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REVIEW

Nanosilver: new ageless and versatile biomedical therapeutic scaffold

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Abstract: Silver nanotechnology has received tremendous attention in recent years, owing to its wide range of applications in various fields and its intrinsic therapeutic properties. In this review, an attempt is made to critically evaluate the chemical, physical, and biological synthesis of silver nanoparticles (AgNPs) as well as their efficacy in the field of theranostics including microbiology and parasitology. Moreover, an outlook is also provided regarding the performance of AgNPs against different biological systems such as bacteria, fungi, viruses, and parasites (leishmanial and malarial parasites) in curing certain fatal human diseases, with a special focus on cancer. The mechanism of action of AgNPs in different biological systems still remains enigmatic. Here, due to limited available literature, we only focused on AgNPs mechanism in biological systems including human (wound healing and apoptosis), bacteria, and viruses which may open new windows for future research to ensure the versatile application of AgNPs in cosmetics, electronics, and medical fields.

Keywords: synthesis of AgNPs, theranostics, antimicrobial properties, biomedical applications of AgNPs

Introduction

"Nano" is a Greek word meaning small or dwarf. Nanoparticles can be defined as the particles ranging in size from 1 to 100 nm in either direction but can be considered as ranging up to several hundred nanometers.[1] These are actually aggregates of atoms, ions, or molecules.[1] In other words, "nano" is used to represent one billion of a meter or can be referred to as 10^{-9} m. The concept of nanotechnology was first defined by Professor Norio Taniguchi in 1974, and since then, the field of nanotechnology has been receiving immense attention, especially from the early 1980s.[2,3]

Various terminologies are used for silver particles such as colloidal silver, nanosilver, silver nanostructures, and silver nanoparticles (AgNPs). For the sake of convenience, we use the abbreviation AgNPs throughout this review. Nanotechnology is an advanced field dealing with the manufacturing of different kinds of nanomaterials having biomedical applications.[4] Due to a wide range of transmittable diseases caused by different pathogenic bacteria and their enhanced antibiotic resistance, many pharmaceutical companies and researchers are striving for synthesizing novel materials with enhanced antibacterial activity and reduced side effects. Currently, nanoscale materials have achieved considerable attention as novel antimicrobial agents due to their high surface area-to-volume ratio and distinct physical and chemical properties.[5–7] The extremely strong broad-spectrum antimicrobial property of AgNPs is the key direction for the improvement of AgNPs-based biomedical products, including bandages, catheters, antiseptic sprayers, textiles, and food storage containers.[8]

Currently, different metals including zinc, titanium and copper,[9] magnesium and gold,[10,11] and alginate[12] are used as antimicrobial agents, but among these AgNPs have been found to be the most efficient due to their outstanding antimicrobial properties.[13] In particular, nanosilver has been verified to have a great medicinal value attributable to its characteristic antibacterial,[13,14] antifungal,[9] antiviral,[15] antiprotozoal,[16] anticatalytic,[17] and antiarthropodal characteristics.[18] In cancer, metastasis is a great challenge to oncologists and clinicians due to the development of resistance to anticancer agents;[19] however, this problem can be overcome by nanoscale materials, especially nanosilver.

Nowadays, the applications of nanoparticles are tremendously increasing as they possess unique optical, chemical, electrical, electronic, and mechanical properties. These properties are attributed to their large surface area-to-volume ratio, which imparts them unique properties as compared to atoms/molecules as well as the bulk of the same material. Metallic particles, specifically AgNPs, are in focus due to their antimicrobial resistance as metal ions, while antibiotics are losing their effectiveness due to development of resistant strains of microbes.[1] Although the antimicrobial properties of AgNPs are extensively studied, their activities against other types of pathogens such as arthropods and different types of cancer cells have been evaluated only recently. AgNPs as therapeutic agents have achieved remarkable attention in the treatment of cancer, leishmania, malaria, and many other human diseases. However, there still remain many questions that are a matter of discussion for future research.

The focus of this review is to provide a comprehensive, well-elaborated, and up-to-date view about what is currently investigated about the antimicrobial and antiparasitic activities and various methods used for the synthesis of AgNPs. Besides, we strive to compile all the most recent investigations about the applications of AgNPs in many fields with a special focus on cancer and viral infection inhibition, and the toxicology of AgNPs. We strongly believe that this review will provide a handy mechanistic framework for the future analysis of AgNPs.

Methods for the synthesis of nanosilver

AgNPs can be synthesized by various methods (Figure 1) including chemical synthesis,[8,20–22] physical techniques,[8,22,23] and green or biological methods.[24–26] Some important examples for biological, physical, and chemical synthesis of AgNPs are mentioned in Table 1.

Silver nanostructure prepared by chemical methods

AgNPs can be synthesized by chemical reduction,[92] electrochemical technique,[20] irradiation-assisted chemical method,[93] and pyrolysis;[21] of these, chemical reduction has been the most common route to synthesize nanosilver. Three main components, namely organic and inorganic reducing agents, capping agents or stabilizers, and metal precursors or silver salts, are used in this method (Figure 2). Hydrogen gas,[94] borohydride,[80,94,95] citrate,[96] ascorbic acid,[97] hydrazine compounds, polyol process, Tollens' reagent, N,N-dimethylformamide, and poly (ethylene glycol) (PEG)-block polymers are the reducing agents most frequently used in this method. These reductants bring about a reduction of silver ions (Ag^+) to metallic silver (Ag^0) followed by agglomeration into oligomeric clusters in aqueous and nonaqueous solutions. Finally, these clusters form metallic colloidal nanosilver.[98–100] Borohydride has been extensively used for reduction process because of its strong and rapid reductant properties as well as its ability to act as a stabilizer to evade aggregation of AgNPs throughout decaying.[94]

The commonly reported stabilizing/capping agents include surfactants and polymeric compounds such as polyvinyl pyrrolidone (PVP), PEG, poly(N-isopropylacrylamide), poly (methyl methacrylate), poly (methacrylic acid), and collagen.[101,102] Among these stabilizers, the alcohols, thiols, amines, acidic functional groups, and surfactants protect the nanoparticles from sedimentation as well as protect them from losing their surface properties. Silver nitrate ($AgNO_3$) is the most significant silver salt frequently used for the preparation of AgNPs, and as compared to other salts, it is chemically stable, easily available, and cost-effective.[103] A detailed summary of reducing, capping, or stabilizing agents and silver salts or metal precursors used in biological, chemical, and physical methods is provided in Table 2.

In their recent study, Zhang et al reported that colloidal silver could be synthesized through the chemical reaction of polymethylene bisacrylamide aminoethyl piperazine with terminal dimethylamine groups (HPAMAM-N $(CH_3)_2$). Later on, it was documented that these groups have strong reducing and stabilizing potential.[104] In another case study, it was demonstrated that polyol process and modified injection technique could produce spherical, highly mono-dispersed AgNPs of controllable size. The reaction temperature and rate of injection were important factors in this method to obtain uniform AgNPs of reduced sized. AgNPs with 17±2 nm diameter were obtained at 100°C and 2.5 mL/s injection rate.[73]
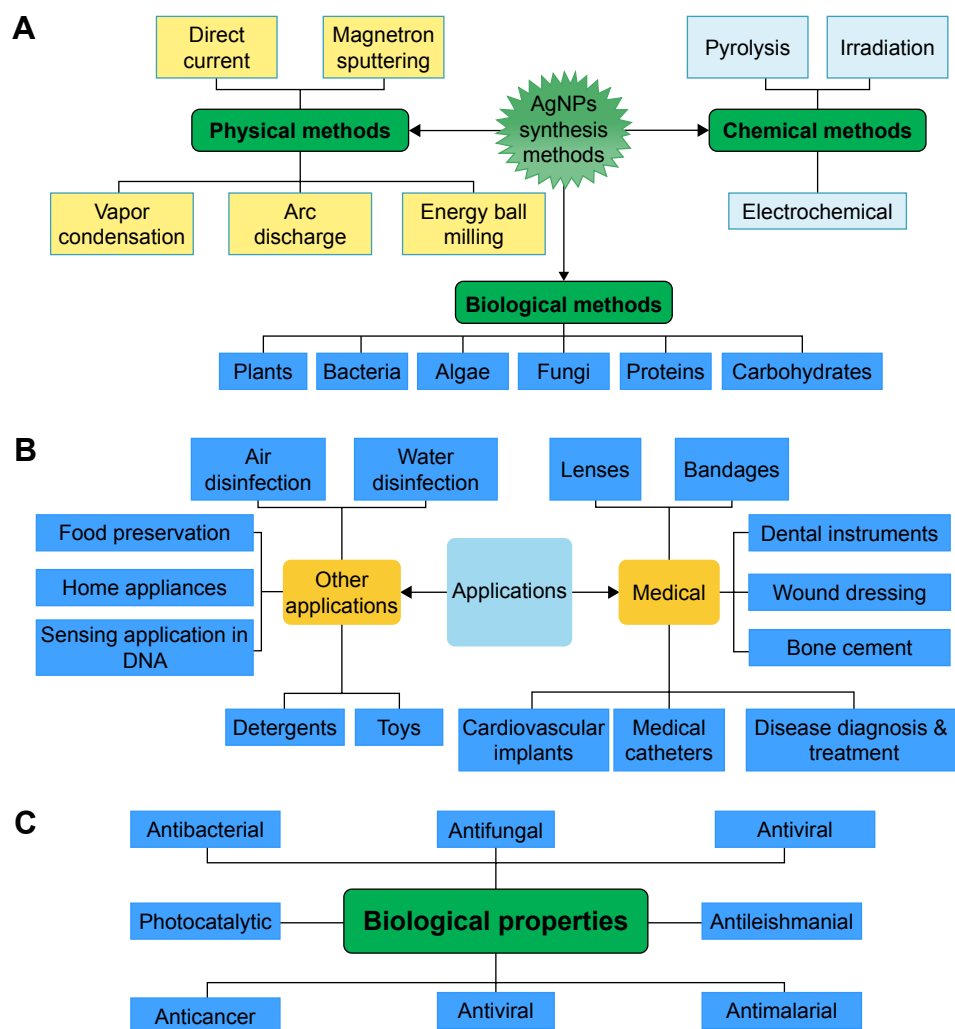
Figure 1 Overall view of (**A**) synthesis methods, (**B**) biological properties, and (**C**) biomedical applications and toxicity of AgNPs.
Abbreviation: AgNPs, silver nanoparticles.

Similar to chemical reduction method, the silver nano-structure can be synthesized by an electrochemical method. Using this approach, small-sized (10–20 nm) AgNPs with spherical shape can be produced.[78] Furthermore, using crystals of zeolite, monodisperse silver nanospheroids of size 1–18 nm have been formed by electrochemical reduction.[105] However, using organic and aqueous interface, polyphenylpyrrole-coated silver nanospheroids of size 3–20 nm can be obtained by electrochemical method.[77]

Irradiation is another method to prepare AgNPs. Abid et al concluded from their study that AgNPs of definite shape and size can be produced using laser irradiation of surfactant and an aqueous solution of silver salt.[106] Sudeep and Kamat successfully induced the synthesis of AgNPs in ethanol/toluene organic solution.[107] However, more investigations are needed to further address the possible in vitro and in vivo

potential toxicities that can be the outcomes of the chemical method used for synthesizing AgNPs.

