



Multifarious global flora fabricated phytosynthesis of silver nanoparticles: a green nanoweapon for antiviral approach including SARS-CoV-2

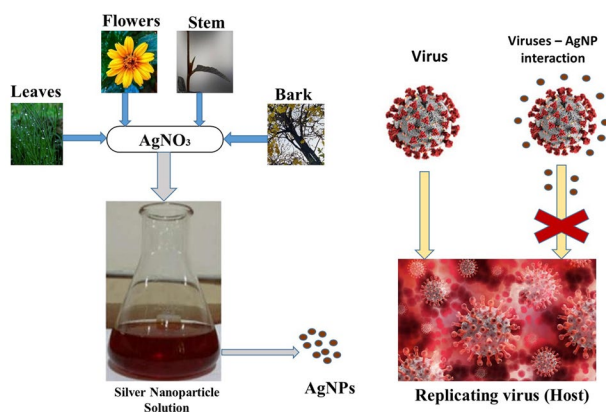
C. Karthik¹ · K. A. Punnaivalavan¹ · S. Pandi Prabha² · D. G. Caroline¹

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Abstract

The progressive research into the nanoscale level upgrades the higher end modernized evolution with every field of science, engineering, and technology. Silver nanoparticles and their broader range of application from nanoelectronics to nano-drug delivery systems drive the futuristic direction of nanoengineering and technology in contemporary days. In this review, the green synthesis of silver nanoparticles is the cornerstone of interest over physical and chemical methods owing to its remarkable biocompatibility and idiosyncratic property engineering. The abundant primary and secondary plant metabolites collectively as multifarious phytochemicals which are more peculiar in the composition from root hair to aerial apex through various interspecies and intraspecies, capable of reduction, and capping with the synthesis of silver nanoparticles. Furthermore, the process by which intracellular, extracellular biological macromolecules of the microbiota reduce with the synthesis of silver nanoparticles from the precursor molecule is also discussed. Viruses are one of the predominant infectious agents that gets faster resistance to the antiviral therapies of traditional generations of medicine. We discuss the various stages of virus targeting of cells and viral target through drugs. Antiviral potential of silver nanoparticles against different classes and families of the past and their considerable candidate for up-to-the-minute need of complete addressing of the fulminant and opportunistic global pandemic of this millennium SARS-CoV2, illustrated through recent silver-based formulations under development and approval for countering the pandemic situation.

Graphical abstract



Keywords Phytochemicals · Green synthesis · Nanosilver · Viral spectra · COVID

C. Karthik and K. A. Punnaivalavan are equal contributors.

✉ C. Karthik
karthikc@stjosephs.ac.in

Extended author information available on the last page of the article



Introduction

‘Nano’ scale that refers to the one-billionth of a meter. Nanotechnology is a multi-disciplinary stream that emphasizes the purposeful design of manipulation of matter at the scale of atomic level utilizing the existing approaches, techniques, and types of equipment available with conventional and modern science and engineering. Nanoparticles do focus on particles that exist in the range of 1–100 nm [1]. Enhancement or acquisition of new characteristics at the nanoscale level compared to the bulk properties gained more interest with research on this avenue within the past 2 decades. Higher ratio of surface area to volume at the nanoscale level and the shift in the laws of physics at the nanometric level are the two important attributes that contribute to effective catalytic activity to various multi-disciplinary applications [2].

Approaches of nanoparticle synthesis include a top–down (TD) approach that encompasses the disintegrative breakdown of bulk materials into finer grain sizes of nanoscale. Synthesis methods such as mechanical milling, laser ablation, and sputtering follow the TD approach. The alternative approach of synthesis encloses gradual consecutive integration of atoms/molecules at various smaller scales that leads to the ‘nucleation’ site formation followed by agglomeration around the nucleation site engenders nanoparticle formation. Spray pyrolysis, sol–gel method & green synthesis methods, etc. are some of the BU route-based nanoparticle synthesis approaches [3].

Various methods for the synthesis of nanoparticles include physical, chemical, and biological methods with their own pros and cons for each. Physical methods utilize higher mechanical energy, high radiation, high temperature, and greater sized apparatus for the synthesis. Grain size control and less manual power are remarkable advantages, whereas parameter optimization and toxicity are notable demerits. Chemical methods involve the usage of chemical reducing and capping agents of organic and inorganic species; sometimes, the same reagents being both. Simple to process and control over scale-up are highlightable merits, whereas environmental unfriendly, lesser biocompatibility are notable demerits. To address the backlogs of physical and chemical methods, shift to biological methods of synthesis enters the research avenue. Environment-friendly, no application of higher temperature, pressure, heat, energy, most supporting biocompatibility, devoid of toxic chemicals, easier handling, and scale-up are all that makes biological synthesis more fascinating than any other [3–5]. Preference of water over any other organic solvents as the major solvent and thereby the greater colloidal stability attainment of the nanoparticle product is the unique property on green synthesis and the fact that water is the most biocompatible solvent is found to be reflected with the application part [6].

