

A Review on Synthesis of Silver Nanoparticles and their Biomedical Applications

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Abstract: The silver (Ag) metal is considered a very useful metal for treating consume wound diseases, open wounds, and cuts, respectively. Nowadays, nanotechnology has created a surprising effect by changing over metallic silver into silver nanoparticles (AgNPs) for better applications. However, according to advanced technology, the synthesis of nanoparticles occurs by using organic or biological techniques rather than physical and chemical techniques. Also, the synthesis of silver nanoparticles (AgNPs) using biological or organic sources is cost-effective and eco-friendly. Silver nanoparticles (AgNPs) are broadly used as antibacterial specialists, helping us cure novel diseases and questionable sicknesses. In biomedicine, silver nanoparticles have huge points of interest because of their physical and synthetic flexibility. The uses of silver nanoparticles (AgNPs) in nano-gels, nano-fluids, silver-based coating over food and medical devices are advancing. Still, there is a need to innovate a better version of silver nanoparticles for vigorous use in an eco-friendly way. So, this review describes the methods of synthesis, activities under various conditions, and different biomedical uses of silver nanoparticles (AgNPs) in detail.

Keywords: silver nanoparticles (AgNPs); larvicidal activity; anti-inflammation; microscopic organisms.

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1. Introduction

Nanotechnology is a quickly developing science technique with very useful roles to human beings, animals, and the environment. Nanoparticles (NPs) are amazing discoveries of nanotechnology to settle the current world's issues. Among the different metallic and non-metallic NPs, silver nanoparticles (AgNPs) have been extensively investigated for their relevance and flexibility [1-6]. The AgNPs have established wide consideration in the fields of wastewater treatment, biomedicine, drug delivery, vector control and agriculture [7, 8-16]. The effective conductivity of AgNPs has amplified their applications in a wide array of products such as electronic devices, inks, gums, pastes and in controlling microbial growth and infections, which has likewise also made them eco-accommodating [17-19].

The physical and synthetic blend of AgNPs has pulled in different biophysical and compound applications attributable to amalgamation's immaculateness. However, both of these syntheses consume high-energy chemicals and are often contaminated with toxic chemicals [20-22]. In this way, the combination of AgNPs utilizing bio-sensible diminishing specialists, such as plants, microorganisms, parasites, and green growth, has prompted green nanofabrication [23].

Biosynthesis of nanoparticles as an arising feature of the convergence of nanotechnology and biotechnology has expanded consideration because of the developing need to grow ecologically amiable innovations in nanomaterial blend [24]. The naturally incorporated NPs are known to have incredible antimicrobial, antimalarial, antiviral and antiparasitic exercises. In a few investigations, bacteria such as *Shewanella oneidensis* and *Lacto-bacillus* sp., etc., have been used to synthesize of AgNPs [25,26]. In previous reports, [27] plant extracts have been used to develop sustainable and eco-friendly approaches for AgNPs synthesis. AgNPs synthesized using plant extracts as reducing agents have also shown effective antibacterial activities against clinical pathogens [23]. Nonetheless, notwithstanding the developing advances in the union of AgNPs, organic sources have consistently portrayed huge possibilities for creating expected AgNPs. Be that as it may, moderate endeavors have been made to popularize organically blended AgNPs for public use. Accordingly, the ebb and flow audit stress the likely biomedical utilization of the organically integrated AgNPs in addressing a wide exhibit of infections and infections.

