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Review Article

Silver Nanoparticles: Biosynthesis and Antimicrobial Potentialities

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Abstract

In recent years, the ever increasing scientific knowledge and research advancements in science have provided a great awareness regarding the use of nanoparticles (NPs). NPs have drawn the researcher's interest to explore new dimensions in biotechnology at large and nanotechnology, in particular, to combat antimicrobial resistance (AMR) and also to present other pharmacological potentialities. Finally, after decades of negligence, the AMR issue has now captured a worldwide attention of the global leaders, public health community, legalization authorities, academia, research-based organizations and medicinal sector of the modern world, alike. The antibiotics utilization has been expedited than ever before driven by increasing access, across the globe. The AMR emergence in microorganisms is considered as a natural phenomenon. However, this health-threatening issue has been driven by those mentioned above faulty human behavior. In this context, metallic nanoparticles (MNPs) are widely used or being engineered with unique potentialities for targetted applications in many fields of medical, engineering and science. Amongst noble metals, the superior attention has been given to silver nanoparticles. Traditionally, different chemical methods have been attempted but criticized due to various biological risks including toxicity that engendered a deep concern to develop some environmental-friendly processes. In this context, biological approaches using biological molecules derived from plant sources in the form of extracts displayed superiority over chemical and biological methods. These plant-based biological molecules undergo highly controlled assemblage to maintain the suitable size of nanoparticles. This critical review mainly focuses on the utilization of vast diversity of plants in the bio-inspired synthesis of silver nanoparticles as well as their potential applications as novel antimicrobial agents.

Key words: Silver nanoparticles, green synthesis, plant extract, antimicrobial potentiality

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INTRODUCTION

In recent years, some fascinating advances and technologies have appeared in the burgeoning field of nanotechnology[1-5]. Remarkably, nanomaterial's (NMs) are playing a vital role in nanotechnology owing to their different properties on their bulk counterparts[6]. Increasing attention is renewed towards metal nanomaterial's (MNMs) particularly common nanoparticles (NPs), nanoclusters (NCs), nanowires (NWS) and related nanostructures due to their unique electrical, catalytic, thermal and magnetic properties[7]. Many new or enhanced properties based on morphology, distribution and size, the NMs and NPS are rapidly growing in various novel fronts such as, biomedical, food, health care, drug-gene delivery, mechanics, optics, chemical industries, electronics, catalysis, single electron transistors, space industry, light emitters, energy science, photochemical applications and nonlinear optical devices[8-10]. Amongst all types of NPs, metallic nanoparticles (MNPs) are conceived to be most tempting for the researcher, since MNPs possess marked antibacterial potentialities presumably due to the large surface area to volume ratio. In modern nanotechnology era, the silver nanoparticles are regarded as for utmost importance amidst all other noble MNPs. Because of their wide-ranging biotechnological applications, the biosynthesis of silver nanoparticles is of great interest to the scientist and researchers. These have been successfully employed in the diagnosis and treatment of cancer therapy[10-12].

Synthesis of nanoparticles: Although the NPs can be synthesized by a variety of physical and chemical methods, these methods are quite expensive and potentially hazardous to the environment. Utilization of a variety of toxic chemicals in these methods leads to various biological disorders. The syntheses of NPs by biologically-inspired processes are evolving into an important branch of nanotechnology. Two approaches are in practice for the development of silver nanoparticles, either from 'top to bottom" approach or a "bottom to up" approach (Fig. 1).

Bottom to top approach: This approach implies the chemical and biological methods for the biosyntheses of NPs. These methods involve the self-assembly of atoms into new nuclei, which grows into a nano-sized particle (Fig. 1a). The chemical reduction is a most commonly used scheme to synthesize the silver nanoparticles. It uses some organic and inorganic reductants such as ammoniacal silver nitrate, poly (ethylene glycol) block copolymer, sodium borohydride, elemental hydrogen, ascorbate and sodium citrate for the reduction of silver ions into aqueous or non-aqueous solutions[13-14]. This method enables the syntheses of a lot of NPs in short period. However, this approach utilized toxic chemicals which lead to the generation of non-eco-friendly by-products. As a consequence, the biosynthesis of the nanoparticles via green route is preferred over the chemical methods because it produces environmental-friendly products without the involvement of toxic chemicals. NPs bio-syntheses via green

