Plant Archives Vol. 20, Supplement 2, 2020 pp. 4326-4336 **e-ISSN:2581-6063 (online), ISSN:0972-5210**

REVIEW ARTICLE
GREEN SYNTHESIZED SILVER NANOPARTICLES AND THEIR POTENTIAL FOR ANTIBACTERIAL APPLICATIONS

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Abstract

Multi-drug resistance is a growing problem in the treatment of infectious diseases and the widespread use of broad-spectrum antibiotics has produced antibiotic resistance for many human bacterial pathogens. Recent advancements in nanotechnology-based medicines have opened new horizons for combating multidrug resistance in microorganisms, allowing the synthesis of nanoparticles that can be assembled into complex architectures. Novel studies and technologies are devoted to understanding the mechanisms of disease for the design of new drugs. The use and search for drugs obtained from plants and other natural products have increased in recent years, but unfortunately infectious diseases continue to be a major health burden worldwide. Since ancient times, silver was known for its anti-bacterial effects and for centuries it has been used for prevention and control of disparate infections. In particular, the use of silver nanoparticles (AgNPs) as a potent antibacterial agent has received much attention. AgNPs exhibits their antimicrobial potential through multifaceted mechanisms. On the other side, AgNPs exposure to human cells induces cytotoxicity, genotoxicity and inflammatory response in human cells in a cell-type dependent manner. This has raised concerns regarding use of AgNPs in therapeutics and drug delivery. This paper aims to critically review AgNPs from the perspectives of research trends, global consumption, synthesis, properties and future challenges. Generally, AgNPs can be synthesized using three methods, namely physical, chemical and biological and the related works as well as their numerous advantages and disadvantages are presented in this review. In addition, AgNPs can be potentially explored for various applications. Future challenges on (AgNPs) synthesis, their release into the environment and scaling up production, as presented in the review, suggest that several potential topics for future works are available to promote a safer and more efficient use of these nanoparticles.
***Keywords*:** Silver nanoparticles, Nanotechnology, Multidrug resistance, Antimicrobial activity, Cytotoxicity, Environmental chemistry.

Introduction

Unresponsiveness of microbes to lethal doses of structurally diverse classes of drugs with different mechanisms of cytotoxic action is generally referred to as multidrug resistance (MDR). Multidrug resistance of the pathogenic microorganisms to the antimicrobial drugs has become a prime concern toward successful diagnosis and treatment of pathogenic diseases of bacterial and fungal origin (Desselberger, 2000). This has led to emergence and re-emergence of infectious diseases. Indeed, exposure of antimicrobials and antibiotics to bacteria are the opportunities for microbes to become less susceptible toward them mainly by altering the cell structure and cellular metabolism. In this way microbes either destroy the antimicrobials and antibiotics or become unresponsive toward them in future exposures (Rai *et al.,* 2012). Four mechanisms have been recognized that account for antibiotic resistance in bacteria: (a) alteration of microbial drug target proteins, (b) enzymatic degradation or inactivation of drug, (c) decreased membrane permeability, and (d) increased efflux of drug (Kumar et al., 2013). Among all, the extrusion of antimicrobial drug by the multidrug efflux pumps contributes maximally for MDR among pathogenic strains (Li *et al.,*1997; Levy, 2002). Although, excessive and irrational use of antibiotics is major factors in development of resistance, the acquisition and dissemination of drug-resistance genes and resistant bacteria have significantly contributed to drug resistance (Levy, 2002; Davies, 1997). Confronted by the increasing doses of antibiotic drugs over many years, pathogens become drug-resistant and respond to antibiotics by generating progenies that are no more susceptible to antimicrobials therapy (Porras & Vega 2012). It is therefore necessary to look for new sources of effective potent drugs. Nature is an inexhaustible source of health-promoting substances. Combination of knowledge in natural medicine with modern technology leads to the discovery of new drugs. One of the most promising sources in recent years has been shown to be plant extracts, which are rich in antioxidant and antimicrobial compounds that have been used as a nanoparticle synthesis agent (Kumari *et al.,* 2015; Franci *et al.,* 2015; Rozzella & Pompa 2014). Recently, development of novel, efficient nanotechnological-based antimicrobial agents against multidrug-resistant bacteria is among one of the priority areas in biomedical research. Nanotechnology is referred to the term for manufacture, portrayal, manipulation, and application of structures by controlling shape and size at nanoscale (Sarsar *et al.,* 2013). The field of nanotechnology is the most dynamic region of research in material sciences and the synthesis of nanoparticles (NPs) is picking up significantly throughout the world. NPs show totally novel or enhanced properties taking into account particular characteristics, i.e., size (1-100 nm), shape, and structure (Jahn, 1999; Slawson *et al.,*1992; Nalwa, 1999). There is a wide range of applications of NPs such as in human health appliances, industrial fields, medical applications, biomedical fields, engineering, electronics, and environmental studies (Hamzeh & Sunahara 2013). NPs can be categorized broadly as inorganic and organic NPs. Inorganic NPs incorporate semi-conductor NPs (like ZnO, ZnS, CdS), metallic NPs (like Au, Ag, Cu, Al), and magnetic NPs (like Co, Fe, Ni), while organic NPs incorporate carbon NPs (like fullerenes, quantum dots, carbon nanotubes). There is a growing enthusiasm for Gold and Ag (noble metal) NPs as they furnish superior characteristics with useful flexibility (Vadlapudi & Kaladhar, 2014). About 5000 years ago, many Greeks, Romans, Persians and Egyptians used silver in one form or other to store food products (Grier, 1968). Use of silver ware during ancient period by various dynasties was common across the globe utensils for drinking and eating and storing various drinkable and eatable items probably due to the knowledge of antimicrobial action (Hill & Pillsburry, 1939). There are records regarding therapeutic application of silver in literature as earlier as 300 BC. In the Hindu religion, till date silver utensils are preferred for the panchamrit preparation using curd, *Ocimum sanctum* and other ingredients. The therapeutic potentials of various metals are mentioned in ancient Indian Aurvedic medicine book medicinal literature named Charak Samhita (Galib *et al.,* 2011). Until the discovery of antibiotics by Alexzander Flemming, silver was commonly used as antimicrobial agent. Silver nanoparticles (AgNPs) are a class of materials with sizes in the range 1-100 nm. The interest in the study of AgNPs with respect to their various different behaviors has recently increased because of their unique and attractive physical, chemical, and biological properties. AgNPs are also known to have unique properties in terms of toxicity, surface plasmon resonance, and electrical resistance. Based on these, intensive works have been conducted to investigate their properties and potential applications for several purposes such as antimicrobial agents in wound dressings, anticancer agents, electronic devices, and water treatment (Achmad *et al.,* 2017). Ag-NPs have a substantial surface zone which results into noteworthy biochemical reactivity, catalytic activity, and atomic behavior compared with bigger particles having same chemical composition (Xu *et al.,* 2006). Among the several metal nanoparticles, silver nanoparticles have received considerable attention due to their broad inhibitory behavior towards nearly 650 species of microbes, and more importantly against antibiotic resistant bacterial strains (Jeong *et al.,* 2005). In one of the findings, it was shown that silver nanoparticles showed superior antibacterial activity against E. coli and S. aureus when compared to gold nanoparticles (Amin *et al.,* 2009). The worldwide production of silver nanoparticles is estimated to be 320 tons per year (Nowack *et al.,* 2011). This paper aims to critically review AgNPs from the perspectives of research trends, global consumption, synthesis, properties, applications and future challenges as presented in the review, suggest that several potential topics for future works are available to promote a safer and more efficient use of silver nanoparticles.