2. Synthesis of Nanoparticles (NPs)

Nanomaterials are classified as non-metallic and inorganic (SiO_2 , TiO_2 , ZnO_2 , Fe_2O_3 , CeO_2 , ZrO_2 , Cu_2O), metallic and metal alloys (Au, Ag, Pd, Cu, Fe, Ni, Co, Mn, Mg), carbon-based nanomaterials (fullerenes, carbon nanotubes, graphene), dendrimers and nano-polymers (polymeric nanotubes and NPs, nanowires, nanorods, nanocellulose, polymer films) and quantum dots (cadmium telluride, cadmium selenide, quantum dots free cadmium) [4,21,28,29]. Nanomaterials are generated either by natural, substance, or actual techniques. Among the various NPs, AgNPs have been generally abused for biomedical applications. Ag nanoparticle combination is performed through two methodologies specifically, start to finish and base to top methodology [30]. In the top to bottom approach, bulk materials are used for NPs synthesis, while in the bottom-to-top approach, NPs are synthesized based on the packaging of atoms, molecules, or clusters [31]. There are various methods employed to synthesize AgNPs; they are classified based on the sources and reducing agents used for the conversion of nano-Ag. The physicochemical methods used to synthesize AgNPs include chemical reduction, gamma-ray radiations, microwave, electrochemical, and laser ablation [32,33]. However, certain restrictions associated with the physical and substance techniques make the organic strategy prevalent for AgNPs amalgamation. Both genuinely and chemically integrated AgNPs have short lives up to 20 min, buildup items are framed as side-effects during amalgamation, sweet-smelling amines are delivered, the cycle of union is exorbitant, it consumes high force, and longtime upkeep is required.

The biological synthesis of AgNPs involves major living resources or organisms. The significant sources utilized for the amalgamation of AgNPs are microscopic organisms, growths, green growth, and plants. During the amalgamation of AgNPs utilizing natural sources, the living organic entities reduce specialists or balance out specialists or covering specialists and decrease Ag^+ to create Ag^0 [34,28]. Plants or plant extracts are effortlessly safe, accessible, and non-toxic concentrates containing many metabolites for the synthesis of AgNPs. However, compared to bacteria, fungi produce higher concentrations of AgNPs due to the high contents of extracellular secondary metabolites used as capping and reducing agents during synthesis. In this way, considering the downsides of physical and substance strategies, an organic technique for synthesizing AgNPs is viewed as a conceivably more secure, non-poisonous, and savvy course.

3. Applications

Although AgNPs are utilized in an assortment of uses, including thin films [35,36], surface coatings [37], batteries [38], energy harvesting [39], and conductors [40], clinical applications have pulled in extraordinary most consideration because of expanding perilous illnesses worldwide and multidrug opposition challenges in vague medication conveyance. Inappropriately, the economic status for the utilization of AgNPs is literally limited. However, the flexibility of AgNPs on a wide scope of contaminations is very much appreciated. Significantly, AgNPs serve as effective antimicrobial agents by moving the proteins and enzymes of the host/pathogenic cells and ultimately cause cell death. The antibacterial impacts of AgNPs are probably going to be exhibited through the particles, which transform into Ag⁺ particles and create receptive oxygen species. They are also liable to upset the development flagging pathway inside the bacterial cells by tweaking the tyrosine phosphorylation of proteins significant for cell practicality [41]. Silver most likely assumes a functioning part in restraining bacterial development by restricting covalently to the cell surfaces and, in the long run, disturbing the cell films [42-46]. The joined antimicrobial specialist upsets the cell layers of the bacterial cells by physical and ionic wonders. Unthinkingly, Ag⁺ particles have been reported to cooperate with the thiol gatherings of compounds and proteins in the films and cytoplasm's that are significant for bacterial breath and the transportation of different substances across the layers. Furthermore, silver particles are notable for being viable in forestalling the diseases of wounds [47,48].

Also, AgNPs directed by functionalizing the surfaces and formed with antimicrobials were viable. Recently, AgNPs were circulated in the polymer lattice [20] for reasonable reactivity. An enormous number of studies have utilized AgNPs for their different biomedical properties, for example, insecticidal, antilarval, antibiofilm, and anticancer properties [28,49-52]. Definitely, this audit could help the peruses to configuration research works and comprehend the adequacy of AgNPs alongside expanded investigations. Schematic portrayal and the table would empower an exhaustive comprehension of different parts of AgNPs in the clinical applications.