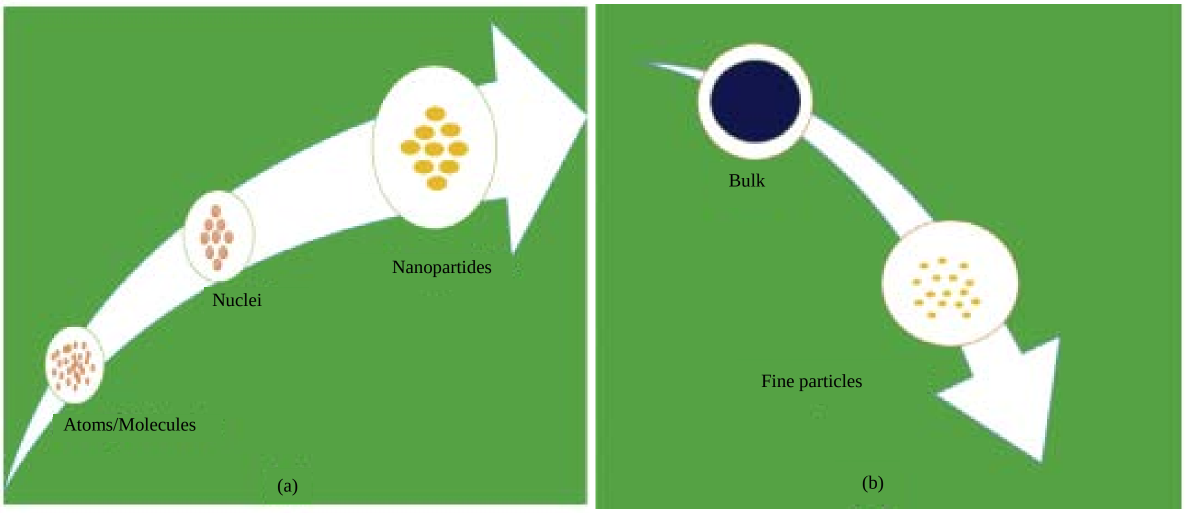

Fig. 1(a-b): Protocols employed for synthesis of nanoparticles (a) bottom to top approach and (b) top to bottom approach (Ahmed *et al.*[68])

route is emerging as a key branch of the nanotechnology, where the exploitation of biological entities (like microorganisms, plant extract or plant biomass) for the development of NPs could be an eco-friendlier substitute to toxic physical-chemical methods[15].

Top to bottom approach: Various size reduction lithographic techniques, such as grinding, sputtering, milling and laser or thermal ablation are used, in this method to break down the bulk size material into fine particles (Fig. 1b). The method utilized for the syntheses of the NPs is evaporation-condensation, by using a tube furnace at atmospheric pressure; the material is converted into a carrier gas by placing it into a boat centered at the furnace. Previously, Au, Ag, PbS and fullerenes NPs have been prepared following vaporization-condensation method. The development of silver nanoparticles using a tube furnace possess numerous drawbacks as it occupies a large space and necessitates an enormous amount of energy. Besides, raising the environmental temperature, it also entails much time to succeed thermal stability[16-17]. Additionally, to acquire a stable operating temperature, a conventional tube furnace requires the power of several kilowatts and a pre-heating time of several hundreds of minutes. One of the biggest limitations of this method is the imperfections in the surface structure of the product and the other physical properties of NPs are highly dependent on the surface structure about surface chemistry[18-19].

It is concluded that, whatever the method is adopted, the chemical methods have certain limitations either in applications or the form of chemical contamination during their syntheses procedures. Nevertheless, no one can neglect their ever growing applications in industrial and biotechnological processes. In every aspect of science and technology including medical fields, the novel silver nanoparticles are striving towards their widespread applications for the service of human beings. Silver nanoparticles have been assimilated into more than 250 consumer products due to their potential antimicrobial and medicinal properties. However, it is a serious concern for the researchers to explore some alternative synthetic routes for the syntheses of cost-effective and environmental responsive NPs. Keeping given the aesthetic sense to provide its potential at the top, the green synthesis is rendering itself as a key procedure for the production of the nanoparticles[20].

Green synthesis of silver nanoparticles: Given large-scale syntheses of nanoparticles, the green syntheses exhibit enormous advantages, i.e., environmentally-friendlier and cost-effective, over the physicochemical methods. Moreover, green synthesis circumvents the prerequisite of high pressure, temperature, energy and toxic chemicals[21]. Based on antioxidant or reducing properties of microorganisms (like bacteria, fungi and plants) for the reduction of metal compounds in their particular nanoparticles, much literature has been reported for the syntheses of silver nanoparticles using biologically-inspired synthesis. Though, amongst the various biological methods, microbes-mediated synthesis of silver nanoparticle is industrially impractical presumably due to the requirements of highly aseptic conditions and their maintenance. As a consequence, the exploitation of plant extracts is potentially advantageous over the microorganisms due to obvious improvement, cell culture maintenance and safety ensurance[22]. This is the best method to synthesize silver nanoparticles since it is free from the toxic chemicals and also provides natural capping agents for the stabilization of silver nanoparticles. Moreover, the use of plant extracts trims down the cost of extraction and isolation of microorganisms and their culture media which enhances the economic feasibility of NPs development by microorganisms. Therefore, the potential comprehensions of bio-inspired synthesis of silver nanoparticles are assembled and critically reviewed on physical-chemical methods in the present review study.

Plants with potential phytochemicals and biosynthesis of silver nanoparticles: In recent years, Phyto nanotechnology has gained a noticeable attention as a potential avenue for the synthesis of nanoparticles with multifunctional characteristics. At contemporary, the single step biosynthesis of silver nanoparticles using plant extracts has gained a considerable research attention because of environmental-friendlier, rapid, economical and non-pathogenic procedure. Figure 2 illustrates a schematic representation of biosynthesis of silver nanoparticles using plant extracts. The combination of bio-macromolecules such as carbohydrates, proteins, amino acids, alkaloids, terpenoids, saponins, tannins, phenolic, etc. plays a vital role in the reduction and stabilization of silver ions. These biomolecular agents are already present in the plant extracts and possess excellent medicinal values in an environmental responsive way[23].