Silver nanoparticles: ‘the unique’

Among the widely explored metallic nanoparticles, silver nanoparticles (AgNPs) have the continuity of being used for centuries in human civilizational history due to their very unique and specific physical, biological, electronic, catalytic, surface, and chemical properties. The strongest biocidal properties against biota of microbial range from bacteria, viruses, fungi, algae to higher nematodes, and helminths. It also possesses non-toxicity toward animal cells and compatibility to human cell lines provides numerous biological product applications. Colloidal stability of AgNPs makes them suitable as preservatives in cosmetics and medicated products, optical plasma-resonance scattering property makes a bio-labeling candidate and sensor, imaging applications, anti-inflammation property-driven wound-healing engineering, surface coating property enhanced paints, reusable catalytic property over the degradation of different classes of dyes, anti-thrombogenic and hemodynamic properties utilized cardiac valves and stents, implants with anti-platelet property and stimulation of vascular endothelial growth factor (VEGF) that promotes angiogenesis, the process of new blood vessel formation and endothelial vasodilation property-driven anti-hypertensive implant, peculiar AgNPs mechanical properties such as elastic modulus and flexural strength improvising of acrylic resin-based removable dental dentures against opportunistic oral pathogens, anti-adhesion and anti-infective property-driven orthodontic brackets against dental caries, metabolonomics intervention and perturbation property with nucleotides, photosynthesis and photorespiration processes, anti-microbial properties, anti-static properties, electrically conducting, and most importantly self-cleaning property. Electro-conductive fibers help to protect from radiation emitted by electronics. Self-cleaning property resists the deepening of stains and dirt from the point of incidence. Nano-functional fibers are used to produce odor-free undergarments, socks and stockings and research over the face masks coated with silver nanoparticles used during the COVID-19 pandemic is contemporary anti-microbial property example [7–20].

Green synthesis of silver nanoparticles

These AgNPs shall be synthesized through various routes out of which biological routes again gain importance due to aforesaid attributes of the produced nanoparticles. The biological route shall be further taken as phyto-mediated, microbe-mediated, and other molecular templates of broader category—inorganic, organic, metals, polysaccharides, proteins & miscellaneous chemical reagents, etc. [21].

Phyto-mediated synthesis of nanoparticles has its own spectrum of source that includes extracts of leaves [22, 23],

bark [24, 25], stem [26, 27], latex [28, 29], fruit [23, 30, 31], flower [32–35], root [36–38], seed [39, 40], and tuber [41, 42]. Different parts of the different plants have their own varying concentration of reductase enzyme that reduces the metal nitrate solution into the nanosized metal particles. Plenty of systems with single reducing agents, dual-reducing agents exist, whereas also a single source of an enzyme that also catalyzes hybrid formation and directs to nanocomposite hybrid system exists [43].

Leaf-mediated synthesis

Leaves are rich source of a larger number of phytochemicals that includes tannins, flavonoids, saponins, alkaloids [44], phlobatannins, carbohydrates, glycosides, terpenoids, anthraquinones [45, 46], coumarines, proteins, emodins [47], anthocyanins [48], xanthoproteins, triterpenoidal sapogenin [49] steroids, phenol, and essential oils. Minerals such as sodium, calcium, iron, phosphorous, magnesium, potassium, and zinc are found in traceable quantity that does serves as the inorganic cofactors for enzymes present in the plants. Essential oils of the leaves can be general and species-specific constituents between which volatile compounds are of greater considerable proportion. Citrus plant leaves possess citreol, burneol, t-Muurolol, humulene, viridiflorol, geraniol, Myrcenol, nerol, valencene, dextro-carvone, linalool, etc., [50] whereas cinnamon species have alcohol [2-nitroethanol, glycerin, cinnamyl alcohol, 1-methoxy-2-propanol], aldehyde [t-cinnamaldehyde, o-methoxy-cinnamaldehyde, benzylidene nemalonaldehyde], alkane [dodecane], carboxylic acid [acetic acid], ester [Isopropyl acetate, ethyl formate], ether [1,1-diethoxy-ethane], and ketonic [coumarine] compounds in the essential oils [51]. All the components shall have a significant to least contributions in the process of phyto (leaf)-mediated nanoparticle synthesis. Table 1 is the list with representative examples of leaves used for the synthesis of silver nanoparticles.

Stem, bark, and latex-mediated synthesis

Stem, bark, and latex of the plants are also utilized as the source of nanoparticle synthesis and its composition ranges with a wide number of constituents alkaloids, flavonoids, tannins, saponins, cardiac glycosides, glycosides, proteins, carbohydrates, steroids, reducing sugars, anthracene glycosides, resins, triterpenes, procyanadines, anthraquinone [161–165], fraxidin, fraxetin, scoparone, 3-acetylaleuritolic acid, beta-sitosterol, and sitosterone [166], etc. were the actual secondary metabolites of various biochemical cycles and some are growth steroids that assist in the regulation of growth and development of the plant assists phyto (stem, bark, and latex)-mediated nanoparticle synthesis. Gums and resins from bark, stem, and latex are also used for NP

synthesis. Table 2 is the list with representative examples of stem, bark, and latex used for the synthesis of silver nanoparticles.

Fruit-mediated synthesis

Fruits are another phyto-source of nanoparticle synthesis. Peels, pulps, and complete fruit can be used for reduction. Usually, they have polyphenols, minerals, vitamins—tocopherols and organic acids (linoleic acid, ascorbic acid, citric acid, etc.), triterpenoids, tannins, carotenoids, phenolics, and flavonoids (rutin, myricetin, luteolin, quercetin, apigenin, and kaempferol). Constituents include moisture, sugars (sucrose, fructose, and glucose), protein, fatty acid [total saturated fatty acids (SFA), monounsaturated fatty acids (MUFA), and polyunsaturated fatty acids (PUFA)], ash contents, and energy contents [186–188]. The same constituents which are metabolic precursors and building blocks of the fruit cell wall that correspond to the texture of the fruit are found to a huge extent in seeds extracts of the fruits in addition to steroids [189]. Table 3 is the list with representative examples of fruits used for synthesis of silver nanoparticles.