3.1. Antimicrobial activity of AgNPs.

AgNPs are natural antimicrobial specialists and their inhibitory impacts on microbes. For example, *Staphylococcus aureus*, *Escherichia coli*, and yeasts, were accounted for AgNPs have critical focal points in the pharmacological business to fix different bacterial and viral dis-facilitates [53]. Specifically, AgNPs target clinical microbes, which incorporate multidrug safe (MDR) and broadened range beta-lactamase (ESBL) microorganisms [20]. AgNPs were found to have higher antibacterial exercises than silver in that capacity, which could be credited to the existence of wide surface regions of AgNPs and more divisions in their surface particles [54]. The previously mentioned highlights of AgNPs would encourage the NPs to enter just into the bacterial cells and initiate cell passing. Also, the section of AgNPs into the bacterial cells causes DNA harm and adjusts their capacities. The limiting of Ag⁺ particles and the sulfur incorpo-appraised proteins cause the breakdown of the bacterial cell dividers and upset the protein union component [55]. In addition, AgNPs advance the creation of responsive oxygen species (ROS, for example, hydrogen peroxide and subsequently cause pathogenic microorganism's restraint [56]. AgNPs delivered utilizing the growth *Fusarium oxysporum* indicated antibacterial action. The NPs consolidated garments can be utilized in clinics to limit the danger of diseases because of *Staphylococcus aureus* [57,58]. Table 1 shows the antibacterial exercises of AgNPs orchestrated utilizing various life

forms against various pathogenic microscopic organisms. Furthermore, the size, shape, and surface charge of AgNPs assume indispensable parts in antibacterial exercises. AgNPs, with the same surface regions yet with unique shapes, display contrasts in antibacterial exercises. Shortened three-sided silver nanoplates have shown the most grounded antibacterial exercises due to their huge surface zone to volume proportions and gem structures [59]. Besides, decidedly charged AgNPs showed expanded inhibitory consequences for gram-negative microscopic organisms, notwithstanding their opposition levels when contrasted with gram-positive microorganisms [28].

3.1. Larvicidal activity of AgNPs

Larviciding is a naturally protected technique to control and slaughter mosquito hatchlings or pupae in water. In recent years, mosquito hatchlings are viewed as significant dangers because of improved protection from existing medications. Then, phytoextracts were additionally utilized as biocontrol specialists against mosquitoes. In such a manner, the biosynthesized AgNPs are considered biocontrol specialists because of their solid efficacies and eco-friendly natures. AgNPs from different plant extracts, such as *Feronia elephantum* [60], *Azadirachta indica* [61], *Agave sisalana* [62], *Eclipta prostrate* [53], *Ficus racemosa* [63] and *Sterculia foetida L.* [64] have been found to possess larvicidal activities against different stages of larvae of *Culex quinquefasciatus*, *Aedes aegypti* and *Anopheles stephensi*. AgNPs synthesized from the mangrove plant *Rhizophora mucronata* were found to have lethal effects on the fourth instar larvae of *Aedes aegypti* and *Culex quinquefasciatus* [65]. A prolonged mosquito repellence was achieved by the large droplets of nanoemulsion with low release rates as compared to the small droplet nanoemulsions [66,67]. Another study reported that the AgNPs synthesized from the *Belosynopsis kewensis* leaf extract had inhibited the fourth instar of *Anopheles stephensi* and *Aedes aegypti*. AgNPs synthesized using the isoamyl acetate extract of *Annona squamosa* were found to exhibit mosquito larvicidal activities against dengue and filariasis vectors, such as *Aedes aegypti* and *Culex quinquefasciatus* [51]. The spherical-shaped Ag NPs integrated utilizing *Eupatorium odoratum* leaf remove indicated larvicidal efficacies against the third and fourth instar hatchlings of *Culex quinquefasciatus* [68]. Subsequently, AgNPs accomplish larvicidal action by the denaturation of the sulfur-containing proteins, or phosphorous-containing intensifies like the DNA present in the cell dividers. This indicated the route to cell organelles' corruption and, finally, cell brokenness and cell demise [69]. Karthiga *et al.* proved to have effective larvicidal activity against *Aedes aegypti* for AgNPs synthesis takes place using *Garcinia mangostana* bark extract [70]. *Holarrhena antidysenterica(L.)* bark's aqueous extract showed larvicidal activity against the third instar larvae of *Aedes aegypti L.* And *Culex quinquefasciatus* [71]. AgNPs synthesized with the help of *Sargassum polycystum* showed high transience of about 80% and 90% after 48hr and 72hr treatment against *Ae.aegypti* and almost 80% *Cx. quinquefasciatus* larvae were killed after 72hr treatment [72].