Briefly, the nanoparticles synthesis procedure implicates the repeated (twice/thrice) washing of target part of the plant with tap water to remove any unwanted necrotic plant and epiphytes, followed by the removal of associated debris using the sterile distilled water. The cleaned parts are shade-dried for 10-15 days and then ground to a fine powder using domestic grinding machines. Adequately, 10 g of the plant powder is boiled with 100 mL of deionized distilled water by

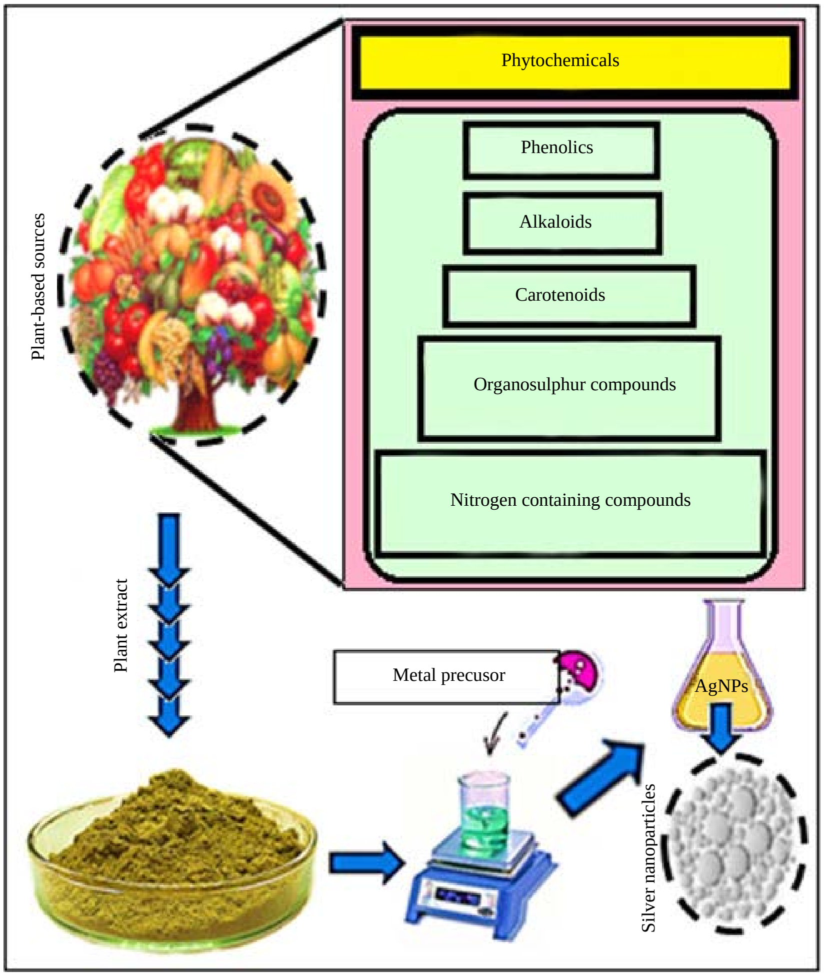

Fig. 2: A schematic illustration of biosynthesis of silver nanoparticles using plant extracts

hot percolation method. The resulting solution was thoroughly filtered to remove all the insoluble materials from the broth. Only a few mL of the plant extract was added to a solution of 10^{-3} M $AgNO_3$ which resulted in the reduction of Ag^+ to Ag^0. This decrease of the silver metal ion was observed by recording the UV-visible spectra of the solution at regular interval of time[24]. Different types of medicinal plants and their respective parts have been utilized for the development of silver nanoparticles; a large segment of flora has also been exploited for the same purpose as well. To investigate the antioxidant, antimicrobial and anticancer effects, the aqueous extract from *Acorous calamus* was employed for the green synthesis of silver nanoparticles[25].

The eco-friendly hydrothermal approach was attempted for the biosynthesis of silver nanoparticles by an aloe vera plant extract solution, which acts as both reducing and stabilizing agent[26]. *Alternanthera dentate* extract was exploited to develop spherical shape silver nanoparticles of dimensions 50-100 nm. This method was observed to be quick, simple and cheaper in contrasted with chemical and microbial processes since plant extract takes only 10 min to reduce silver ions to silver nanoparticles. The phyto-assisted aynthesis of silver nanoparticles using *Solanum nigrum* displayed pronounced antibacterial activities against *Salmonella Typhi* and *Staphylococcus*[27]. In another study, *Boerhaavia diffusa* was utilized as a reducing agent for green synthesis of 25 nm silver nanoparticles having a face-centered cubic shape as deliberated by X-ray diffraction (XRD) and Transmission electron microscopy (TEM) analysis. Among three bacterial strains (such as *Pseudomonas fluorescens, Aeromonas hydrophila* and *Flavobacterium branchiophilum*) tested, the maximum antibacterial activity of these NPs was recorded to be against *F. Branchiophilumin*. Most of the carbohydrates, flavonoids, sapogenins and steroids act as reducing agents and phytoconstituent as capping agents for the stability of silver nanoparticles. The tea extract was used as a capping agent to develop 20-90 nm size silver nanoparticles of the crystalline structure; the quantity of tea extract and reaction temperature exhibited a substantial effect on the synthetic efficiency of NPs[28]. Aqueous extract of *Nyctanthes arbortristis* (aka night jasmine) was examined for the stable synthesis of silver nanoparticles by Basu and co-workers[29]. UV-visible spectroscopy confirmed surface plasmon resonance of silver nanoparticles at 420 nm, XRD results showed peaks at 111, 200, 220, which confirmed the presence of AgNPs with face-centered cubic structure. The uniform spherical nature of the AgNPs and size (between 50 and 80 nm) were further corroborated by scanning electron microscope (SEM) analysis. Ali *et al*.[30] use an aqueous extract of *Artemisia absinthium* to investigate its reducing potential. During the study, the UV-visible spectroscopy, dynamic light scattering (DLS), TEM and energy dispersive X-ray analysis (EDX) were used to find out the appropriate concentration of AgNPs. The significant effect on size, yield and stability of AgNPs was observed by varying the concentration of plant extract (10 mg mL^{-1}) and silver nitrate (2 mM). The highest conversion efficiency of $AgNO_3$ to AgNPs was noticed by reacting them in 6: 4 v/v which results in the size of AgNPs > 100 nm. The TEM reveals the polydispersed particle (PDP) size in the range of 5-20 nm. EDX shows the characteristic peaks of silver in NPs.

