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INVITED REVIEW PAPER

Phyto-synthesized silver nanoparticles for biological applications

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Abstract−Silver nanoparticles (AgNPs) are valuable metal nanoparticles that exhibit exceptional properties compared to their bulk materials. Pronounced surface area, quantum confinement effect complemented by small particle dimension, and many other extraordinary characteristics make AgNPs suitable in a variety of applications. Different methods have been adopted to synthesize AgNPs. Biological methods can formulate AgNPs in an environmentally friendly manner without producing toxic waste. Among the biological methods, plants are simple and attractive sources for AgNP synthesis. Compared to AgNPs produced via other modes of synthesis, phyto-synthesized AgNPs, due to their safety features, have been found to be advantageous for a variety of applications, especially biological applications. Strong research efforts have investigated the utility of phyto-synthesized AgNPs for different applications. Investigators are coming up with innovative applications of phyto-synthesized AgNPs for the development of science and technology and to benefit humankind. The present article focuses on phyto-synthesized AgNPs for biological applications, with a brief review of their synthesis, mechanism, and size/shape control.

Keywords: Plants, Biosynthesis, Silver Nanoparticles, Mechanism, Bioapplications

INTRODUCTION

Silver nanoparticles (AgNPs) have unique properties that are proving valuable in biomedical applications employing antibacterial, antiviral, antifungal, anticancerous, antivector, and antiinflammatory activities; this is on top of their utility in fields such as drug delivery, wound dressing, topical creams, antiseptic sprays, and fabrics [1-6]. They have distinctive physico-chemical properties such as catalytic activity, conductivity, chemical stability, non-linear optical behavior, and Raman scattering [7,8]. These properties make them vital in electronic components, cosmetic products, the food industry, composite fibers, cryogenic superconducting materials, and medical imaging [9-11]. They are becoming increasingly beneficial in textiles [12], biosensors [13], agriculture [14], and pest management [4].

Different strategies have been adopted to synthesize AgNPs. Biological methods of synthesis do not require high temperature, pressure, energy, or toxic chemicals; furthermore, these methods are eco-friendly, cost effective, and scalable. Therefore, biological modes of AgNP synthesis are relatively simple and convenient [15]. Plants, yeasts, bacteria, and fungi, and metabolites derived from these materials can be used to synthesize different nanoparticles [15,16]. The AgNP synthesis approach using microorganisms involves isolation of the microorganisms, and maintenance of aseptic working conditions and culture media for pure cultures. This requires specialized equipment and expert manpower to avoid biohazard during maintenance and handling of cell cultures [17]. Comparatively, plant mediated AgNP synthesis methods are relatively simple, fast, economical, and environmentally friendly. The stabilization of AgNPs occurs via plant metabolites as capping agents, which makes them appropriate for numerous uses including biomedical applications [15].

Many reviews are available that provide summary information on the plant species and morphological and microscopic characteristics of the synthesized AgNPs. After a brief review of the synthesis, mechanism, and size/shape control of phyto-synthesized AgNPs, we discuss a sample of selected investigations on plant synthesized AgNPs with specific bioapplications.

PHYTO-SYNTHESIS AND CHARACTERIZATION OF SILVER NANOPARTICLES

Diverse plants around the world have been investigated for their abilities to synthesize AgNPs. A general scheme of AgNP synthesis is displayed in Fig. 1. Different phytochemicals present in plants reduce and stabilize silver ions. These phytochemicals have medicinal properties and are mostly ecofriendly [15]. Wide-ranging methods involving plant-based AgNP synthesis include plant material collection and plant extract preparation. The plant materials are first properly washed with tap water. Fresh plant materials can be used or dried under shade or in an oven. Fine powder is prepared using a grinder. Extracts are prepared from ground/powdered materials in water or other solvents at room temperature or after boiling. The extracts are filtered to remove undesirable big plant particles. The prepared plant extract is used as a reducing agent for addition to precursor silver salt solution (e.g. 1 mM $AgNO_3$). The color change of the solution indicates reduction of Ag(I) ions to Ag(0); synthesis of AgNPs can be monitored via UV-visible spectra of the reaction solution [6,15]. For purification of the AgNPs, the solutions are generally centrifuged at 15,000 rpm for 15-30 min and