AgNPs preparation by physical methods

The most important physical techniques frequently used for the preparation of AgNPs include evaporation/vapor condensation,[22,102,108] arc discharge,[109] energy ball milling,[110] and direct current magnetron sputtering method.[23] Compared to chemical methods, physical methods are generally less time consuming and do not involve any type of hazardous chemicals.[110] However, high energy consumption and requirement of long time for thermal stability are still the bottlenecks of these methods.[22,111,112]

Tsuji et al used the small ceramic heater and laser ablation method, respectively, to synthesize AgNPs.[116] Later on, investigators successfully synthesized colloidal AgNPs in a

Table 1 Biologically, physically, and chemically synthesized AgNPs

Methods and organisms/ process used	Shape	Size (nm)	Reference
Biological			
Bacteria			
Acinetobacter calcoaceticus	Spherical	8–12	27
Enterobacter aerogenes	Spherical	25–35	28
Klebsiella pneumoniae	Spherical	15–37	29
Proteus mirabilis	Spherical	10–20	30
Shewanella oneidensis MR-1	Spherical	2–16	31
Stenotrophomonas maltophilia	Cuboidal	93	32
Vibrio alginolyticus	Spherical	50–100	33
Bacillus licheniformis	Spherical	50	34
Brevibacterium casei	Spherical	10–50	35
Exiguobacterium spp.	Spherical	5–50	36
Rhodococcus spp.	Spherical	10–15	37
Thermoactinomyces spp.	Spherical	20–40	38
Bacillus thuringiensis	ND	43.52–142.97	39
Plants			
Chenopodium murale	ND	30–50	40
Fraxinus excelsior	Spherical	25–40	41
Moringa oleifera	Spherical	100	42
Hypnea musciformis	Cubic	40–60	43
Nyctanthes arbortristis	Spherical and oval	5–20	44
Turmeric	Spherical	5–10	45
Lantana camara	ND	11–24	46
Jasminum nervosum	Spherical	9.4	47
Psidium guajava	Spherical	26	48
Saraca indica	Spherical	22	49
Leucas aspera	Spherical	25–80	50
Dalbergia spinosa	Spherical	18	51
Melia dubia	Spherical	30–50	51
Citrus sinensis	Spherical	7.36	52
Chrysanthemum indicum	Spherical	37.71–71.99	53
Acacia leucophloea	Spherical	17–29	54
Aegle marmelos	Spherical	34.7	55
Alpinia galanga	Spherical	20.82	56
Antigonon leptopus	Spherical	10–60	57
Artemisia princeps	Spherical	10–40	58
Caesalpinia coriaria	Triangle, hexagonal, and spherical	40–98	59
Cassia auriculata	Spherical	20	60
Eclipta prostrata	Spherical	34	61
Fungi			
Penicillium expansum	ND	14 and 25	62
Aspergillus terreus	ND	10–18	62
Fusarium oxysporum	Spherical	40.3±3.5	63
Cryphonectria spp.	Spherical	30–70	64
Cochliobolus lunatus	Spherical	3–21	65
Fusarium culmorum	Spherical	5–25	66
Pestalotia spp.	Spherical	10–40	67
Phoma glomerata	Spherical	60–80	68
Aspergillus niger	Spherical	03–30	69
Algae			
Spirulina platensis	Spherical	07–16	70

(*Continued*)

Table 1 (*Continued*)

Methods and organisms/ process used	Shape	Size (nm)	Reference
Physical			
Using arc discharge	ND	10	71
By laser ablation	ND	20–50	72
By physical deposition of metal	Round	3.5	73
Using electrical arc discharge	Nanospheres	~10	74
Using electrical arc discharge	Nanospheres	14–27	73
Chemical			
Using polyol process	Spherical	17±02	75
By photoinduced method	Triangle	30–120	76
Using UV light irradiation	ND	02–08	77
By electrochemical reduction	ND	03–20	78
Using electrochemical method	Spherical	10–20	79
Using plasma gas	Spherical	10–80	80

Abbreviations: AgNPs, silver nanoparticles; ND, not detected; UV, ultraviolet.

metal solution with no chemical reagent added. Furthermore, using arc discharge method, Tien et al produced AgNPs having 20–30 nm size in pure water without the addition of any stabilizers or surfactants.[103]

Some studies documented that AgNPs were formed when bulk materials in solution were subjected to laser ablation technique.[22,113–115] Meanwhile, it was also found that silver nanospheroids sized 20–50 nm can be obtained by the same technique in pure water with femtosecond laser pulses at 800 nm.[71] Laser ablation method has an advantage over other techniques because there is no need to add any reagent to solutions. Thus, laser ablation technique is useful for the production of uncontaminated and pure metal colloids.[116]
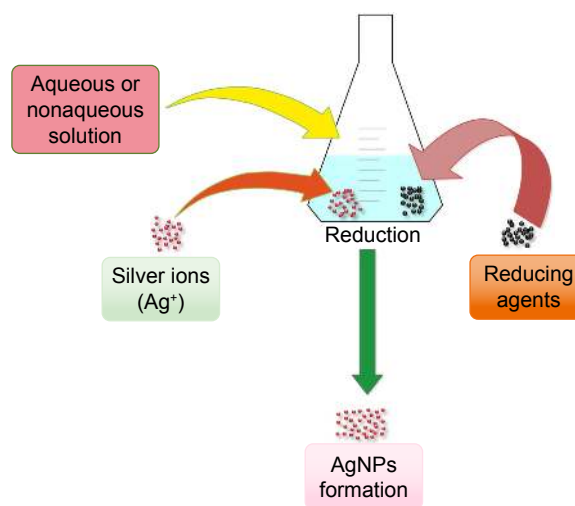

Figure 2 Chemical synthesis of AgNPs.
Abbreviation: AgNPs, silver nanoparticles.

Table 2 Widely used reducing agents, metal precursors/salts, and capping/stabilizing agents in AgNPs synthesis

Methods	Common reductants or reducing agents	Important metal precursors/salts	Stabilizing/capping agents
Biological	Proteins	$AgNO_3$	Proteins
	Peptides	Ag_2S	Peptides
	Carbohydrates	Ag_2O	Carbohydrates
	Bacteria		Bacteria
	Fungi		Fungi
	Yeast		Yeast
	Algae		Algae
	Plants		Plants
Chemical	Sodium citrate ($Na_3C_6H_5O_7$)	$AgNO_3$	Polyvinyl pyrrolidone (($C_6H_9NO)_n$)
	Ascorbic acid ($C_6H_8O_6$)	$AgClO_4$	Poly (ethylene glycol) ($C_{2n}H_{4n+2}O_{n+1}$)
	Sodium borohydride ($NaBH_4$)	Ag_2SO_4	Poly (methacrylic acid) (($C_4H_6O_2)_n$)
	Hydrogen gas (H_2)		Poly (methyl methacrylate) (($C_5H_8O_2)_n$)
	Tollens' reagent ($Ag(NH_3)_2NO_3$)		Poly(N-isopropylacrylamide) (($C_6H_{11}NO)_n$)
	N,N-Dimethylformamide (C_3H_7NO)		Collagen
	Poly (ethylene glycol)-block copolymers ($C_{2n}H_{4n+2}O_{n+1}$)		Trisodium citrate ($Na_3C_6H_5O_7$)
	Dextrose ($C_6H_{12}O_6$)		Dodecanoic acid ($C_{12}H_{24}O_2$)
	Hydrazine compounds (N_2H_4)		Oleylamine ($C_{18}H_{35}NH_2$)
	β-D-Glucose ($C_6H_{12}O_6$)		Gluconic acid ($C_6H_{12}O_7$)
	m-Hydroxy benzaldehyde ($C_7H_6O_2$)		Carboxymethylated chitosan
	Carboxymethylated chitosan		Sodium dodecyl sulfate ($NaC_{12}H_{25}SO_4$)
	Alcohols (R–OH)		Bis(2-ethylhexyl) sulfosuccinate (AOT) ($C_{20}H_{37}NaO_7S$)
Physical	Electric arc discharge and water	Ag wires and $AgNO_3$	Sodium citrate ($Na_3C_6H_5O_7$)

Abbreviation: AgNPs, silver nanoparticles.

UV-initiated photoreduction

A simple and effective method, ultraviolet (UV)-initiated photoreduction, has been reported for the synthesis of AgNPs in the presence of citrate, PVP, poly (acrylic acid), and collagen. For instance, Huang and Yang produced AgNPs via photoreduction of $AgNO_3$ in layered inorganic laponite clay suspension which served as a stabilizing agent for the prevention of NPs aggregation. The properties of produced NPs were studied as a function of UV irradiation time. Bimodal size distribution and relatively large AgNPs were obtained using UV irradiation for 3 h. Further irradiation disintegrated the AgNPs into smaller-sized particles with a single distribution mode until a relatively stable size and size distribution were obtained.[117] Silver NPs (nanosphere, nanowire, and dendrite) have been prepared by UV irradiation photoreduction technique at room temperature using poly (vinyl alcohol) (PVA) (as protecting and stabilizing agent). The concentration of both PVA and $AgNO_3$ played a significant role in the growth of the nanorods and dendrites.[118]

Previous studies demonstrated that UV light can assist in the reduction of silver ions to immobilize AgNPs on the surface of the polymer. Synthesis approach was applied to immobilize AgNPs in situ on the surface of sericin gel with the assistance of UV light. Scanning electron microscopy (SEM), X-ray diffractometry, Fourier-transform infrared spectroscopy, and differential scanning calorimetry were applied to characterize the surface tomography and structure of the AgNPs-modified sericin materials. Sericin gel was cut into small sheets and then soaked into 50 mM $AgNO_3$ solution. At the same time, sericin gel sheets were irradiated with a 365 nm UV light lamp (24 W) for 10, 30, and 60 min to make AgNPs immobilize on the surface of sericin gel, respectively. The collected AgNPs-modified sericin gel sheets were dried at room temperature, and then their surface tomography, structure, and antimicrobial activity were studied.[119]

The sonoelectrochemistry technique utilizes the ultrasonic power primarily to manipulate the material mechanically. The pulsed sonoelectrochemical synthetic method involves alternating sonic and electric pulses. Electrolyte composition plays a crucial role in shape formation.[120] It was reported that silver nanospheres could be prepared by sonoelectrochemical reduction using a complexing agent, nitrilotriacetate, to avoid aggregation.[120]

Silver nanostructure synthesis using biological systems

The bio-based or green synthesis of AgNPs has great advantages over chemical and physical methods. Biologically synthesized AgNPs are eco-friendly, as no toxic reductants or stabilizing agents are used during the synthesis of nanoparticles.

In biological systems, the health hazardous reducing and stabilizing agents can be substituted by essential biomolecules such as proteins[121] and carbohydrates,[122] which are locally produced by microbes including bacteria,[23,123–125] fungi[24,62,126,127] and yeast,[127–129] plants,[25,127,130,131] and lower organisms like algae.[127,130,131] The different reducing, capping, or stabilizing agents and silver salts or metal precursors which are used during biological method are presented in Table 2. Herein, we summarize some important biogenic synthesis or biological systems such as plants, bacteria, fungi, and algae using proteins and polysaccharides as reducing and stabilizing agents for the synthesis of AgNPs.