Flower-mediated synthesis

Phyto-constituents of flower extracts are found to contain flavonoids, tannins, phlobatannins, cardiac glycosides, alkaloids and triterpenes, saponins, anthraquinone, phenol, protein and amino acids, carbohydrates, oil, fats & resins, coumarine, phytosterol, gums, and mucilages [219–223]. Table 4 is the list with representative examples of flowers used for synthesis of silver nanoparticles.

Root-mediated synthesis

Root system constantly serves as the transport hub for water and dissolved minerals to all the aerial parts of the plants and exploitation of these roots as phyto-source for metallic nanoparticle synthesis includes products of tubers in the list. Steroids, saponins, alkaloids, glycosides, flavonoids, tannins, traces of myricetin, cholesterol and beta sitosterol, carbohydrates, phenol, anthraquinone, ellagic acid, coumarine, and phytosterol [240–243]. Table 5 is the list with representative examples of roots and tubers used for synthesis of silver nanoparticles.

Seed-mediated synthesis

Seeds serve as the germination hub for any plantlet at favorable conditions for growth and development. They have constituents such as moisture, fat, protein, carbohydrate, fiber, minerals like calcium, phosphorus, magnesium, sodium, potassium, zinc, and many other minerals with varying



Table 1 Representative examples of leaves used for synthesis of silver nanoparticles

Name of the plant	Nanoparticle size (nm)	Nanoparticle shape	References
<i>A. indica</i> (neem)	20	Triangular	[52]
<i>Actaea racemosa</i> (Black bugbane)	3–9	Spherical	[53]
<i>Aegle marmelos</i> (Vilvam)	14–28	Spherical	[54]
<i>Aloe</i> sp.,	5	Spherical	[53]
<i>Aloe vera</i>	70–192	Spherical	[55]
<i>Aloe vera</i>	10–30	Spherical	[56]
<i>Alternanthera dentata</i> (Purple Joyweed)	10–80	Spherical	[57]
<i>Amaranthus gangeticus</i> (Elephant head)	11–15	Spherical	[58]
<i>Anisomeles indica</i> —Indian Catmint	18–35	Spherical	[59]
<i>Annona squamosa</i> (Sugar apple)	200–500	Irregularly spherical	[60]
<i>Anthemis atropatana</i> (plant) extract	10–80	Spherical	[61]
<i>Arbutus Unedo</i> (Strawberry)	20–30	Spherical	[62]
<i>Argemone mexicana</i>	10–50	Cubic, hexagonal	[63]
<i>Artemisia turcomanica</i> (Wormwood)	4–42	Spherical	[64]
Banana leaves	50	Spherical	[52]
<i>Berberis vulgaris</i> (Barberry)	40	Spherical	[65]
black pepper leaf	5–50	Spherical	[66]
<i>Boerhaavia diffusa</i> (Mookarati saarai)	24–25	Spherical	[67]
<i>Buddleja globosa</i>	2–5	Spherical	[68]
<i>Butea monosperma</i> —(Palash teak)	10–100	Spherical, triangular, hexagonal	[69]
<i>Cadaba indica lam</i> (Viluthi leaf)	30–60	Spherical	[70]
<i>Carica papaya</i>	10–50	Cubical	[71]
<i>Carica papaya</i>	50–250	Spherical	[72]
Carob leaf extract	5–40	Spherical	[73]
<i>Cassia Roxburghii</i> (Ceylon senna)	57–95	Spherical, triangular, truncated triangular, decahedral	[74]
<i>Chamomile</i> (a tea plant)	20–70	Spherical	[75]
<i>Chrysanthemum indicum</i> (Saamanthi)	38–72	Spherical	[76]
<i>Citrullus colocynthis</i> (Kumatti)	1–60	Spherical	[77]
<i>Coleus aromaticus</i>	25–27	Spherical	[78]
<i>Coleus aromaticus</i> —Mexican Mint	20–30	Spherical	[79]
<i>Commelina benghalensis</i>	13–51	Spherical	[80]
<i>Crocus Haussknechtii Bois</i>	16	Spherical	[81]
<i>Cycas circinalis</i> ,	13–51	Spherical	[80]
Cycas Leaf (Panai Peyarani)	2–6	Spherical	[82]
<i>Cynodon dactylon</i> (Arugampul)	25–60	Spherical	[56]
Datura metel (Oomaththai)	16–40	Spherical	[83]
<i>Diopyros kaki</i>	32	Spherical	[84]
Eclipta leaf	2–6	Spherical	[82]
Eucalyptus	4–60	Spherical	[85]
<i>Eucalyptus angophoroides</i>	3–15	Spherical	[53]
<i>Eucalyptus chapmaniana</i>	60	–	[86]
<i>Eucalyptus globulus</i>	1.9–25	Spherical, oval	[87]
<i>Eucalyptus leucoxylon</i>	50	Spherical	[88]
<i>Eucalyptus oleosa</i>	14–26	Spherical	[89]
<i>Ferocactus Echidne</i> (Mexican Cactus)	20–60	Elliptical	[90]
<i>Ficus amplissima</i>	13–51	Spherical	[80]
<i>Ficus benghalensis</i> (Banyan)	16	Spherical	[91]
<i>Fraxinus excelsior</i>	25–40	Spherical	[92]