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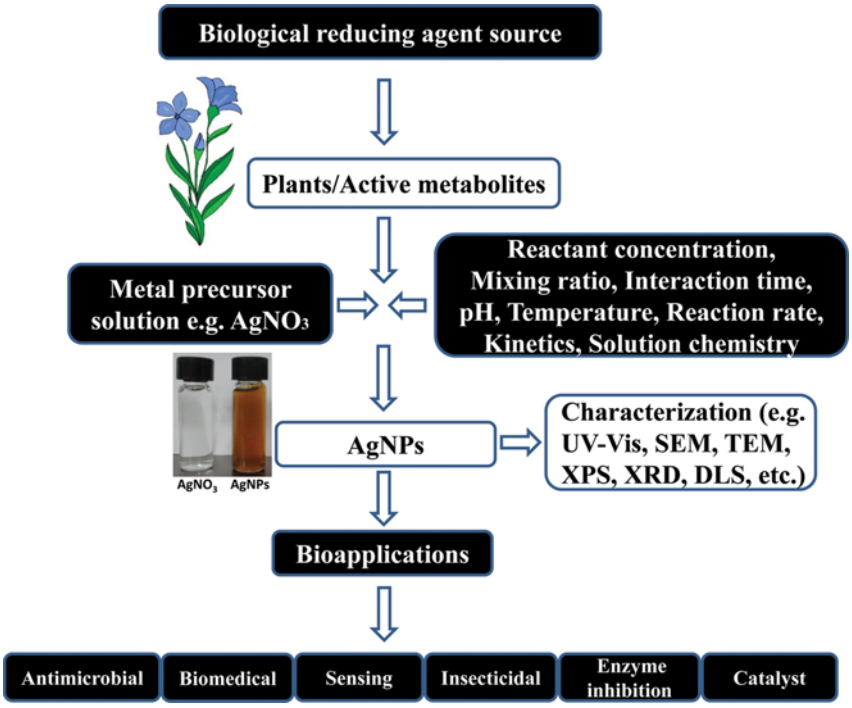

Fig. 1. General scheme of phyto-synthesis of silver nanoparticles and their bioapplications.

Table 1. Properties and applications of phyto-synthesized AgNPs

Plants	Shape	Size (nm)	UV-vis peak (nm)	Applications	Reference
Acalypha indica	-	20-30	420	Antibacterial against water borne pathogens	[29]
Aloe vera	Spherical	25	-	Antibacterial	[67]
Alstonia macrophylla	Spherical	50-163	420-450	Mosquito larvicidal	[68]
Alternanthera tenella	Spherical	≈48	430	Anticancer	[37]
Anogeissus latifolia	Spherical	5.7±0.2	412	Antibacterial	[21]
Azadirachta indica	Spherical	15-20	400	Copper sensing	[13]
Beetroot extract	Spherical	15	438	Catalytic activity	[54]
Breynia rhamnoides	Spherical, anisotropic	64	428	Catalyst	[69]
Cacumen platycladi	Spheroidal	18.4±4.6	411, 425, 431	Antibacterial	[70]
Cajanus cajan	Spherical	5-60	470	Antibacterial	[71]
Calliandra haematocephala	Spherical	70	414	Antibacterial and H_2O_2 sensing	[50]
Cassia auriculata	Spherical	20-40	450	Synthesis	[72]
Cassia auriculata	Spherical	10-70	460	Antibacterial	[73]
Casuarina equisetifolia	Spherical	9-22	-	Photcatalytic	[57]
Catharanthus roseus	-	67-48	418	Antibacterial	[74]
Catharanthus roseus	Spherical	35-55	-	Antiplasmodial	[75]
Citrullus colocynthis	Spherical	31	-	Anticancer	[35]
Coleus aromaticus	Spherical	40-50	340-740	Bactericidal	[76]
Cucumis sativus	Spherical	8-10	450	Photcatalytic and Antibacterial	[56]
Cymbopogan citratus	Spherical	32	430	Antimicrobial	[77]
Dimocarpus Longan Lour	Spherical	9-32	412, 427, 438, 440	Antibacterial and Anticancer	[38]
Dioscorea bulbifera	Spheres, triangles, and hexagons	8-20	450	Antimicrobial	[78]
Erythrina indica	-	-	262	Drug delivery	[39]
Euphorbia hirta	Spherical	263	520, 396, 228	Antibacterial	[5]

