Zhang[5] presented his findings on the effects of nanoparticles on respiratory toxicity and inflammation. Some of the particle features such as size, surface chemistry, and oxidative stress functions play important roles in nanotoxicity. Other features such as crystallinity, coating, and the longevity of particles have also been studied as important parameters. By gaining control over dangerous particles, we can increase the use of nanoparticles by reducing their harmful effects, and thus allowing them to be used in the curing of diseases[7].

What is Nanosilver?

Silver is a well-known metal used by humans for centuries. Recent advances in nanosciene (the science and manipulation of chemical and biological materials with dimensions in the range from 1-100 nanometers) led to the development of silver nanoparticle. A silver nanoparticle consists of many silver atoms or ions clustered together to form a particle 1-100nm in size. Due to their small size, these nanoparticles are able to invade bacteria and other microorganisms and kill them.

***Corresponding Author:**
Dr. S. Janardana Reddy,
Head, Department of Fishery Science and Aquaculture,
College of Sciences, Sri Venkateswara University,
Tirupati - 517 502, India.

Silver nanoparticles (or nanosilver) are now widely impregnated into a wide range of consumer products, including textiles such as socks, sportswear, underwear and bedding, vacuums, washing machines, toys, sunscreens, and a host of others (Figure-1).

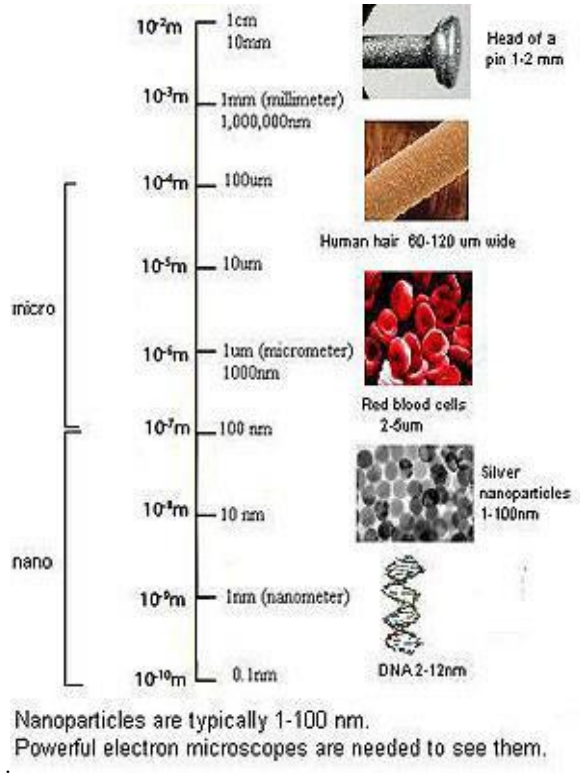

Figure 1: Different sizes of Nanoparticles

However, the chronic impacts of this new technology to human health and the environment are still unknown. Recent studies have found permeated textiles, when laundered, release silver nanoparticles into the wash cycle and eventually into wastewater systems and the environment. In the environment, these nanoparticles become dangerous to microbes essential for ecologic systems. There have been some reports demonstrating that nanoparticles can cross the blood-brain barrier to enter the brain[8].

The nanosilver formulations disclosed in the preceding section have not only been used by scientists and described in the patent literature, but have persistently found their way into the market. In the early part of the 20th century, the commercial sale of medicinal nanoscale silver colloids, known under disparate trade names such as Collargol, Argyrol, and Protargol, began and over a 50-year period their use became widespread[4]. These nanosilver products were sold as over-the-counter medications and also used by medical doctors to treat various diseases such as syphilis and other bacterial infections Nanotechnology has many useful and prpitious applications that can benefit mankind, but nanotechnologies are still new and even though they are having commercial success in the market place, there are big unanswered questions about their potentially harmful effects on our health and the environment.

Nano-Silver is pure de-ionized water with silver (Ag) in suspension. Approximately 80% of the silver is in the form of metallic silver nano-particles. The remaining silver is in ionic form. Though similar to colloidal silver, generally, a colloid is a suspension of particles of from 10 nm to 1 micron in diameter and the silver particles in Nano-Silver are less than 2 nm in diameter and therefore too small to be considered in "colloidal" suspension. They are rather, in a "nano-suspension," a much more stable state.

Because of the small size of the particles, the total surface area of the silver exposed in solution is maximized, resulting in the highest possible effect per unit of silver. As a result, the 20 PPM concentration of silver in Nano-Silver provides more productiveness inside the body than silver solutions in the colloidal class, of many times greater concentration.

The distinctive feature of Nano-Silver which amplifies its effectiveness inside the body above that of common colloidal silver products is the high percentage of silver in particulate (metallic) form. This relationship is key because ionic silver becomes silver chloride in the stomach or bloodstream. Silver chloride is only slightly soluble and far less effective than metallic or ionic silver. Were it not for this chemical reaction, ions would be preferable to metallic particles as they are in vitro. Only metallic particles survive the hydrochloric acid of the stomach to remain effective inside the bloodstream and body tissue. Most colloidal silver solutions are no more than 5-10% particles with the remainder in the form of ions.

What is Nanotechnology?

Nano silver technology uses Silver particles of nano size (1m = 109 nano meters), which are impregnated on activated carbon. Silver is a bacteriostatic agent, which inhibits growth of bacteria and activated carbon removes odour, organic impurities and improves taste of water[9].

Nano silver technology unites micro particles of ceramic and silver increasing their concentration levels for enhanced performance. Nano Silver's unique properties help to promote healthy, shiny hair. Silver is known for its natural antibacterial and antifungal properties helping to minimize the spread of bacteria. Nano ceramic emits negative ions and far infrared heat in their most beneficial form, quickly sealing the cuticle layer and eliminating frizz for smooth, silky hair. Far infrared heat penetrates the hair from within, for gentle styling without damaging hair. Look for nano silver flat irons, curling irons and blow dryers.

A reduction in the size of nano-sized particles results in an increase in particle surface area. Therefore more chemical molecules may attach to this surface, which would enhance its reactivity and result in an increase in its toxic effects. Many studies on the absorption of nanoparticles from the mucus have examined these effects. After absorption, nanoparticles reach the blood stream and then spread through the tissue. In one study, 33% of 50 nm, 26% of 100 nm, and 10% of 500 nm particles were discovered in mucosal and lymphatic tissues of the intestine[10]. Nanoparticles larger than 1 μm were weakly

observed and nanoparticles larger than 3 µm were occasionally seen in lymphatic tissues. Researchers have concluded that:

- Nanoparticles smaller than 100 nm are absorbed by the cells of the intestine but not the larger nanoparticles (300 nm).
- The absorption of smaller nanoparticles (100 nm) in the lymphatic tissue is greater than in intestinal cells.
- Intestinal cells cannot absorb nanoparticles larger than 400 nm.
- Only nanoparticles smaller than 500 nm can enter the circulatory system.

Scientists are discussing the relationship between particle sizes and their penetration into mesenteric lymphatic glands, but so far have reached no agreement. In addition to being able to cross cell membranes, and reach the blood and various organs because of their small size, nanoparticles have a bigger surface to volume ratio than larger particles. Therefore more molecules of the chemical are present on the surface, which may be one of the reasons why nanoparticles are generally more toxic than larger particles of the same composition[11].

In vitro studies have shown that very small particles have more pathological and destructive power on the lungs rather than the same particles of smaller size due to their larger surface area, greater tendency to conjugate, and energy sustainability.