Table 1 (continued)

Name of the plant	Nanoparticle size (nm)	Nanoparticle shape	References
<i>Galega officinalis</i> (Professor weed)	23–220	Spherical	[93]
<i>Ginkgo biloba</i>	32	Spherical	[84]
<i>Glaucium corniculatum</i>	45–53	Spherical	[94]
Green and Black tea leaves	10–20	Spherical	[95]
Green tea	6–8.5	Spherical	[96]
Green tea leaves	25–75	Spherical	[97]
<i>Hamamelis virginiana</i> Leaf (American Witch hazel)	8–35	Spherical	[98]
<i>Heritiera fomes</i>	20–100	–	[99]
<i>Hydrilla verticillata</i>	–	Spherical	[100]
<i>Iresine herbstii</i> (Chicken Gizzard)	44–64	Spherical	[101]
<i>Ixora coccinea</i> leaves (Jungle Geranium)	13–57	Spherical	[102]
<i>Justicia glauca</i> (thavasi murungai)	10–20	Spherical	[103]
<i>Lantana camara</i> (Unni Chedi)	20–34	Spherical	[104]
<i>Leptadenia reticulata</i> (Palaikkodi)	50–70	Spherical	[105]
<i>Lippia nodiflora</i>	13–51	Spherical	[80]
<i>Lonerica japonica</i>	20–60	Spherical, hexagonal	[106]
<i>Lysiloma acapulcensis</i> (Legume Plant)	1.2–62	Spherical	[107]
<i>M. pudica</i> —Thottal sinungi (Mimosaceae)	20–60	Spherical	[108]
<i>Magnolia grandiflora</i>	32	Spherical	[84]
Mangosteen leaf	6–57	Spherical	[109]
<i>Mentha piperita</i> (Peppermint)	20–50	Spherical	[110]
<i>Mimusops elengi</i> Leaf (Spanish Cherry)	55–83	Spherical	[111]
<i>Moringa oleifera</i> —Drumstick tree	9–11	Spherical	[112]
Mulberry Leaves	20–40	Spherical	[113]
<i>Murraya koenigii</i> (Kari Vembu)	20–35	Spherical	[114]
<i>Murraya Koenigii</i> Leaf (Kari vembu)	10–20	Spherical	[115]
<i>Mussaenda glabrata</i>	11–51	Spherical	[116]
<i>Myrica esculenta</i> (Box berry)	45–80	Spherical	[117]
<i>Nelumbo nucifera</i> (Yellow Lotus)	25–80	Spherical, triangle, decahedral	[118]
<i>Nicotiana tobaccum</i>	7–9	Irregularly spherical	[119]
<i>O.sanctum</i> (tulsi)	50	cuboidal	[52]
<i>O. tenuiflorum</i> (black tulsi)	20	Hexagonal, pentagonal	[52]
<i>Ocimum sanctum</i>	40–50	Spherical	[120]
<i>Ocimum gratissimum</i>	17	Cuboidal	[121]
<i>Ocimum sanctum</i>	6–110	Triangular	[122]
<i>Ocimum Sanctum</i> (Tulsi)	11–17	Spherical	[123]
<i>ocimum</i> sp.,	3–20	Spherical	[124]
Olive leaf	20–25	Spherical	[125]
<i>Origanum heracleoticum</i>	30–40	Spherical	[126]
<i>Osmanthus Fragrans</i> (Olive Variety)	2–30	Spherical	[127]
<i>Padina tetrastromatica</i>	10–100	Spherical	[128]
<i>Paederia foetida</i> (Gandha Prasarini)	4–15	Spherical	[129]
<i>Parkia speciose</i> (Bitter bean/Avara Paruppu)	26–39	Spherical	[130]
Parthenium leaf	30–80	Irregular	[131]
<i>Pedaliium murex</i> (Yanai Nerunjil)	20–50	Spherical	[132]
Pine roxburghii	32	Spherical	[84]
Pineapple leaf	7080	Spherical	[133]
<i>Piper nigrum</i>	7–50	Spherical	[134]
<i>Piper nigrum</i>	5–50	Spherical	[68]



Table 1 (continued)