Table 1. Continued

Plants	Shape	Size (nm)	UV-vis peak (nm)	Applications	Reference
Euphorbia heterophylla	Grain and triangular shapes	13-50	422, 405	Restriction endonuclease inhibition, Mercury sensing	[47,49]
Euphorbia hirta	Spherical	30-60	410	Mosquito larvicidal	[79]
Euphorbia ingens	Spherical	276	420, 211	Antibacterial	[5]
Euphorbia milii	Spherical	105	606, 526, 426, 200	Antibacterial	[5]
Euphorbia prostrata	Rod	25-80	420	Pesticidal activity	[80]
Euphorbia tirucalli	Spherical	50-163	420-450	Mosquito larvicidal	[68]
Euphorbia. lacteal	Spherical	186	420, 385, 200	Antibacterial	[5]
Ficus benjamina	Spherical	20-30	415-440	Apoptosis	[34]
Ficus carica	Spherical	21	422	Urease inhibition	[48]
Fissidens minutus	Spherical	-	412.8	Antibacterial	[81]
Gliricidia sepium	Spherical	10-50	440	Antibacterial	[30]
Glycyrrhiza glabra	Spherical	7-45	404	*In-vitro* antiulcer	[40]
Helicteres isora	Cubic shape	25.55-45.55	430	Catalytic degradation of dyes	[55]
Hibiscus sabdariffa	Spherical	5-30	366-625	Sensing of metal ions and Antimicrobial	[51]
Hovenia dulcis	Spherical	33	433	Antibacterial	[6]
Jatropha curcas	Spherical	73	420, 389, 212	Antibacterial Antiparasitic	[5] [45]
Jatropha gossypifolia	Spherical	18-62	419, 420, 450, 550	Antibacterial, Mosquito larvicidal, Antiparasitic, Sensing of melamine	[5,68,45,53]
Kalopanax pictus	Spherical	10-30	430	Antibacterial	[82]
Kalopanax septemlobus	Mixture of different shapes	30.8	430	Antibacterial	[83]
Lactuca sativa	Spherical	40-70	440	Antibacterial	[84]
Magnolia kobus	Spherical	15-500	430	Rapid synthesis	[85]
Malus pumila (Apple)	Spherical	30.25±5.26	420-450	Antibacterial	[86]
Mimosa pudica	Spherical	25-60	420	Antiparasitic	[24]
Murraya koenigii	Cubic and spherical	20-35	410	Mosquito larvicides and pupaecide	[87]
Musa acuminata	Agglomerated form	-	420	Bioactive product development	[88]
Nicotiana tobaccum	Crystalline	8	418	Antibacterial	[20]
Ocimum canum	Rod	25-110	426	Acaricidal	[46]
Ocimum sanctum	Circular	4-30	413	Antimicrobial	[89]
Pedilanthus tithymaloides	Spherical	123	420, 393, 211	Antibacterial	[5]
Pergularia daemia	Spherical	44-255	456	Mosquito larvicides	[4]
Pinus thunbergii	Triangular and hexagonal	5-50	414-464	Antibacterial	[90]
Plumeria rubra	Spherical	32-220	456	Mosquito larvicides	[4]
Polyalthia longifolia	Spherical	15 and 20	422, 425, 435, 451	Antibacterial	[91]
Prosopis farcta	Spherical	10.8	433	Antibacterial against multidrug resistant bacteria	[28]
Psidium guajava	-	24	400, 450, 460	Antibacterial	[92]
Satureja hortensis	Spherical	15±7.402	-	Antibacterial	[93]
Setaria verticillata	-	24	-	Electrochemical/Sensing	[52]
Solanum torvum	Spherical	14	434	Antibacterial	[94]
Spinacia oleracea	Spherical	40-70	450, 480	Antibacterial	[84]
Tagetes erecta	Spherical, hexagonal and irregular	10-90	430	Antibacterial and antifungal	[95]
Tinospora cordifolia	Aggregated	55-80	420	Pediculocidal and larvicidal	[42]
Trianthema decandra	Cubic, hexagonal	10-50	450	Antibacterial	[96]
Vitex negundo	-	10-30	-	Antibacterial	[97]
Zingiber officinale	Spherical	6-20	424	Antiplatelet agent	[36]

purified by repeated washings. Powders of settled AgNPs can be prepared by freeze drying. These powdered AgNPs can be used for different types of characterizations.

After preliminary indication from color reactions and UV-visible spectroscopic analyses, AgNPs are commonly further characterized through X-ray diffractometry (XRD), dynamic light scattering (DLS), X-ray photoelectron spectroscopy (XPS), scanning electron microscopy (SEM), transmission electron microscopy (TEM,) atomic force microscopy (AFM), and Fourier transform infrared spectroscopy (FTIR) [6,15,18]. Characterizations via these approaches provide information on crystallinity, size, shape, surface area, pore size, and fractal dimensions, as well as orientation, intercalation, and dispersion of nanoparticles. UV-visible spectroscopic analyses through plasmon resonance give information on sample formation. Size distribution of particles is understood through DLS and using TEM and SEM. Evidence of the crystallinity of particles can be obtained through XRD. Morphological features and size of particles can be understood through AFM, SEM, and TEM. Three-dimensional images in AFM provide information on volume and height of particles.

Plants of diverse species and their different plant parts have been reported for the synthesis of AgNPs. Table 1 provides information on a sample of plant species investigated for their AgNP synthesis ability and morphological and microscopic characteristics of the synthesized AgNPs. The information in Table 1 suggests that most plants synthesize spherical AgNPs with average size less than 100 nm. Some plants can synthesize triangular, rod, cubic, and hexagonal AgNP shapes, as well as a mixture of different shapes.