Geiser *et al.,* [12] studied the interaction between particle surface chemistry and the lung's surface-lining layer. They found that, regardless of the nature of the surface, the particles will be submersed into the lining layer after deposition in the small airways and alveoli. This displacement is promoted by the surfactant film itself as its surface tension falls temporarily to relatively low values.

Chemical components of the particle surface have important effects on nanoparticles as they can react with metals. Iron can be affected by nanoparticles, which increases the induction of ROS in the free cell system. The surface modification of nanoparticles can reduce toxicity. Researchers have also shown that the toxicity of super paramagnetic iron oxide nanoparticles could be reduced by coating them with pullulan.

Silver Nanoparticles – Effect on Humans

Nanoparticles released into the environment interact with air, water and soil. This often changes the surface properties of the particles which can result in particle aggregation or changes in particle charge and other surface properties. These effects have been studied in water ecosystems and soil[11] and show the importance of understanding nanoparticles and their environmental setting as a "complex" that needs to be looked at in its entirety in order to understand particle behaviour in the environment[13]. A current debate addresses whether nanoparticles can cause toxicity as a contaminant in, for example, soil or water, via a **"piggyback"** mechanism on natural organic matter[15].

In order to assess nanoparticle toxicity, *in-vitro* models are insufficient alone to predict possible hazards to humans, so *in-vivo* studies are necessary to elucidate mechanisms, pathways and entry routes of nanoparticles in a complex multicellular organism. This is required not only for nanomaterials used in industrial processes, where human exposure could occur via the environment but also for nanomaterials where human exposure is part of the design, e.g. nanomedicines. For nanoparticles produced on an industrial scale, the extent to which factory workers, specific population subgroups or the public in general are exposed needs to be established. Several nanomaterials currently fall into this category: silicon dioxide, zinc oxide, silver, titanium dioxide, carbon nanotubes, and cerium dioxide[15,16] , to name the most prominent ones. Gold nanoparticles are and will be increasingly used for nanotherapeutical applications due to their outstanding bioconjugation properties. Research shows that, apart from the intrinsic nanotoxicological potential of the "bare" particle, coating and surface properties have to be taken more seriously in order to understand and predict toxicological effects at the in-vivo level. To know the entry routes and vulnerabilities—get into the body, it has been demonstrated and identify that nanoparticles gain access to the body mainly via the airways, the skin or via ingestion[17,18] (Figure-2). They are also able to translocate to secondary organs, however this has only been demonstrated in small quantities.

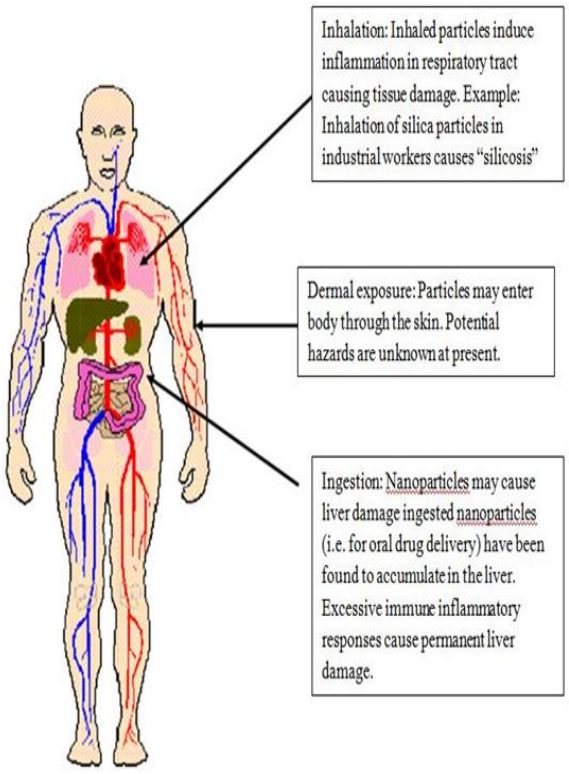

Figure 2: Entry of Nanoparticles in to the body mainly via the airways, the skin or via ingestion.

The main entry route for airborne particles to the body is through the respiratory system. Substantial data on ultrafine particles (dust, carbon black and other pollutants) and their effects to the airways and lungs is available[19]. Data on translocation of nanoparticles via the lungs are

increasing. The main question is whether particles can cross the air-blood-barrier in the lungs and therefore gain access to the rest of the body. The body has certain defense mechanisms against particles (mucus and mucociliary escalator), however nanoparticles seem to be able to translocate from the lung into liver, spleen, heart and possibly other organs. The main mechanism for nanoparticle translocation appears to be via endocytosis of alveolar epithelial cells[20]. Apart from exposure to the lungs, inhaled nanoparticles can also gain access to other organs via the olfactory bulb[12, 21]. This is potentially hazardous from a neurotoxicological point of view, as particles would also be able to gain direct access to the central nervous system via this route. Another potential exposure route in humans is via the skin. Titanium dioxide nanoparticles are, for example, often used in sunscreen products and may gain access through hair follicles or wounds and lesions[22]. However, the literature on dermal absorption and translocation into the body of titanium dioxide is inconclusive and further research is required. Other particles such as fullerenes and quantum dots seem to be able to penetrate the dermis, dependent on size and surface coatings[23]. Since nanoparticles are increasingly used as food additives or in food processing and packaging, there are concerns that nanoparticles could gain access to the blood stream via gastro-intestinal assimilation. It has been demonstrated that nanoparticle uptake via the gut is possible and seems to be size dependent. However, further research is required to shed more light on gastro-intestinal assimilation. The major concern however is that nanoparticles could gain access to other organs once having entered the body and reached the bloodstream[24]. Great importance is attached to natural barriers in the body, for example the air-blood barrier in the lung, the blood-brain barrier or the materno-foetal barrier. Biodistribution studies of nanoparticles have found low concentrations of them in liver, spleen, heart and the brain[25]. Further concerns are the bioaccumulation of nanoparticles in certain organs. It is not yet clear to what extent the body is able to excrete nanoparticles via urine or whether residual nanoparticles bioaccumulate in certain organs and may even block the body's excretion systems.

Synthesis of Silver nanoparticles

Nanotechnology is rapidly growing by producing nanoproducts and nanoparticles (NPs) that can have novel and size-related physico-chemical properties differing significantly from larger matter. The novel properties of NPs have been exploited in a wide range of potential applications in medicine, cosmetics, renewable energies, environmental remediation and biomedical devices[26]. Among them, silver nanoparticles (Ag-NPs or nanosilver) have attracted increasing interest due to their unique physical, chemical and biological properties compared to their macro-scaled counterparts. Ag-NPs have distinctive physico-chemical properties, including a high electrical and thermal conductivity, surface-enhanced Raman scattering, chemical stability, catalytic activity and non linear optical behavior[27,28]. These properties make them of potential value in inks, microelectronics, and medical imaging. Besides, Ag-NPs exhibit broad spectrum bactericidal and fungicidal activity that has made them extremely popular in a diverse range of consumer products, including plastics, soaps, pastes, food and textiles, increasing their market value.

a. Physical approach

In physical processes, metal nanoparticles are generally synthesized by evaporation–condensation, which could be carried out using a tube furnace at atmospheric pressure. The source material within a boat centered at the furnace is vaporized into a carrier gas. Nanoparticles of various materials, such as Ag, Au, PbS and fullerene, have previously been produced using the evaporation/condensation technique[29, 30]. However, the generation of silver nanoparticles (AgNPs) using a tube furnace has several drawbacks, because a tube furnace occupies a large space, consumes a great deal of energy while raising the environmental temperature around the source material, and requires a lot of time to achieve thermal stability. A typical tube furnace requires power consumption of more than several kilowatts and a preheating time of several tens of minutes to attain a stable operating temperature.