Research trends

The increased popularity of research on AgNPs in the past decades is strongly evident. This highlights the related works that use silver nanoparticle as keyword (Cao, 2004). It is a clear proof that studies on AgNPs are interesting and being continually pursued even today. In the first 20 decades, studies on AgNPs were more focused on synthesizing and characterizing them using chemical approaches. Physical and biological approaches were further proposed because of their safe and green nature. Today, many works are concentrated on biological procedures and applications for several purposes. It is worth noting that materials science is the dominant subject area of AgNPs. In addition, the Journal of Nanoparticle Research has published more topics on AgNPs than others. The top six institutions that have published on this topic are the Chinese Academy of Sciences, Seoul National University, Nanjing University, Jilin University, Northwestern University, and Hanyang University. Furthermore, China, the United States, India, South Korea, Japan and Germany are the top six countries active in publishing works on AgNPs. It is interesting to see that publications on AgNPs are generally dominated by the developed countries. Besides the studies on AgNPs, the developments of nanotechnology are widely explored in and originate from these countries. This trend is closely associated with their national income, intellectual property policies, and human resources. India and China are the two developing countries that have shown recently activity in developing nanotechnology. In this regard, the Department of Science and Technology, India, has invested $20 million for nanomaterials science and technology development (Iravani *et al.,* 2014). China ranks the third in the number of nanotechnology patent applications filed. Furthermore, it is important to note that nanotechnology development can be achieved through knowledge transfer by means of research collaboration and international funding. Also, serious awareness and close involvement of the national government are essential.

Global consumption

Global consumption of AgNPs is predicted to increase owing to their increasing industrial demand. Intensive use in various industries such as electronics, appliances, textiles, and medical applications is due to their remarkable properties and behaviors compared to other nanomaterials. Moreover, recent literature reports that AgNPs can be easily synthesized at room temperature using physical, chemical, or biological procedures. Their characterization has been well established using various methods. Also, their behavior has been simulated and verified using experimental data. Healthcare shows the fastest growing trend compared to other applications. Increasing demand for antibacterial and antifungal medications as well as in the prevention of other diseases is the contributing factor responsible for the growth of AgNPs. This is supported by the fact that AgNPs are effective against gram-positive and gram-negative bacteria as well as antifungal and antimicrobial agents (Tan *et al.,* 2009; Lee & Kang 2004; Jung *et al.,* 2006; Tien *et al.,* 2008; Siegel *et al.,* 2012; Kim *et al.,* 2006; Sun & Xia 2002; Chen *et al.,* 2007). Growing demand for AgNPs in the electronics and electrical fields is predicted to see significant growth until 2022. The increasing demand for products having high performance, high processing capability, more stability, and more conductivity is responsible for the growth of AgNPs in these areas. For textiles, their increase in demand is due to the expanding applications in sportswear, underwear, military clothing, and medical textiles. In addition, their growth in the food and beverages industry is mainly due to increased demand for materials for food storing and processing so that food can stay fresh for longer perids and hygienic. Moreover, the stable rise in demand for other applications of AgNPs is attributed to their utilization in the production of jewelry, coins, photography, and photovoltaics. The aforementioned trend of global AgNP consumption clearly indicates that

AgNPs exist widely in the environment. Therefore, environmental effects caused by AgNP release from a wide range of products should be considered.

Synthesis of silver nanoparticles

A top-down approach to nanofabrication is based on the synthesis of the nanomaterials from the bulk system (Dang & Le 2012), while bottom-up synthesis of nanomaterials is based on packing of several atoms, or molecules with molecules, or clusters with clusters (Dang & lee 2012; Patil *et al*., 2012). A representation of the top down and bottom up approach is shown in Figure (1). Procedures used in top-down synthesis of nanoparticles include etching, grinding, ball milling, laser ablation, photo-lithography, and electron beam lithography. Unlike top-down approach, bottom up approach is based on organization of small constituents (atoms or molecules). This method is guided by physicochemical interaction of neighboring constituents, the surface chemistry and self assembly principles of the constituents that makeup the nanoscopic material. Bottomup approach offers a better chance to obtain nanostructures with less defects, more homogeneous chemical composition, potentially better short and long range order. Some examples of bottom-up approach include biological, photochemical, and chemical synthetic routes. Here, we describe the bottom up method which is the primary focus of the study.

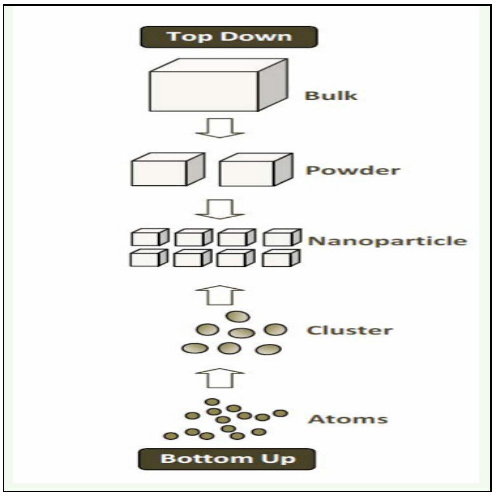

Fig. 1 : Schematic representation of formation of nanostructure via Top-down Vs. Bottom-up.

Physical method

In the physical synthesis process of Ag-NPs, usually, the physical energies (thermal, ac power, and arc discharge) are utilized to produce Ag-NPs with a narrow size particle distribution. This approach can permit us to produce large quantities of Ag-NPs samples in a single process. Under the physical methods, the metallic NPs can be generally fabricated by evaporation-condensation process that could be carried out in a tube furnace at atmospheric pressure. The large space of tube furnace, consumption of large amount of energy, raising the environmental temperature around the source material and a lot of time for achieving thermal stability, are the few drawbacks of the method. Another physical method of synthesis of Ag-NPs is a thermal decomposition method that used to synthesize the powdered Ag-NPs (Nazeruddin *et al.,* 2014). In particular case, Ag-NPs (particles with particle size of 9.5 nm with a standard deviation of 0.7 nm) were formed by thermal decomposition of an Ag^{1+}–oleate complex, at high temperature of 290^0C. This indicates that the Ag-NPs were prepared with a very narrow size distribution. (Rashid *et al.* 2013) reported a small ceramic heater (with a local heating area) for synthesizing the metal NPs and by evaporating the source materials under the flow of carrier gas, i.e., air. It had been reported that the geometric mean diameter, the geometric standard deviation, and the total concentration of spherical NPs without agglomeration increases with the temperature of the surface of the heater. The testimony given by (Solomon *et al.,* 2007) reveal the fabrication technique for the Ag-NPs by employing the electrical discharge machining (EDM) without addition of any surfactants. Where, pure silver wires were submerged in deionized water and treated as electrodes. The stability of suspension, concentration of particles, particle size, solution properties, electric conductivity, and pH are the factors that may affect the synthesis of NPs by enhancing the complex interactions to the nanofluid, in the form of van der Waals combination force and electrostatic Coulomb repulsion force. Metallic Ag-NPs of the 10 nm size and ionic silver of approximate concentrations 11-19 ppm were obtained by silver rod at the consumption rate ~ 100 $mgmin^{-1}$. More recently, (Niu & Li 2014) reported an unconventional approach for the physical synthesis of gold-NPs and Ag-NPs by the direct metal sputtering into the liquid medium (glycerol-to-water).