MECHANISM OF PHYTO-SYNTHESIS OF SILVER NANOPARTICLES

In most studies, AgNP synthesis by plant extracts has been linked with the phyto-constituents or active principles of the plants. Saponins [19], amines [20], arabinose, galactose [21], aldehydes, ketones [22], starch [23], terpenoids, flavonoids, and polyphenols [24] have been used for the synthesis of AgNPs. Enzymes and proteins have also been reported to be useful for the synthesis of AgNPs. Peptide and protein carbonyl groups have strong metal binding ability. *Jatropha curcas* latex curcain (enzyme), curcacyclin A (octapeptide), and curcacyclin B (nonapeptide) have been found to play roles in AgNP synthesis [25]. Euphorbian plant latex proteins can lead to the formation of AgNPs [5]. Claims regarding the roles of proteins in most studies have been demonstrated by FTIR study, which shows shifting of bands and binding of (NH)C=O group with AgNPs.

As a result of the vast diversity in plant systems, ascertaining the precise mechanism of AgNP synthesis is challenging. The exact mechanism of reduction and capping of AgNPs in plant mediated synthesis is not yet clear. The progression of AgNP synthesis happens with an initial dissociation of the metal precursor, such as $AgNO_3$ to Ag^+ and NO^{3-}. The hydroxyl and ketonic groups containing bioactive plant metabolites may provide stability against agglomeration due to their ability to bind to metals and reduce metal salts. Plant extracts may be able to impart proteins/plant metabolites and enzymes to the $AgNO_3$ solution, in which Ag^+ ions may combine with the enzyme to form an enzyme substrate complex. The enzyme released from the plant extract may act on the silver ions to synthesize AgNPs. Proteins/plant metabolites from plant extracts may combine with released AgNPs to yield protein/plant metabolites capped AgNPs.

SIZE AND SHAPE CONTROL OF SILVER NANOPARTICLES VIA PHYTO-SYNTHESIS APPROACH

Nanoparticles hold some exclusive optical, chemical, and electronic properties in comparison to their bulk materials. With variation in the monodispersity, shape, and size, the properties of nanoparticles also change. Some nanoparticles display certain unique size- or shape-dependent properties. Therefore, the research focus has been geared exclusively toward obtaining nanoparticles with desired controlled morphologies. Different parameters such as the type of plant, plant part, solvent for extraction, and synthesis conditions are important for the formulation of controlled morphologies. Temperature, pH, reaction time, source compound of target nanoparticle, and substrate concentrations all have impacts on nanoparticle morphology.

Kajani et al. [26] utilized *Taxus baccata* plant extracts as capping and reducing agents to formulate anisotropic AgNPs with controlled size and shape morphologies of narrow size distribution with an average size of 75.1 nm. They considered various parameters such as the type and concentration of plant extract, the silver nitrate concentration, and the temperature and pH used to manufacture the desired shape and size AgNPs. Plant extract type was found to be the most important parameter, with an impact on the chemical, physical, and cytotoxic properties of the AgNPs. TEM and AFM results revealed the synthesis of spherical AgNPs through the use of aqueous extracts and hexagonal and truncated triangular shaped stable AgNPs through the use of ethanolic extracts at high concentration. The aqueous extract formulated AgNPs exhibited compelling anticancer effects on MCF-7 cells, with an IC_{50} value of 0.25 mg/mL within 48 h as determined using an MTT assay. That study indicated the promise of AgNPs for cancer therapy, imaging, and tracking cells. Sahni et al. [27] attempted an investigation of the controlled synthesis of AgNPs using *Musa acuminata* and *Allium cepa* plant extracts. They studied the influence of various parameters such as the temperature, time, and pH on the AgNP synthesis and reported a simple strategy for kinetics control of metal ion interactions with reducing agents; they attained sub-10 nm AgNPs with narrow size distribution via stabilization by ammonia. The AgNPs were characterized by TEM and UV-visible spectral analyses. These obtained AgNPs displayed remarkable antimicrobial activity at very low concentration versus *Fusarium oxysporum*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, and *Escherichia coli*, indicating their significance as innovative nanoproducts for agricultural and biomedical applications.

Research on achieving precise morphology and monodispersity using plants is still in its infancy. Extensive research efforts are needed to accomplish controlled synthesis by optimizing the different process parameters. Investigations focusing on parameters such as choice of specific plant by species, growth phase, growing conditions, plant part, extraction solvent, conditions of synthesis, reac-

tion time, temperature, substrate concentrations, pH, precursor salts, ultrasonication, shaking, irradiation, and several other parameters will need to be carried out and optimized to ascertain a trustworthy process for the synthesis of uniform size and shaped AgNPs. As plant extracts are mixtures of different bioactive chemicals, controlling the size and shape using only extracts may be difficult. Isolation of pure compounds from plants and their utilization may give more reproducible size and shape control than would be possible with crude extracts.

BIOAPPLICATIONS OF PHYTO-SYNTHESIZED SILVER NANOPARTICLES

Phyto-synthesized AgNPs have been investigated for their different activities such as antimicrobial, mosquito larvicidal, antiparasitic, antiplasmodial, pesticidal, acaricidal, pediculocidal, anticancer, restriction endonuclease inhibitory, catalytic, and sensing (Table 1). Some of the selected bioapplications are discussed below.