Silver applies to the slaughter of organisms and parasites utilizing various instruments, such as interruption of cell dividers, inactivation of cell digestion systems, and harming hereditary materials [73,74]. A couple of works have detailed the antimalarial movement of silver and its metal edifices until now. Synthetically combined silver (I) protoporphyrin IX indicated antimalarial movement under in vitro conditions against a CQ-delicate FCR-3 strain [75]. Mono and bis(N-heterocyclic-carbene) (NHC)- based ligands advanced murdering activities against the chloroquine-safe strain of *P. falciparum* [76]. Although artificially combined

AgNPs are proficient, their poisonousness remaining parts a worry. In this manner, organic sources are being abused for the blend of AgNPs. Natural sources give a reasonable and eco-friendly stage for the combination of AgNPs and advance compelling antimalarial activities. Rajakumar and Rahuman reported that AgNPs were synthesized using the aqueous extract of *Eclipta prostrate* and were tested against the larvae of the filariasis vector, *Culex quinquefasciatus* say and the malarial vector, *Anopheles subpictus* Grassi (Diptera: Culicidae) [77]. The blended AgNPs demonstrated LC50 = 27.49 and 4.56 mg/L; LC90 = 70.38 and 13.14 mg/L, individually against *C. quinquefasciatus* and LC50 = 27.85 and 5.14 mg/L; LC90 = 71.45 and 25.68 mg/L, respectively against *A. subpictus*. AgNPs synthesized using the leaves of *Catharanthus roseus* showed anti-plasmodial activity against *Plasmodium falciparum* [78]. AgNPs synthesized using the aqueous extract of *Cocus nucifera* showed effective anti-larvicidal activity against the larvae of *Anopheles stephensi* and *C. quinquefasciatus* [79]. AgNPs synthesized using β -caryophyllene isolated from the leaf extract of *Murraya koenigii* showed potential toxicity towards chloroquine-sensitive *Plasmodium falciparum* (IC50: 2.34 \pm 0.07 μ g/mL). Recently, it has been proved that the AgNPs synthesized from the leaf extracts of *Leucas aspera* and *Hyptis suaveolens* possessed promising larvicidal activities against malarial, dengue and filariasis vectors. Hence, the mosquitocidal and larvicidal exercises of AgNPs integrated utilizing a substance and natural techniques indicated the effectiveness of AgNPs to kill the danger of intestinal sickness and malaria-related infections [80]. Further, the focal point of scientists ought to be on lessening the harmfulness of AgNPs, which will advance their applications in the climate in a more secure and eco-friendly way.

Table 1. Silver nanoparticles and their antimicrobial activities.

| Organisms used for AgNPs Synthesis | Pathogenic Bacteria | References |
|---|--|------------|
| Fungus <i>Alternaria</i> sp. | <i>Bacillus subtilis</i> , <i>Staphylococcus aureus</i> , <i>Escherichia coli</i> and <i>Serratia marcescens</i> | [81] |
| Actinobacteria <i>Streptacidiphilus durhamensis</i> | <i>Pseudomonas aeruginosa</i> , <i>Staphylococcus aureus</i> and <i>Proteus mirabilis</i> | [82] |
| <i>Lysinibacillus varians</i> | <i>Candida albicans</i> and <i>Candida glabrata</i> | [83] |
| Root extract of <i>Helicteres isora</i> | <i>Bacillus subtilis</i> and <i>Micrococcus luteus</i> | [84] |
| Bacterium <i>Ochrobactrum anhtropi</i> | <i>Salmonella typhi</i> , <i>Salmonella paratyphi</i> , <i>Vibrio cholerae</i> and <i>Staphylococcus aureus</i> | [85] |
| Fruit <i>Dimocarpus Longan Lour. peel</i> | <i>Escherichia coli</i> and <i>Staphylococcus aureus</i> | [86] |