Ahmed *et al*.[31] attempted to synthesize silver nanoparticles using aqueous leaf extract of *Azadirachta indica* followed by characterization through FTIR, dynamic light scattering (DLS), photoluminescence (PL) UV-visible spectroscopy and TEM. The silver nanoparticles exhibited antibacterial activities against both Gram-positive (*Staphylococcus aureus*) and gram negative (*Escherichia coli*) microorganisms. Photoluminescence and absorbance peak at 436-446 nm were also evaluated. The short time (15 min) reveals that the process is simple, rapid, eco-friendly and nontoxic.

Without using the external reducing and capping agents, Nayak *et al*.[32] synthesized the AgNPs by bark extracts of *Ficus benghalensis* and *Azadirachta indica*. The absorbance peak by UV-visible spectroscopy indicates the complete formation of AgNPs. Field emission scanning microscopy (FE-SEM), AFM, XRD and ATR-FTIR were used to validate the morphology, crystalline phase and role of various functional groups. The synthesized AgNPs showed promising antimicrobial activities against both Gram-negative (*Escherichia coli, Pseudomonas aeruginosa and Vibrio cholerae*) and Gram-positive (*Bacillus subtilis*) bacteria. The anti-proliferative activity was determined against MG-63 cells. Thus, it was inferred that these synthesized AgNPs could be used as broad spectrum therapeutic agents against osteosarcoma and microorganisms. Biosynthesis of silver nanoparticles using different plant extracts and their antimicrobial activities against representative microorganisms are summarized in Table 1.

An eco-friendly and profitable green synthesis was undertaken by Tarnam *et al*.[45] to investigate the hypoglycemic effect of AgNPs using ethanolic leaf extract of *Clausena anisata (Willd.) Hook f. ex Benth*. Different characterization techniques including UV-visible spectrophotometry (UV-Vis), FE-SEM, XRD, EDS and FTIR were used for the validation of experimental data. DPPH assay was performed to determine the antioxidant activity, whereas *in-vitro* hypoglycemic activity was appraised by alpha-amylase inhibition assay, adsorption capacity and glucose diffusion assay. The average size of AgNPs was 60.67 nm. The NPs exhibited the alpha-amylase inhibitory activity of 80.32% at 500 µg mL^{-1} and IC_{50} 100 µg mL^{-1}. The maximum glucose uptake was found to be 68.29% at 10 mM concentration. The molar concentration of glucose was directly proportional to the glucose binding capacity of extracts. The rate of glucose diffusion across the membrane was found to increase from 30-180 min. The DPPH scavenging activity was found to be potent (71.60%) at extract concentration of 500 µg mL^{-1}. The sample revealed the hypoglycemic effect exhibited by the AgNPs in vitro model of yeast cells, mediated by glucose absorption, increasing glucose diffusion and glucose transport across the cell membrane.

Recently, Sanchez *et al*.[46] synthesized AgNPs adopting an easy, cost-effective and eco-friendly green method, by using an aqueous extract of Peumus boldus (Boldo), a medicinal plant. The moderate reaction conditions, low concentration and short reaction time, were sufficient for biosynthesizing the AgNPs. The characterization techniques used for the validation of results were UV-visible spectroscopy, XPS and hydrodynamic size. In another study, Rao *et al*.[47] synthesized the AgNPs by reducing silver acetate with the help of crude methanolic root extract of Diospyros paniculata. A surface plasmon peak was shown at 428 nm by UV-visible spectroscopy. XRD confirmed face centered cubic crystal of metallic Ag. The average diameter of AgNPs was found to be 17 nm by TEM which is in agreement with the average size calculated by XRD. The synthesized AGNPs showed remarkable activity against thepathogenic strains (Gram-positive, Gram-negative and fungi).