Chemical method

Among the various known methods, the chemical method has been the most widely studied because of the general versatility of the technique. For example, silver nanocubes in large amounts have been synthesized by reducing silver nitrate with ethylene glycol in the presence of stabilizing agent, the so-called polyol process (Nogueira *et al.,* 2014). Ethylene glycol serves as both reductant and solvent. Based on the molar ratio of stabilizer relative to silver nitrate and the experimental conditions used in the synthesis, the geometric shape and size of the nanoparticles could be varied significantly. The polyol process has also been used to synthesize spherical silver nanoparticles with a controllable size and high monodispersity (Li *et al.,* 2013). Alternatively, spherical silver nanoparticles can be synthesized using oleyl amine-liquid paraffin mixture (Brewer *et al.,* 2005). The use of a high boiling point liquid e.g. paraffin, offers the flexibility to effectively use reaction temperature to generate silver nanoparticles of varying size without changing the solvent. The size of nanoparticles in the solution is strongly dependent on the duration of the individual stages of synthesis i.e., synthesis of silver nuclei and subsequent growth accompanying nuclei formation. For the synthesis of monodispered silver nanoparticles with uniform size distribution, it is preferable to form the nuclei at similar time. The initial nucleation and the subsequent growth step of initial nuclei can be controlled by adjusting the reaction parameters such as reaction temperature, pH, type of metal precursors, reducing agents (e.g. $NaBH_4$, ethylene glycol, glucose) and stabilizing agents (e.g. sodium citrate) (henglein, 1998; Roberto *et al.,* 2009; Nowack *et al.,* 2011). Reduction of silver salts to form nanoparticles has been achieved using sodium citrate and/or borohydride. The use of sodium borohydride (a strong reductant) usually results in the formation of somewhat monodispersed smaller sized silver nanoparticles while the use of only citrate (a weaker reductant) usually results in the formation of somewhat polydispersed larger sized silver nanoparticles because of slower reduction rate (Ghosh *et al.,* 2003). Reduction of silver ion by sodium citrate is shown below (Huang *et al.,* 2008).

$$4Ag^{+} + C_6H_5O_7Na_3 + 2H_2O \rightarrow 4Ag^{0} + C_6H_5O_7H_3 + 3Na^{+} + H^{+} + O_2 \uparrow \quad ...(4)$$

Reactions 5, 6, and 7 provide the individual steps and overall reaction step in the formation of silver nanoparticles upon reduction with sodium borohydride.

$$2Ag^{+} + 2e^{-} \rightarrow 2Ag \quad ...(5)$$

$$2BH_4^{-} \rightarrow B_2H_6 + H_2 + 2e^{-} \quad ...(6)$$

$$2AgNO_3 + 2NaBH_4 \rightarrow 2Ag + 2H_2 + B_2H_6 + NaNO_3 \quad ...(7)$$

(Sakamoto *et al.,* 2009) proposed a mechanism of nanoparticle formation based on sodium borohydride reduction and stabilization (without stabilizing agent). The nanoparticle formation is based on the temporary stabilization of smaller sized silver nanoparticles by excess BH_4^- species. However, with time, there is the collapse of the stabilized shell around the nanoparticles that causes the nanoparticles to aggregate which is largely attributed to the degradation of $BH4^-$ accompanied by hydrogen gas evolution as mentioned in equation 8.

$$BH_4^{-} + 4H_2O \rightarrow B(OH)_4 + 4H_2 \quad ...(8)$$

Given the borohydrydate anion degradation in sodium borohydride capped nanoparticles, a number of alternative capping agents have been studied to stabilize nanoparticles with or without dispersants. A nice review on the common capping agents commonly used in nanoparticle synthesis and their impact is presented by (Chouhan & Ameta *et al.,* 2107). Recently aminosilanes have been used as capping agent to stabilize the nanoparticles as well as serve as coupling agent to couple with other moieties (Roy *et al.,* 2013). took a different approach to stabilize nanoparticle by dispersing oleic acid capped silver nanoparticles with different dispersion agents. Interactions between dispersant and capping agent determine the extent of dispersion of silver nanoparticles. H-bonding between dispersant and capping agent effectively results in enhanced agglomerations of Ag nanoparticles (Thakur *et al.,* 2010). Other studies have evaluated the stability of stabilized silver nanoparticles at various pH conditions. It was established that citrate anion as capping molecule may not be enough to maintain the stability of citrate stabilized nanoparticles over a wide pH range (Sadeghi & Gholamhoseinpoor 2015). There is a strong likelihood for the nanoparticles to aggregate depending upon the pH despite the nanoparticles stabilized by small molecules such as citrate anion. Therefore alternative routes to stabilize nanoparticles have been studied.

Photochemical synthesis

In the photochemical approach, the nanoparticles are synthesized from ionic precursors. For example, when an aqueous solution of silver salt, acetone, propanol and polymer stabilizer is UV irradiated, polymer capped silver nanoparticles are formed. UV illumination is believed to generate ketyl radicals via initial excitation of acetone and subsequent hydrogen atom abstraction from 2-propanol according to Equation 1: (Perni *et al.,* 2014).

$$CH_3COCH_3{*} + (CH_3)_2CHOH \rightarrow 2(CH_3)_2C^{\cdot}OH \quad ...(1)$$

The short lived radicals serve as strong reductants. It releases electron and a proton in the process of regeneration of acetone. The electrons could subsequently reduce silver salt to form silver atom, according to Equation 2 and 3. Polymers effectively stabilize the clusters of silver atoms to form polymer capped nanoparticles.

$$(CH_3)_2C^{\cdot}OH \rightarrow CH_3COCH_3 + H^{+} + e^{-} \quad ...(2)$$

$$(CH_3)_2C^{\cdot}OH + Ag^{+} \rightarrow (CH_3)_2CO + H^{+} + Ag0 \quad ...(3)$$

Alternatively, the synthesis of silver nanoparticles may involve direct photo-reduction of AgNO3 in the presence of sodium citrate with different light sources at room temperature [56]. It was demonstrated that depending upon the wavelength of light source used in photochemical reduction i.e. UV or white or green light, nanoparticle suspension with distinctive optical properties could be formulated (Kora *et al.,* 2010). These nanoparticles differed in size and shape. Occasionally, in a UV photo-activation method, a reagent is used in the preparation of stable silver nanoparticles which serves as reducing agent as well as stabilizing agent. In fact, when silver nanoparticles were prepared along with aqueous Triton X-100, Triton X-100 served the dual purpose of reducing agent and stabilizing agent (Jha *et al.,* 2009). Likewise, when silver nanoparticles were synthesized in an alkaline solution of $AgNO_3$ carboxymethylated chitosan (CMCTS) with UV light, CMCTS served the dual role as a reducing agent for silver cation reduction and a stabilizing agent/ surfactant for silver nanoparticles (Sista *et al.,* 2016). Studies have shown that surfactants play an important role in the photochemical reduction of silver salt solution to form uniform sized nanoparticles. The surfactant solution acts as stabilizer in the preparation of well defined nanoparticles (by increasing the surface tension at the solvent- nanoparticles interface). The major merits of the photochemical synthesis route are: (i) clean, (ii) controlled formation of nanoparticles triggered by the photo irradiation and (iii) significant versatility in the photochemical synthesis of nanoparticles in various mediums including emulsion, surfactant micelles, etc. (Neelu, 2001). Some of the factors that can influence the overall composition of synthesized nanoparticles include the wavelength and intensity of irradiation beam, and exposure time of the reagent solution to irradiation. In the absence of proper control, there is a possibility of localized heating of the reagent solution leading to in homogeneity in synthesized nanoparticles composition.

Biological synthesis

Usually, wet-chemical or physical method is used to prepare the metal nanoparticles. However, the chemicals used in physical and chemical methods are generally expensive, harmful and inflammable but the bogenic methods are a cost effective, energy saver and having environmentally benign protocols technique for green synthesis of silver nanoparticles from different microorganisms (yeast, fungi and bacteria, etc) and plant tissues (leaves, fruit, latex, peel, flower, root, stem, etc). Pytochemicals (lipids, protiens, polyphenols, carboxylic acids, saponins, aminoacids, polysachccarides amino cellulose, enzymes, etc.) present in plants are used as reducing and capping agent. The use of agro waste and micro-orgamisms materials not only reduces the cost of synthesis but also minimizes the need of using hazardous chemicals and stimulates green synthesis way for synthesizing nanoparticles (Russell & Hugo 1994; Kokila *et* *al.,* 2016). This method of biosynthesis is very simple, requiring less time and energy in comparison to the physical and chemical methods with predictable mechanisms. The other advantages of biological methods are the availability of a vast array of biological resources, a decreased time requirement, high density, stability, and the ready-to-soluble as-prepared nanoparticles in water. Therefore, biogenic synthesis of metal NPs unwraps up enomorus opportunities for the use of biodegradable or waste materials.