Plants

Plant-based production is one of the most cost-effective and valuable alternative large-scale method for synthesizing AgNPs.[132] Researchers have put attempts and focused to synthesize AgNPs of varying size and shape using different plant extracts with a broad range of antimicrobial, anticancer, antiviral, and anticatalytic activities as shown in Table 3. *Euphorbia hirta* leaf extract was used for the synthesis of AgNPs resulting in the production of spherical nanoparticles sized 40–50 nm. These AgNPs showed strong activity against *Bacillus cereus* and *Staphylococcus aureus* bacterial strains.[133] Krishnaraj et al and Veerasamy et al were able to synthesize AgNPs of size 20–30 and 35 nm, respectively, using leaf extracts of the medicinal plants *Acalypha indica* and *Garcinia mangostana*.[134,135]

In a recent study, the leaf extract of *Ocimum sanctum* was found to reduce Ag$^+$ ions into crystalline AgNPs having a size of 4–30 nm in 8 min. However, due to the presence of ascorbic acid in the plant leaves, the silver ions were readily reduced to metallic silver. The authors related the stability of the particles to the presence of proteins which played an important role as capping agents. The resulted AgNPs were effective against *Escherichia coli* and *S. aureus*.[136]

The cubic- and hexagonal-shaped AgNPs of 31–40 nm size were obtained using the bark extract of *Cinnamon zeylanicum*.[137] Spherically shaped nanosilver sized 1–10 nm was synthesized from geraniol ($C_{10}H_{18}O$) compound isolated from two important medicinal plants, namely *Pelargonium graveolens* and *Azadirachta indica*. These AgNPs ablated fibrosarcoma Wehi 164 cancer cells.[86] In another study, ten different *Cassia* medicinal plant species were screened for the biosynthesis of AgNPs. It was also found that the leaves of *P. graveolens* and *Cinnamomum camphora* contained

Table 3 Biological properties of phytogenic AgNPs

Plants name	Part used	Shape of AgNPs	Size of AgNPs (nm)	Biological properties	Reference
Caesalpinia coriaria	Leaf	Spherical, triangle, and hexagonal	40–98	Antibacterial	81
Chenopodium murale	Leaf	ND	30–35	Antibacterial	40
Chrysanthemum indicum	Flowers	Spherical	37.71–71.99	Antibacterial	53
Dalbergia spinosa	Leaves	Spherical	18	Antibacterial, antioxidant, and anti-inflammatory	51
Melia dubia	Leaf	ND	30–50	Antibacterial and larvicidal	82
Azadirachta indica	Leaf	Hexagonal and spherical	200	Antibacterial	83
Andrographis paniculata	Leaf	Cubic	40–60	Antibacterial	84
Acacia leucophloea	Bark	Spherical	17–29	Antibacterial	54
Chrysanthemum indicum	Flowers	Spherical	37.71–71.99	Cytotoxicity	53
Aegle marmelos	Fruit	Spherical	34.7	Antibacterial	55
Alpinia galanga	Rhizome	Spherical	20.82	Antifungal and antibacterial	56
Lantana camara	Leaf	ND	11–24	Antibacterial	46
Moringa oleifera	Leaf	Spherical	100	Antibacterial	85
Pelargonium graveolens		Spherical	6	Anticancer	86
Psidium guajava	Leaves and fruit	Spherical	60 and 26	Antifungal and antibacterial	48, 87
Turmeric	Root	Spherical	5–10	Antioxidant	45
Morinda citrifolia	Root	ND	32–55	Anticancer	88
Fraxinus excelsior	Leaf	Spherical	25–40	Antioxidant	41
Ficus carica	Latex	Spherical	163.7	Antioxidant	89
Euphorbia nivulia	Stem latex	Spherical	<100	Anticancer	90
Cassia auriculata	Leaf	Spherical	20	Anticancer	60
Artemisia princeps	Leaf	Spherical	10–40	Anticancer and antibacterial	58
Alternanthera sessilis	Leaf	Spherical	32.81	Anticancer	58
Albizia adianthifolia	Leaf	Spherical	4–35	Anticancer	91

Abbreviations: AgNPs, silver nanoparticles; ND, not detected.

terpenoids which were responsible for the biosynthesis of AgNPs.[130,138] Among them, only the aqueous leaf extract of *Cassia roxburghii* supported the synthesis of stable AgNPs (35 nm size). These nanoparticles were further tested against human and plant pathogenic fungi, and they exhibited excellent result as compared to tested standard drugs.[139]

Chandran et al[140] and Li et al[141] reported the synthesis of AgNPs from the leaf extracts of *Aloe vera* and *Capsicum annum* plants, respectively. The rapid synthesis of AgNPs using the fruit extract of *Carica papaya* was demonstrated, and it was found that the synthesized nanoparticles were highly toxic against different multidrug-resistant (MDR) human pathogens.[142] Begum et al[143] were able to synthesize stable AgNPs of various shapes using black tea leaf extract. Extracellular synthesis of AgNPs was also carried out using leaf extract of Pine, Persimmon, *Ginkgo*, *Magnolia*, and *Platanus* plants.[144] In addition, AgNPs were successfully synthesized using the latex and seed extract of *Jatropha curcas*.[145] The compatibility of the bark and powder extracts of *Curcuma longa* was also checked towards the formation of AgNPs, and it was reported that bark extract could produce a higher amount of AgNPs compared to the powder extract.[146]

Babu and Prabu described the AgNP synthesis using a leaf extract of *C. camphora*, while the reduction was considered to be due to presence of the phenolics, terpenoids, polysaccharides, and flavonoids in the extract.[147]

A simple, environmental-friendly, and cost-effective method has been developed to synthesize AgNPs using tea leaf extract. The synthesized AgNPs showed a good stability in terms of time-dependent release of silver ions. Due to the larger size and less silver ion release, the synthesized NPs showed low antibacterial activity against *E. coli*.[148]

The biosynthesis of AgNPs was reported for the first time using identified antimicrobial molecules (gallic acid + apocynin) and (gallic acid + apocynin + quercetin) from the medicinal plant *Pelargonium endlicherianum* Fenzl., and these AgNPs had dramatically enhanced antimicrobial activity.[149]

Bacteria

Klaus et al were the first to explore the ability of the bacterium *Pseudomonas stutzeri* AG259 to synthesize AgNPs. The bacteria exhibited a remarkable property of surviving in an extreme silver-rich environment, which might be the possible explanation for the accumulation of nanosilver.[150] Nanosilver particles have been synthesized using both Gram-positive and Gram-negative bacteria including the silver-resistant bacteria to form AgNPs.[151] Some bacteria have the ability to produce extracellular AgNPs, while others can synthesize intracellular

AgNPs. Interestingly, some bacteria including *Calothrix pulvinata*, *Anabaena flos-aquae*,[152] *Vibrio alginolyticus*,[33] *Aeromonas* spp. SH10,[153] *Plectonema boryanum* UTEX 485,[154] and *Lactobacillus* spp.[155] have the ability to produce both extra- and intracellular AgNPs.

Like other methods, metal precursors or silver salts are also used in the preparation of silver nanostructure from bacterial cultures. The production of AgNPs using sulfide (Ag_2S) and oxide (Ag_2O) of silver has also been reported by various studies.[31,156] In a recent report, the culture supernatant of bacterium *Bacillus licheniformis* was used to produce 40 and 50 nm AgNPs, respectively.[157,158] AgNPs of 1–6 nm size has also been produced using visible light emission from the supernatants of *Klebsiella pneumoniae*.[159] Furthermore, it was also found that *Lactobacillus* strains can be used for the production of AgNPs.[155,160] Recently, the bacterial strains of *Aeromonas* spp. SH10 and *Corynebacterium* spp. SH09 were screened for the biosynthesis of AgNPs. The authors concluded from their results that the bio-reduction of $[Ag(NH_3)_2]^+$ resulted in the production of monodispersed and stable AgNPs.[153]

Fungi

Green and/or biogenic synthesis of any type of nanoparticles involves natural processes occurring in microorganisms like fungi, bacteria, and plants, as shown in Figure 3. These organisms generate biocompatible nanostructures having excellent therapeutic potential.[131] Fungi-based synthesis of AgNPs is also eco-friendly and of low cost. In a recent study, two fungal strains, namely *Penicillium expansum* HA2N and *Aspergillus terreus* HA1N, were reported for the synthesis of AgNPs. The transmission electron microscopy result showed that 14–25 nm AgNPs were obtained from *P. expansum*, while 10–18 nm AgNPs were obtained from *A. terreus*. The efficacy of these AgNPs was further examined against different fungal species which demonstrated their strong antifungal potential.[62]

Recent studies showed that AgNPs of size 5–25 and 5–50 nm could be extracellularly synthesized using *Aspergillus fumigatus* and *Fusarium oxysporum*, respectively.[161,162] The authors further reported that most of the nanoparticles were spherical in shape; however, rare triangular-shaped nanoparticles were also noticed.[161]

Balaji et al used an extracellular solution of *Cladosporium cladosporioides* for the reduction of $AgNO_3$ to form spherical-shaped AgNPs of 10–100 nm size. They further reported that *C. cladosporioides* released some organic materials, including polysaccharides, organic acids, and proteins, which were responsible for the formation of spherical crystalline
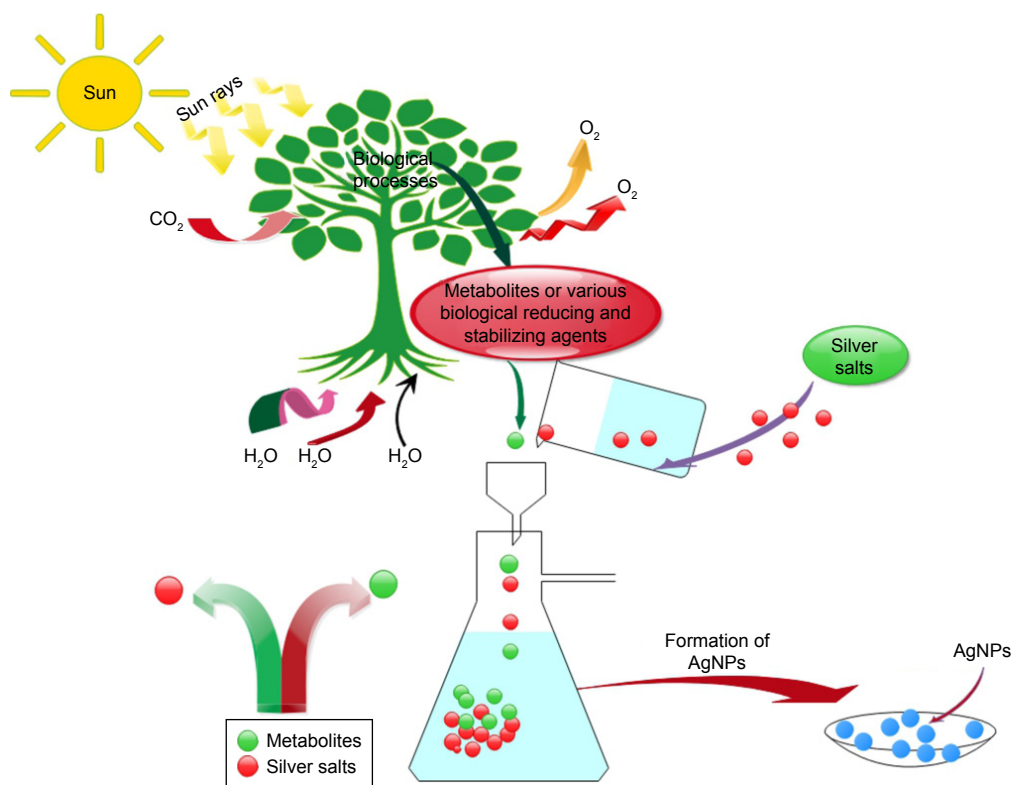
Figure 3 Biogenic or green synthesis of AgNPs.
Abbreviation: AgNPs, silver nanoparticles.

AgNPs.[126] *Penicillium* spp. were also used for the production of AgNPs.[163] Soil-isolated *Penicillium* spp. J3 which has the ability to produce silver nanoparticles was used for the synthesis, and the AgNPs formation took place on the surface of the cells in which proteins acted as stabilizing agents.[164]

The spherical nanosilver can also be synthesized using *Coriolus versicolor*, but the reduction of AgNPs is time consuming (ie, 72 h; however, the duration could be reduced to 1 h by tailoring the reaction conditions using alkaline media at pH 10). The alkaline media play a vital role in the bio-reduction of silver ions, water hydrolysis, and interaction with protein functionalities. Furthermore, the S–H group from the protein plays an excellent role in the bio-reduction, whereas glucose molecule also plays a significant role in the reduction of AgNPs.[165] *Aspergillus flavus* can also be used to obtain stable nanosilver with more than 3 months of stability in aqueous solution. Meanwhile, the stabilizing agents released by fungal species ensure prevention of aggregation.[166]

Algae

Algae have been recently studied for the synthesis of AgNPs. Venkatpurwar and Pokharkar reported the formation of AgNPs from aquatic red algae using sulfated polysaccharides. These AgNPs were highly constant at broad pH range (2–10) and showed effective antibacterial activity against Gram-negative than Gram-positive bacteria.[167] El-Rafie et al extracted water-soluble polysaccharides from aquatic microalgae. These polysaccharides were used as both reducing and stabilizing agents for AgNPs formation. The colloidal solutions imparted antimicrobial activity when tested on cotton fabrics.[168] More recently, Salari et al were able to synthesize AgNPs from macroalgae *Spirogyra varians* through bio-reduction of silver ions. These AgNPs functioned as efficient bactericidal mediators in response to many pathogenic bacteria.[169] Some other algal species, namely *Tetraselmis gracilis*, *Chaetoceros calcitrans*, *Isochrysis galbana*, and *Chlorella salina*, can be successfully used for the AgNPs biosynthesis.[170]