A rapid and green procedure was reported by Nabikhan *et al*.[44] for the biosynthesis of silver nanoparticles using the extract of a marshy plant, *sesuvium portulacastrum.* As confirmed by TEM, the spherical shape silver nanoparticles in the range of 5-20 nm were developed. Gopinath *et al*.[48]

Table 1: Biosynthesis of silver nanoparticles using different plant extracts and their antimicrobial activities against representative microorganisms

		Silver nanoparticles		Antibacterial activity		
Plants	Plant's part	Shape	Size (nm)	Test microorganisms	Inhibition zone (mm)	Authors
Azadirachta indica	Leaf	Spherical	34.00	*Staphylococcus aureus*	9	Ahmed *et al.*[31]
				Escherichia coli	9	
Ficus benghalensis	Bark	Crystalline	85.95	*Escherichia coli*	12	Nayak *et al.*[32]
				Pseudomonas aeruginosa	12	
				Vibrio cholerae	12	
				Bacillus subtilis	12	
Azadirachta indica	Bark	Crystalline	90.13	*Escherichia coli*	12	Nayak *et al.*[32]
				Pseudomonas aeruginosa	12	
				Vibrio cholerae	12	
				Bacillus subtilis	12	
Coffea arabica	Seed	Crystalline	20-30	*Escherichia coli*	3.1	Dhand *et al.*[33]
				Staphylococcus aureus	2.7	
Diospyros paniculata	Root	Crystalline	17-19	*Bacillus subtilis*	Good	
				Escherichia coli	Good	
Artocarpus altilis	Leaf	Spherical	34.00	*Escherichia coli*	10	Ravichandran *et al.*[34]
				Pseudomonas aeruginosa	9	
				Staphylococcus aureus	8	
				Aspergillus vesicolor	3	
Anigozanthos manglesii	Leaf	Cubes, triangular and hexagonal	50-150	*Deinococcus*	16	Shah *et al.*[35]
				Escherichia coli	9	
				Staphylococcus epidermis	10	
Heritiera fomes	Bark	Spherical	400	*Staphylococcus aureus*	12	Thatoi *et al.*[36]
				Shigella flexneri	No	
				Vibrio cholera	9	
				Staphylococcus epidermidis	10	
				Bacillus subtilis	15	
				Escherichia coli	14	
Sonneratia apetala	Leaf	Spherical	20-30	*Staphylococcus aureus*	16	Thatoi *et al.*[36]
				Shigella flexneri	13	
				Vibrio cholera	10	
				Staphylococcus epidermidis	12	
				Bacillus subtilis	14	
				Escherichia coli	10	
Ocimum tenuiflorum	Leaf	Irregular	28	*Staphylococcus aureus*	25	Logeswari *et al.*[37]
				Pseudomonas aeruginosa	20	
				Escherichia coli	30	
				Klebsiella pneumoniae	19	
Solanum tricobatum	Leaf	Irregular	22.3	*Staphylococcus aureus*	30	Logeswari *et al.*[37]
				Pseudomonas aeruginosa	12	
				Escherichia coli	12	
				Klebsiella pneumoniae	18	Logeswari *et al.*[37]
Syzygium cumini	Leaf	Irregular	26.5	*Staphylococcus aureus*	26	
				Pseudomonas aeruginosa	25	
				Escherichia coli	26	
				Klebsiella pneumoniae	24	
Centella asiatica	Leaf	Irregular	28.4	*Staphylococcus aureus*	26	Logeswari *et al.*[37]
				Pseudomonas aeruginosa	15	
				Escherichia coli	21	
				Klebsiella pneumoniae	20	
Citrus sinensis	Leaf	Irregular	65	*Staphylococcus aureus*	27	
				Pseudomonas aeruginosa	18	
				Escherichia coli	17	
				Klebsiella pneumoniae	16	
Potentilla fulgens	Root	Spherical	10-15	*Escherichia coli* MTCC 433	9.5	Mittal *et al.*[38]
				Bacillus subtilis MTCC 44	9.7	
Solanum trilobatum	Fruit	Spherical	12.50-41.90	*Escherichia coli*	18	Ramar *et al.*[39]
				Klebsiella pneumoniae	19	
				Streptococcus mutans	17	
				Enterococcus faecalis	16	

Table 1: Continue

		Silver nanoparticles		Antibacterial activity		
Plants	Plant's part	Shape	Size (nm)	Test microorganisms	Inhibition zone (mm)	Authors
Abelmoschus esculentus (L.)	Pulp	Spherical	3-11	*Bacillus subtilis*	33	Mollick *et al.*[40]
				Bacillus cereus	18	
				Escherichia coli	19	
				Micrococcus luteus	40	
				Pseudomonas aeruginosa	26	
Musa paradisiaca	Peel	Crystalline	23.7	*Bacillus subtilis*	10	Ibrahim,[41]
				Staphylococcus aureus	14	
				Pseudomonas aeruginosa (ATCC)	17	
				Pseudomanas aeruginosa (isolate)	15	
				Escherichia coli	13	
Acorus calamus	Rhizome	Spherical	31.83	*Bacillus subtilis*	1.7	Nakkala *et al.*[25]
				Bacillus cereus	1.6	
				Staphylococcus aureus	1.5	
Cocous nucifera	Inflorescence	Spherical	22	*Vibrio alginolyticus*	19	Mariselvam *et al.*[42]
				Plesiomonas shigelloides	21	
				Klebsiella pneumoniae	24	
				Salmonella paratyphi	16	
				Staphylococcus aeruginosa	14	
				Vibrio harveyi	14	
				Bacillus subtilis	14	
				Escherichia coli	12	
				Vibrio mimicus	0	
				Staphylococcus aureus	0	
Syzygium cumini	Leaf powder	Irregular	53	*Staphylococcus aureus*	15	Logeswari *et al.*[43]
				Pseudomonas aeruginosa	12	
				Escherichia coli	14	
				Klebsiella pneumonia	15	
Citrus sinensis	Leaf powder	Irregular	41	*Staphylococcus aureus*	15	Logeswari *et al.*[43]
				Pseudomonas aeruginosa	16	
				Escherichia coli	14	
				Klebsiella pneumonia	16	
Solanum tricobatum	Leaf powder	Irregular	52	*Staphylococcus aureus*	12	Logeswari *et al.*[43]
				Pseudomonas aeruginosa	12	
				Escherichia coli	13	
				Klebsiella pneumonia	12	
Centella asiatica	Leaf powder	Irregular	42	*Staphylococcus aureus*	No	
				Pseudomonas aeruginosa	11	
				Escherichia coli	11	
				Klebsiella pneumonia	No	
Sesuvium portulacastrum L.	Callus	Spherical	5-20	*Pseudomonas aeruginosa*	20	Nabikhan *et al.*[44]
				Klebsiella pneumonia	20	
				Staphylococcus aureus	23	
				Listeria monocytogenes	18	
				Micrococcus luteu	18	
Sesuvium portulacastrum L.	Leaf	Spherical	5-20	*Pseudomonas aeruginosa*	18	Nabikhan *et al.*[44]
				Klebsiella pneumoniae	12	
				Staphylococcus aureus	22	
				Listeria monocytogenes	20	
				Micrococcus luteu	12	