Separation of AgNPs

Centrifugation technique is mostly used by researchers to obtain the pellet or powder form of synthesized silver nanoparticles. The AgNPs suspensions were also oven dried to obtain the product in powder form (Chopade *et al.,* 2913; Shriniwas & Subhash 2017). Some common characterizations of AgNPs include UV-Vis Spectra, SEM, TEM, FTIR, XRD and EDAX or EDX/EDS. DLS study is mostly used for AgNPs synthesized from bio-polymers rather than plant extracts and microorganisms. Zeta potential values indicate the stability of synthesized AgNPs. Thermo-Gravimetric Analysis (TGA) is used to find the effect of $AgNO_3$ and L-cystine on the organic composition of AgNPs (El & Attie 2014; Dakal *et al.,* 2016) to find out the amount of organic material in synthesized AgNPs (Ahmad *et al.,* 2016) and predict the thermal stability of AgNPs (Nakkala *et al.,* 2017). Inductive Coupled Plasma (ICP) analysis was performed to analyze the concentration and conversion of AgNPs.

Mechanism of AgNPs synthesis

The synthesis of AgNP by biological entities is due to the presence of large number of organic chemical like carbohydrate, fat, proteins, enzymes& coenzymes, phenols flavanoids, terpenoids, alkaloids, gum, etc capable of donating electron for the reduction of Ag^+ ions to Ag^0. The active ingredient responsible for reduction of Ag^+ ions varies depending upon organism/extract used. For nano-transformation of AgNPs, electrons are supposed to be derived from dehydrogenation of acids (ascorbic acid) and alcohols (catechol) in hydrophytes, keto to enol conversions (cyperaquinone, dietchequinone, remirin) in mesophytes or both mechanisms in xerophytes plants (Gurunatham 2015). The microbial cellular and extracellular oxidoreductase enzymes can perform similar reduction processes. A schematic diagram showing the silver ion reduction, agglomeration and stabilization to form a particle of nano size is shown in Figure 2.

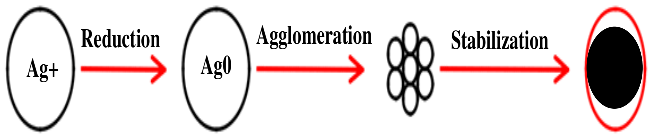

Fig. 2 : Synthesis mechanism of AgNPs

Factors affecting AgNPs synthesis

The major physical and chemical parameters that affect the synthesis of AgNP are reaction temperature, metal ion concentration, extract contents, pH of the reaction mixture, duration of reaction and agitation. Parameters like metal ion concentration, extract composition and reaction period largely affect the size, shape and morphology of the AgNPs. Most of the authors have reported suitability of basic medium for AgNPs synthesis due to better stability of the synthesized nanoparticles in basic medium. Some other advantages reported under basic pH are rapid growth rate, good yield and mono dispersity and enhanced reduction process. Small and uniform sized nanoparticles were synthesized by increasing pH of the reaction mixture. The nearly spherical AgNPs were converted to spherical AgNP by altering pH, However, very high pH (pH > 11) was associated with the drawback of formation of agglomerated and unstable AgNPs. The Reaction conditions like time of stirring and reaction temperature are important parameters. Temperatures up to 100˚C were used by many researchers for AgNP synthesis using bio-polymers and plant extracts, whereas the use of mesophilic microorganism restricted the reaction temperature to 40˚C. At higher temperatures the mesophilic microorganism dies due to the inactivation of their vital enzymes. The temperature increase (30˚C-90˚C) resulted in increased rate of AgNPs synthesis and also promoted the synthesis of smaller size AgNPs. On the whole, most of workers have synthesized AgNPs at room temperature (25˚C to 37˚C) range. It has been found that the size range of AgNPs synthesized from algae, bryophytes, pteridophytes, gymnosperms and bio-polymer sources lie below 50 nm and that of AgNPs synthesized using from angiosperms, algae and bacterial sources ranged between 100 nm and more. The reaction mixture synthesizing AgNP using microorganisms and bio-polymers were continuously agitated to protect agglomeration compared to plant extracts without any suitable reason by the authors. Reaction mixture agitation achieved by applying external mechanical force might accelerate the formation of nanoparticles. Aging of the synthesized AgNP solution changed spherical nanoparticles into flower like structure (Ge *et al.,* 2014).

Characterization of AgNPs and Their Properties

Characterization of AgNPs is important to understand and control nanoparticles synthesis and applications. Various techniques are used for determination of different parameters. At the nanoscale, particle-particle interactions are either dominated by weak Vander Waals forces, stronger polar and electrostatic interactions or covalent interactions. Characterization of nanoparticles is vital part of determination of the phase purity, shape, size, morphology, electronic transition plasmonic character, atomic environment and surface charge, etc. By using advanced analytical techniques such as electron microscopic techniques (atomic force microscopy (AFM), electron energy loss spectroscopy (EELS), surface enhanced Raman scattering (SERS), scanning electron microscopy (SEM) and transmission electron microscopy (TEM) and their corresponding energy-dispersive X-ray spectroscopy (EDX), and selected area electron diffraction (SAED for crystallinity). Properties like surface morphology, size, and overall shape are determined by electron microscopy techniques and elemental composition by SEM-/TEM-/EELS-supported EDX. Optical analysis techniques such as Fourier transform infrared (FTIR) spectroscopy, fluorescence correlation spectroscopy (FCS, diffusion coefficients, hydrodynamic radii, average concentrations, and kinetic chemical reaction), X-ray diffraction (XRD for phase purity with crystal parameters and particle size), diffuse light scattering (DLS can probe the size distribution of small particles), UV-Vis spectroscopy (band gap, particle size electronic interaction), XPS (X-ray photon spectroscopy, surface environment of elemental arrangement), Raman spectroscopy (it provides submicron spatial resolution average size and size distribution through analysis of the spectral line broadening and shift), nuclear magnetic resonance (NMR can detect structure, compositions, diffusivity of nanomaterials, dynamic interaction of species under investigation), small-angle X-ray scattering (SAXS; from 0.1^0 to 3^0 can evaluate the size distribution, shape, orientation, and structure of a variety of polymers and nanomaterials), zeta potential with a value of ±30 mV is generally chosen to infer particle stability. Above analysis can be used to determine the properties of nanomaterials such as the size distribution, dispersibility, average particle diameter, and charge affect the physical stability and the in vivo distribution of the nanoparticles (Pal *et al.,* 2007).

Antibacterial activity of AgNPs

Antimicrobial activity of silver is well known. Silver has been used for treatment of several diseases since from ancient time (Sadeghi *et al.,* 2012). The AgNPs synthesized by different methods were widely tested against number of pathogenic bacteria with evidence of strong antimicrobial activity against a broad-spectrum bacteria including both Gram-negative and Gram-positive. Some researchers have been reported that the AgNPs are more effective against Gram-negative bacteria (Sheng & Liu, 2017; Duran *et al.,* 2016), while opposite results have also been found (Rajesh & Bharath, 2013). The difference in sensitivity of Gram-positive and Gram-negative bacteria against AgNPs may result from the variation in the thickness and molecular composition of the membranes. Gram-positive bacteria cell wall composed of peptidoglycan is comparatively much thicker than that of Gram-negative bacteria (Sintubin *et al.,* 2012). The importance of antibacterial activity study on different bacterial strains becomes from the importance of understanding the mechanism, resistance and future application. Although the antibacterial effect of silver nanoparticles has been widely studied, there are some factors affecting the antimicrobial properties of AgNPs, such as shape, size, and concentration of nanoparticles and capping agents (Morones *et al.,* 2005). analyzed AgNPs with the average size of 21 nm, and the size distribution was found to be 1-69 nm prepared by medicinal plant *Ficus religiosa*. These nanoparticles showed excellent antibacterial activity in *P. fluorescens*, *S. typhi*, *B. subtilis*, and *E. coli*. Bacterial cells exposed to lower concentration of AgNPs exhibited delays of growth which may be due to the bacteriostatic effect, while at the higher concentration (of 60 and 100 μg), the AgNPs were found to exhibit bactericidal effect as no growth was observed. The smaller particles with a larger surface-to-volume ratio were able to reach bacterial proximity most easily and display the highest microbicidal effects than larger particles (Le & Stellacci 2015). Normally, a high concentration leads to more effective antimicrobial activity, but particles of small sizes can kill bacteria at a lower concentration. Furthermore, apart from size and concentration, shape also influences the interaction with the Gram-negative organism E. coli (Lee *et al.,* 2014). (Chopade *et al.,* 2013) Discussed about depending of nanoparticles' shape and size on antibacterial activity against Gram-negative bacteria *E. coli*. They found that observed interaction between nanoparticles of silver with various shapes and *E. coli* was similar and the inhibition results were variable. They speculated about the fact that AgNPs with the same surface areas, but different shapes, may have unequal effective surface areas in terms of active facets. Gurunathan 2015 found different antimicrobial effects of nanosilver shapes (nanoparticles, nanorods, and nanoplates) for *S. aureus* and *E. coli*. SEM analysis indicated that both strains were damaged and extensively inhibited by Ag-nanoplates due to the increasing surface area in AgNPs.