1. Antimicrobial

AgNPs display antimicrobial properties versus many pathogenic microorganisms. Both Gram negative and Gram positive bacteria have been reported to be susceptible to AgNPs. Regardless of their Gram characteristics in bacteria, antagonist effects of AgNPs were found on enzymes and proteins [5]. In the wake of augmented antibiotic resistance of pathogenic microbes and hospital infection cases, AgNPs show promise for use in antimicrobial therapy. Spherical AgNPs with mean diameter of 10.8 nm were synthesized using extract of *Prosopis farcta* at room temperature; this process showed greater antibacterial action versus clinical isolates with multi drug resistance [28]. AgNPs synthesized from different plants were effective against water borne pathogens: AgNPs synthesized from *Acalypha indica* against *Escherichia coli* and *Vibrio cholerae* [29]; AgNPs synthesized from *Gliricidia sepium* against *Staphylococcus aureus* [30]; AgNPs synthesized from Euphorbian plant latex of *Jatropha gossypifolia*, *Jatropha curcas*, *Euphorbia milii*, *Euphorbia hirta*, *Pedilanthus tithymaloides*, etc. against *Micrococcus luteus*, *Staphylococcus epidermis*, *S. aureus*, and *E. coli* [5]. Antimicrobial features of AgNPs are desirable for their utility in water purification [31]. Filtration of water through filters of polypropylene coated with silver removed all *E. coli* bacterial load within 7 h at a level of 3 L/h with 10^3 cfu/mL [32]. The uniform coating of AgNPs on cotton fibers imparted antifungal characteristics to the textiles [33]. Salunke et al. [6] reported the enhancement of the antibacterial potential of *Hovenia dulcis* medicinal plant mediated biosynthesized AgNPs after their combination with ten different antibiotics; diverse mode of action was also documented for these compounds. The investigators observed synergistic antibacterial effects of AgNP in combination with antibiotics, with the highest synergistic effects for penicillin against *Bacillus cereus* (3.04 folds) and for tetracycline against *E. coli* (1.55 folds). They suggested that the distinctive properties of AgNPs can be therapeutically valuable for fabrication of innovative hybrid drugs to enhance the effectiveness of antibiotics' ability to kill bacteria.

2. Biomedical

Bhakat et al. [34] used thermal and microwave reduction to synthesize AgNPs using *Ficus benjamina* leaf extract. AgNPs (20-30 nm size) showed apoptotic (anticancer) potentials against cervical cancer cells (HeLa) and variable effects on normal body cells (HEK293) *in vitro*. AgNPs synthesized using *Citrullus colocynthis* calli cells showed anticancerous potential on Hep-2 cells [35]. AgNP inhibitory concentration for survival of 50% cells was 500 ppm. Apoptosis of cells occurred after AgNP treatment due to an increase in the caspase-3 activity. *Zingiber officinale* plant extract synthesized AgNPs displayed high blood compatibility, which is an encouraging sign for biosensor and drug delivery applications involving direct blood contact [36]. *Alternanthera tenella* leaf extract synthesized AgNPs (average size ≈48 nm) inhibited MCF-7 cells (Human breast adenocarcinoma) in a dose-dependent manner (IC_{50} 42.5 μg/mL) and significantly reduced MCF-7 cell migration [37]. *Dimocarpus longan* peel extract synthesized AgNPs (size range 9-32 nm with a face-centered cubic structure) were cytotoxic to PC-3 cells (human prostate cancer) in a dose-dependent manner via increasing caspase-3 and decreasing survivin, bcl-2, and stat 3 [38]. These results show a prospective anticancer application of AgNPs in therapy for prostate cancer. *Erythrina indica* leaf extract synthesized AgNPs were integrated in gelatin and investigated to determine their capability of sustained drug release [39]. Gelatin was used as a medium for binding and sustained release of drug. Gelatin amalgamated AgNPs were loaded along with Atorvastatin calcium (ATVC) and characterization for sustained drug release was carried out through thermogravimetric, FTIR, and UV-visible spectral analyses. The investigators recorded comprehensive drug release for AgNP-gelatin with ATVC in comparison to cases that did not integrate AgNPs with gelatin-ATVC. This study outcome recommended AgNPs as an effective drug carrier. Via assays of broth micro dilution and agar disc diffusion, *Glycyrrhiza glabra* root extract manufactured AgNPs were investigated for their anti-ulcer potential versus *Helicobacter pylori*; the studies revealed the promise of phyto-synthesized AgNPs for gastric ulcer therapy [40].

Detailed understanding of the toxicity mechanism for precise determination of the bioactivity of phyto-synthesized AgNPs is needed. To understand the real mechanism behind bioactivity, control studies should involve investigation of the biomedical effects of AgNPs and plant extracts, as well as the extent of released Ag^+ ions. This will help in determining the actual deciding factors of the toxicity to be AgNPs, Ag^+ ions, or some other mechanism.