amalgamated the dried fruit body extract of the plant, *Tribulus terrestris* with silver nitrate to fabricate spherical shaped silver nanoparticles with a diameter ranging from 16-28 nm. The antibacterial potential of these NPs was investigated against multidrug resistant bacteria such as *Streptococcus pyogens, Pseudomonas aeruginosa, Bacillus subtilis, Escherichia coli* and *Staphylococcus aureus.* The silver nanoparticles (size 22 nm) synthesized from the extract of tree *cocous nucifera* in ethyl acetate and methanol (40: 60) displayed noteworthy antibacterial potentiality against human bacterial pathogens such as *Salmonella paratyphi, Klebsiella pneumoniae, Bacillus subtilis* and *Pseudomonas aeruginosa*[42]. Singh *et al.*[49] successfully synthesized stable silver nanoparticles using an endophytic fungal supernatant of *Raphanus sativus* which

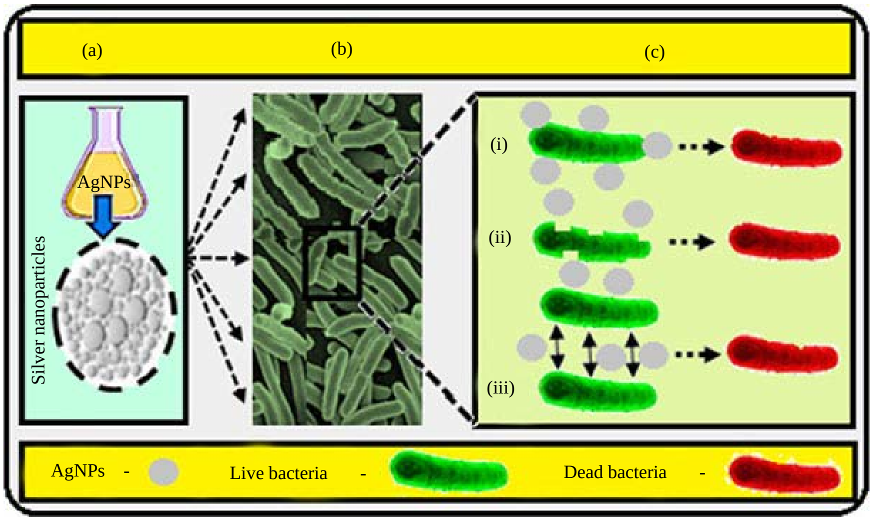

Fig. 3: A schematic illustrations of potential antimicrobial routes of silver nanoparticles, (a) AgNPs delivery/dispersion, (b) Target site/microbially infected area and (c) Death mechanisms i.e.
(i) Bacterial death by contact/attachment, (ii) Cell-wall deformation that cause cell lysis and ultimately leads to death and (iii) Bacterial death by inhibiting cell-cell interaction network (quorum sensing)

presented high antibacterial activity. Sadeghi and Gholamhoseinpoor[50] developed spherical and uniform shape silver nanoparticles in the range of 8-40 nm utilizing *Ziziphoratenuior* leaves. FTIR was used to analyze the functionalization of different biomolecules containing carboxyl, primary amines and hydroxy groups.

Ulug *et al.*[51] reported the synthesis of silver nanoparticles by using the aqueous extract of *Ficuscarica* leaf in a shorter incubation time of 3.0 h using 5 mM silver nitrate solution. The strong antimicrobial effect was shown against *P. aeruginosa, P. mirabilis, E. coli, Shigella flexaneri, S. Somenei and Klebsiella pneumonia*. Similarly, Krishnaraj *et al.*[52] managed to synthesize silver nanoparticles within 30 min from the leaf extract of *Acalypha indica*. The facile and rapid biosynthesis of the silver nanoparticles was also documented by Dwivedi and Gopal[53] using an obnoxious weed *Chenopodium album*. Silver and gold nanoparticles ranging from 10-30 nm were admirably synthesized by using the leaf extract and characterized completely using TEM analysis. *Azadirachta indica leaves* were used to synthesize the silver nanoparticles, while aqueous silver nitrate solution and natural rubber latex obtained from *Hevea brasilensis* were thermally treated to form the colloidal nanoparticles ranging from 2-10 nm, having a face-centered cubic structure with spherical shape[54].