3.2. Insecticidal Activity of AgNPs.

Insects and illnesses on food creating and business crops are significant dangers to farming. Creepy crawlies which rely upon plants for food are called bothers. Vermin harms youthful leaves; foods are grown from the ground. Expanded utilization of synthetic insect sprays may make unfavorable and extreme outcomes to the biological systems, for example, influencing human wellbeing [87], loss of biodiversity, loss of nitrogen obsession [88], and obliteration of environments [89]. As of late, nano-pesticide plans have been recommended for crop nuisance and infection administrations. Accordingly, there is a more prominent favorable position in utilizing biosynthesized silver and lead nanoparticles [90,91] because they are effectively realistic, safe (not cancer-causing) and hold various metabolites [92,93]. Euphorbia prostrate watery leaf separate intervened AgNPs have insecticidal movement against *Sitophilus oryzae* bother, which for the most part influences rice, wheat and maize grains [94]. Insecticidal exercises of AgNPs and sulfur nanoparticles (S NPs) from various sources on larval, pupal and

grown-ups of the organic product fly *Drosophila melanogaster* [95] were accounted. Even though both the NPs showed insecticidal exercises, the AgNPs incorporated from olive and mulberry exhibited high mortality and a considerable decline in larval longevity.

3.2. Antibiofilm Activity of AgNPs

Thickly pressed microbial cell networks structure self-blended polymeric lattices on biotic or abiotic surfaces, known as biofilms [96]. Biofilm development is considered the superb method of life for microorganisms because most of the world's biomass is set up in a biofilm state and organisms are profoundly lenient to exogenous pressure [97]. Biofilms of pathogenic microscopic organisms cause huge clinical diseases. The utilization of NPs for the advancement of antibiofilm specialists is very much reported [98]. The antibiofilm activities of various biosynthesized NPs were studied using clinically important pathogenic bacteria such as *Klebsiella pneumoniae*. Electrostatic communications of NPs with the bacterial layers cause disturbance of the films. NPs can enter profound into the developed biofilm due to their high surface-to-volume proportions. Biosynthesized gold and AgNPs have been accounted for to uncover antibiofilm exercises at lower fixations [99-101]. 0.2 µg/mL of AgNPs synthesized using the fungus *Aspergillus flavus* effectively reduced the formation of *Escherichia coli* and *Pseudomonas aeruginosa* biofilms up to 70%. In a similar manner, 4 µg/mL of *Emericella nidulans* mediated AgNPs inhibited more than 50% biofilm formation % in *Staphylococcus aureus* and *Pseudomonas aeruginosa* [100]. Absolute inhibition of *Klebsiella pneumoniae* and *Staphylococcus aureus* biofilms was achieved with a trivial amount (0.0596 µg/mL and 0.0683 µg/mL, respectively) of AgNPs synthesized using the plant *Zingiber officinale* [102]. Another examination demonstrated that 0.2 mM convergence of AuNPs blended utilizing a bacteriophage repressed 80 % of biofilm form in *Pseudomonas aeruginosa*.

3.3. Anticancer Activity of Silver Nanoparticles.

Currently, there are a few anticancer medications on the lookout for restorative alternatives and to oversee malignancy mortality; however, significant results and fundamental harmfulness has been accounted for [103]. Examining disease is a fascinating subject regarding nanomedicine's field for finding new restorative, anticancer materials to overcome dangerous tumors [104-108]. Nanobiotechnology intervened cancer treatments have high specificities as they are less obtrusive [109,110].