Polysaccharides

Polysaccharides have been widely used for biomedical applications, as they are biocompatible and biodegradable. Polysaccharides are considered as excellent templates for the preparation of nanosilvers. Polysaccharides play a dual role, that is, reductants and/or capping agents, in the synthesis of AgNPs. For more than a decade, gentle heating of starch (capping agent) and β-D-glucose (reducing agent) has resulted in the formation of AgNPs.[171]

The starch solution (reducing/capping agent) and AgNO$_3$ (salt) have been used for the synthesis of AgNPs, and using these agents, stable AgNPs sized 10–34 nm were formed. These nanoparticles were stable in the aqueous solution at 25°C for around 3 months.[172] Similarly, small-sized AgNPs (5–20 and ≤10 nm) can be prepared using starch (stabilizer and capping agent) and NaOH solution having glucose (reducing agent).[173,174] Small-sized (1–21 nm) and spherical-shaped AgNPs have been synthesized using carboxymethyl starch in aqueous solution with a stability of more than 3 months at 25°C.[175] The alkaline solutions can also be used for solubilization of spherical nanoparticles in starch.[176] Recent studies revealed that ester of alginic acid (sodium and calcium alginate) can be used for the preparation of AgNPs.[177,178] Some studies also reported that the spherical-shaped and small-sized (1–4 nm) AgNPs can be obtained in 1 min from sodium alginate using water as solvent at 70°C.[179]

It was also found that gum ghatti and gum kondagogu can be used as stabilizer and reducing agent for the synthesis of AgNPs.[180,181] Using gum ghatti, narrow-sized (4.8–6.4 nm)

AgNPs were produced, whereas gum kondagogu produced 2–9 nm AgNPs.[181] Moreover, AgNPs of undetectable size to 25 nm (spherical) were also obtained from alkali-soluble xanthan and acacia.[182,183] Schizophyllan[184] and hyaluronic acid (HA)[185] were used as reducer and stabilizing agent for the synthesis of AgNPs. HA was analyzed chemically and thermally, and the results showed that 5–30 nm AgNPs can be obtained.[185] Similarly, carboxymethyl chitosan and N-phthaloyl chitosan were also used in the preparation of nanosilver.[186–188] In a recent report, it was investigated that under acidic medium, silver chitosan film was formed due to the mixing of both silver salts and chitosan.[189] Also, acidic medium and chitosan were used as chelating agents for AgNPs.[190]

Cellulose is also one of the most important groups of polysaccharides, and due to its unique properties, cellulose is considered as an excellent template for the nanosilver formation. Both soluble and insoluble cellulose have been employed for the preparation of AgNPs, where alcohol and aldehyde groups performed an important role in the stabilization and reduction of silver ions[191] as presented in Figure 4.
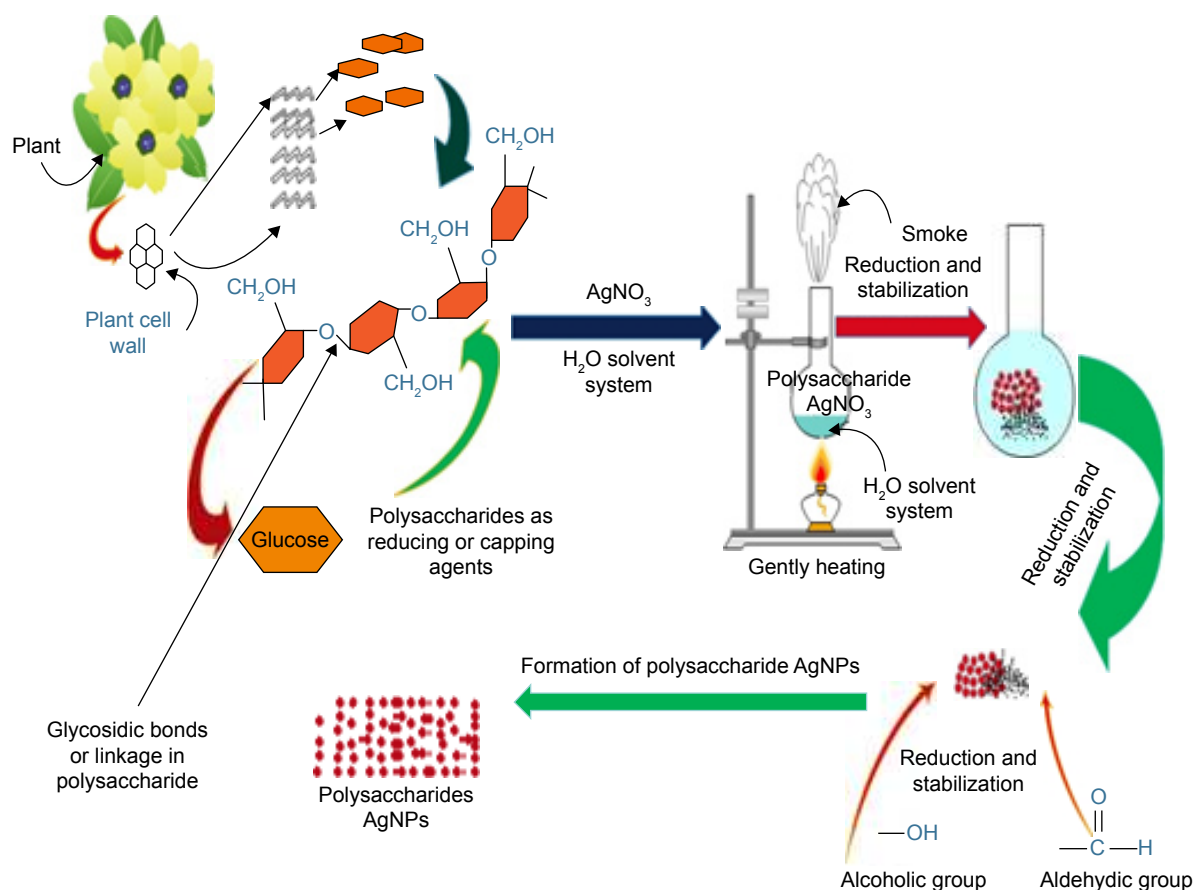

Figure 4 Polysaccharides-based synthesis of AgNPs in which polysaccharides (cellulose), alcohol, and aldehyde groups act as stabilizing agents.
Abbreviation: AgNPs, silver nanoparticles.

Recently, the green synthesis of AgNPs using hydroxyl propyl cellulose (HPC) has also been reported. HPC plays a dual role (reducer and stabilizer) in the synthesis of AgNPs.[192,193] Insoluble cellulose was also investigated for the synthesis of AgNPs. Furthermore, it was indicated that various types of fibers were used in the silver salt solution. Meanwhile, experimental results showed that AgNPs of undetectable size to 160 and 50 nm were deposited on cotton and viscose fibers, respectively. Recently, cotton fabrics were investigated for the synthesis of the AgNPs. Trisodium citrate was used as a reducing agent at 90°C. Experimental results indicated that 20–90 nm AgNPs can be obtained.[194]

Synthesis of AgNPs by proteins and DNA

Sericin, a globular glue protein, is exclusively produced in the middle silk gland of silkworm when silkworm spins a cocoon for protective and adhesive effects.[195] Silkworm cocoon is usually composed of about 75% fibroin and 25% sericin. However, sericin has been disposed of as a waste during the silk reeling process in the past few thousand years. It is not only a great waste of natural resources but also causes serious environmental pollution. Modern studies propounded that sericin performs a variety of biological activities, such as anticoagulation, antioxidant, antibacterial, and mitogenic effects, on mammalian cells. In regenerative medicines, it is usually mingled with functional polymers to form various scaffolds for biomedical purposes.[195]

Silk fibroin is a natural protein present in silkworm silk and is a common biomacromolecule with a unique sequence-specific self-assembling behavior.[119,196]

Over the past decade, silk fibroin has been applied in tissue engineering as a degradable surgical suture and scaffold[197,198] for its good biocompatibility, controllable biodegradability, and easy fabrication into different forms, such as fibers, films, gels, and three-dimensional scaffolds.[199] Silk fibroin is a good candidate for biomineralization. Previous works have indicated that silk fibroin regulates the morphologies of inorganic nanoparticles during the biomineralization process.[200,201] Silk fibroin contains 18 types of amino acid residues, including some polar amino acids such as tyrosine (Tyr). Tyr endows silk fibroin with the electron-donating property. The electron-donating property of the phenolic hydroxyl group of Tyr could directly reduce silver ion to AgNP.[202] Thus, it is possible to synthesize AgNPs through the reduction of Ag$^+$ by silk fibroin in situ to prepare the antibacterial silk film. Biopolymer film such as AgNPs silk is limited in its packaging application due to its poor mechanical property. To improve the mechanical property,

biopolymer–polymer interaction is developed by blending natural biopolymers with polymers. PVA is a biodegradable, biocompatible, water-soluble, and nontoxic semicrystalline polymer. It offers good thermomechanical property, thermal stability, mechanical strength, and flexibility, as well as good optical and physical properties that are crucial for packaging application.[203,204] Moreover, PVA is approved by the US Food and Drug Administration as an indirect food additive for flexible food packaging.[205,206] The combination of AgNPs, silk fibroin, and PVA will be promising for active packaging.

Graphene oxide (GO), an oxidized form of graphene, has been extensively used for various applications since the discovery of graphene in 2004.[207] Recently, GO has been utilized as a platform for growing NPs or attaching pre-synthesized NPs on its surface to produce NP-GO nanocomposites (NCs). Interestingly, NP-GO NCs exhibit enhanced surface enhanced Raman scattering, catalytic, and antibacterial properties compared to bare GO and NP.[208–213] Recent studies reported the fabrication of AgNPs-decorated GO as an effective antibacterial agent.[213–216]

Synthesis of AgNPs decorated on magnetic GO NCs was demonstrated, which showed highly effective inhibitory property and reusability even at the very low concentration (12.5 ppm).[217]

Biomedical applications of AgNPs
Bactericidal property of AgNPs

Antimicrobial activities of AgNPs as presented in Figures 1 and 5 have been known for many centuries, but their assessment on a scientific basis has only been realized in recent years. Sondi and Salopek-Sondi for the first time depicted AgNPs performance against *E. coli*, to propose a possible enlightenment of the observed action of AgNPs on bacteria. The authors revealed that the appearance of "pits" in bacterial cell wall and accumulation of AgNPs in the cellular membrane resulted in an enhanced permeability of cell wall and eventually induced bactericidal activity.[218]

Devi and Joshi evaluated 53 strains of various fungi for the mycosynthesis of AgNPs and showed considerable effectiveness of AgNPs against *Streptococcus pyogenes*, *Salmonella enterica*, *S. aureus*, and *Enterococcus faecalis*.[219] Moreover, the mycosynthesized nanoparticles also exhibited potential antibacterial activity and synergistic effect with erythromycin, chloramphenicol, methicillin, and ciprofloxacin against *Enterobacter aerogenes* and *K. pneumoniae*[66] and with antibiotics ampicillin, tetracycline, gentamycin, and streptomycin against *E. coli*, *S. aureus*, and *Pseudomonas aeruginosa*.[220] The antibacterial activity of AgNPs strongly

depends on the size of the silver particles as reported in previous reports. AgNPs with a smaller size have high activity due to a relative increase in contact surface.[221]

Shameli et al reported size-based bactericidal potential of various AgNPs prepared in PEG against *S. aureus* and *Salmonella typhimurium* bacteria using disc diffusion method. AgNPs were found to be very effective and cause momentous inhibition of both strains. They summarized that the bactericidal potential of AgNPs in PEG can be tuned by controlling the size of nanoparticles, since smaller particles have a relatively greater contact surface area than larger particles. The factors that are influencing the activity of AgNPs (size, shape, concentration, UV radiation, and combination with different antibiotics) should be taken into account during the preparation processes and medicinal applications of AgNPs.[222] Similarly, investigations by Raheman et al and Gade et al had already demonstrated the biocidal potential of AgNPs, respectively.[67,223] Silver bionanocomposite films having a size less than 20 nm were tested against *E. coli*, *P. aeruginosa*, *S. aureus*, and *Micrococcus luteus*. These silver composites exhibited satisfactory antibacterial properties.[224]

In recent studies, spherical-shaped 20, 18, and 15 nm AgNPs were prepared. The experimental result showed that all AgNPs were active against different strains of bacteria.[13,17] In another study, AgNPs having a spherical shape and ranging in size from 5 to 30 nm and crude latex aqueous extract were tested against different bacterial pathogens such as *Enterococci* spp., *B. cereus*, *Shigella* spp., *P. aeruginosa*, *S. aureus*, *K. pneumoniae*, and *E. coli*. These biosynthesized AgNPs were found to have the capability of enhancing the antimicrobial activity compared to crude latex aqueous extract.[225] The nanoparticles assumed spherical geometry and were often aggregated into small particles with quite a uniform size of 12.50–41.90 nm. These AgNPs showed exceptional antibacterial property against different strains of bacteria. Afterwards, they were found to be more effective against *E. coli* and *K. pneumoniae* than against *E. faecalis* and *S. mutans*. This differential activity may possibly be due to the difference in bacterial cell wall structure.[226]

Recently, AgNPs with an average uniform size of 5 nm were tested against bacteria. Results indicated that the efficiency of antibiotics was improved in the presence of AgNPs against test strains. The activity of AgNPs was more pronounced with ampicillin against the Gram-negative bacteria *Shigella flexneri* and *P. aeruginosa*, and vancomycin against the Gram-positive bacteria *Streptococcus pneumoniae* and *S. aureus*. More interestingly, these antibiotics exhibited higher antimicrobial efficiency in association with AgNPs.