Antimicrobial mechanism of silver nanoparticles: Silver metal has extensively been used for different purposes, such as jewelry, Cutlery and ornaments. The use of silver in cutlery equipment and jewelry is considered to be beneficial for health. The long history of silver as the anti-microbial agent has discouraged the contamination of microbes to the users. In recent years, the use of silver as an antimicrobial agent against different classes of microbes such as gram positive, gram negative, fungi and viruses in the form of nanoparticles has drawn considerable attention. Usually, silver is used in the form of silver nitrate solution to induce the antimicrobial effects. Figure 3 illustrates various antimicrobial routes of silver nanoparticles. Different plant extracts have been used to synthesize the silver nanoparticles and their mechanisms of action against various bacterial strains[55]. Various authors have suggested several mechanisms of action of silver nanoparticles and the most validated are summarized in Table 2.

Various factors such as pH, size, ionic strength and capping agent influence the antimicrobial properties of the silver nanoparticle. The mechanism of antimicrobial properties and toxicity of silver nanoparticles is still controversial and debatable. To act as a potential antimicrobial candidate, the silver ion must be in its ionized form as positive charge on silver is considered to be vital for the antimicrobial properties. Silver displays an inert behavior in its ionized form but it releases the silver ion (Ag^+) when it comes in contact with water or moisture[80]. These silver ions can easily conjugate with nucleic acids to form complexes as compared to phosphate groups of nucleic acids. In some reports, the interaction between positively charged NPs and negatively charged bacterial cells are supposed to be most suitable antibacterial agents[81-82]. The NPs accumulate and can penetrate into the cell wall or membrane resulting in the formation of a stable S-Ag bond with the compounds containing thiol (-SH) groups and

Table 2: Details of silver nanoparticles and their mechanisms of action against various bacterial strains (Franci *et al*.[55])

Bacteria	Mechanism of action	References
Acinetobacter baumannii	Alteration of cell wall and cytoplasm	Dhas *et al*.[56], Junqueira *et al*.[57]
Escherichia coli	Alteration of membrane permeability and respiration	Kumar *et al*.[58], Lysakowska *et al*.[59], Manjumeena *et al*.[60], Morones *et al*.[61], Muhsin and Hachim[62], Naraginti and Sivakumar[63], Pal *et al*.[64], Paredes *et al*.[65], Shrivastava *et al*.[66], Sondi and Salopek-Sondi[67], Vazquez-Munoz *et al*.[68], Wang *et al*.[69], Zhou *et al*.[70] and Meire *et al*.[71]
Enterococcus faecalis	Alteration of cell wall and cytoplasm	Wu *et al*.[72] and Tamayo *et al*.[73]
Listeria monocytogenes	Morphological changes, separation of the cytoplasmic membrane from the cell wall	Wang *et al*.[74]
Nitrifying bacteria	Inhibits respiratory activity	Biel *et al*.[75]
Pseudomonas aeruginosa	Irreversible damage on bacterial cells, alteration of membrane permeability	Morones *et al*.[61], Wei *et al*.[76], Zhang *et al*.[77] and Jain *et al*.[78]
Proteus mirabilis	Alteration of cell wall and cytoplasm	Junqueira *et al*.[57] and Manjumeena *et al*.[60]
Staphylococcus aureus	Irreversible damage on bacterial cells	Shameli *et al*.[79]
Staphylococcus epidermidis	Inhibition of bacterial DNA replication, bacterial cytoplasm membranes damage, modification of intracellular ATP levels	Sondi and Salopek-Sondi[67] and Jain *et al*.[78]
Salmonella typhi	Inhibition of bacterial DNA replication, bacterial cytoplasm membranes damage, modification of intracellular ATP levels	Wang *et al*.[74], Zhang *et al*.[77] and Jain *et al*.[78]
Vibrio cholerae	Alteration of membrane permeability and respiration	Tamayo *et al*.[73]

eventually, causes the deactivation of the enzyme in the cell. It was anticipated that Ag^+ ion penetrates into the cell and intercalates with the purine and pyrimidine base pairs disturbing the H-bonding between the two anti-parallel strands and denaturing the DNA molecule. Bacterial cell lysis could be one of the reasons for its antibacterial property.

One antimicrobial phenomenon could be elucidated by cell wall thickness of the gram-positive and gram-negative bacteria. Due to the presence of a thicker layer of peptidoglycan, the cell wall of gram gram-positive bacteria is less vulnerable to silver ions as compared to Gram-negative bacteria. The peptidoglycan possesses negative charge and silver ions are positively charged, so more silver ions are trapped in the peptidoglycan of the gram-positive bacteria. Other mechanisms involving the interaction of silver ions with biological macromolecules (enzymes, DNA) can be explained by electron release mechanism[83] and free radical production mechanism[84]. With current medication, the multi-resistant behavior of the pathogens due to antigenic shifts becomes a significant problem in public health, thus compelling the important development of new pathways for bactericidal and virucides. Silver has a long history, in this regard, as a potential antibacterial, antiseptic and disinfectant agent. The interference of silver nanoparticles and silver with disulfide bonds can change the 3-dimensional structure of cell glycoproteins and consequently, many functional operations of the microorganisms impede[85-86]. The use of environmentally-non-threatening materials like bacteria, fungi, plant extracts and enzymes for the syntheses of silver nanoparticles ensures several advantages of eco-friendly and compatibility for pharmaceutical and other biomedical applications since they do not use toxic chemicals for the bio-synthetic procedures. These disadvantages asserted the use of innovative and well-developed methods that opened doors to discover compassionate and green routes for synthesizing nanoparticles [84].