Name of the plant	Nanoparticle size (nm)	Nanoparticle shape	References
<i>Platanus orientalis</i>	32	Spherical	[84]
<i>Plukenetia volubilis</i> (Ankaaravalli)	4–25	Spherical	[135]
<i>Portulaca oleracea</i> (Tharai keerai)	15–40	Spherical	[56]
<i>Prangos ferulacea</i> (Medicinal plant)	10–20	Spherical	[136]
<i>Prunus japonica</i> —Japan bush cherry tree	24–26	Spherical	[137]
<i>Prunus persica</i>	40–98	Spherical	[138]
<i>Rhizophora mucronata</i> (Mangrove plant)	4–26	Spherical	[139]
<i>Rosa rugosa</i> (Rose)	10–35	Triangular, hexagonal	[140]
<i>Rosmarinus officinalis</i> (Rosemary)	10–33	Spherical	[141]
<i>Salvia spinosa</i> (Mint family)	19–125	Spherical	[142]
<i>Salvinia molesta</i>	1–35	Spherical	[143]
<i>Saraca indica</i> (Ashoka tree)	51–230	Spherical	[144]
<i>Securinega leucopyrus</i> (Plant)	11–20	Spherical, oval	[145]
<i>Sesbania grandiflora</i> (Agaththi)	10–25	Spherical	[146]
<i>Sida acuta</i> —Arivaalmanai Poundu	20–60	Triangular, pentagonal, hexagonal	[147]
<i>Skimmia laureola</i> (Ornamental Shrub)	38–46	Spherical, hexagonal	[148]
<i>Sonneratia apetala</i>	20–100	–	[99]
<i>Strychnos potatorum</i> (Thethan Kottai)	20–62	Cubical, hexagonal	[149]
<i>Taxus baccata</i> (English Yew)	75–91	Spherical	[150]
Tea leaf	20–90	Spherical	[151]
<i>Tecomella undulata</i>	32–46	Spherical	[22]
<i>Terminalia arjuna</i> (Marudha maram)	10–50	Spherical	[152]
<i>Terminalia arjuna</i> (Marudha maram)	8–16	Irregular-shaped	[153]
<i>Terminalia chebula</i>	10–30	Spherical	[154]
Terrestrial fern— <i>Gleichenia Pectinata</i>	4–10	Spherical	[155]
<i>Thymbra spicata</i> (Plant)	20–50	Spherical	[156]
<i>Vitex Negundo</i> Leaf (Vellai nochchi)	10–30	Cubical	[157]
Water hyacinth	3–10	Spherical	[158]
Wheatgrass	21–32	Spherical	[159]
<i>Ziziphora tenuior</i> (Turkey herb)	8–40	Spherical	[160]

concentrations corresponding to the needs of that particular species. Saponins, tannins, triterpenoids glycosides, and alkaloids are also present in the seeds [261]. Table 6 shows the list with representative examples of seeds used for synthesis of silver nanoparticles.

Microbe-mediated synthesis

Microbes and metal interaction were greatly explored already in the discipline of environmental biotechnology through bioremediation, biomineralization, and bioleaching. Microbe-mediated synthesis of metallic nanoparticles (MNPs) includes prokaryotic bacteria, eukaryotic fungi, and some viral particles that in turn takes place either intracellular or extracellular. Interaction of positive metal ions in the solution with the negatively charged cell wall facilitates the transportation of ions to intracellular space

and further reduction by the cellular enzyme system produces metallic nanoparticles which shall further diffuse out of the cell is the mechanism of intracellular microbe-mediated green synthesis of MNPs. Experiments that tend to chemical treatment of cell wall charge alteration show more favorable NP synthesis that proves the interaction of cell wall charge and cellular transportation in this process. The alternate synthesis mechanism includes nitrate-reductase enzymes of the microbes that reduce the metal ions extracellularly [276]. Tables 7, 8, and 9 show the list with representative examples of bacteria, fungi, and algae used for synthesis of silver nanoparticles.

Miscellaneous agent-mediated synthesis

Apart from the phyto-mediated and microbe-mediated routes, the macromolecules such as carbohydrates, organic

Table 2 Representative examples of bark, stem, and latex used for synthesis of silver nanoparticles

Name of the plant	Part of the plant	Nanoparticle size (nm) and shape	References
<i>Azelaia quanzensis</i> (Lucky bean tree)	Bark	10–80, spherical	[167]
<i>Butea monosperma</i> (Palash teak)	Bark	18–50, spherical	[168]
<i>Cochlospermum gossypium</i> (gum Plant)	Stem	3–56, spherical	[169]
<i>Euphorbia milii</i> (Kireeda kalli)	Latex	10–50, spherical	[170]
<i>Euphorbia tirucalli</i>	Latex	20–30, spherical, cubical	[171]
<i>Ficus benghalensis</i> (Banyan tree)	Bark	68–74, spherical	[172]
Garlic clove	Stem	4–22, spherical	[173]
Gum Arabic	Latex	10–50, spherical	[174]
Gum ghatti (<i>Anogeissus latifolia</i>)	Stem	11–52, spherical	[175]
<i>Hevea brasiliensis</i>	Latex	2–100, spherical	[176]
<i>Jatropha curcas</i> (Barbodos nut)	Latex	10–20, irregularly spherical	[177]
<i>Picrasama. quassinoids</i>	Bark	17.5–66.5, spherical	[178]
<i>Pinus eldarica</i> (Pine tree)	Bark	10–40, spherical	[179]
<i>Piper nigrum</i>	Stem	9–30, spherical	[134]
<i>Prosopis juliflora</i> (Mexican tree)	Bark	10–50, spherical	[180]
<i>Salacia chinensis</i> (Pon Korandi)	Bark	100–200, spherical	[181]
<i>Salvadora persica</i>	Bark	2–100, spherical	[182]
<i>Seidlitzia rosmarinus</i> (Desert plant)	Stem	16, spherical	[183]
<i>Terminalia cuneata</i> (Kadukkai)	Bark	25–50, spherical	[184]
<i>Thevetia peruviana</i> (Persian nut)	Latex	10–30, spherical	[185]

acids, proteins, and other miscellaneous chemicals are also used in the reduction and capping of silver nanoparticles. Table 10 gives the list with representative examples of macromolecules that have been employed as reducing agents for silver nanoparticle synthesis.