These results suggested that AgNPs could be used as an adjuvant for curing various infectious diseases caused by bacteria.[4] AgNPs which were synthesized by the green method and their antibacterial properties were studied using diffusion method. The concentration of AgNPs was varied as 25, 50, 75, and 100 µg/mL. The highest efficiency of AgNPs was found against *S. aureus* (23 mm) and *E. coli* (28 mm). The moderate activity was obtained against *Salmonella typhi* (18 mm) followed by *M. luteus* (15 mm) and *P. aeruginosa* (13 mm).[19]

AgNPs, having a size of 26 nm, have been reported to be efficient against *E. faecalis* CCM 4224, *S. aureus* CCM 3953, *E. coli* CCM 3954, and *P. aeruginosa* CCM 3955. The modified antibacterial activity of silver NPs was considerably improved as confirmed by minimum inhibitory concentration (MIC) values ranging from 6.75 down to 0.84 µg/mL.[227] In another study, the growth rates of bacteria were studied under varying AgNPs concentrations, incubation temperatures, times, and pH. *E. coli* and *S. aureus* were shown to be substantially inhibited by AgNPs, and the antibacterial activity of AgNPs did not change with pH or temperature.[228]

AgNPs in montmorillonite were prepared, and their antibacterial activities against *S. aureus* and methicillin-resistant *S. aureus* (Gram-positive bacteria) and *E. coli*, *E. coli* O157:H7, and *K. pneumoniae* (Gram-negative bacteria) were tested by the disc diffusion method using Mueller–Hinton agar. The smaller AgNPs exhibited significantly higher antibacterial activity.[229] More recently, cream formulations of AgNPs and AgNO$_3$ were prepared, and their antibacterial activity was evaluated on human pathogens (*S. aureus*, *Proteus vulgaris*, *E. coli*, *P. aeruginosa*, and *Candida albicans*) and a plant pathogen (*Agrobacterium tumefaciens*). The antimicrobial studies concluded that AgNPs have 200 times more inhibitory effect compared to AgNO$_3$. The AgNPs act by damaging the cell membrane of *E. coli*, which was confirmed by SEM study.[230]

The antibacterial activity of AgNPs was tested against nine human diseases-causing Gram-negative bacteria and one Gram-positive bacteria. AgNPs extracts had the capability to enhance antibacterial activity against all tested strains compared to the extracts alone. AgNPs were more bactericidal in liquid than in solid medium, probably due to better contact with bacterial cells in a liquid state. Maximum zone of inhibition was 19 mm for nanoparticles of leaves on *P. aeruginosa* (ATCC278223) and 18 mm for latex nanoparticles on *S. flexneri* (ATCC12022). The minimum zone of inhibition was 7 mm for both nanoparticles of leaves

and latex on *S. typhi* (ATCC19430) and *S. typhimurium* (ATCC14028), respectively.[231]

The leaf extract of *Lantana camara* was used for the biosynthesis of AgNPs. These nanoparticles were evaluated for catalytic and antibacterial activities. The biosynthesized nanosilver had excellent potential against the tested strains including *E. coli*, *Pseudomonas* spp., *Bacillus* spp., and *Staphylococcus* spp. Moreover, these AgNPs also showed higher catalytic activity in the reduction of methylene blue observed using UV–vis spectrophotometer.[232] Spherical nanosilver sized 10–15 nm was synthesized from fresh spinach leaves. These nanoparticles had strong bactericidal potential and good catalytic property toward methyl red and methylene blue.[233]

A recent study on the effect of AgNPs (13.4 nm) against *E. coli* and *S. aureus* found their MIC values to be below 6.6 nM and above 33 nM, respectively.[234] Another study was conducted against the bacterium *E. coli*. The results showed that AgNPs (16 nm) had the ability to inhibit *E. coli* colony-forming unit at a concentration of 60 µg/mL.[235] Furthermore, the activity of some important dendrimer (polyamidoamine) Ag-composites has also been reported against *E. coli*, *S. aureus*, *P. aeruginosa*, *Klebsiella mobilis*, and *Bacillus subtilis*.[104]

The antimicrobial property of AgNPs is most exploited in the medical field, though their anti-inflammatory nature is also considered immensely useful. Initial studies have suggested that the acceleration of wound healing in the presence of nanoparticles is due to the reduction of local matrix metalloproteinase activity and the increase in neutrophil apoptosis within the wound.

Recent evidence suggests that nanosilver has a potent anti-inflammatory effect[236–238] and accelerates wound healing.[239,240] Silver has long been known to possess antibacterial activity and has been used throughout history, from Hippocrates' early treatment of ulcers to C.S.F. Crede's treatment of gonococcal infections in newborns. Silver is still used clinically, and nanosilver is emerging as a valuable tool in the therapeutic armory (Figure 5). Silver sulfadiazine is the gold standard for the topical treatment of burn patients.[241] The resurgent interest in silver and nanosilver has been motivated by the emergence of rampant antibiotic-resistant bacteria and the increasing prevalence of hospital-acquired bacterial infections. The use of silver has been severely limited by the toxicity of silver ions to humans; however, nanotechnology has facilitated the production of smaller silver particles with increasingly large surface area-to-volume ratios, greater efficacy against bacteria,[242,243] and most importantly, lower toxicity to humans.[244]

Nanocrystalline silver wound dressings have been commercially available for over a decade (eg, Acticoat™) and are in current clinical use for the treatment of various wounds, including burns,[240,245,246] toxic epidermal necrolysis,[247] Stevens–Johnson syndrome,[248] chronic ulcers,[237] and pemphigus.[248]
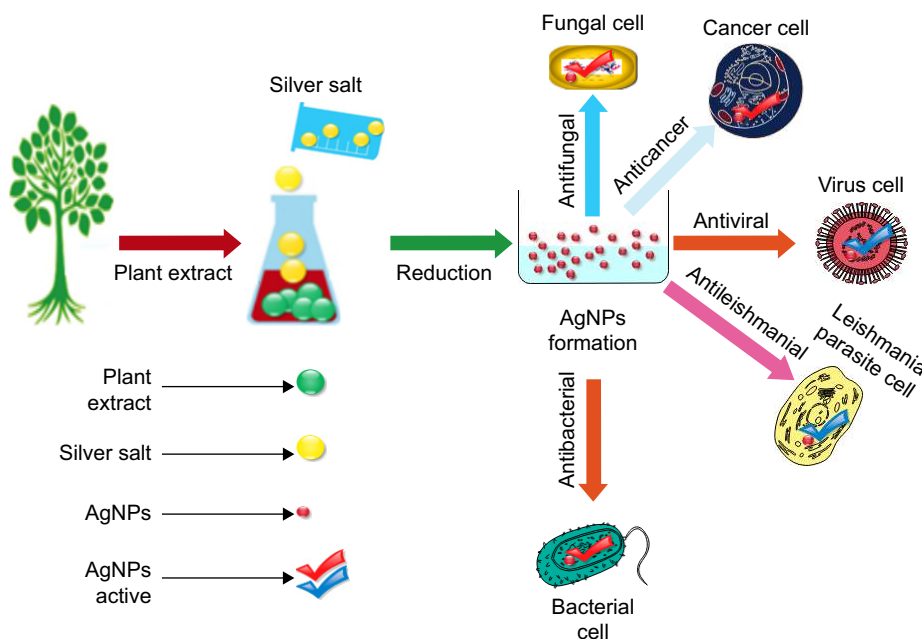

Figure 5 Graphical abstract representing the synthesis (green) and the biocidal potential of AgNPs against various microbes.
Abbreviation: AgNPs, silver nanoparticles.

Typical dressings consist of two layers of polyethylene mesh forming a sandwich around a layer of polyester gauze. Typical nanocrystalline coatings are 900 nm thick with a crystallite size of 10–15 nm[236] and are applied to the polyethylene layer.

Antifungal property of AgNPs

In 2008, Kim et al demonstrated the potential of AgNPs against 44 strains of six fungal species, namely *Candida tropicalis*, *C. albicans*, *Candida glabrata*, *Candida krusei*, *Candida parapsilosis*, and *Trichophyton mentagrophytes*. The AgNPs were found active against various strains of *T. mentagrophytes* and *Candida* spp.[249] Similarly, Velluti et al found that nanosilver complexes [Ag$_2$(SMX)$_2$] showed good activity against 10 fungal strains, namely *C. tropicalis* (C 131), *C. albicans* (ATCC 10231), *Cryptococcus neoformans* (ATCC 32264), *Saccharomyces cerevisiae* (ATCC 9763), *A. fumigatus* (ATCC 26934), *A. flavus* (ATCC 9170), *Aspergillus niger* (ATCC 9029), dermatophytes including *Trichophyton rubrum* (C 113), *T. mentagrophytes* (ATCC 9972), and *Microsporum gypseum* (C 115).[250]

Gajbhiye et al reported the efficiency of biogenic AgNPs against *Pleospora herbarum*, *Phoma glomerata*, *Fusarium semitectum*, *Trichoderma* spp., and *C. albicans*. Furthermore, they also reported the synergistic effects of AgNPs in association with fluconazole.[251] In 2009, Jo et al demonstrated the antifungal potential of silver ions and nanoparticles against two plant pathogenic fungi, *Magnaporthe grisea* and *Bipolaris sorokiniana*. The fungicidal potential of AgNPs in combination with various heterocyclic compounds like phthalazine, thiazolidine, hydrazide, pyrazolo, tetrazolo, and pyridazine derivatives was studied against *C. albicans* and *A. flavus*, and the AgNPs were found to have significant fungicidal activity against tested organisms.[252]

Recently, six fungal species, namely *Penicillium brevicompactum*, *A. fumigatus*, *Mortierella alpina*, *C. cladosporoides*, *Chaetomium globosum*, and *Stachybotrys chartarum*, were selected for the study of the antifungal activity of AgNPs. The growth rates of all tested fungal species, except *Mortierella* spp., were affected by the addition of AgNPs, which caused the limitation of *Chaetomium* and *Stachybotrys* on gypsum products. Each fungus showed a distinct response to applied AgNPs depending upon the concentration and the rate of Ag ions released into the environment.[253]