Antimicrobial exploitation of AgNPs: In recent years, with an ever-increasing scientific knowledge of infectious diseases caused by various microorganisms, more attention is now being focused towards alternative approaches to control or limit such deadly infections. In this context, novel constructs with antimicrobial activities are attracting the considerable attention of both academia and industry, especially in the biomedical and other health-related areas of the modern world[87-92]. It has been well-documented in the literature that many biological materials are suitable media for growth of microorganisms such as bacteria. Such a high survival rate of pathogens on the materials having great potential to be used in medical applications may contribute to transmissions of diseases at increased risk[93-95]. Because of the growing consciousness and demands of legislative authorities, the manufacture, to reduce bacterial population in healthcare facilities and possibly to cut pathogenic infections, development of novel anti-microbial constructs is considered to be a potential solution to such a problematic issue.

Given excellent antimicrobial properties, silver nanoparticles have been used in some environmental processes, food and health industry as well as in textile and pharmaceutical industry, from last several decades. Due to greater catalytic functionality, the silver nanoparticles are well known in the area of dye reduction and their elimination from textile industry wastewater. Zou *et al.*[96] have reported an effective removal of methylene blue using silver nanoparticles. Mallick *et al.*[97] highlighted the catalytic potential of silver nanoparticles for the reduction of pheno-safranine. The antimicrobial activity of silver nanoparticles has been investigated against yeast, *Escherichia coli* and *Staphylococcus aureus* by Kim *et al.*[98]. The Antimicrobial activities of silver nanoparticles were investigated by growing the *E. coli* on agar plates and LB medium. The bio-inspired syntheses of silver nanoparticles using aqueous *piper longum* fruit extract have revealed potential antimicrobial, biomedical as well as antioxidant properties in *in-vitro* assays[99]. Silver nanoparticles demonstrated antiviral activities as well against HIV-1 at their non-cytotoxic concentrations but the exact mode of action underlying their HIV-inhibitory activity has been not fully elucidated[100]. In recent days, particular interest has been geared at providing enhanced biomolecular diagnostics, including SNP detection gene expression profiles and biomarker characterization. These strategies have been focused on the development of nanoscale devices and platforms that can be used for single molecule characterization of nucleic acid, DNA or RNA and protein at an increased rate when compared to traditional techniques[101]. Several authors have used different strategies to engineer novel constructs with antimicrobial potentialities [102, 103].

Futuristic view and research gaps: Though the plethora of information is available about many potential aspects including bio-inspired green routes for NPs synthesis, multifunctional characteristics and natural plants with medicinal potentialities; however, much of critiques including the distribution profile of NPs, *in vivo* insertion, clearance and excretion are still outstanding and need to be addressed in future studies. Despite current advancements in NPs related investigations, the bioavailability, biocompatibility and biodegradability issues are still at early stages. Thus, a substantial scientific research with proven employability of NPs is needed in this particular line of research. Similarly, many other unsolved questions are posing a big research gap that needs to be addressed comprehensively. Major research gaps include but not limited to the, (1) NPs yield variation with different biological sources, (2) NPs stability variation with different biological sources and same metal precursors, (3) polydispersion of NPs during biosynthesis, (4) size and shape-dependent efficiency of MNPs, (5) stable and efficient *in vivo* profile and (6) activity mechanisms and futuristic applications in human.

CONCLUSION

In conclusion, the above-discussed literature shows the potential of MNPs as potent antimicrobial bullets with proven advantages. However, there is a dire need to engineer multifunctional NPs on a pilot scale. In this context, many researchers have directed or redirected their interest to explore new dimensions in biotechnology at large and nanotechnology in particular. The green biosynthesis of NPs has following major advantages among others i.e. (1) natural plants which are renewable and eco-friendlier, (2) NPs synthesis process is easy to scale up, (3) overall cost-effective ratio is net positive, (4) carbon neutral, (5) stable formulations with adjustable sizes and shapes, (6) no or less consumption of harsh chemicals and (7) no or less toxic contaminants/by-products, etc. In summary, the present review work aimed at combatting AMR and research that underpins the development of strategies to mitigate the effects e.g. through novel alternatives to antimicrobials. Through sophisticated design, multifunctional characteristics of NPs can be modified to achieve optimal infective capability and therefore enhanced antibacterial control.

SIGNIFICANCE STATEMENT

Nanoparticles (NPs) particularly silver nanoparticles with potent functionalities have gained particular attention in the research arena, consumer product and biomedical communities, alike. NPs engineered via Green routes offer important antibacterial activities against a wider spectrum of pathogenic microbes. The recent advancements from the biotechnology sector at large and nanotechnology arena, in particular, have contributed major role in combating antimicrobial resistance along with other biomedical, pharmacological, cosmeceutical and nutraceutical potentialities.

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