Antimicrobial activity of silver nanoparticles and nanocomposites

Antibacterial activity

Silver has always been widely preferred to treat various diseases; it is used as an antiseptic and anti-microbial against Gram-positive and Gram-negative bacteria. Although the highly antibacterial effect of AgNPs has been widely described, silver-based nanocomposites also have gained more attention in many different areas, including antibacterial applications. Generally, the nanocomposite material supports the extended release of silver nanoparticles by adhering to either large-sized or small-sized surface of support materials and thereby increases the anti-microbial activity [364]. The interaction of NPs with polymers not only makes the nanoparticles more compatible with polymer matrix, but also change their properties. The use of polymers in functionalization provides a large surface area and mechanical strength of nanoparticles, which transfers into increased durability and extended use. Moreover, it limits unintended release of nanoparticles into the environment

and thereby preventing its loss and aggregation. Among the support materials investigated (Table 11), small-sized SiO₂ NPs are cheap and release high quantity of AgNPs per unit volume [365].

Antiviral activity

Viruses: infection and targeting

Viruses are the minuscule obligate microbes that infect all form of lives ranging from bacterial pathogens to humans where generation of energy, synthesis and assembly of replication, and other factors for central dogma take place within the host making avail of the host cell machineries for the above process. The gene core material shall be either single or double stranded, ribonucleic acid (RNA), or deoxy-ribo nucleic acid (DNA) encapsulated with proteins made the layer of capsomeric subunits assembly to form either helical or spherical sphere [381].

Infection of viruses has unique stages in the process of viral replication into the host cell starting with attachment to host cell, accumulation of viral load and penetration, the release of viral nucleic acid, processing of nucleic acid as replicative template form and its entry into the host cell nucleus, viral genome replication, transcription and translation of the replicated viral nucleic acid, assembly and release of virions, attachment to the closer proximal cells, and repetition of the cycle [382].



Table 3 Representative examples of fruits used for synthesis of silver nanoparticles

Name of the plant	Nanoparticle size (nm)	Nanoparticle shape	References
Apple extract	24–36	Spherical	[190]
<i>Averrhoa bilimbi</i> Fruit (Cucumber)	50–150	Hexagonal, rhomboidal	[191]
Banana peel	21–25	Spherical	[192]
Bitter apple (<i>Citrullus colocynthis</i>)	20–80	Spherical	[193]
<i>Brucea javanica</i> (Ayurvedic plant)	24–58	Spherical	[194]
Capuli cherry	40–100	Spherical	[195]
<i>Carica papaya</i>	25–50	Cubical	[71]
<i>Citrullus lanatus</i> (Watermelon)	17–20	Spherical	[196]
<i>Coccinia grandis</i> (kawai guard)	–	Spherical	[197]
Coconut	7080	Cubical	[198]
<i>Cordia dichotoma</i> (Naru valli)	2–60	Spherical	[199]
<i>Crataegus douglasii</i> (hawthorn)	40–60	Spherical	[200]
<i>Dillenia Indica</i> (Uvaa thaekku)	40–100	–	[201]
<i>Emblica Officinalis</i> fruit (Nellikaai)	10–70	Spherical	[202]
European black elderberry	20–80	Spherical	[203]
<i>Feronia elephantum</i> (Vilaam palam)	20–60	Triangular, pentagonal, hexagonal	[204]
<i>Gmelina arborea</i> (Kumil)	8–32	Spherical	[205]
Green carambola (star fruit)	8–19	Spherical	[206]
<i>Kigelia africana</i> fruit (Mara suraikkai)	10	Spherical	[207]
Locust bean gum (LBG)	16–28	Irregularly spherical	[208]
<i>M. balbisiana</i> (Banana)	20	Spherical, pentagonal	[52]
<i>Malus domestica</i> fruit (Apple)	20	Spherical	[209]
Oak fruit hull (Jaft)	40	Spherical	[210]
Orange peel	1–15	Spherical	[211]
Peels of <i>Punica Granatum</i> (Pomegranate)	4–7	Spherical	[212]
<i>Phyllanthus emblica</i> (Nelli- gooseberry)	–	Spherical	[197]
Pine cone	20–100	Triangular, hexagonal	[213]
<i>Solanum xanthocarpum</i>	4–18	Spherical	[214]
Tamarind fruit	6–8	Spherical	[215]
<i>Terminalia chebula</i> (kadukkai)	25	Spherical	[184]
<i>Terminalia chebula</i> fruit (Kadukkai)	20–50	Spherical, triangular	[216]
<i>Ananas comosus</i>	10–300	Sharp corners	[217]
<i>Citrus sinensis</i>	10–300	Spherical	[217]
<i>Trachyspermum ammi</i> (Omam)	60–87	Spherical	[218]

Therapeutic targeting shall be with any one of the above steps and sometimes combinatorial drug targeting two or more steps of the viral load increase. Targeting component shall be fusion inhibitors, channel blocking compounds, transcription blocking compounds, nucleotide polymerase inhibitor, reverse transcriptase and helicase inhibitors, protease and virion assembly inhibitors, neuraminidase inhibitors, and combination from any of the above [383].