Table 2. Role of bio-synthesized AgNPs in anti-inflammation

| Organisms used for AgNPs Synthesis | Constituents as Stabilizing Agents | Production of Anti-inflammatory Agents | References |
|--|---|--|------------|
| Terminalia sp. (<i>T. bentazoe</i> , <i>T. bellerica</i> , <i>T. mellueri</i> and <i>Terminalia catapa</i>) leaves | Polysaccharides, protein, polyphenolic and flavonoid compounds | Reactive oxygen species (ROS) | [116] |
| Leaf extract of <i>Pteris tripartita</i> Sw | Phenolics, flavonoids, terpenoids, tannins, proteins and glycosides | Histamine, serotonin, and prostaglandins | [117] |
| Plant <i>Leucas aspera</i> (willd.), <i>Abutilon indicum</i> | Terpenoids, alkaloids, flavonoids, phenol, tannins, phytosterols, carbohydrates, aromatics, aldehydes, alkenes, aromatics, alkyl halides, aliphatic amines, amines, alkyl halides | Indomethacin | [118] |

Curiously, metallic NPs address an alluring stage for potential disease diagnostics and treatment because of their interesting, appropriate ties for high infiltration and target particularity for diagnostics and therapeutics, separately [111-113]. Also, the metallic NPs

could likewise be formed into natural compartments, including peptides, monoclonal antibodies, DNA/RNA, and additionally tumor markers to explicitly target cell surface proteins or receptors on disease cells [114,115].

3.4. Anti-inflammatory Activity of AgNPs.

The reaction of the immune system against contaminations and harm to body cells is known as inflammation. It works for the disposal of illegal factors and helps get sorted out the tissues and reestablish the cells' elements [119]. Disappointment in this intricate cycle can prompt the improvement of various fiery disorders [120]. A calming reaction is an interaction of the production of safe, responsive mixtures, for example, interleukins and cytokinins by keratinocytes [121]. In spite of the fact that the endocrine framework secretes certain fiery arbiters, for example, catalysts and antibodies, other forthcoming mitigating specialists, including cytokines, IL-1, IL-2 are emitted by the essential insusceptible organs. These calming middle people prompt the recuperating interaction [3]. Bio-combined gold and platinum NPs accomplished positive injury mending and tissue recovery [122]. Certain AgNPs which have calming exercises are introduced in Table 2. AgNPs synthesized from plants were found to animate the creation of cytokines because the alkaloids or flavonoids present in the plants would go about as covering specialists, hence giving extra pharmacological properties [120]. Higher dosages of nanosilver have been reported to accomplish a solid creation of Th1 cells followed by the emission of fiery cytokines IL-2, INF- γ , which assume an indispensable part in cell insusceptibility [123]. AgNPs covered by the alkaloids of the unripe products of *Flautist nigrum* improved the calming action in human fringe blood mononuclear cells [120]. In addition, the AgNPs synthesized from plants, such as *Pteris tripartite* [117], *Acalypha indica*, *Garcinia mangostana* [123], *Centratherum punctatum* Cass, *Rosa damascene* [95], and *Abutilon indicum* [122], exhibited anti-inflammatory activities.

4. Conclusions

This review gives a complete investigation of the general and attentive biomedical uses of AgNPs. These have been used as surface covering agents or thin films in emergency clinics for many decades. Silver has shown predictable applications against microbes to cells specifically. The physicochemical characteristics of silver nanoparticles like adherence, shape, size and SPR make them appropriate to target pathogenic microorganisms to tainted mammalian cells. The developing threat of multidrug-safe microbes (MDR) to resist antibiotics and other manufactured compounds has redirected more consideration towards NPs. The objective explicit and simple infiltration of AgNPs makes them an appropriate alternative to antibiotics against MDR and ESBL forming bacteria. Apart from pathogenic microbes, silver nanoparticles have conceivably demonstrated to repress or execute illness-causing vectors or agents like insects, mosquito larvae, crustaceans, and biofilm-forming microorganisms. Consequently, the current survey has been focused on providing comprehensive details on the potential and adaptable biomedical uses of AgNPs.

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Conflicts of Interest

The author declares no conflict of interest regarding the publication of this article.

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