Mechanism of action

In the past decade, silver nanoparticles as antimicrobial agents have attracted much attention in the scientific field. Although several reviews have described the AgNPs' mechanism in detail, the exact mechanism of the antibacterial effect of silver and AgNPs remains to be not fully elucidated. Most studies considered multiple mechanisms of action but simplified the main tree of different mechanisms determine the antimicrobial activity of silver nanoparticles: (1) irreversible damage of bacterial cell membrane through direct contact; (2) generation of reactive oxygen species (ROS); and (3) interaction with DNA and proteins [83-86]. The damage of cell membranes by AgNPs causing structural changes renders bacteria more permeable and disturbs respiration function (panacek *et al.,* 2016). Interestingly, *Morones et al.* demonstrated the existence of silver in the membranes of treated bacteria as well as in the interior of it by transmission electron microscopy (TEM) analysis. Another aspect of mechanism is the role of Ag^+ ions release. Research has shown that the Ag^+ ions at a lower concentration than that of AgNPs can exert the same level of toxicity. Several evidences suggest that the silver ions are important in the antimicrobial activity of silver nanoparticles (Akram *et al.,* 2016). *Durán et al.* discussed that silver ions react with the thiol groups of proteins, producing bacterial inactivation, and inhibit the multiplication of microorganisms. Ag^+ in μmol/L levels had weakened DNA replication due to uncoupling of respiratory electron transport from oxidative phosphorylation, which inhibits respiratory chain enzymes and/or interferes with membrane permeability. On the other side, silver ion can interact with the thiol groups of many vital enzymes and inactivate them and generate reactive oxygen species (ROS). The AgNPs can act as a reservoir for the monovalent silver species released in the presence of an oxidizer (Tram *et al.,* 2013). Ag^+ release was found to correlate with AgNP size, the silver nanoparticles antibacterial activity below 10 nm is mainly caused by the nanoparticle itself, while at larger sizes, the predominant mechanism occurs through the silver ions (Hwang *et al.,* 2012). *Lee et al.* studied the mechanism of antibacterial action on *Escherichia coli*. A novel mechanism for the antibacterial effect of silver nanoparticles, namely the induction of a bacterial apoptosis-like response was described. They observed accumulation of reactive oxygen species (ROS), increased intracellular calcium levels, phosphatidylserine exposure in the outer membrane which indicate early apoptosis, disruption of the membrane potential, activation of a bacterial caspase-like protein and DNA degradation which is the sign of late apoptosis in bacterial cells treated with silver nanoparticles (Figure 3). Antimicrobial activity of silver nanoparticles combined with various antibiotics is currently being studied, and the synergistic antibacterial effect has been found. *Singh et al.* studied individual and combined effects of AgNPs with 14 antibiotics. They found that synergistic action of AgNPs and antibiotics resulted in enhanced antibacterial effect. Exposure of bacteria in combination of AgNPs and antibiotics reduced the MICs significantly, and the bacteria were found to be susceptible to all of the tested antibiotics, except cephalosporins, where no change was observed. The significant reduction of required antibiotic dose up to 1000-fold in combination with small amount of AgNPs could achieve the same effect. The study on bacterial strains resistant to one or more antibiotics belonging to the β-lactam class indicated that the addition of AgNPs decreased MIC on the susceptibility range, therefore, addition of AgNPs not only reduced MIC, but also caused bacteria sensitivity to antibiotic. Briefly, simultaneous action of AgNPs with antibiotics could prevent the development of bacterial resistance. These results are in accordance with findings reported by *Gurunathan* [91], who observed synergistic effects of silver nanoparticles in the presence of conventional antibiotics on Gram-negative bacteria *E. coli* and *K. pneumoniae*. The viability of bacteria was significantly reduced by more than 75% in combination of sublethal dose of meropenem and AgNPs. Evidence of a synergistic effect resulting from the combination of silver nanoparticles with five different antibiotics was declared by reducing MIC against multiresistant, β-lactamase, and carbapenemase producing Enterobacteriaceae (deng *et al.,* 2016). The resistance on antibiotic treatment of *S. aureus* is fast growing global problem due to slow development of new effective antimicrobial agents. *Akram et al.* investigated synergic affects of five various antibiotics and AgNPs applied in combination with blue light against methicillin-resistant *S. aureus* (MRSA). These triple combinations of blue light, AgNPs, and the antibiotic considerably enhanced the antimicrobial activity against MRSA, in comparison with treatments involving one or two agents. The biofilm formation is adjunctive problem of resistance on antimicrobial agents and chronic bacterial infections. It was proposed that Ag-NPs can impede biofilm formation. *Hwang et al.* found that combination of AgNPs with ampicillin, chloramphenicol, and kanamycin against various pathogenic bacteria inhibits the formation of biofilm. *Deng et al.* examined the synergistic antibacterial mechanism of four different classes of conventional antibiotics in combination with AgNPs against the multidrug-resistant bacterium Salmonella typhimurium. The antibiotics enoxacin, kanamycin, neomycin, and tetracycline interact with AgNPs strongly and forming antibiotic-AgNPs complex, while no such effects were observed for ampicillin and penicillin. This complex with AgNPs interacts more strongly with the Salmonella cells and causes more Ag^+ release, thus creating a temporal high concentration of Ag^+ near the bacterial cell wall that ultimately causes cell death.