In 2010, Jaidev and Narasimha demonstrated the antifungal (*A. niger*) and antibacterial (*Staphylococcus* spp., *E. coli*, *Bacillus* spp.) activities of AgNPs. They reported that nanosilver has excellent inhibitory activity against *A. niger*

confirming the maximum activity as compared to *Bacillus* spp. (0.8 cm), *Staphylococcus* spp. (0.9 cm), and *E. coli* (0.8 cm).[69] Meanwhile, Nasrollahi et al studied the fungicidal potential of AgNPs against *S. cerevisiae* and *C. albicans*. Their results were productive confirming the excellent potential of AgNPs as compared to standard antifungal agents (viz. fluconazole and amphotericin B).[254] Savithramma et al prepared AgNPs using a different extract of medicinal plants, *Shorea tumbuggaia*, *Boswellia ovalifoliolata*, and *Svensonia hyderobadensis*, to evaluate their antifungal activity against *A. niger*, *Curvularia* spp., *A. flavus*, *Fusarium* spp., and *Rhizopus* spp. The results confirmed that all biogenic AgNPs showed considerable antifungal activity against various fungal spp. The AgNPs synthesized with *S. hyderobadensis* exhibited higher activity as compared to AgNPs synthesized using the other two plants.[255]

Kaur et al reported the fungicidal potential of silver and chitosan nanoparticles against *A. flavus*, *Rhizoctonia solani*, and *Alternaria alternata* from chickpea seeds.[256] In 2012, Arjun and Bholay also demonstrated the momentous efficiency of AgNPs against *T. rubrum*, *C. albicans*, and *A. fumigatus*.[257] Xu et al also tested nanosilver and natamycin against 216 strains of fungi from patients suffering from severe keratitis. These included 82 isolates of *Aspergillus*, 112 isolates of *Fusarium*, and 10 isolates of *Alternaria*. Results demonstrated that AgNPs had higher activity as compared to natamycin.[258] Similarly, Dar et al studied the biocidal potential of AgNPs synthesized from *Cryphonectria* spp. against *S. typhi*, *E. coli*, *S. aureus*, and *C. albicans*, concluding that AgNPs can be used as potential antifungal agents.[64]

More recently, the antifungal activity of mycosynthesized AgNPs was tested for the first time against plant pathogenic fungi. AgNPs displayed good antifungal activity against *Colletotrichum* spp. (12.63 mm) followed by *R. solani* (12.03 mm) and *Cochliobolus lunata* (11.23 mm) at 1 mg/mL concentration. The nanoparticles were less effective against *Fusarium* spp. (9.37 mm).[259] In another study, AgNO$_3$ was tested against three fungi namely *Trichoderma* spp. (ATCC 18648), *Mucor* spp. (ATCC 48559), and *A. niger* (ATCC 6275), and it was found to exhibit good antifungal activity.[260]

The antifungal activity of AgNPs against *C. tropicalis* and *C. albicans* was also investigated. Stable nanoparticles of size 12.5±4.9 nm (mean ± SD) were obtained, which presented high activity against *Candida* spp.[261] The spherical and polydispersed AgNPs, ranging in size from 4 to 36 nm and 8 to 60 nm, respectively, were applied against superficial mycoses caused by *T. rubrum*, *Malassezia furfur*, *C. albicans*,

and *C. tropicalis*. The AgNPs exhibited highest antifungal activity against *T. rubrum* and the least against *M. furfur* and *C. albicans* as compared to others.[262]

C. glabrata and *C. krusei* were exposed to spherical nanoparticles (19 nm) with positive surface charge. The MIC50 values were 0.1–l g mL^{-1} AgNPs, and minimum fungicidal concentration (MFC) values were 0.25 and 0.5 g mL^{-1} for *C. glabrata* and *C. krusei*, respectively.[263] Meanwhile, another research confirmed that concentrations of AgNPs between 10 and 25 µM reduced the growth rates of the tested fungus and bacteria and showed the bactericidal/fungicidal activity by delaying the exponential and stationary phases. However, complete inhibition of the growth of *C. albicans* MTCC183 was found at a concentration of 10 µM AgNPs.[264]

A more recent report showed that AgNPs (spherical, 1–40 nm) had excellent antifungal activity against *R. solani* cultures by inhibiting 83% of the mycelium growth at 25 µg/mL concentration.[265] In another study, several essential oils were tested for their antifungal activity. The oil isolated from the bark of *Cinnamomum cassia* had the highest activity against MIC and MFC values for all tested strains in the range of 0.0006%–0.0097% (v/v) and 0.0012%–0.019% (v/v), respectively.

Further studies were carried out about the antifungal activity of AgNPs against some *Candida* spp. The fungicidal efficacy of AgNPs functionalized with PVP was established. The PVP-functionalized silver particles demonstrated no damage to fungi until the exposure time was 24 h. After 24 h, no viability of fungal cells was observed. The work revealed that Ag particles aggregate outside the fungal cells, releasing free silver ions and thus inducing cell necrosis through the reduction process.[266] Naz et al synthesized silver particles capped with 5-amino-β-resocyclic acid hydrochloride dehydrate (AR). They analyzed their nanostructures before and after conjugation to silver metal for in vitro antifungal, antibacterial, antioxidant, and enzyme inhibitory properties. The results indicated that the fungicidal activity of Ag, AR, and Ag AR were not momentous as compared to the dithane-M45 (standard fungicide).[267]

Anticancer property of AgNPs

AgNPs have been popular for their antibacterial and antifungal activities. However, recent studies have exploited AgNO$_3$ potential in neoplastic maladies. Recently, eco-friendly AgNPs were synthesized from the leaf extracts of *Vitex negundo*[268] and *Sesbania grandiflora*, and their efficacy was tested against human colon cancer cell lines HCT15 and MCF-7, respectively. The results demonstrated that AgNPs obtained from *V. negundo* showed antiproliferative effects on cancer cell line, reduced DNA synthesis, and induced apoptosis.[268] Similarly, nanosilver obtained from *S. grandiflora* also caused cytotoxicity, oxidative stress, and apoptosis in tumor cells.[269] Moreover, green-synthesized AgNPs from the leaves extract of *Podophyllum hexandrum* and *Suaefa monoica* were examined and found to show cytotoxic activity and apoptotic effect, respectively.[270,271]

Piao et al demonstrated that OH radicals released by the AgNPs attacked cellular molecules including DNA, proteins, and lipids to induce oxidative damages.[272] In another report, it was shown that AgNPs exhibited toxicity due to some factors such as dose, size of particles, and time. In the case of MCF-7 cell culture, the toxicity was due to the dose of AgNPs. AgNPs also caused cellular damage in Human Epidermoid Larynx (Hep-2) cell line through reactive oxygen species (ROS) formation.[273] Lima et al greenly synthesized nanosilver and evaluated its genotoxicity and cytotoxicity.[63] Also, Durán et al studied the potential of biosynthesized AgNPs. These nanosilver particles interacted with DNA, proteins, and cellular organelles via ROS, and induced necrosis and apoptosis in the tumor cells.[274]

New nanocrystalline silver with a structural size of 8 nm customized with TAT cell penetrating peptide (AgNP-TAT) exhibited higher antitumor property in both nonresistant and MDR cells without any discrimination. The AgNP-TAT displayed outstanding efficacy in killing tumor cells, that is, up to 24-fold higher than pristine AgNO$_3$ without TAT alteration. Moreover, the AgNP-TAT also displayed considerable reduction in adverse toxic effects, in vivo.[275]

Dimocarpus longan Lour. peel aqueous extract (acts as reducing and stabilizing agent) was evaluated for the synthesis and anticancer and antibacterial effects of AgNPs. The antibacterial activities of AgNPs were evaluated using dilution method, whereas their efficacy against human prostate cancer (PC-3) cells was in vitro evaluated via blue assay and Western blot by the expression of phosphorylated stat 3, caspase-3, bcl-2, and survivin. These nanoparticles had the face-centered cubic structure (size 9–32 nm) and exhibited great bactericidal potential against both Gram-positive and Gram-negative strains of bacteria.[276]

In another study, *Malus domestica* and *Origanim vulgare* extracts were used for the synthesis of nanosilver. The *M. domestica* extract-biosynthesized silver had considerable effects on MCF-7 breast cancer cells, whereas silver synthesized from *O. vulgare* aqueous extracts showed dose-dependent response against human lung cancer A549 cell line.[277,278]

In a recent study, AgNPs were obtained from the stem bark extract of *Moringa olifera*. These biosynthesized AgNPs were tested for anticancer properties. The flow cytometry results showed apoptosis induced through ROS generation in HeLa cells.[279] The rhamnolipids were isolated from *P. aeruginosa* strain JS-11 and used for the biosynthesis of Rh-AgNPs. These nanosilver particles were tested against MCF-7 human cells.[280] Furthermore, caffeic acid-mediated spherical nanosilver particles of 6.67±0.35 nm size were used against cancer cells. The results showed that AgNPs efficiently inhibited the growth of HepG2 cells via apoptosis induction.[281]

Recently, spherical-shaped (6.2±0.2 nm) silver-(protein-lipid) nanoparticles (Ag-LP-NPs) were obtained using the seed extract of *Sterculia foetida*. These eco-friendly Ag-LP-NPs showed antiproliferative activity against HeLa cancer cell lines and also showed potential toxicity in a dose-dependent manner.[282] More recently, biogenic AgNPs were obtained from the flower extract of *Plumeria alba* (frangipani) known as frangipani AgNPs (FS NPs). These FS NPs had a cytotoxic effect on COLO 205 which was determined by MTT assay, and after 24 and 48 h of incubation, the IC_{50} concentration was found at 4 and 5.5 µg/mL, respectively. Furthermore, the FS NPs cytotoxic affect on COLO 205 cells was associated with the loss of membrane integrity and chromatin condensation that have a great role in the induction of apoptosis as evidenced by acridine orange/ethidium bromide staining.[283]

On the other hand, it was also demonstrated that $AgNO_3$ and metal-based nanoparticles (AgNPs) had strong potential for cytotoxic, antiproliferative, and apoptotic property in H-ras 5RP7 cells and cervical cancer, respectively.[284,285]

Biosynthesized nanosilver from the extract of *Pterocladiella capillacea* (11.4±3.52 nm) and *P. aeruginosa* (13–76 nm) showed great potential against human hepatocellular carcinoma (HepG2) cell lines and human cervical cancer cells (HeLa), respectively.[286,287] In another study, it was found that green-synthesized nanosilver (45±0.15 nm) from novel *Nocardiopsis* spp. had potent activity against in vitro human cervical cancer cell line. The IC_{50} value was recorded in the range of 200 µg/mL of AgNPs against HeLa cancer cells.[288] It was also found that the plumbagin-caged nanosilver induced ~80% cell death at a concentration of 2.5 µM, whereas no cytotoxicity was observed for normal cells.[289]

A study published by Yeasmin et al demonstrated that AgNPs with controlled shape are more effective against many types of cancer cell lines. They stabilized the shape of spherical silver nanoparticles by interaction with natural gum and then screened against cervical cancer cell lines (HeLa), lung cancer (A549), and mice macrophage or RAW 264.7 and found that the particles effectively killed these cell lines in a dose-dependent manner.[290] Venil et al reported flexirubin (a bacterial pigment)-mediated silver nanoparticles for the first time that were highly cytotoxic (IC_{50} value of 36 µg/mL) against human breast cancer cell lines (MCF-7).[291]

Nowadays, chitosan-based biosynthesized silver nanoparticles are mostly synthesized and used against different cancer cell lines. A study performed by Venkatesan et al demonstrated that porous chitosan-alginate-biosynthesized AgNPs exhibited cytotoxic effects against breast cancer cell line MDA-MB-231 (IC_{50}=4.6 mg).[292] A recent study demonstrated that loaded quinazolinone polypyrrole/chitosan silver chloride NC had active anticancer efficacy against Ehrlich ascites carcinoma cells.[293] The chitosan-silver hybrid nanoparticles were proven to induce apoptosis in HepG2 cells by downregulating BCL2 gene and upregulating P53.[294]

Antiviral property of AgNPs

AgNPs have received enormous attention for their bactericidal potential, while the antiviral activities of metal nanoparticles remain an emergent area. The potential of AgNPs was studied in both prokaryotic and eukaryotic organisms,[295] and it was reported that small-sized AgNPs of around 25 nm or less had outstanding potential in viral infection inhibition.[296] The aqueous extract of *Ricinus communis* was used for the synthesis of nanoparticles, which resulted in AgNPs sized 1,000 nm. Smaller-sized (5–20 nm) AgNPs were obtained from fungi. The results indicated that the small-sized AgNPs had an excellent ability to decrease the infection potential of herpes simplex virus types (HSV) 1/2 and human parainfluenza virus type 3.[297]