Jung *et al.,* [31] synthesized AgNPs via a small ceramic heater that has a local heating area. Because the temperature gradient in the vicinity of the heater surface is very steep in comparison with that of a tube furnace, the evaporated vapor can cool at a suitably rapid rate. This makes possible the synthesis of small nanoparticles in high concentration. This method might be suitable for a variety of applications, including utilization as a nanoparticle generator for long-term experiments for inhalation toxicity study and as a calibration device for nanoparticle measurement equipment [29, 32].

Moreover, AgNPs have been synthesized with laser ablation of metallic bulk materials in solution[33, 34]. The characteristics of the metal particles formed and the ablation efficiency strongly depend upon many parameters[35-37], such as the wavelength of the laser impinging the metallic target, the duration of the laser pulses (in the femto-, pico- and nanosecond regime), the laser fluence, the ablation time duration and the effective liquid medium, with or without the presence of surfactants.

The laser fluence is one of the most important parameters. Indeed, the ejection of metal particles from the target requires a minimum power or fluence. The mean size of the nanoparticles has been found generally to increase with increasing laser fluence and is generally smallest for fluencies not too far above the laser breakdown threshold. Besides the laser fluence, the number of laser shots. influences the concentration and the morphology of metal particles released in a liquid. For longer times under the laser beam the metal particle concentration is expected to increase, but it can saturate due to light absorption in the colloid highly concentrated in metal particles. Moreover, nanoparticles can be modified in size and shape due to their further interaction with the laser light passing through[35, 38, 39]. Also, the formation of nanoparticles by laser ablation is terminated by the surfactant coating. The nanoparticles formed in a solution of high surfactant concentration are

smaller than those formed in a solution of low surfactant concentrate. One advantage of laser ablation compared to other conventional method for preparing metal colloids is the absence of chemical reagents in solutions. Therefore, pure colloids, which will be useful for further applications, can be produced by this method[40].

b. Chemical synthesis

Currently, many methods have been reported for the synthesis of Ag-NPs by using chemical, physical, photochemical and biological routes. Each method has advantages and disadvantages with common problems being costs, scalability, particle sizes and size distribution. Among the existing methods, the chemical methods have been mostly used for production of Ag-NPs. Chemical methods provide an easy way to synthesize Ag-NPs in solution. Monodisperse samples of silver nanocubes were synthesized in large quantities by reducing silver nitrate with ethylene glycol in the presence of polyvinylpyrrolidone (PVP), the so-called polyol process. In this case, ethylene glycol served as both reductant and solvent [41]. It showed that the presence of PVP and its molar ratio relative to silver nitrate both played important roles in determining the geometric shape and size of the product. It suggested that it is possible to tune the size of silver nanocubes by controlling the experimental conditions. Spherical Ag-NPs with a controllable size and high monodispersity were synthesized by using the polyol process and a modified precursor injection technique[41]. In the precursor injection method, the injection rate and reaction temperature were important factors for producing uniform-sized Ag-NPs with a reduced size. Ag-NPs with a size of 17 ± 2 nm were obtained at an injection rate of 2.5 ml s−1 and a reaction temperature of 100◦C. The injection of the precursor solution into a hot solution is an effective means to induce rapid nucleation in a short period of time, ensuring the fabrication of Ag-NPs with a smaller size and a narrower size distribution.

Nearly monodisperse Ag-NPs have been prepared in a simple oleylamine-liquid paraffin system. It was shown that the formation process of Ag-NPs could be divided into three stages: growth, incubation and Oatwald ripening stages. In this method, only three chemicals, including silver nitrate, oleylamine and liquid paraffin, are employed throughout the whole process.

The higher boiling point of 300◦C of paraffin affords a broader range of reaction temperature and makes it possible to effectively control the size of Ag-NPs by varying the heating temperature alone without changing the solvent. Otherwise, the size of the colloidal Ag-NPs could be regulated not only by changing the heating temperature, or the ripening time, but also by adjusting the ratio of oleylamine to the silver precursor.

Generally, the chemical synthesis process of the Ag-NPs in solution usually employs the following three main components: (i) metal precursors, (ii) reducing agents and (iii) stabilizing/capping agents. The formation of colloidal solutions from the reduction of silver salts involves two stages of nucleation and subsequent growth. It is also revealed that the size and the shape of synthesized Ag-NPs are strongly dependent on these stages. Furthermore, for the synthesis of monodispered Ag-NPs with uniform size distribution, all nuclei are required to form at the same time. In this case, all the nuclei are likely to have the same or similar size, and then they will have the same subsequent growth. The initial nucleation and the subsequent growth of initial nuclei can be controlled by adjusting the reaction parameters such as reaction temperature, pH, precursors, reduction agents (i.e. NaBH4, ethylene glycol, glucose) and stabilizing agents (i.e. PVA, PVP, sodium oleate)[42].

c. Biological synthesis

As mentioned above, when Ag-NPs are produced by chemical synthesis, three main components are needed: a silver salt (usually AgNO3), a reducing agent (i.e. ethylene glycol) and a stabilizer or aping agent (i.e. PVP) to control the growth of the NPs and prevent them from aggregating. In case of the biological synthesis of Ag-NPs, the reducing agent and the stabilizer are replaced by molecules produced by living organisms. These reducing and/or stabilizing compounds can be utilized from bacteria, fungi, yeasts, algae or plants[43]. A facile biosynthesis using the metal-reducing bacterium, *Shewanella oneidensis,* seeded with a silver nitrate solution, was reported[44]. The formation of small, spherical, nearly monodispersed Ag-NPs in the size range from ∼2 to 11 nm (average size of 4±1.5 nm) was observed. The Ag-NPs exhibit useful properties such as being hydrophilic, stable, and having a large surface area. This bacterially based method of synthesis is economical, simple, reproducible, and requires less energy when compared to chemical synthesis routes.

In another study, the use of the fungus *Trichoderma viride* (*T. viride*) for the extracellular biosynthesis of Ag-NPs from silver nitrate solution was reported. In this regard *T. viride* proves to be an important biological component for extracellular biosynthesis of stable Ag-NPs. The morphology of Ag-NPs is highly variable, with spherical and occasionally rod-like NPs observed on micrographs. The obtained diameter of Ag-NPs was in the range of from 5 to 40 nm. In another study, stable Ag-NPs of 5–15 nm in size were synthesized by using an airborne bacteria (Bacillus sp.) and silver nitrate[45]. The biogenic NPs were observed in the periplasmic space of the bacterial cells, which is between the outer and inner cell membranes. Also, the Ag-NPs were produced by using the Lactobcillus spp. as reducing and capping agent. The smallest NPs were produced by *L. fermentum* and had a diameter of 11.2 nm. The recovery of silver and the reduction rate were pH dependent. On the other hand, Naik *et al.,* [46] have demonstrated the biosynthesis of biogenic Ag-NPs using peptides selected by their ability to bind to the surface of silver particles. By the nature of peptide selection against metal particles, a 'memory effect' has been imparted to the selected peptides. The silver-binding clones were incubated in an aqueous solution of 0.1 mM silver nitrate for 24–48 h at room temperature. The silver particles synthesized by the silver-binding peptides showed the presence of silver particles 60–150 nm in size.