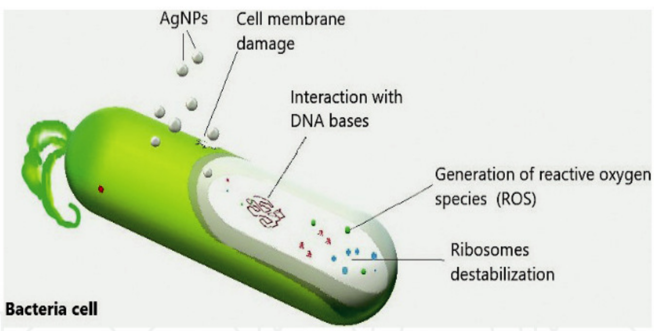

Fig. 3: Schematic visualization of AgNPs' mechanism of action

Applications of AgNPs

Silver nanoparticles are one of the most attractive nanomaterials for commercialization applications. They have been used extensively as electronic products in the industry, anti-bacterial agents in the health industry, food storage, textile coatings and a number of environmental applications. As anti-bacterial agents, silver nanoparticles were used for a wide range of applications from disinfecting medical devices and home appliances to water treatment. Moreover, this encouraged the textile industry to use AgNPs in different textile fabrics. In this direction, silver nanocomposite fibers were prepared containing AgNPs incorporated inside the fabric. The cotton fibers containing AgNPs exhibited high anti- bacterial activity against Escherichia coli. Silver nanoparticles were found to catalyze the chemiluminescence from luminal-hydrogen peroxide system with catalytic activity better than Au and Pt colloid. Recently, inkjet technology has been used to produce flexible electronic circuits at low cost, and many studies regarding this application have been reported in recent years. To fabricate flexible electronic displays via inkjet printing, it is necessary to develop suitable inks. Nano-sized metal particles such as Au or Ag are useful for producing electronic circuits because of the uniformity of the small metal particles dispersed in the inks and their high electrical conductivity. For example, using our methods described above, AgNPs with small size and uniform can be prepared easily, and have high electrical conductivity, indicating that they are useful for producing electronic circuits. In the manufacture of electronic circuits, nanoparticles must be sintered to obtain high electrical conductivity. It is preferable to perform sintering at the lowest temperature possible. However, the use of polymeric materials as dispersing agents means that a high temperature is required for sintering. In our method, polymeric compound PVP was used as a dispersing agent in the synthesis of AgNPs-A. The use of PVP with high molecular weight resulted in a high temperature (>200°C) being required for sintering. In contrast, low molecular weight compounds such as sodium gluconate have good protecting function similar to polymeric compounds, which can produce uniform, small AgNPs-B with high conductivity and also allow them to be sintered at a relatively low temperature of 150°C. The lowering of the sintering temperature in 50 degrees is very important and useful from the perspective of industrial manufacturing. In particular, a simple approach to synthesize AgNPs is developed using benzoic acid and amines as reducing agents. A film with high electrical conductivity can be obtained using AgNPs-C prepared only by drying at room temperature. This is very important to prepare silver nanoparticles in industry and medical applications (Jun *et al.,* 2015). In short AgNPs used in medical: diagnosis and treatment of aliment, food industry, catalyst, air disinfection (biosols filter), drinking water purification, and general/ health care.

Future challenges

Synthesis of different NPs is done by different techniques like chemical, physical and photochemical methods. Among all, synthesis of silver nanoparticles by a green method is more attractive because the process is simple, cost effective, easy to operate and time-saving. The production methods generally use bacteria and fungus, and other creatures since and they include growth, isolation of strains, which demand some complex steps. Commonly, this type of procedure is a challenge in relation to retaining the standard culture as compared to the chemical & physical conditions. Synthetic methods of synthesis of different NPs using seeds, leaves, roots, and some fruits are well recognized. Availability of roots and seeds is little difficult as they may be associated with grasses and some fruits. For nanoparticle formation, biological production uses different greenery for producing the significant spherical shape. The characteristics of nanoparticles are remarkably reliant on complete morphology. For example, production of AgNPs in different forms, production using *Prunus yedoensis, Azadirachta indica, Musa balbisiana, Bauhinia variegate, Ocimum tenuiforum* etc. (Velmurugam *et al.,* 2015; Banerjee *et al.,* 2014). So, future tasks in green production process lies in how this method can be applied uniformly to obtain the other forms like truncated, decahedral, pyramidal shapes, cubical and triangular. Moreover, still there is a need to find out the best approach by which the efficiency regarding the product yield becomes high so that the biological approach can work at a larger scale.

Conclusions

This paper has critically reviewed AgNPs from the perspectives of research trends, global consumption, synthesis, properties, and future challenges. Generally, there are three methods for synthesizing AgNPs, namely physical, chemical, and biological. The physical approach has several drawbacks, such as large space requirement, high energy consumption, and long time consumption to achieve thermal stability. The chemical approach provides an easy way to produce AgNPs although the toxicity of their by-products is a primary concern. Green synthesis of AgNPs is becoming more popular since it is environmentally friendly and cheap. In green synthesis, the challenges that should be considered are simplicity, cost, and time consumption. Also, how this technique can be employed to produce shapes other than spherical is a matter worth exploring. AgNPs released into the environment should be clearly investigated, starting from their sources, mechanisms, and transportation to their effects, by means of better models than the existing ones. A continuous-flow tubular microreactor prototype is potentially an alternative for scaling up AgNP production.

References

Achmad S.; Salmiati M. R. S.; Ahmad B. H. K.; Tony H.; Hadi N. (2017). A Review of Silver Nanoparticles: Research Trends, Global Consumption, Synthesis, Properties, and Future Challenges. J. Chin. Chem. Soc. 64, 732–756.

Ahmed S.; Ahmad M.; Swami B. L.; Ikram S. (2016). A review on plants extract mediated synthesis of silver nanoparticles for antimicrobial applications: A green expertise. Journal of Advanced Research. 7(1):17-28.

Akram F. E.; El T. T.; Abou A. K.; El A. M. (2016). A combination of silver nanoparticles and visible blue light enhances the antibacterial efficacy of ineffective antibiotics against methicillin-resistant Staphylococcus aureus (MRSA). Annals of Clinical Microbiology and Antimicrobials. 15(1):48.

Amin R. M.; Mohamed M. B.; Ramadan M. A.; Verwanger T.; Krammer B. (2009). Rapid and sensitive microplate assay for screening the effect of silver and gold nanoparticles on bacteria. Nanomedicine (Lond). 637-643.

Banerjee P.; Satapathy M.; Mukhopahayay A.; Das P. (2014). Leaf extract mediated green synthesis of silver nanoparticles from widely available Indian plants: synthesis, characterization, antimicrobial property and toxicity analysis. Bioresour Bioprocess 1(1):3.

Brewer S. H.; Glomm W. R.; Johnson M. C.; Knag M. K.; Franzen S. (2005). Probing BSA binding to citrate-coated gold nanoparticles and surfaces. Langmuir. 21: 9303-9307.

Cao G. (2004). Nanostructure and Nanomaterials: Synthesis, Properties and Applications, Imperial College Press: London, 1: 448.

Chen M.; Feng Y. G.; Wang X.; Li T. C.; Zhang J. Y.; Qian D. J.; et al. (2007). Silver nanoparticles capped by oleylamine: formation, growth, and selforganization. Langmuir. 23: 5296-304.

Chen S. F.; Zhang H. (2012). Aggregation kinetics of nanosilver in different water conditions, Adv. Nat. Sci.: Nanosci. Nanotechnol. 3: 1-4.

Chopade B. A.; Singh R.; Wagh P.; Wadhwani S.; Gaidhani S.; Kumbhar A.; et al. (2013). Synthesis, optimization, and characterization of silver nanoparticles from *Acinetobacter calcoaceticus* and their enhanced antibacterial activity when combined with antibiotics. International Journal of Nanomedicine. 8:4277.

Chopade B. A.; Singh R.; Wagh P.; Wadhwani S.; Gaidhani S.; Kumbhar A.; et al. (2013). Synthesis, optimization, and characterization of silver nanoparticles from *Acinetobacter calcoaceticus* and their enhanced antibacterial activity when combined with antibiotics. International Journal of Nanomedicine. 8:4277.

Chouhan N.; Ameta R.; Meena R. K. (2017). Biogenic silver nanoparticles from Trachyspermum ammi (Ajwain). seeds extract for catalytic reduction of p-nitrophenol to p-aminophenol in excess of NaBH4. Journal of Molecular Liquids. 230:74-84.

Dakal T. C.; Kumar A.; Majumdar R. S.; Yadav V. (2016). Mechanistic basis of antimicrobial actions of silver nanoparticles. Frontiers in Microbiology. 7: 1-17.

Dang T.; Le T.; (2012). Fribourg-Blanc E, Dang M, Influence of surfactant on the preparation of silver nanoparticles by polyol method. Adv Nat Sci: Nanosci. Nanotechnol. 3: 1-4.

Davies J. E. (1997). Origins, acquisition and dissemination of antibiotic resistance determinants. Ciba. Found. Symp. 207: 15–27.

Deng H.; McShan D.; Zhang Y.; Sinha S. S.; Arslan Z.; Ray P. C.; *et al*. (2016). Mechanistic study of the synergistic antibacterial activity of combined silver nanoparticles and common antibiotics. Environmental Science & Technology. 50(16): 8840-8848.