Nanosilver: the most unique antiviral

Silver nanoparticles have efficacious anti-microbial properties, which have been taken advantage of for addressing the evolving hyper virulence spikes of different families of

viruses during different times. Silver nanoparticles with its exceptional surface area and binding properties exhibit anti-viral attributes through interaction either at the binding stage of virus with the host cell (viral entry inhibition) or interference with the viral genome expression cycle inside the cell (virucidal). The out of the ordinary porosity property of silver nanoparticles facilitates the movement and interaction of different other smaller molecules and particles with the viral factor and cellular factors of the viral genome [384, 385].

Silver nanoparticles have a different mechanism of action and activity against viruses such as the affinity of binding to glycoprotein-120, strong competitive binding of cell attachment with the viral strain, interference and inhibitory blocking of viral binding and penetration, viral DNA

Table 4 Representative examples of flowers used for synthesis of silver nanoparticles

Name of the plant	Nanoparticle size (nm)	Nanoparticle shape	References
<i>Achillea biebersteinii</i> (Yarrow)	5–35	Spherical	[224]
<i>Calotropis gigantea</i>	50	Spherical	[225]
<i>Calendula officinalis</i>	5–10	Spherical	[226]
<i>Cassia auriculata</i> Flower (Pea family)	10–35	Spherical	[227]
<i>Chrysanthemum morifolium</i> (Saamanthi)	20–50	Spherical	[228]
<i>Cinnamon zeylanicum</i> (Lavangam pattai)	31–40	Spherical	[229]
<i>Crocus sativus</i>	10–25	Spherical	[81]
<i>Crocus sativus</i> L (Kunguma Poo)	12–20	Spherical	[230]
<i>Fritillaria</i> flower	5–10	Spherical	[231]
<i>Hibiscus rosa-sinensis</i>	5–14	Spherical	[232]
Inflorescence of <i>Cocos nucifera</i> (Coconut)	22	Spherical	[233]
Marigold flower	10–90	Spherical, Hexagonal	[234]
<i>Nyctanthes arbor-tristis</i> (Night flowering Jasmine)	5–20	Spherical, oval	[235]
<i>Piper nigrum</i> (Black Pepper)	1–29	Spherical	[236]
<i>Rosa damascena</i> petals (Damask rose)	74–94	Spherical	[237]
<i>Syzygium aromaticum</i> (Clove)	20–149	Spherical	[238]
<i>Tithonia diversifolia</i> (Mexican Sunflower)	10–26	Spherical	[239]

Table 5 Representative examples of roots and tubers used for synthesis of silver nanoparticles

Name of the plant	Nanoparticle size (nm)	Nanoparticle shape	References
<i>Berberis vulgaris</i> (Barberry)	30–70	Spherical	[244]
Beetroot extract	10–15	Spherical	[245]
<i>Cassia toral</i> (Senna tora)	20–100	Spherical	[246]
<i>Cibotium barometz</i> root	6–23	Spherical	[247]
<i>Curcuma longa</i> tuber (Turmeric)	4–9	Spherical	[248]
<i>Delphinium denudatum</i> (Ayurvedic—Nirbasi)	2–85	Spherical	[249]
<i>Diospyros Paniculata</i> —(karunthuvarai)	8–10	Spherical	[250]
<i>Diospyros Sylvatica</i> (Forest Ebony)	10–40	Spherical	[251]
Garlic	3–12	Spherical	[252]
Garlic and turmeric extracts	6–8.5	Spherical	[96]
Garlic extract	4–20	Spherical	[253]
<i>Nepeta leucophylla</i> (White leaved catmint)	40–100	Spherical	[254]
<i>Parthenium hysterophorus</i> root	-	Spherical	[255]
<i>Phytolacca Decandra</i> (PokeWeed)	91	Spherical	[256]
<i>Rheum palmatum</i> (Rhubarb plant)	11–210	Spherical, hexagonal	[257]
Root of <i>Zingiber officinale</i>	10–20	Spherical	[258]
<i>Thalictrum foliolosum</i>	15–30	Spherical	[259]
<i>Zingiber officinale</i>	10–20	Spherical	[260]

interaction and inactivation of the viral strain before entry into the host cell, etc. The mechanism for antiviral property of silver metallic nanoparticles with respect to virus entry inhibition includes interaction of metal ions with the host cell-binding surface glycoproteins of the virus and inhibition of the host–virus physical attachment. The denaturation of the protein coat of the virus by irreversible modification of the integrity of the coat frame through reduction of the

disulfide bonds and hence diminish the infectivity of the viral residues. The silver nanoparticles are capable of targeting the genetic material of the virus irrespective of the nature of genetic material (DNA, RNA) and their type of strand (single, double). Due to their natural affinity with the phosphate groups of the nucleic acid interacts with the disassembled viral nucleic acid and cellular replication factors thereby preventing the viral replication and or propagation



Table 6 Representative examples of seed extract used for synthesis of silver nanoparticles