Characterization of silver nanoparticles

Characterization of nanoparticles is important to understand and control nanoparticles synthesis and applications. Characterization is performed using a variety of different techniques such as transmission and scanning electron microscopy (TEM, SEM), atomic force microscopy (AFM), dynamic light scattering (DLS), X-ray photoelectron spectroscopy (XPS), powder X-ray diffractometry (XRD), Fourier transform infrared spectroscopy (FTIR), and UV–Vis spectroscopy [47-51].

These techniques are used for determination of different parameters such as particle size, shape, crystallinity, fractal dimensions, pore size and surface area. Moreover, orientation, intercalation and dispersion of nanoparticles and nanotubes in nanocomposite materials could be determined by these techniques.

For instance, the morphology and particle size could be determined by TEM, SEM and AFM. The advantage of AFM over traditional microscopes such as SEM and TEM is that AFM measures three-dimensional images so that particle height and volume can be calculated. Furthermore, dynamic light scattering is used for determination of particles size distribution. Moreover, X-ray diffraction is used for the determination of crystallinity, while UV–Vis spectroscopy is used to confirm sample formation by showing the Plasmon resonance[50].

Antibacterial effects

The Ag-NPs have been demonstrated as an effective biocide against broad-spectrum bacteria including both Gram-negative and Gram-positive bacteria, in which there are many highly pathogenic bacterial strains[50]. I herewith summarized the exhibited antibacterial activities of some of the Ag-NPs, the data were collected from recent publications (Table-1). In 2004, Sondi and Salopeck-Sondi[53] reported the antimicrobial activities of Ag-NPs against the growth of *E. coli* on Luria–Bertani agar plates. In this study, the *E. coli* bacterial strain served as a model of Gram-negative bacteria. Results showed that the growth inhibition of *E. coli* was dependent on the concentration of Ag-NPs and the initial concentration of cultivated bacteria. The growth inhibitory concentrations were found to be about 50–60 and 20μg cm−3 for 105 CFU and 104 CFU of *E. coli,* respectively. Noticeably, the bacterial cells were damaged and destroyed along with the accumulation of Ag-NPs in the bacterial membrane. Morones *et al.,* [54] have also used different types of Gram-negative bacteria to test the antibacterial activities of Ag-NPs in the range of 1–100 nm.

Table 1: Antimicrobial effects, Antifungal effects and Antiviral effects of Ag-NPs.

S.No.	Characterization of Ag-NPs			Microbial Stains	Major Outcomes
	Size	Particle size	Surface stability		
I. Antibacterial effects					
1.	Ag-NPs Powder	12 nm	None	*E. coli*	Growth inhibitory concentration: 50–60μg cm−3(105 CFU), and 20μg cm−3(104 CFU)
2.	Ag-NPs	1–100 nm	Carbon matrix	*E. coli, V. cholera, P Aeruginosa* and *Salmonella typhus*	Growth inhibitory [45] powder concentration: 75μg ml−1 *P. aeruginosa* and *V. cholera* were more resistant than *E. coli* and *S. typhus.*
3.	Ag-NPs in aqueous Media	10–15 nm	None	*E. coli*, ampicillin- resistant *E. coli,* multi-drug resistant *Salmonella typhi* and *S. aureus*	Growth inhibitory, concentration: 25μg ml−1 for *E. coli*, and multi-drug resistant strains of *S. typhi* ndetermined data for *S. aureaus.*
4.	Ag-NPs	NA	NA	*E. coli* and *S. aureus*	Minimum inhibitory powder concentration: 100μg ml^{-1}
II. Antifungal effects					
5.	Ag-NPs	~3 nm	None	44 strains of 6 fungal species from clinical isolates and ATCC strains of *T. mentagrophytes* and *C. albicans*	IC80: 1–7μg ml^{-1}
6.	Ag-NPs	~5 nm	None	*C. albicans* and *Candida glabrata*	Minimum inhibitory concentration: 0.4–3.3μg ml^{-1}
7.	Ag-NPs	28.2–100nm	None	*T. rubrum*	*Minimum* inhibitory *Concentration:* 10μg $m1^{-1}$
III. Antiviral effects					
8.	Ag-NPs	10, 50 and 800 nm	None	HBV	Inhibition of HBV replication [69] (Ag-NPs,10 nm)
9.	Ag-NPs	10–80 nm	None, or polysaccharide coating	Monkeypox virus (MPV)	Ag-NPs of approximately 10 nm inhibit MPV infection *in vitro*
10.	Ag-NPs	11.2 nm	Biogenic Ag^0	MNV^{-1}	Addition of 31.25 mg biogenic Ag0 m−2 on the filter caused a3.8-log decline of the virus as compared with a 1.5-log

It was reported that the antibacterial activity of Ag-NPs against Gram-negative bacteria divided into three steps:

(i) Nanoparticles mainly in the range of 1–10 nm attach to the surface of the cell membrane and drastically disturb its proper functions, such as permeability and respiration;
(ii) They are able to penetrate inside the bacteria and cause further damage by possibly interacting with sulfur- and phosphorus-containing compounds such as DNA.
(iii) Nanoparticles release silver ions, which will have an additional contribution to the bactericidal effect of Ag-NPs. In addition, Kim *et al.,* [55] have used a model of both Gram-negative (*E. coli*) and Gram-positive (*S. aureus)* bacteria to investigate the antibacterial activities of Ag-NPs.

Shrivastava *et al.,* [56] described the strong antibacterial potency of novel Ag-NPs in the range of 10–15 nm with increased stability against some strains of non-resistant and drug-resistant bacteria. It was concluded that the antibacterial effect is dose-dependent and is more pronounced against Gram-negative than Gram-positive bacteria; it was also independent of acquisition of resistance by the bacteria against antibiotics. It was also suggested that the major mechanism in which Ag-NPs manifested antibacterial properties was by anchoring to and penetrating the bacterial cell wall, and modulating cellular signaling by dephosphorylating putative key peptide substrates on tyrosine residues.

Kvitek *et al.,* [55] have reported that the antibacterial activity of Ag-NPs is also dependent on surface modifications (surfactant/polymers). In their study, different types of surfactants/polymers (sodium dodecyl sulfate-SDS and polyoxyethylenesorbitane monooleate-Tween 80), and one polymer (polyvinylpyrrolidone-PVP 360) were used. These stabilized Ag-NPs were tested with some bacterial strains including S. aureus, E. faecalis, E. coli and P. aeruginosa, and other strains isolated from human clinical samples such as P. aeruginosa, methicillin-susceptible *S. epidermidis*, methicillin-resistant *S. epidermidis,* methicillin-resistant *S. aureus,* vancomycin-resistant *E. faecium* and *K. pneumonia.* The obtained results showed the minimum inhibitory concentrations (MICs) of Ag-NPs in the range of 1.69–13.5μg ml−1, depending on bacterial strains, and the use of surfactants/polymers. Specifically, the antibacterial activity of the Ag-NPs was significantly enhanced when modified by SDS where the MIC decreased under the **'magical value'** of 1μg ml−1. Furthermore, Guzman *et al.,* [58] have reported the results of antibacterial activities of synthesized Ag-NPs against *E. coli, P. aeruginosa* and *S. aureus* around 14.38, 6.74, and 14.38 ppm, respectively.