Desselberger U. (2000). Emerging and re-emerging infectious diseases. J. Infect. 40, 3–15.

Durán N.; Durán M.; de Jesus M. B.; Seabra A. B.; Fávaro W. J.; Nakazato G. (2016). Silver nanoparticles: A new view on mechanistic aspects on antimicrobial activity. Nanomedicine: Nanotechnology, Biology, and Medicine. 12: 789-799.

El K. H. Y.; Attia A. A. (2014). Bactericidal application and cytotoxic activity of biosynthesized silver nanoparticles with an extract of the red seaweed Pterocladiella capillacea on the HepG 2 cell line. Asian Pacific Journal of Cancer Prevention. 15(3): 1299-1306.

Franci G.; Falanga A.; Galdiero S.; Palomba L.; Rai M.; Morelli G.; *et al*. (2015). Silver nanoparticles as potential antibacterial agents. Molecules. 20(5): 8856-8874.

Galib B. M.; Mashru M.; Jagtap C.; Patgiri B. J. Prajapati P. K. (2011). Therapeutic Potentials of Metals in Ancient India: A Review through Charaka Samhita. Journal of Ayurveda and Integrative Medicine, 2: 55-63.

Ge L.; Li Q.; Wang M.; Ouyang J.; Li X.; Xing M. M. Q. (2014). Nanosilver particles in medical applications: Synthesis, performance, and toxicity. International Journal of Nanomedicine. 9(1): 2399-2407.

Ghosh S.; Kundu S.; Mandal M.; Nath S.; Pal T. (2003). Studies on the evolution of silver nanoparticles in micelle by UV-photoactivation. J. Nanopart. Res. 5: 577-583.

Grier N. (1968). Silver and Its Compounds. In: Block, S.S.; Ed.; Disinfection, Sterilization and Preservation, Lee and Febiger, Philadelphia, 375-398.

Gurunathan S. (2015). Biologically synthesized silver nanoparticles enhances antibiotic activity against Gram-negative bacteria. Journal of Industrial and Engineering Chemistry. 29: 217-226.

Gurunathan S. (2015). Biologically synthesized silver nanoparticles enhances antibiotic activity against Gram-negative bacteria. Journal of Industrial and Engineering Chemistry. 29: 217-226.

Hamzeh M.; Sunahara G. I. (2013). In vitro cytotoxicity and genotoxicity studies of titanium dioxide (TiO2). nanoparticles in Chinese hamster lung fibroblast cells. Toxicol In vitro 27: 864–73.

Henglein A. (1998). Colloidal Silver Nanoparticles: Photochemical Preparation and Interaction with O2, CCl4, and Some Metal Ions, Chem. Mater. 1998; 10: 444-450.

Hill W. R. Pillsbury D. M. (1939). Argyria-The Pharmacology of Silver. Williams and Williams, Baltimore.

Huang L.; Zhai M.; Long D.; Peng J.; Xu L.; et al. (2008). UV-induced synthesis, characterization and formation mechanism of silver nanopareticles in alkalic carboxymethylated chitosan solution. J. Nanopart. Res. 10: 1193-1202.

Hwang I.; Hwang J. H.; Choi H.; Kim K. J.; Lee D. G. (2012). Synergistic effects between silver nanoparticles and antibiotics and the mechanisms involved. Journal of Medical Microbiology. 61: 1719-1726.

Iravani S.; Korbekandi H.; Mirmohammadi S. V.; Zolfaghari B. (2014). Synthesis of silver nanoparticles: chemical, physical and biological methods. Res Pharm Sci. 9: 385-406.

Jahn W. (1999). Review: chemical aspects of the use of gold clusters in structural biology. J Struct Biol. 127: 106–112.

Jeong S.; Yeo S.; Yi S. (2005). The effect of filler particle size on the antibacterial properties of compounded polymer/silver fibers. J. Mater. Sci. 40: 5407-5411.

Jha A. K.; Prasad K.; Prasad K.; Kulkarni A. R. (2009). Plant System: Natures Nanofactory. Colloids and Surfaces B: Biointerfaces, 73: 219-223.

Jun N.; Toshiaki N.; Yoshio H. (2015). A Review of Silver Nanoparticles: Synthesis Methods, Properties and Applications. International Journal of Materials Science and Applications 4(5): 325-332.

Jung J. H.; Oh H. C.; Noh H. S.; Ji J. H.; Kim S. S. (2006). Metal nanoparticle generation using a small ceramic heater with a local heating area. Journal of Aerosol Science. 37(12): 1662-1670.

Kim D.; Jeong S.; Moon J. (2006). Synthesis of silver nanoparticles using the polyol process and the influence of precursor injection. Nanotechnology. 17: 4019-4024.

Kokila T.; Ramesh P. S.; Geetha D. (2016). Biosynthesis of AgNPs using Carica Papaya peel extract and evaluation of its antioxidant and antimicrobial activities. Ecotoxicology and Environmental Safety. 134: 467-473.

Kora A. J.; Sashidhar R. B. Arunachalam J. (2010). Gum Kondagogu (*Cochlospermum gossypium*): A Template for Green Synthesis and Stabilization of Silver Nanoparticles with Antibacterial Application. Carbohydrate Polymers, 82: 670-679.

Kumar S.; Mukherjee M. M. Varela M. F. (2013). Modulation of bacterial multidrug resistance efflux pumps of the major facilitator superfamily. Int. J. Bacteriol. 2013:204141.

Kumari A.; Guliani A.; Singla R.; Yadav R.; Yadav S. K (2015). Silver nanoparticles synthesised using plant extracts show strong antibacterial activity. IET Nanobiotechnology, 9(3): 142-152.

Le O. B.; Stellacci F. (2015). Antibacterial activity of silver nanoparticles: A surface science insight. Nano Today. 10(3):339-354.

Lee D. K.; Kang Y. S. (2004). Synthesis of silver nanocrystallites by a new thermal decomposition method and their characterization. ETRI Journal. 26(3): 252-256.

Lee W.; Kim K. J.; Lee D. G. (2014). A novel mechanism for the antibacterial effect of silver nanoparticles on Escherichia coli. Biometals. 27(6): 1191-1201.

Levy S. B. (2002). Factors impacting on the problem of antibiotic resistance. J. Antimicrob. Chemother. 49: 25–30.

Li C. C.; Chang S. J.; Su F. J.; Lin S. W.; Chou Y. C. (2013). Effects of capping agents on the dispersion of silver nanoparticles. Colloids and Surfaces A: Physicochemical and Engineering Aspects 419: 209-215.

Li X. Z.; Nikaido H.; Williams K. E. (1997). Silver-resistant mutants of Escherichia coli display active efflux of Ag^+ and are deficient in porins. J. Bacteriol. 179: 6127–6132

Morales-Sanchez E.; Guajardo-Pacheco J.; Noriega-Trevino M.; Quintero-Gonzalez C.; Compean-Jasso M.; LopezSalinas F.; Gonzalez-Hernandez J. Ruiz F. (2011). Synthesis of Silver Nanoparticles Using Albumin as Reducing Agent. Materials Sciences and Applications, 2: 578-581.

Morones J. L.; Elichiguerra A.; Camacho K.; Holt J. B.; Kouri J. T.; Ramirez M. Y. (2005). The bactericidal effect of silver nanoparticles. Nanotechnology. 16(10):2346-2353.

Nakkala J. R.; Mata R.; Sadras S. R. (2017). Green synthesized nano silver: Synthesis, physicochemical profiling, antibacterial, anticancer activities and biological in vivo toxicity. Journal of Colloid and Interface Science. 499: 33-45.

Nalwa H. S. (1999). Handbook of Nanostructured Materials and Nanotechnology, Five-Volume Set. Academic Press.

Nazeruddin G.; Prasad N.; Prasad S.; Garadkar K.; Nayak A. (2014). In-vitro biofabrication of silver nanoparticle using Adhathoda vasica leaf extract and its anti-microbial activity. Physica E. 61: 56-61.