Baram-Pinto et al investigated the inhibitory effect of AgNPs against HSV-1 and demonstrated that sulfonate-capped nanosilver inhibited HSV-1 infection. Furthermore, they demonstrated that AgNPs prevented the attachment and entry of virus into a cell or prevented the cell from spreading the virus. The heparan sulfate is a cellular primary acceptor of HSV, and thus competes with the virus for attaching to the cell and the potential was enhanced due to the presence of the inner core AgNPs.[298] This study also demonstrated the virucidal action of AgNPs. These nanoparticles exhibited anti-HIV activity at an early stage of viral infection and also prevented the further replication of HIV-1.[299] Furthermore, the viruses and other microbial strains were grown under multicycler growth condition in the absence or presence of colloidal

silver to check the antimicrobial property. As expected, no viral growth was seen with any strains tested.[300]

A recent study also showed that T lymphocyte (T)-tropic and macrophage (M)-tropic strains of HIV-1 were extremely susceptible to the AgNPs coated with polyurethane condom.[15]

In a recent study, different types of nanosilver particles were biosynthesized from *F. oxysporum* (4–13 nm), *Curvularia* spp. (5–23 nm), and *Alternaria* and *Phoma* spp. (7–20 nm). Silver particles produced from *F. oxysporum* and *Curvularia* spp. had exceptional antiviral activity but were less cytotoxic to Vero cells, whereas particles produced from *Alternaria* and *Phoma* spp. showed moderate virucidal action. This study also confirmed that small-sized nanoparticles have excellent ability to inhibit the replication of virus as compared to larger ones.[297]

More recently, the tannic acid-modified AgNPs in the range of 13, 33, and 46 nm were found to reduce HSV-2 infectivity in vivo and in vitro. In particular, tannic acid in the same amount also showed somewhat in vivo potential against the virus. Therefore, tannic acid-modified nanosilver was used as an antimicrobial agent in addition to cream or protective gel used for oral herpes infections treatment.[301]

Antiprotozoal property of AgNPs

According to the WHO, leishmaniasis is the sixth most infectious disease.[302] Leishmaniasis is one of the most abandoned tropical infections around the globe, with occurrence in 88 countries and a predictable number of 500,000 cases of visceral form and 1.5 million cases of cutaneous leishmaniasis.[303] Rossi-Bergmann et al demonstrated the potential function of biosynthesized AgNPs (using *F. oxysporum*) against *Leishmania amazonensis* promastigotes both in vivo and in vitro. They also compared the biologically and chemically synthesized AgNPs. Their results demonstrated that biosynthesized nanosilver was four times more active as compared to chemically produced AgNPs in vitro, while the in vivo results showed it was even more effective.[304]

The protozoal vector-borne diseases are the most common and important infections in developed regions, resulting in over one million deaths from malaria on yearly bases, worldwide.[305] To control the malaria vector, researchers strive to discover innovative approach against antimalarial agents. Among various antimalarial drugs, AgNPs have also been evaluated against malarial parasites and reported with promising potential against malaria. In recent studies, the biologically synthesized AgNPs from *Andrographis paniculata* Nees. (Acanthaceae) ~55 nm in size[306] and *Catharanthus*

roseus leaves (approximate size 35–55 nm) were tested against *P. falciparum*.[307] In another study, the higher antimalarial potential of AgNPs was reported. The AgNPs were bio-reduced in 5% *Cassia occidentalis* leaf broth against chloroquine-sensitive and chloroquine-resistant strains of *P. falciparum* and malarial vector *Anopheles stephensi*.[232]

Mechanism of action of AgNPs in biological systems

To date, there is no proper mechanism for the synthesis of AgNPs. A proposed hypothetical mechanism behind the synthesis of nanoparticles is an enzymatic reaction in which the complex of reducing enzymes present in the plant, fungal, or bacterial extract reduces the chemicals such as $AgNO_3$ into silver ions and nitrate ions.[308]

Plants contain a complex network of antioxidant metabolites and enzymes that work together to prevent oxidative damage to cellular components. It was reported that plant extracts contain biomolecules including polyphenols, ascorbic acid, flavonoids, sterols, triterpenes, alkaloids, alcoholic compounds, polysaccharides, saponins, β-phenylethylamines, glucose and fructose, and proteins/enzymes which could be used as reductants to react with silver ions and therefore used as scaffolds to direct the formation of AgNPs in the solution. Hypothetically, biosynthetic products or reduced cofactors play an important role in the reduction of respective salts to nanoparticles. However, it seems probable that some glucose and ascorbate reduce $AgNO_3$ and $HAuCl_4$ to form nanoparticles.[131,140,308,309] In neem leaf broth, terpenoids are the surface-active molecules stabilizing the nanoparticles, and reaction of the metal ions is possibly facilitated by reducing sugars.[310] A study using *Capsicum annuum* extract also indicated that the proteins which have amine groups played a reducing and controlling role during the formation of AgNPs in the solutions and that the secondary structure of the proteins changed after reaction with silver ions.[141] *Ficus benghalensis* leaf contains antioxidants and polyphenols (flavonoids), and it can also directly scavenge molecular species of active oxygen. Antioxidant action of flavonoids resides mainly in their ability to donate electrons or hydrogen atoms, that is, change keto group to enol form. Proteins, enzymes, phenolics, and other chemicals within plant leaf extract reduce silver salts and also provide excellent tenacity against agglomeration, which can be further studied to understand the mechanism of evolution by biological systems.[309,311]

The precise and accurate mechanism of action of AgNPs is still far from being understood completely. However based

on previously reported studies, we summarize the AgNPs mechanism in different biological systems such as bacteria, human, fungi, virus, leishmania, and protozoa.

Figure 6 shows the mechanism of action of AgNPs in a biological system. The antiviral mechanism of AgNPs, as depicted in Figure 6A, begins after the attachment of the virus to host cell during which the virus inserts its genetic material into the cell. Silver particles bind to the genetic material and block its replication which ultimately leads to translational inhibition, and in this way, viral growth is inhibited. Wound healing and antibacterial mechanism of AgNPs are shown in Figure 6B. Although not reported in the literature, we assume that AgNPs may react with free oxygen in the wound portion followed by its ionization. This ionized active silver may regulate FOXO1 which is a transcription factor stimulating wound healing molecule, TGF-β1. Furthermore, active silver has also been reported to generate ROS. In the eukaryotic system, the ROS activate JNK and p53 proteins which induce Bax proteins to migrate to the mitochondrial surface resulting in cytochrome C release from mitochondria which subsequently results in PARP cleavage. This phenomenon leads to apoptosis. The antibacterial mechanism of AgNPs starts with adhesion of AgNPs to bacterial cell followed by pit formation through which AgNPs enter the cell. These AgNPs

then bind to nuclear material residing inside the bacteria. This leads to transcriptional and translational disruption and subsequently leads to ROS generation, which results in antibacterial activity.

Antibacterial activity

As reported for other metals, it is assumed that AgNPs may undergo redox reaction leading to the generation of free radicals (ROS, reactive nitrogen species) which triggers cytotoxicity in bacterial cells. The AgNPs first adhere to the bacterial cell wall leading to destabilization of cell membrane potential and low levels of ATPs in the cell followed by cell death.[312,313] There are some assumptions regarding AgNPs-induced bacterial cell death.

First, silver ions produced from AgNPs inside bacterial cells may interact with cellular glutathione and oxidize it. This phenomenon leads to the generation of ROS which consequently triggers bacterial growth inhibition.[314] Second, the oxidized glutathione may result in an increased lipid peroxidation leading to membrane disruption, thereby resulting in leakage of cellular constituents.[272] Third, DNA contains sulfur and phosphorous groups. AgNPs may bind to these groups leading to unwinding of DNA which may lead to transcriptional and translational
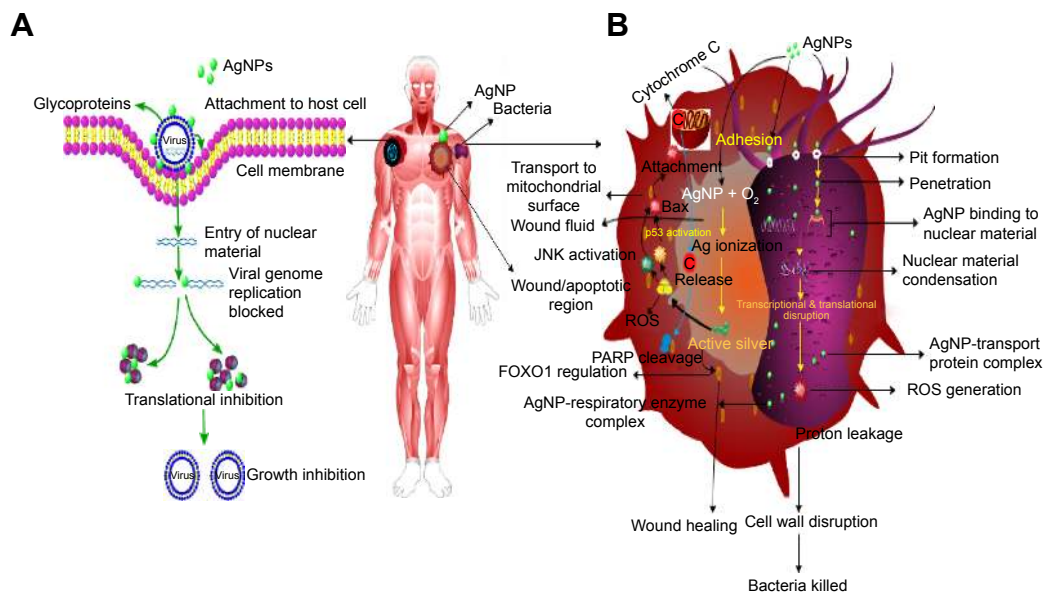

Figure 6 Mechanism of action of AgNPs in a biological system. (**A**) AgNPs antiviral mechanism. After attachment to host cell, the virus inserts its genetic material into the cell. Silver particles bind to the genetic material and block its replication which ultimately leads to translational inhibition, and in this way, viral growth is inhibited. (**B**) Wound healing and antibacterial mechanism of AgNPs. Although not reported in the literature, we assume that AgNPs may react with free oxygen in the wound portion followed by its ionization. This ionized active silver may regulate FOXO1 which is a transcription factor stimulating wound healing molecule, TGF-β1. Furthermore, active silver has also been reported to generate ROS. In the eukaryotic system, the ROS activate JNK and p53 proteins which induce Bax proteins to migrate to the mitochondrial surface resulting in cytochrome C release from mitochondria which subsequently results in PARP cleavage. This phenomenon leads to apoptosis. The antibacterial mechanism of AgNPs starts with adhesion of AgNPs to bacterial cell followed by pit formation through which AgNPs enter the cell. These AgNPs then bind to nuclear material residing inside the bacteria. This leads to transcriptional and translational disruption and subsequently leads to ROS generation, which results in antibacterial activity.
Abbreviations: AgNPs, silver nanoparticles; ROS, reactive oxygen species.

disruption, thereby leading to the production of ROS as shown in Figure 6.