Recently, the increasing number of drug-resistant bacteria has become a major challenge endangering human health. Ag-NPs have been also demonstrated as an effective biocide against these drug-resistant strains[59]**.** In a study, Lara *et al.,* [59] have tested the antibacterial activities of commercial Ag-NPs (100nm), and results revealed a minimum inhibitory concentration (on average) at 79.4nM for drug-resistant bacteria such as Erythromycin-resistant Streptococcus. pyogenes (66.7 nM), ampicillin-resistant *E. coli* O157:H7 (83.3nM) and multidrug-resistant *P. aeruginosa* (83.3 nM), and at 74.3 nM for drug-susceptible tested bacterial strains. To date, there have been many studies on the effects of Ag-NPs against different bacterial strains. Although some articles proposed different ways to explain the growth inhibition and death of bacterial cells acted on by Ag-NPs[55]**,** but the exact antibacterial mechanism of Ag-NPs has not been fully understood. In a recent review, Jones and Hoek[52] summarized three most common antibacterial mechanisms of Ag-NPs as follows: (i) uptake of free silver ions followed by disruption of ATP production and DNA replication, (ii) Ag-NPs and silver ion generation of reactive oxygen species (ROS) and (iii) Ag-NPs' direct damage to cell membranes. However, further investigations are still needed to demonstrate more clearly this mechanism, especially our question concerning the affinity of Ag-NPs to sulfur- and phosphorus-containing proteins of bacteria, and the effects of this affinity to the functions of bacterial proteins.

Antifungal Properties

Silver nanoparticles (NPs), exhibiting very strong bactericidal activity against both gram-positive and gram-negative bacteria including multi resistant strains. In addition, silver NPs kill bacteria at low concentrations (units of mg/L) [60, 61]**,** which do not reveal acute toxic effects on human cells[62, 63]**.** Besides, silver NPs have not been shown to cause bacterial resistance currently complicating antibiotic therapy of bacterial infections. Regards to mycoses, NPs can be considered as potential antifungal agent[64]**.** I herewith summarized the exhibited antifungal activities of some of the Ag-NPs, the data were collected from recent publications (Table-1).

Antiviral Properties

Ag-NPs have shown effective activities against microorganisms including bacteria and fungi as mentioned above. However, the antiviral activities of Ag-NPs are still open questions to researchers. Very little research have been carried out the effects of Ag-NPs against viruses, indicated in Table 2. As the first report, Elechiguerra *et al.,* [65] have investigated the interaction between Ag-NPs and HIV-1. It was reported that Ag-NPs undergo a size-dependent interaction, with NPs exclusively in the range of 1–10 nm attached to the virus. It was also suggested that Ag-NPs interact with the HIV-1 virus via preferential binding to the exposed sulfur-bearing residues of the gp120 glycoprotein knobs, resulting in the inhibition of the virus from binding to host cells. This mechanism was then demonstrated by Lara *et al.,* [59]. In this article, it was reported that Ag-NPs exert anti-HIV activity at an early stage of viral replication, most likely as a virucidal agent or as an inhibitor of viral entry.

Lu *et al.,* [66] investigated the effects of Ag-NPs of different sizes (10, 50 and 800 nm) on the hepatitis B virus (HBV), and using a HepAD38 cell line as infection model. Their study showed that only Ag-NPs could inhibit production of HBV RNA and extracellular virions in vitro. In summary of the antiviral effects of Ag-NPs, available

literature has suggested that Ag-NPs could bind to outer proteins of viral particles, resulting in inhibition of binding and the replication of viral particles in cultured cells. Although the antiviral mechanism of Ag-NPs has not been fully known yet, Ag-NPs are still suggested as potential antiviral agents in the future.

Applications of Silver Nanoparticles

AgNPs have been used extensively as anti-bacterial agents in the health industry, food storage, textile coatings and a number of environmental applications. It is important to note that despite of decades of use, the evidence of toxicity of silver is still not clear. Products made with AgNPs have been approved by a range of accredited bodies, including the US FDA, US EPA, SIAA of Japan, Korea's Testing and Research Institute for Chemical Industry and FITI Testing and Research Institute[67]. As anti-bacterial agents, AgNPs were applied in a wide range of applications from disinfecting medical devices and home appliances to water treatment[68]. Moreover, this encouraged the textile industry to use AgNPs in different textile fabrics. In this direction, silver nanocomposite fibers were prepared containing silver nanoparticles incorporated inside the fabric[69].

The cotton fibers containing AgNPs exhibited high anti-bacterial activity against *Escherichia coli* [70]. Furthermore, the electrochemical properties of AgNPs incorporated them in nanoscale sensors that can offer faster response times and lower detection limits. For instance, Manno *et al.,* [71] electrodeposited AgNPs onto alumina plates gold micro-patterned electrode that showed a high sensitivity to hydrogen peroxide. Catalytic activities of nanoparticles differ from the chemical properties of the bulk materials. For instance, Ko¨hler *et al.,* showed that the bleaching of the organic dyes by application of potassium peroxodisulphate in aqueous solution at room temperature is enhanced strongly by the application of silver containing nanoparticles. Furthermore, AgNPs was found to catalyze the chemiluminescence from luminol–hydrogen peroxide system with catalytic activity better than Au and Pt colloid. Moreover, Liu and Zhao[72] used silver nanoparticles supported halloysite nanotubes (Ag/HNTs), with Ag content of about 11% to catalyze the reduction of 4-nitrophenol with NaBH4 in alkaline aqueous solutions.

The optical properties of a metallic nanoparticle depend mainly on its surface plasmon resonance, where the Plasmon refers to the collective oscillation of the free electrons within the metallic nanoparticle. It is well known that the Plasmon resonant peaks and line widths are sensitive to the size and shape of the nanoparticle, the metallic species and the surrounding medium. For instance, nanoclusters composed of 2–8 silver atoms could be the basis for a new type of optical data storage. Moreover, fluorescent emissions from the clusters could potentially also be used in biological labels and electroluminescent displays[73].

Applications of Silver Nanoparticles in Medicine

The availability of silver nanoparticles has ensured a rapid adoption in medical practice. Their application can be broadly divided into diagnostic and therapeutic uses. Early diagnosis to any disease condition is vital to ensure that early treatment is started and perhaps resulting in a better chance of cure. This is particularly true for cancer. Lin et al reported silver nanoparticle based Surface-enhanced Raman spectroscopy (SERS) in non-invasive cancer detection[74]. This approach is highly promising and may prove to be an indispensable tool for the future.

In terms of therapeutics, one of the most well documented and commonly used application of silver nanoparticles is in wound healing. Compared with other silver compounds, many studies have demonstrated the superior efficacy of Ag NPs in healing time, as well as achieving better cosmetic after healing. Although the exact mechanisms for these biological effects has not yet been elucidated, an article by Kwan et al did shed some light on this subject[75]. Here, it was shown that in wounds treated with Ag NPs, there was better collagen alignment after healing when compared to controls, which resulted in better mechanical strength.

For oncology, Tse *et al.,* [76] presented a novel method to selectively destroy cancer cells. Human epidermoid cancer cell line was targeted with folated silver-dendrimer composite nanodevices and the labeled cancer cells were subsequently destroyed by the microbubbles generated through increased uptake of laser light energy by AgNPs.