3. Insecticidal

AgNPs formulated using the latex of one plant, *Plumeria rubra*, as compared to crude latex extract, showed more toxicity to second and fourth larval instars of two mosquito species, *Aedes aegypti* and *Anopheles stephensi* [4]. The investigators reported LC_{50} values of 1.49 and 1.82 ppm against *A. aegypti* and 1.10 and 1.74 ppm against *A. stephensi* for the AgNPs synthesized after 24 h against second and fourth larval instars, respectively. For crude latex extract, the LC_{50} values were 143.69 and 170.58 ppm against *A. stephensi* and 181.67 and 287.49 ppm against *A. aegypti*. Characterization by TEM, particle size analysis, zeta potential, and UV-visible spectrophotometry revealed spherical AgNPs with sizes in a range of 32-200 nm; these AgNPs also showed dose dependent mortality. The pesticidal activity of *Euphorbia prostrata* synthesized AgNPs was studied against *Sitophilus oryzae* adult insects [41]. Pesticidal activity was investigated at different doses for 14 days with rod shaped AgNPs with a size range between 25-80 nm (average size 52.4 nm). The LD_{50} and

LD_{90} values for the AgNPs were 44.69 and 168.28 mg/kg, respectively. On the other hand, the LD_{50} and LD_{90} values were 213.32 and 1,648.08 mg/kg for aqueous extract, and 247.90 and 2,675.13 mg/kg for $AgNO_3$ solution, respectively. These observations suggest the use of AgNPs as biocontrol agents against *S. oryzae*. Jayaseelan et al. [42] found that *Tinospora cordifolia* Miers (Menispermaceae) leaf aqueous extract synthesized AgNPs can control the head louse *Pediculus humanus* (Phthiraptera: Pediculidae) and the fourth instar larvae of *Anopheles subpictus* and *Culex quinquefasciatus*. Using direct contact assay to assess the pediculocidal activity, the investigators exposed lice and mosquito larvae to different doses of aqueous extracts and AgNPs for 24 h. Their observations revealed mortalities of 33%, 67%, and 100% after 5 min, 15 min, and 1 h, respectively for the formulated AgNPs. The LC_{50} values of the AgNPs were 12.46, 6.43, and 6.96 mg/L versus lice, *A. subpictus*, and *C. quinquefasciatus*, respectively. These outcomes suggest that AgNPs have exceptional anti-lice and mosquito larvicidal action, and so they have good prospects to become head lice and vector control agents. *Euphorbia hirta* phyto-synthesized AgNPs were also found to be effective as mosquito larvicides against *Anopheles stephensi* [43].

4. Antiparasitic

AgNPs in a size range between 35-55 nm were synthesized using *Catharanthus roseus* aqueous leave extracts; the synthesized AgNPs showed antiplasmodial activity against the malarial parasite, *Plasmodium falciparum* [44]. *Jatropha curcas* and *Jatropha gossypifolia* synthesized AgNPs, pigments violacein, prodigiosin, and their mixtures with AgNPs were investigated for growth inhibitory studies of *Plasmodium falciparum* and *Trypanosoma brucei* gambiense [45]. For both parasites, a significant reduction of the IC_{50} values (2.7 to 3.6 fold) for prodigiosin-metal nanoparticle combinations was observed without mammalian cell cytotoxicity elevation. The antiparasitic efficacy of *Ocimum canum* formulated AgNPs (average size 95 nm, rod structures) was explored against *Hyalomma anatolicum* and *Hyalomma marginatum* (Acari: Ixodidae) larvae at various concentrations for 24 h [46]. LC_{50} and LC_{90} values of 15.31 and 13.85 mg/L, and 62.41 and 48.86 mg/L for *O. canum* crude leaf extracts in water were found against *H. a.* anatolicum and *H. m.* isaaci larvae, respectively. Values of LC_{50} of 12.25 and 12.17 mg/L, and values of LC_{90} of 49.17 and 46.52 mg/L were found against *H. a. anatolicum* and *H. m. isaaci* for 1 mM $AgNO_3$ solution. AgNPs were most effective with values of LC_{50} and LC_{90} of 0.78 and 1.00 mg/L, and 1.51 and 1.68 mg/L against *H. a. anatolicum* and *H. m. isaaci*, respectively. This method is considered a good alternative for controlling parasites.

5. Enzyme Inhibition

Medicinal plant *Euphorbia heterophylla* (*E. heterophylla*) synthesized AgNPs with average size of 13 nm were found to inhibit restriction endonuclease DNA cutting activity (*Bam*HI, *Eco*RI, and *Hin*dIII) in agarose gel electrophoresis [47]. This property of AgNPs has promise for augmenting the efficiency of phage therapy by inhibiting bacterial restriction endonuclease. Borase et al. [48] studied a fast, economical, and environmentally friendly synthesis of stable AgNPs by utilizing *Ficus carica* leaves extract. The AgNPs were spherical, with an average size of 21 nm and a crystalline nature. FTIR analyses was used to determine that *F. carica* proteins were responsible for the synthesis and stabilization of AgNPs. Through evaluation of ammonia release, the investigators observed that AgNPs are able to inhibit the enzyme urease. This is a crucial enzyme for the pathogenesis and survival of *Helicobacter pylori* bacteria. The potential of AgNPs to inhibit urease can give rise to new drug molecules for *H. pylori* treatment after their combination with other standard drugs.