Anticancer action

The available literature about the anticancer potential of AgNPs strongly suggests that ROS generation is a result of the interaction of AgNPs with cancer cells. A study reported the anticancer potential of AgNPs against A549 and B16 cells. The interaction of AgNPs with A549 and B16 cells resulted in the production of superoxide anion ($O^{\bullet-}$) and hydrogen peroxide (H_2O_2) species which arrested the uncontrolled cell division of the cancer cells. A plentitude of studies also suggests the antitumor activity of colloidal silver and gold nanoparticles on cancer cells due to the formation of ROS inside the cells.[315–317] The increased formation of superoxide and hydrogen peroxide species also affects signal transduction pathways triggering apoptosis.[318] Superoxide radicals also contribute to uncoupling of respiration with ATP synthesis.[319]

Another possible reason for cancer cells death is the release of silver ions from AgNPs because the concentration of silver ions determines cell death distinguishing between normal and cancer cells.[320] Furthermore, the release of silver ions from AgNPs is also dependent on the pH of the medium (the lower the pH, the higher the release of ions). It is well established that the pH of tumor cells is slightly acidic than normal cells.[321]

In tumor cells where the pH is slightly acidic than normal cells, AgNPs release more silver ions followed by formation of ROS leading to cancer cell death. However Asharani et al reported silver ions as a downstream signal of ROS. They reported that the interaction of AgNPs with cancer cells results in the generation of ROS followed by silver ions release form AgNPs through the oxidative dissolution process in acidic pH (5.0–6.4).[322]

Cytotoxicity of AgNPs on normal cells

Considering the distribution of AgNPs in multiple tissues, recent studies have revealed that cell types can influence responses to AgNPs. When fibroblast cells (NIH3T3) and colon cancer epithelial cells (HCT116) were exposed to AgNPs, the two types of cells showed distinct responses.[323] For the fibroblast cells, exposure to AgNPs resulted in high expression of ROS and c-Jun N-terminal kinases, which activated mitochondrial apoptotic pathways. However, the epithelial cells showed less of a response to AgNPs because the expression of antiapoptotic protein bcl-2 was activated to protect against apoptotic stimuli. Starch-coated

AgNPs can cause different genotoxicities to fibroblast cells (IMR-90) and glioblastoma cells (U251). For both types of cells, AgNPs can diffuse into mitochondria and the nucleus, induce mitochondrial dysfunction, and increase the level of ROS, and subsequently cause DNA damage, chromosomal aberrations, and cell cycle arrest. However, fibroblast cells are more resistant to AgNPs, while the glioblastoma cells are more sensitive to AgNPs because fibroblast cells can recover from cell cycle arrest.[324]

Although AgNPs are widely used nanoparticles in the biomedical field, safety in the uses of AgNPs is still controversial.[325] Conventional AgNPs had a strong affinity towards extracellular membranes and can accumulate in tissues in excess amount for a long time causing several toxic effects to normal cells.[326] The most common effects of AgNPs had been observed on erythrocytes, where they can lyse the membrane[327] and induce oxidative stress-related responses such as induction of heme oxygenase I or formation of protein carbonyls.[328] AgNPs and the ions released from the oxidized nanosilver surface directly bind to sulfur- and phosphorus-containing cellular constituents such as proteins and DNA, potentially causing damage to cellular machinery.[234] The toxic effects of nanosilver on macrophages had been studied in the past.[329] Upon uptake by the macrophage, silver metal could be further dissolved to Ag^+ ions in the lysosomes due to the lower pH. Such Ag^+ ions are highly toxic to mitochondria and induce apoptosis.[329] Moreover, AgNPs had been reported to be toxic to the liver,[330] skin,[331] lung,[332] and neural cells.[333] In conclusion, the AgNPs show toxic effects to all kinds of cells by interfering with their metabolic pathways, induction of apoptosis, and producing superoxides, genotoxicity, or other cytological consequences. However, there is still not enough data available to conclude what the toxic effects of AgNPs are due to the different sizes, shapes, and features of AgNPs. Therefore, extensive research is needed in this field to explore the proper mechanism of action of AgNPs in normal and carcinoma cell lines.

Preparation of AgNPs to function in a specific tumor site

Surface chemistry can influence the interaction of AgNPs with target tumor cells. The surface charges should be negative or neutral on AgNPs to target the specific tumor site. Also, the surface modification of AgNPs with a different biomarker of cancer can make them target the specific tumor site. The particle sizes are also a very important factor in targeting tumor site.[334,335]

Antiviral mechanism

During viral infection, the virus first comes in contact with the host cell and introduces its nuclear material through binding and fusion events into susceptible cells. Though the mechanism is not fully understood, AgNPs are assumed to interfere with this phenomenon by interacting with the viral surface glycoproteins in susceptible cells. Furthermore, AgNPs have also been reported to inhibit the post-entry stages of the HIV-1 life cycle, because AgNPs maintained their antiviral activity even after they were added to the cells already infected with HIV. The mechanism behind this event is that AgNPs may have blocked other functional HIV-1 proteins, and lessened reverse transcription rates through direct binding to sulfur and phosphorous groups of nuclear material. PVP-coated AgNPs efficiently inhibit respiratory syncytial virus (RSV) possibly by binding to evenly distributed surface glycoproteins on RSV virion's envelope.[336] A different capping agent, namely mercaptoethanesulfonate, has been used for AgNPs tested against HSV-1.[298] Sulfonate-coated AgNPs either block the attachment and entry of HSV-1 virus into cell or cell-to-cell proliferation of the virus. Their anti-HSV-1 activity depends on their ability to mimic heparan sulfate (the cellular primary receptor for HSV) and thus compete with the virus for binding to the cell and is amplified by the presence of the inner core of nanosilver. The understanding of antiviral mechanism of AgNPs is still in its early stages; hence, further studies are needed to explore the mechanisms of action of AgNPs, which may render the conceivable antiviral development of AgNPs to fill the vital niche of a wide range of antiviral agents.

Antifungal and antiprotozoal mechanism

AgNPs may disrupt membrane integrity and inhibit normal budding process in yeast. As stated before, the AgNPs result in the generation of ROS, and the protozoans, viz. leishmania parasites, exhibit sensitivity to ROS.[337] Studies related to antifungal and antiprotozoal activities of AgNPs are very rare, so further investigations are required to document the detailed antifungal and antiprotozoal mechanisms of AgNPs.

Comparison of advantages and disadvantages of different synthesis methods

Various routes are employed for the synthesis of AgNPs (Figure 1), and so we aimed to explore the merits and demerits of each above-mentioned method. Chemical synthesis is one of the important methods for AgNPs preparation. In chemical method, the major drawback is the use of highly deleterious organic solvents. These solvents have lower biocompatibility which limits their natural applications.[25] In contrast, the physical techniques have no harmful substances employed during preparation of AgNPs, and thus uncontaminated and pure AgNPs can be obtained.[116] Generally, physical methods are fast, and narrow-sized nanostructure formulations are produced which is another advantage of physical technique over chemical method.[23,102] However, the use of furnace tubes in the physical method has some disadvantages such as consumption of high energy,[8,22,102,112] and requirement of more time for thermal stability[22,111,112] and more space.[111,112]

An advantage of biogenic methods over physical and chemical approaches is that they do not require deleterious solvents, while biopolymers play an important role as stabilizing and reducing agents.[8,338] Green synthesis also has other advantages such as higher stability for longer time,[338] and is facile, biocompatible, and cost-effective, and biogenically synthesized nanostructures have good applications in biomedical realm. Applications of biosynthesized AgNPs have been reviewed in many studies.[25,339,340] Furthermore, it is very interesting that AgNPs produced by biosynthesis methods can be used in a lot of applications; however, the main disadvantage of these methods is purification. During purification procedure, there is a chance of bacterial contamination and transfection which may be considered as a major constraint in their biomedical applications.[129]

Significance and toxicity of silver nanostructure

Silver is considered as one of the most imperative metals which can be used in various fields, for instance, in magnetics, optics, and electronics.[341] Besides these, it has also been used as an anticancer, antiviral, bactericidal, fungicidal, and antiprotozoal agent.[342] It has been reported that low amount of silver has excessive potential against microorganisms, while the AgNPs at high concentration (>10 µM) are toxic to mammals as well as host organisms.[343] However, some reports demonstrated nanosilver as pharmaceutically sound and nontoxic to humans.[342]

Silver nanostructures have emergent role and versatility in various fields; however, some momentous evidence has also been reported in the literature regarding the toxicity of Ag nanostructures toward a number of hosts ranging from microorganisms to complex animals.

The AgNPs also inactivate microorganisms such as bacteria, algae, viruses, and fungi. Some metals like silver (Ag), tellurium (Te), and mercury (Hg) are very toxic to the majority of bacteria and exhibit aberrant antimicrobial

property even at small amount.[344] Some reports have also proven the effective nature of AgNPs against fungi such as *S. cerevisiae*,[345] algae such as *Chlamydomonas reinhardtii*,[346] and viruses such as hepatitis B virus[347] and HIV-1.[348]

The toxicity of silver nanostructure against complex organisms has also been reported in fish (zebrafish),[349] humans,[323,324] mice, rats,[350,351] and *Diptera* spp. (*Drosophila melanogaster*).[352] The detailed investigation of toxicity of $AgNO_3$ can be found in some studies.[26,320]

Miscellaneous applications of AgNPs

Combination of nano- and metallic silver has been found to possess strong antimicrobial and antiparasitic properties. Hence, $AgNO_3$ has been used in a wide range of applications in multiple disciplines. Silver has historical biomedical applications, such as silver foil, and $AgNO_3$ sutures are used to prevent infections of surgical wounds, treat gonorrheal eye in newborns, repair vaginal tear after childbirth, and treat burns.[344,353–356]

Recently, AgNPs have displayed a tremendous cytotoxic effect against leukemia cells,[357,358] breast cancer cells,[359,360] hepatocellular carcinoma, and human liver HepG2 cells[330,361] and lung cancer cells.[362,363] Furthermore, AgNPs have been widely used in medical devices and consumer products such as surgical instruments, sterilizers, medical catheters, artificial teeth or orthodontics, bone coating, skin donation, creams, lotions, household sprays, home appliances, toys, detergents, toothpastes, soaps, containers for food storage and preservations, and antiseptic paints.[364–370] Moreover, AgNPs have wide applications in electronics, such as data storage and optical devices, inks, nano- and optoelectronics, and nonlinear and sub-wavelength optics.[368,371,372] Several investigators have demonstrated that AgNPs and silver composites possess the ability to catalyze chemical reactions, for example, oxidation of CO,[373] oxidation of benzene to phenol,[374] photodegradation of gaseous acetaldehyde,[375] and reduction of p-nitrophenol to p-aminophenol.[369] AgNPs have sensing applications in DNA sequencing[376] and also play an important role in water filtration.[1,377] The detailed application of AgNPs is demonstrated in Figure 1.

Conclusion and future remarks

From the forgone discussion, it can be concluded that AgNPs have gained remarkable interest, as they possess a wide range of applications in different fields including material science, biotechnology, and environmental and medical fields. Attributable to their distinctive physiochemical properties, AgNPs have been extensively used against bacteria, fungi, virus,

leishmania, malaria, and neoplastic cells. Moreover, AgNPs have been prepared by different procedures such as chemical, physical, and biological methods. In biosynthetic methods, the potential of nature-gifted environmental-friendly reducers and stabilizers has been explored. The biogenic method is considered eco-friendly and handy to be applied in various realms, for instance, medical, cosmetic, and pharmaceutical fields. There still exist some open questions regarding silver-based nanotechnology, and each synthetic method has critical limitations which require special attention to eradicate. Furthermore, the toxic effects of AgNPs targeting from microorganisms to higher organisms including human is another interesting aspect that has also been outlined in this review.

Although reports regarding the potential of AgNPs against cancer, malaria and leishmania, and other human diseases are available, it will be a great revolution to find out the potential role of AgNPs against world's leading diseases with high mortality like AIDs and chronic hepatitis, which still need proper treatment. The biological systems including bacteria, fungi, and plants maintain a tight regulation of various metabolic machineries such as photosynthesis, respiration, and transport mechanism for several ions across membranes, and cell architecture (organization of lipids and proteins in the cell membrane and other endomembranes and cell wall). How AgNPs could take a promising part in regulating these metabolic pathways operating simultaneously will be an interesting facet of AgNPs mechanism of action which awaits elucidation. Furthermore, as evident from many studies, cancer cells use glucose, glutamine, asparagine (in some cases), lipids, and proteins as fuels for their uncontrolled proliferation. Now the question is whether AgNPs prevent the growth of cancer cells either by activation of the expression of glucosidase, lipase, or proteinase enzymes or by clinging to the mitotic and meiotic apparatus during cell division to block the whole metabolic machinery of the abnormal cells. For a certain type of cancer like acute lymphoblastic leukemia where asparagine is the main nutrient reservoir, if AgNPs control its levels by regulating the expression of L-asparaginase, then pH change (ie, from neutral to acidic) of the medium (blood) would occur which could cause hindrance to the cancer cell proliferation. In short, in-depth handy mechanistic studies are required to fill these gaps.

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Disclosure

The authors report no conflicts of interest in this work.

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