Toxicity of nanoparticles

Knowledge of the toxicity effects of these small substances is limited, but is rapidly growing. Many studies have shown that some nanoparticles demonstrate toxicity in biological systems. Thus research in the internal and external environment is needed; external studies can direct the internal studies. Some researchers have shown that most of the nanoparticles can release active oxygen and cause oxidative stress and inflammation by the RES (reticoendothelial system). Acute toxicity resulting from nanoparticles has been investigated in the mouths of rats. The results indicate that toxicity depends on the size, coating, and chemical component of the nanoparticles. Also, the systemic effects of nanoparticles have been shown in different organs and tissues. The effects on inflammatory and immunological systems may include oxidative stress or pre-inflammatory cytotoxin activity in the lungs, liver, heart, and brain. The effects on the circulatory system can include prethrombosis effects and paradox effects on heart function. Genotoxicity, carcinogenicity, and teratogenicity may occur as a result of the effects of nanoparticles. Some nanoparticles could pass the blood–brain barrier and cause brain toxicity of course more studies are required[76, 77]. Due to the high loading of nanoparticles, macromolecule absorption will increase, so that they can cross through the digestive tract. Because, for example, lectin is such an immunologic material for coating, it can be toxigenic and also cause inflammatory responses or digestive stimulation.

With the use of silver nanoparticles in many clinical conditions, potential toxicity remains a concern. Indeed, hypersensitivity reactions have been reported in a

small proportion of burn patients who received ionic silver treatment[78, 79]. A few in-vitro studies have also showed some evidence of nanoparticles being harmful to some cell lines. The toxicity seems to correlate with smaller particle size. In contrast, others have shown the relative non-toxic nature of Ag NPs, and the overall significance and toxicity in the in vivo setting, and the applicability to human are not known.

Currently, silver nanoparticle based wound dressings are used in the clinics and these have been commonly used for many years with no reported systemic toxicity to the FDA thus far. Taken together, it would seem that silver nanoparticles would be safe to use at low doses[80,81].

CONCLUSION

The field of nanotechnology has grown rapidly over the past few years and has even ventured into all scientific fields including clinical medicine. Out of all kinds of nanoparticles, silver nanoparticles (Ag NPs) seem to have attracted the most interests in terms of their potential application. Ag-NPs are one of the most attractive nanomaterials for commercialization applications. They have been widely used for antimicrobial, electronic and biomedical products. Ag-NPs are one of the most attractive nanomaterials for commercialization applications. In this review, we provide a comprehensive understanding of the Ag-NPs from synthesis methods, antimicrobial effects and possible toxicology considerations of Ag-NPs. The advance in nanotechnology has enabled us to utilize particles in the size of the nanoscale. This has created new therapeutic horizons, and in the case of silver, the currently available data only reveals the surface of the potential benefits and the wide range of applications. We have yet to elucidate the exact cellular pathway of silver nanoparticles. Nonetheless, a bright future holds for this precious metal. Although over the past few years, the knowledge of potential interactions between nanoparticles and biological systems has increased rapidly, it is still very difficult to draw a clear conclusion about the underlying toxicity mechanisms responsible for toxic actions of nanoparticles. Several toxicity studies have demonstrated that the toxicity of nanoparticles maybe significantly associate with a number of unique physiochemical characteristics such as extremely small size distribution and large surface area. As research and business communities continue to invest heavily on nanoparticles, more research is also needed to explore the toxicology of nanoparticles supporting standard setting process as a critical requirement of nanotechnology development.

REFERENCES

1. Nowack B, and Bucheli TD. "Occurrence, behavior and effects of nanoparticles in the environment." *Environ Pollut* 150 (2007): 5–22.
2. Cha KE, and Myung H, "Cytotoxic Effects of Nanoparticles Assessed In Vitro and *In Vivo." J Microbiol Biotechnol* 17.9 (2007): 1573–1578.
3. Bernd Nowack, Harald F Krug, and Murray Height. "120 Years of Nanosilver History: Implications for Policy Makers." *Environ Sci Technol* 45 .4 (2011): 1177–1183.
4. Lewinski N, Colvin V, and Drezek R. "Cytotoxicity of Nanoparticles." *Small* 4 (2008): 26–49.
5. Zhang QW, Kusaka Y, Sato K, Nakakuki K, Kohyama N, and Donaldson K. "Differences in the extent of inflammation caused by intratracheal exposure to three ultrafine metals: role of free radicals." *J Toxicol Env Heal* 53 (1998): 423–438.
6. Oberdorster G, Ferin J, and Lehnert BE. Correlation between particle-size, in-vivo particle persistence and lung injury." *Environ Health Persp* 102 (1994): 173–179.
7. Holsapple MP, Farland WH, and Landry TD. "Research strategies for safety evaluation of nanomaterials, Part II: Toxicological and safety evaluation of nanomaterials, current challenges and data needs." *Toxicol Sci* 88 (2005): 12–17.
8. Handy RD, Von der Kammer F, JR Lead, M Hassellov, R Owen, and M Crane. "The ecotoxicology and chemistry of manufactured nanoparticles." *Ecotoxicology* 17 (2008): 287–314.
9. Quik JT, Lynch I, Van Hoecke K, CJ Miermans, KA De Schamphelaere, CR Janssen, KA Dawson, MA Stuart, and D Van De Meent. "Effect of natural organic matter on cerium dioxide nanoparticles settling in model fresh water." *Chemosphere* 81(2010): 711–715.
10. Kiser MA, Ryu H, Jang H, Hristovski K, and Westerhoff P. "Biosorption of nanoparticles to heterotrophic wastewater biomass." *Water Res* 44 (2010): 4105–4114.
11. Geiser M. "Update on macrophage clearance of inhaled micro and nanoparticle." *J Aerosol Med Pulm Drug Deliv* 23 (2010): 207–217.
12. Garnett MC, and P Kallinteri. "Nanomedicines and nanotoxicology: some physiological principles." *Occup Med (Lond)* 56 (2006): 307–311.
13. Yacob NR, Malmstadt N, Fazlollahi F, DeMaio L, Marchelletta R, Hamm-Alvarez SF, Borok Z, Kim KJ, and Crandall ED. "Mechanisms of alveolar epithelial translocation of a defined population of nanoparticles." *Am J Respir Cell Mol Biol* 42 (2010): 604–614.
14. Wiesner MR, Hotze EM, Brant JA, and Espinasse B. "Nanomaterials as possible contaminants: the fullerene example." *Water Sci Technol* 57 (2008): 305–310.
15. Aitken RJ, Chaudhry MQ, Boxall AB, and Hull M. "Manufacture and use of nanomaterials: current status in the UK and global trends." *Occup Med (Lond)* 56 (2006): 300–306.
16. Oberdorster G. "Safety Assessment for Nanotechnology and Nanomedicine: concepts of Nanotoxicology." *Intern Med* 267 (2010): 89–105.
17. Stern ST, and McNeil SE. "Nanotechnology safety concerns revisited." *Toxicol Sci* 101 (2008): 4–21.
18. Sperling RA, Rivera Gil P, Zhang F, Zanella M, and Parak WJ. "Biological applications of gold nanoparticles." *Chem Soc Rev* 37 (2008): 1896–1908.
19. Bennett WD. "Rapid translocation of nanoparticles from the lung to the bloodstream?" *Am J Respir Crit Care Med* 165 (2002): 1671–1672.
20. Greulich C, Diendorf J, Simon T, Eggeler G, Epple M, and Koller M. "Uptake and intracellular distribution of silver nanoparticles in human mesenchymal stem cells."*Acta Biomater* 7 (2011): 347–354.
21. Yacobi NR, Phuleria HC, Demaio L, Liang CH, Peng CA, and Sioutas C. "Nanoparticle effects on rat alveolar epithelial cell monolayer barrier properties." *Toxicol In Vitro* 21(2007): 1373–1381.
22. Crosera M, Bovenzi M, Maina G, Adami G, Zanette C, Florio C, and Filon Larese F. "Nanoparticle dermal absorption and toxicity: a review of the literature." *Int Arch Occup Environ Health* 82 (2009): 1043–1055.