6. Sensing

Azadirachta indica synthesized AgNPs showed good sensitivity for detection of copper metal at minimal levels [13]. AgNPs of spherical shape and narrow size range (20-50 nm) were synthesized using biologically active latex from *Euphorbia heterophylla* (Poinsettia) [49]. These latex-synthesized AgNPs showed good potential and sensitivity for selective Hg^{2+} ion detection, with a 100 ppb detection limit. Addition of Hg^{2+} led to a marked deviation in the color and AgNP surface plasmon resonance (SPR) spectra. Raja et al. [50] manufactured AgNPs utilizing *Calliandra haematocephala* leaf extract and demonstrated the hydrogen peroxide detection capacity of AgNPs. The study suggested that AgNPs can be useful to develop innovative biosensors to sense the existence of hydrogen peroxide in different samples. AgNPs produced using *Hibiscus sabdariffa* plant extract were investigated for selective sensing of metal ions of Pb^{2+}, Cd^{2+}, and Hg^{2+} in aqueous solutions at the ppm level [51]. AgNPs synthesized from various plant parts showed different levels of sensitivity and selectivity. The investigation endorses the utility of AgNPs for diverse applications as a result of selective colorimetric toxic metal ion sensing. Prabhu et al. [52] validated the thermal stability, optical property, and electrochemical properties of *Setaria verticillata* plant extract formulated AgNPs (average size 24 nm). AgNP-modified glassy carbon electrodes (GCE) decreased the over potential and displayed well-defined cyclic voltammetry (CV) peaks. Modified GCE presented long-term stability, good selectivity, and great sensitivity. A new way of designing electrochemical sensors for metal impurity and organic effluent sensing is possible through this approach. *Jatropha gossypifolia* leaf extract synthesized spherical and grain shaped AgNPs (size range 18-30 nm) were used to selectively and rapidly detect melamine present in raw milk [53]. The detection was possible due to changed color, SPR spectral deviation, and absorption ratio (A500/A419) changes after interactions of AgNPs and melamine. Various thermal and physicochemical studies were carried out to optimize the sensing of melamine using AgNPs. The investigators achieved a 252 ppb (2 μM) limit of melamine detection using AgNPs. This limit is relatively lower as compared to the regulatory body safety level recommendations, indicating the sensitivity of the method. DLS and TEM suggested hydrodynamic diameter and AgNP size increase after interaction of melamine and AgNPs.

7. Catalytic

Spherical, well dispersed AgNPs (average diameter of 15 nm) were formulated using beetroot aqueous extract as a reducing agent [54]. A blue shift of the absorption spectra was witnessed after increase in beetroot extract concentration, indicating particle size decrease. The catalytic actions of the synthesized AgNPs were investigated for 4-nitrophenol to 4-aminophenol reduction by $NaBH_4$. The prepared AgNPs revealed faster catalytic action. As 4-nitrophenol is toxic, mutagenic, and carcinogenic, use of AgNPs is an effective

method for its removal. Bhakya et al. [55] synthesized AgNPs using the different parts of *Helicteres isora*. AgNPs displayed organic dye degradation catalytic activity in a size and extract dependent manner. *Cucumis sativus* (cucumber) fruit extract synthesized AgNPs exhibited good photocatalytic activity under solar irradiation for methylene blue dye degradation [56]. Similarly, AgNPs formulated using *Casuarina equisetifolia* leaf extract demonstrated methylene blue dye degradation under sunlight irradiation via photocatalytic activity [57]. This was established using a UV-visible spectrophotometer to observe the methylene blue dye specific absorbance decrease over time. With an exposure time of 5 h, almost 35.13% of the methylene blue dye was efficiently degraded by the AgNPs. Adverse effects occurring due to exposure of methylene blue dyes, such as methymoglobinemia and painful micturition, can be prevented via application of AgNPs for dye degradation in the pharmaceutical and textile industries as well as for water treatment plants.

CURRENT SCENARIO AND FUTURE PROSPECTS OF PHYTO-SYNTHESIZED SILVER NANOPARTICLES

Plant systems are more economically scalable than other biomodes of nanosynthesis and have opened wide areas in nanotechnology research. AgNP synthesis employing plant extracts has been described in many reports. Optimization of the production process to obtain stable, small nanoparticles can be achieved via systematic studies of the pH and plant extract to the precursor silver salt concentration. Trustworthy, economical, eco-friendly, and commercially viable methods using natural reducing constituent to produce AgNPs are needed. Active components from plants like enzymes, tannins, phenolics, alkaloids, terpenoids, saponins, flavonoids, vitamins, polysaccharides, amino acids, proteins, etc. can be responsible for AgNP synthesis [19-23]. AgNP synthesis efficiency utilizing the same species of plant can change due to the significant variation in chemical compositions of plant extracts of the same species in various parts of the world. Therefore, ascertaining the biomolecules involved in AgNP synthesis and their use for rapid and large scale production in a single step protocol can be good approach. Advancements in modifications of plant genomes, the engineering of genes, plant part regeneration *in vitro*, precise metabolite yield increase, and plant specific constituent extraction and separation method improvements will help in the development of nanoparticle production systems in the near future.