Neelu C. Silver Nanoparticles: Synthesis, Characterization and Applications. http://dx.doi.org/10.5772/intechopen.75611

Niu Z.; Li Y. (2014). Removal and Utilization of Capping Agents in Nanocatalysis. Chem. Mater. 26: 72-83.

Nogueira A. L.; Machado R. A. F.; de Souza A. Z.; Martinello F.; Franco C. V.; Dutra G. B (2014). Synthesis and Characterization of Silver nanoparticles Produced with a Bifunctional Stabilizing Agents. Ind. Eng. Chem. Res. 53: 3426-3434.

Nowack B.; Krug H.; Height M. (2011). 120 years of nanosilver history: implications for policy makers, Environ. Sci. Technol. 45: 1177- 1183.

Pal S.; Tak Y. K.; Song J. M. (2007). Does the antibacterial activity of silver nanoparticles depend on the shape of the nanoparticle? A study of the gram-negative bacterium Escherichia coli. Applied and Environmental Microbiology. 73(6): 1712-1720.

Panáček A.; Smékalová M.; Večeřová R.; Bogdanová K.; Röderová M,. Kolář M, et al. (2016). Silver nanoparticles strongly enhance and restore bactericidal activity of inactive antibiotics against multiresistant Enterobacteriaceae. Colloids Surfaces B Biointerfaces. 142: 392-399.

Patil R. S.; Kokate R. M.; Jambhale C.; Pawar S.; Han S.; Kolekar S.; et al. (2012). One-pot synthesis of PVA-capped silver nanoparticles their characterization and biomedical application, Adv Nat Sci Nanosci Nanotechnol. 3: 1-7.

Perni S.; Hakala V.; Prokopovich K. (2014). Biogenic Synthesis of Antimicrobial Silver Nanoparticles Caped with L-Cystine. Colloids and Surfaces A: Physicochemical and Engineering Aspects, 460: 219-224.

Porras-Gomez M.; Vega-Baudrit J. (2012). Overview of Multidrug-Resistant Pseudomonas aeruginosa and novel therapeutic approaches. J. Biomater. Nanobiotechnology 3, 519.

Rai M. K.; Deshmukh S. D.; Ingle A. P.; Gade A. K. (2012). Silver nanoparticles: the powerful nanoweapon against multidrug-resistant bacteria. J. Appl. Microbiol. 112: 841–852.

Rajesh K. S.; Bharath L. V. (2013). Mechanism of plant-mediated synthesis of silver nanoparticles – A review on biomolecules involved, characterization and antibacterial activity. Chemico-Biological Interactions. 273: 219-227.

Rashid M. U.; Bhuiyan K. H.; Quayum E. M. (2013). Synthesis of Silver Nano Particles (Ag-NPs). and their uses for Quantitative Analysis of Vitamin C Tablets. J. Pharm, Sci. 12: 29-33.

Rizzello L.; Pompa P. P (2014). Nanosilver-based antibacterial drugs and devices: Mechanisms, methodological drawbacks, and guidelines. Chemical Society Reviews. 43(5):1501- 1518.

Roberto S. B.; Rocío R.; América V. O.; José M. (2009). Saniger. Silver nanoparticles synthesized by direct photoreduction of metal salts: Application in surface-enhanced Raman spectroscopy. J. Raman Spectrosc. 40: 376-380.

Roy N.; Gaur A.; Jain A.; Bhattacharya S.; Rani V. (2013). Green synthesis of silver nanoparticles: An approach to overcome toxicity. Environmental Toxicology and Pharmacology 36(3): 807-812.

Russell A. D.; Hugo W.B. (1994). Antimicrobial activity and action of silver. Progress in Medicinal Chemistry. 31(C): 351-370.

Sadeghi B.; Garmaroudi F. S.; Hashemi M.; Nezhad H. R.; Nasrollahi A.; Ardalan S. *et al*. (2012). Comparison of the anti-bacterial activity on the nanosilver shapes: Nanoparticles, nanorods and nanoplates. Advanced Powder Technology. 23(1): 22-26.

Sadeghi B.; Gholamhoseinpoor F. (2015). A Study on Stability and Green Synthesis of Silver Nanoparticles Using *Ziziphora tenuior* (Zt). Extract at Room Temperature. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 134: 310-315

Sakamoto M.; Fujistuka M.; Majima T. (2009). Light as a construction tool of metal nanoparticles: Synthesis and mechanism. J. of Photochem. and Photobiol. C: Photochemistry Reviews. 10: 33-56.

Sarsar V.; Selwal K.K.; Selwal K. (2013). Green synthesis of silver nanoparticles using leaf extract of Mangifera indica and evaluation of their antimicrobial activity. J Microbiol Biotech Res. 3: 27–32.

Sheng Z.; Liu Y. (2017). Potential impacts of silver nanoparticles on bacteria in the aquatic environment. Journal of Environmental Management. 191:290-296.

Shriniwas P.P. and Subhash K.T. (2017). Antioxidant, antibacterial and cytotoxic potential of silver nanoparticles synthesized using terpenes rich extract of Lantana camara L. leaves. Biochemistry and Biophysics Reports. 10: 76-81.

Siegel J.; Kvítek O.; Ulbrich P.; Kolská Z.; Slepička P.; Švorčík V. (2012). Progressive approach for metal nanoparticle synthesis. Materials Letters. 89: 47-50.

Sintubin L.; Verstraete W.; Boon N. (2012). Biologically produced nanosilver: Current state and future perspectives. Biotechnology and Bioengineering. 109(10): 2422-2436.

Sista K. S.; Deen D. G.; Dan BP.; Pradeep K. M.; Siddh N. U. (2016). Green Synthesis of Silver Nanoparticles: A Review. Green and Sustainable Chemistry, 6, 34-56.

Slawson R. M.; Trevors J. T.; Lee H. (1992). Silver accumulation and resistance in Pseudomonas stutzeri. Arch Microbiol. 158: 398–404.

Solomon S. D.; Bahadory M.; Jeyarajasingam A.; Rutkowsky S.; Boritz S.; Mulfinger L (2007). Synthesis and Study of Silver Nanoparticle. Journal of Chemical Education. 84: 322-325.

Sun Y.; Xia Y. (2002). Shape-controlled synthesis of gold and silver nanoparticles. Science. 298: 2176-2179.

Tan G. L.; Yu X. F. (2009). Capping the ball-milled CdSe nanocrystals for light excitation. J. Phys. Chem. C. 113: 8724-8729.

Thakkar K. N.; Mhatre S. S.; Parikh R. Y. (2010). Biological synthesis of metallicnanoparticles. Nanomedicine: Nanotechnology, Biology and Medicine. 6(2): 257-262.

Tien D. C.; Tseng K. H.; Liao C. Y.; Huang J. C.; Tsung T. T. (2008). Discovery of ionic silver in silver nanoparticle suspension fabricated by arc discharge method. Journal of Alloys and Compounds. 463(1): 408-411.

Tran Q. H.; Nguyen V. Q.; Le A. T. (2013). Silver nanoparticles: Synthesis, properties, toxicology, applications and perspectives. Advances in Natural Sciences: Nanoscience and Nanotechnology. 4(3): 33001.

Vadlapudi V.; Kaladhar D. (2014). Review: green synthesis of silver and gold nanoparticles. Middle East J Sci Res. 19: 834–842.

Velmurugan P.; Cho M.; Lim S. S.; Seo S. K.; Myung H.; Bang K. S.; Sivakumar S.; Cho K. M.; Oh B. T. (2015). Phytosynthesis of silver nanoparticles by Prunus yedoensis leaf extract and their antimicrobial activity. Mater Lett 138: 272–275.

Xu Z. P.; Zeng Q. H.; Lu G. Q.; Yu A. B. (2006). Inorganic nanoparticles as carriers for efficient cellular delivery. Chem Eng Sci. 61: 1027–1040.