23. Ryman-Rasmussen JP, Riviere JE, and Monteiro-Riviere NA. "Penetration of intact skin by quantum dots with diverse physicochemical properties." *Toxicol Sci* (2006): 91159–165.

24. Hagens WI, Oomen AG, de Jong WH, Cassee FR, and Sips AJAM. "What do we (need to) know about the kinetic properties of nanoparticles in the body?." *Regul Toxicol Pharmacol* 49 (2007): 217–229.

25. Nemmar A, Hoet PHM, Vanquickenborne B, Dinsdale D, Thomeer M, Hoylaerts MF, Vanbilloen H, Mortelmans L, and Nemery B. "Passage of inhaled particles into the blood circulation in humans." *Circulation* 105 (2002): 411–414.

26. Torreggiani A, Jurasekova A, D'Angelantonio M, Tamba M, Garcia-Ramos JV and Sanchez-Cortes S. "Colloids and Surfaces A: Physicochemical and Engineering Aspects." *Colloids and Surfaces A Physicochemical and Engineering Aspects* 3391–3 (2009): 1-246, A 339 60.

27. Lee Y, Choi JR, Lee KJ, Stott NE, and Kim D. "Large-scale synthesis of copper nanoparticles by chemically controlled reduction for applications of inkjet-printed electronics." *Nanotechnology* 1519.41 (2008): 415604.

28. Dongjo Kim, Sunho Jeong, and Jooho Moon. "Synthesis of silver nanoparticles using the polyol process and the influence of precursor injection." *Nanotechnology* 17 (2006):4019–4024.

29. Kruis F, Fissan H, and Rellinghaus B. "Sintering and evaporation characteristics of gas-phase synthesis of size-selected PbS nanoparticles." *Mater Sci Eng B* 69 (2000): 329–334.

30. Magnusson M, Deppert K, Malm J, Bovin J, and Samuelson L. "Gold nanoparticles: production, reshaping, and thermal charging." *J Nanoparticle Res* 1 (1999): 243–251.

31. Jung J, Oh H, Noh H, Ji J, and Kim S. "Metal nanoparticle generation using a small ceramic heater with a local heating area." *J Aerosol Sci* 37 (2006):1662–1670.

32. Hagens WI, Oomen AG, de Jong WH, Cassee FR, and Sips AJAM. "What do we (need to) know about the kinetic properties of nanoparticles in the body?" *Regul Toxicol Pharmacol* 49 (2007): 217–229.

33. Kabashin AV, and Meunier M. "Synthesis of colloidal nanoparticles during femtosecond laser ablation of gold in water." *J Appl Phys* 94 (2003): 7941–7943.

34. Sylvestre JP, Kabashin AV, Sacher E, Meunier M, and Luong JHT. "Stabilization and size control of gold nanoparticles during laser ablation in aqueous cyclodextrins." *J Am Chem Soc* 126 (2004): 7176–7177.

35. Link S, Burda C, Nikoobakht B, and El-Sayed M. "Laser-Induced shape changes of colloidal gold nanorods using femtosecond and nanosecond laser pulses." *J Phys Chem B* 104 (2000): 6152–6163.

36. Kawasaki M, and Nishimura N. "1064-nm laser fragmentation of thin Au and Ag flakes in acetone for highly productive pathway to stable metal nanoparticles." *Appl Surf Sci* 253 (2006): 2208–2216.

37. Tarasenko N, Butsen A, Nevar E, and Savastenko N. "Synthesis of nanosized particles during laser ablation of gold in water." *Appl Surf Sci* 252 (2006): 4439–4444.

38. Mafune F, Kohno J, Takeda Y, Kondow T, and Sawabe H. "Structure and stability of silver nanoparticles in aqueous solution produced by laser ablation." *J Phys Chem B* 104 (2000): 8333–8337.

39. Korbekandi H, Iravani S, Abbasi S. "Optimization of biological synthesis of silver nanoparticles using *Lactobacillus casei* subsp. casei. *J ChemTechnol Biotechnol* 87 (2012):932–937.

40. Tsuji T, Iryo K, Watanabe N, and Tsuji M. "Preparation of silver nanoparticles by laser ablation in solution: influence of laser wavelength on particle size." *Appl Surf Sci* 202 (2002): 80–85.

41. Dongjo Kim, Sunho Jeong, and Jooho Moon. "Synthesis of silver nanoparticles using the polyol process and the influence of precursor injection." *Nanotechnology* 17.16 (2006): 4019-24.

42. Dang TMD, Le TTT, Blance EF, and Dang MC. "Influence of surfactant on the preparation of silver nanoparticles by polyol method." *Adv Nat Sci Nanosci Nanotechnol* 3 (2012): 035004-1-4.

43. Sintubin L, Verstraete W, and Boon N. "Biologically produced nanosilver: current state and future perspectives." *Biotechnol Bioeng* 109.10 (2012): 2422-36.

44. Suresh AK, Pelletier DA, Wang W, Moon JW, Gu B, Mortensen NP, Allison DP, Joy DC, Phelps TJ, and Doktycz MJ. "Silver nanocrystallites: biofabrication using *Shewanella oneidensis*, and an evaluation of their comparative toxicity on gram-negative and gram-positive bacteria." *Environ Sci Technol* 44 (2010): 5210–5.

45. Pugazhenthiran N, Anandan S, Kathiravan G, Udaya Prakash NK, Simon Crawford S, and Ashokkumar M. "Microbial synthesis of silver nanoparticles by Bacillus sp." *J Nanopart Res* 11 (2009):1811–1815.

46. Naik RR, Stringer SJ, Agarwal G, Jones SE, and Stone MO. "Biomimetic synthesis and patterning of silver nanoparticles." 2002, *Nat Mater* 1.3 (2002): 169-72.

47. Yoosaf K, Ipe BI, Suresh CH, Thomas KG. "In situ synthesis of metal nanoparticles and selective naked-eye detection of lead ions from aqueous media." *J Phys Chem C* 111 (2007): 12839-12847.

48. Vilchis-Nestor AR, Sanchez-Mendieta V, Camacho-Lopez MA, Gomez-Espinosa RM, and Camacho-Lopez MA. "Solventless synthesis and optical properties of Au and Ag nanoparticles using Camellia sinensis extract." *Mater Lett* 62 (2008): 3103-3105.

49. Bhainsa KC, and D'Souza SF. "Extracellular biosynthesis of silver nanoparticles using the fungus *Aspergillus fumigatus*," *Colloids Surf B Biointerfaces* 47 (2006): 160-164.

50. Zhang W, Qiao X, Chen J, and Wang H. "Preparation of silver nanoparticles in water-in-oil AOT reverse micelles." *J Colloid Interface Sci* Oct 1. 302. 1 (2006):370-3.

51. He B, Tan JJ, Liew KY, Liu H. Synthesis of size controlled Ag nanoparticles, *Journal of Molecular Catalysis A Chemical* 221 (2004):121-126.

52. Jones CM, and Hoek EMV. "A review of the antibacterial effects of silver nanomaterials and potential implications for human health and the environment." *J Nanopart Res* 12 (2010):1531–1551.

53. Sondi Ivan, and Branka Salopek-Sondi. "Silver nanoparticles as antimicrobial agent: a case study on *E. coli* as a model for Gram-negative bacteria." *Journal of Colloid and Interface Science* 275 (2004): 177–182.