As a result of their exclusive properties, AgNPs are promising for a number of beneficial applications. They are valuable in the development of nanoscale devices and platforms for single molecule characterization at a faster rate than is possible using traditional techniques. Their excellent electrochemical properties make them suitable for the development of nanoscale sensors at faster response times and lower detection limits. Catalytic activities exhibited by these materials makes them suitable for utilization in the faster degradation of complex materials. Many innovative applications are progressively emerging. The presence of AgNPs is already being felt in applications in the textile, health industry, food storage, and environmental sectors. Considering their potential and promise, these materials can become integral components of major science and technology applications in the near future.

Suspected environmental and human health toxicity raise concerns for the practical utility of AgNPs. Although silver has been used for decades, there is no clear evidence on its toxicity. Different investigators have reported variable toxicity effects of AgNPs on different living systems. Some investigators have reported AgNPs to be toxic; however, some others have found them to be nontoxic. The toxic effects of AgNPs were observed in the zebrafish *Danio rerio*, triggering injuries to embryos and reducing zebrafish survival at LC_{50} values of 6.04-8.28 (7.07) mg/L for adults and 5.9-8.6 (7.20) mg/L for juveniles; similar results were obtained for algae *Pseudokirchneriella subcapitata*, *Ceriodaphnia dubia* neonates, and *Daphnia pulex* [58,59]. Smaller sized AgNPs (5.5±2 nm), compared to that of relatively large AgNPs (9.2±2.7 nm) on agar strips, showed enhanced repellent activity of the active streaming form of *plasmodium* of *Physarum polycephalum* slime mold [60]. However, no noticeable toxic effects in fish, *Poecilia reticulate*, were observed after 24 to 48 h exposure to the synthesized AgNPs. Toxicity studies of *Euphorbia heterophylla* (Poinsettia) synthesized AgNPs on aquatic non-target species *Daphnia magna* showed that latex-synthesized AgNPs (20.66±1.52% immobilization) were comparatively much less toxic than chemically synthesized AgNPs (51.66±1.52% immobilization) [49]. Similarly, comparative toxicity study on human red blood cells showed lower hemolysis (4.46±0.01%) by latex-synthesized AgNPs than was the case for chemically synthesized AgNPs, which caused 6.14±0.01% hemolysis. More detailed investigations focusing on optimization of the concentrations and determination of AgNP impacts on living systems will be needed to make judgements about the toxicity of AgNPs. Different accredited bodies such as FITI Testing and Research Institute, the Testing and Research Institute for Chemical Industry Korea, the SIAA in Japan, the US EPA, and the US FDA have permitted some goods to be prepared using AgNPs [61-66].

CONCLUSIONS

Well-designed and resourceful means of producing very effective and useful nanomaterials are available in nature. Enormous natural wealth exists on earth as natural factories of enzymes, metabolites, antibiotics, and foods. There is vast diversity of plants in the world. These plants offer a wide array of chemical, morphological, and genetic variation. Exploration of prospective plants for AgNP synthesis requires widespread plant survey in diverse habitats. Data acquired from such surveys and identification of potent nanoparticle-producing plants can be valuable. There is increasing awareness of the need for the development of environment-friendly techniques for AgNP synthesis. Extracts of plants are the best candidates for the synthesis of AgNPs, much better than physical, chemical, and microbial methods. Use of plants is more beneficial than the use of other biological agents, such as using microbes; further, plant culture maintenance is not needed. Plants are rich bio-resources of medicinally important metabolites, which can act as capping and reducing agents for the synthesis of AgNPs. The approach of utilizing extracts of plants for AgNP synthesis is economical, energy efficient, and trustworthy. This strategy will also provide better work environments, protecting human health and the environment and

producing safer products with less waste. Phyto-synthesized nanoparticles have diverse applications. Large scale synthesis study, the determination of the mechanism of nanoparticle synthesis, and plant genetic engineering for active principle production of reducing and capping agents are promising areas of research. Rigorous quality control for synthesis and procedures for safe measurement of nanoparticles *in vivo* will be needed to certify their utilization for animal and human health applications.

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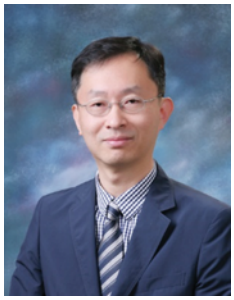

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