54. Morones Jose Ruben, Jose Luis Elechiguerra, Alejandra Camacho, Katherine Holt, JuanBKouri, Jose Tapia Ramırez, and Miguel Jose Yacaman. "The bactericidal effect of silver nanoparticles." *Nanotechnology* 16 (2005): 2346 – 2353.

55. Kim JS, Kuk E, Yu KN, Kim JH, Park SJ, Lee HJ, Kim SH, Park YK, Park YH, Hwang CY, Kim YK, Lee YS, Jeong DH, and Cho MH. "Antimicrobial effects of silver nanoparticles." *Nanomedicine* 3.1 (2007):95-101.

56. Shrivastava S, Singh SK, Mukhopadhyay A, Sinha ASK, Mandal RK, and Dash D. "Negative regulation of fibrin polymerization and clot formation by nanoparticles of silver." *Colloids Surf B Biointerfaces* 82 (2011): 241-246.

57. Kvitek L, Ales Panacek, Jana Soukupova, Milan Kolar, Renata Vecerova, Robert Prucek, Mirka Holecova, and Radek Zboril. "Effect of Surfactants and Polymers on Stability and Antibacterial Activity of Silver Nanoparticles (NPs)." *Phys Chem C* 112. 15.(2008): 5825–5834.

58. Guzman M, Dille J, and Stephane Godet S. "Synthesis and antibacterial activity of silver nanoparticles against gram-positive and gram-negative bacteria." *Nanomedicine Nanotechnology Biology and Medicine* 8. 1 (2012): 37-45.

59. Lara HH, Ayala-Nunez NV, del Carmen Ixtepan Turrent L, and Rodrìguez Padilla C. "Bactericidal effect of silver nanoparticles against multidrugresistant bacteria." *World Journal of Microbiology and Biotechnology* 26 (2010): 615-621.

60. Panacek A, Kvitek L, Prucek R, Kolar M, Vecerova R, and Pizurova N. "Silver colloid nanoparticles: synthesis, characterization, and their antibacterial activity." *Journal of Physical Chemistry*: *Part B* 110 (2006):16248–53.

61. Roe D, Karandikar B, Bonn-Savage N, Gibbins B, and Roullet JB. "Antimicrobial surface functionalization of plastic catheters by silver nanoparticles." *Journal of Antimicrobial Chemotherapy* 61 (2008): 869–76.

62. Asha Rani PV, Mun GLK, Hande MP, and Valiyaveettil S. "Cytotoxicity and genotoxicity of silver nanoparticles in human cells." *ACS Nano* 3 (2009):279–90.

63. Carlson C, Hussain SM, Schrand AM, Braydich-Stolle LK, Hess KL, and Jones RL. "Unique cellular interaction of silver nanoparticles: sizedependent generation of reactive oxygen species." *Journal of Physical Chemistry Part B* 112 (2008): 13608–19.

64. Ales Pana C, Milan K, Renata V, Robert P, Jana S, Vladimir K, Petr H, Radek Z, and Libor K. "Antifungal activity of silver nanoparticles against Candida spp." *Biomaterials* 30 (2009): 6333–6340.

65. Elechiguerra JL, Justin L Burt, Jose R Morones, Alejandra Camacho-Bragado, Xiaoxia Gao, Humberto H Lara, and Miguel Jose Yacaman. "Interaction of silver nanoparticles with HIV-1."*Journal of Nanobiotechnology* 3: (2005) 6.

66. Lu L, Sun RWY, Chen R, Hui CK, Ho CM, Luk JM, Lau GKK, and Che CM. "Silver nanoparticles inhibit hepatitis B virus replication." *Antivir Ther* 13 (2008): 253–262.

67. Jia X, Maa X, Wei D, Dong J, and Qian W. "Direct Formation of Silver Nanoparticles in Cuttlebone Derived Organic Matrix for Catalytic Applications." *Coll Surf A Phys Cochem Aspects* 330 (2008): 234.

68. Jain P, and Pradeep T. "Potential of silver nanoparticle-coated polyurethane foam as an antibacterial water filter." *Biotechnol Bioeng* 90.1(2005):59-63.

69. Sang Young Yeo, Hoon Joo Lee, and Sung Hoon Jeong. "Preparation of nanocomposite fibers for permanent antibacterial effect." *J Mat Sci* 38.10 (2003): 2143-2147.

70. Chen CY, and Chiang CL. "Preparation of cotton with antibacterial silvernanoparticles." *Mater Lett* 62 (2008): 3607–3609.

71. Manno D, Filippo E, Giulio Di M, and Serra A. "Synthesis and characterization of starch-stabilized Ag nanostructures for sensors applications." *Journal of Non-Crystalline Solids* 354.52–54.15 (2008): 5515–5520.

72. Liu Peng, and Mingfei Zhao. "Silver nanoparticle supported on halloysite nanotubes catalyzed reduction of 4-nitrophenol (4-NP)." *Appl Surf Sci* 255 (2009): 3989-3993.

73. Berciaud S, Cognet L, Tamarat P, and Lounis B. Observation of intrinsic size effects in the optical response of individual gold nanoparticles." *Nano Lett* 5. 3 (2005):515-8.

74. Lin J, Chen R, Feng S, Pan J, Li Y, and Chen G. "A novel blood plasma analysis technique combining membrane electrophoresis with silver nanoparticle-based SERS spectroscopy for potential applications in noninvasive cancer detection Nanomedicine." *Nanotechnology Biology and Medicine* 7.5 (2011): 655-663.

75. Kwan KHL, Liu XL, To MKT, Yeung KWK, Ho CM, and Wong KKY. "Modulation of collagen alignment by silver nanoparticles results in better mechanical properties in wound healing. Nanomedicine." *Nanotechnology Biology and Medicine* 7.4 (2011): 497-504.

76. Tse C, Zohdy MJ, Ye JY, O'Donnell M, Lesniak W, and Balogh L. "Enhanced optical breakdown in KB cells labeled with folate-targeted silver-dendrimer composite nanodevices. Nanomedicine." *Nanotechnology Biology and Medicine* 7.1 (2011): 97-106.

77. Unrine JM, Tsyusko OV, Hunyadi SE, Judy JD and Bertsch PM "Effect of particle size on chemical speciation and bioavailability of copper to earthworms (*Eisenia fetida*) exposed to copper nanoparticles." *J Env Qual* 39 (2010): 1942–53.

78. Hill G T, Mitkowski NA, Aldrich-Wolfe L, Emele LR and Jurkonie DD. "Methods for assessing the composition and diversity of soil microbial communities." *Appl Soil Ecol* 15 (2000): 25–36.

79. Muhlfeld C, Gehr P, and Rothen-Rutishauser B. "Translocation and cellular entering mechanisms of nanoparticles in the respiratory tract." *Swiss Med Wkly* 138 (2008):387–39.

80. Rutishauser R, Muhlfeld C, Blank F, Musso C, and Gehr P. "Translocation of particles and inflammatory responses after exposure to ine particles and nanoparticles in an epithelial air-way model." *Part Fibre Toxicol* 4 (2007):9–15.

81. Nel A, Xia T, Madler L, and Li N. "Toxic Potential of Materials at the Nano level." *Sci* 311 (2006):622–627.

CITE THIS ARTICLE AS:

S. Janardana Reddy. Silver nanoparticles - synthesis, applications and toxic effects on humans: a review. *International Journal of Bioassays* 4.11 (2015): 4563-4573.

Source of support: Nil

Conflict of interest: None Declared