Name of the plant	Nanoparticle size (nm)	Nanoparticle shape	References
<i>Artocarpus heterophyllus</i> (Jackfruit)	3–25	Spherical	[262]
<i>Brassica nigra</i>	41	–	[263]
<i>Coffea arabica</i>	20–30	Spherical, ellipsoidal	[264]
<i>Ducrosia Anethifolia</i> (oil plant)	4–42.13	Spherical	[265]
<i>Embelia ribes</i> (False black Pepper)	5–35	Spherical	[266]
Grape seed extract	54.8	Spherical	[267]
<i>Jatropha curcas</i>	15–50	Spherical	[268]
<i>Macrotyloma Uniflorum</i> (Horse gram)	12–17	Spherical	[269]
<i>Nyctanthes arbor-tristis</i> (Night Jasmine)	50–80	Spherical	[270]
<i>Papaver somniferum</i> (Kasa kasa)	60–87	Spherical	[218]
<i>Pistacia atlantica</i>	10–50	Spherical	[271]
Seeds of <i>acranythes aspera</i> (Naaiyuruvi)	5–50	Spherical	[272]
<i>Sinapis arvensis</i> seed (Wild mustard)	1–35	Spherical	[273]
<i>Tectona grandis</i> (Teak/thaekku)	10–30	Spherical	[274]
<i>Trifolium resupinatum</i> (Persian Clover)	5–10	Spherical	[275]

Table 7 Representative examples of Bacterial strains used for synthesis of silver nanoparticles

Name of the bacteria	Nanoparticle size (nm)	Nanoparticle shape	References
<i>Acetobacter xylinum</i>	40–60	Spherical	[277]
<i>Actinobacteria Rhodococcus</i>	5–30	Spherical	[278]
<i>Anabaena doliolum</i> (Cyanobacteria)	10–50	Spherical	[279]
<i>Bacillus amyloliquefaciens</i>	5–24	Triangular	[280]
<i>Bacillus methylotrophicus</i>	10–30	Spherical	[281]
<i>Bacillus safensis</i>	5–30	Spherical	[282]
<i>Escherichia coli</i>	65	Spherical	[283]
<i>E. fergusonii</i> (Bacteria)	10–80	Spherical	[284]
<i>Mutant Bacillus licheniformis</i>	10–30	Spherical	[285]
<i>Proteus mirabilis strain</i> (Bacteria)	10–20	Spherical	[286]
<i>Spore crystal of Bacillus thuringiensis</i>	10–20	Cubical, hexagonal	[287]
<i>Weissella oryzae</i> (Bacteria)	10–30	Spherical	[288]

taking place within the host cell and hence block further progeny or virion expression [384–390].

Antiviral spectra of silver nanoparticles

Silver nanoparticles possess a diverse extent of interactive mechanism with every family and classes of virus. Human immunodeficiency virus (HIV), herpes virus, influenza virus, coxsackie, and dengue virus including a range of enveloped, non-enveloped viruses to RNA- and DNA-based virus titer against varying concentrations of silver nanoparticles were studied, and with fold reduction virucidal activity against all the viral classes, the enveloped and positive sense RNA viruses have greater reduction than non-enveloped and negative sense RNA viruses [391, 392].

Lara et al. substantiated the activity of silver nanoparticles against HIV in both the cell-free and cell-associated forms, and found to reduce many fold of the viral gp-120 interaction, accumulative fusion, and virulent factor infectivity with the CD-4 cell receptor of the host cell. With the interaction hypothesis, the AgNPs also tends to denature and weaken the disulfide regions of CD-4-binding domain present in the gp-120 of the viral cell-surface receptor which was reflected with the multi-fold reduced fusion and infectivity making it a suitable candidate for early stage and post-entry target [385].

The novel SARS-CoV2, a member of the family of coronaviridae being the enveloped, single-stranded RNA virus shall be tackled and targeted using silver nanoparticle on the basis of previous works done against epidemic and pandemic of the long past to later past that includes H5N1,

Table 8 Representative examples of fungal strains used for synthesis of silver nanoparticles

Name of the fungi	Nanoparticle size (nm)	Nanoparticle shape	References
<i>Aspergillus niger</i> (Fungus)	5–26	Spherical	[289]
<i>Aspergillus terreus</i>	1–20	Spherical	[290]
<i>Candida albicans</i> (Fungus)	5–10	Spherical	[291]
<i>Fusarium oxysporum</i>	15–84	Spherical	[292]
<i>Fusarium solani</i> (Fungus)	5–35	Spherical	[293]
<i>Macrophomina Phaseolina</i> (Fungus)	5–40	Spherical	[294]
<i>Metarhizium Anisopliae</i> (Fungus)	28–38	Rod shaped	[295]
<i>Mushroom Fungus Schizophyllum</i>	51–99	Spherical	[296]
<i>Penicillium citrinum</i>	90–120	Spherical	[297]
<i>Penicillium duclauxii</i>	3–32	Spherical	[298]
<i>Penicillium purpurogenum</i>	8–10	Spherical	[299]
<i>Phoma glomerata</i> (Fungus)	19–65	Spherical	[300]
<i>Sclerotinia sclerotiorum</i> (Fungus)	25–30	Spherical	[301]
<i>Trichoderma harzianum</i>	51.10	Irregularly Spherical	[302]
<i>Trichoderma viride</i>	1–50	Spherical	[303]

Table 9 Representative examples of algal strains used for synthesis of silver nanoparticles

Name of the algae	Nanoparticle size (nm)	Nanoparticle shape	References
Boiled Algae (<i>Desmosus</i> sp.)	3–6	Spherical	[304]
<i>Caulerpa racemosa</i>	5–25	Spherical	[305]
<i>Chaetomorpha linum</i> (Macroalgae)	3–44	Cubical	[306]
<i>Chlorella vulgaris</i>	15–47	Spherical	[307]
<i>Colpomenia sinuosa</i>	16	Spherical	[308]
<i>Jania rubens</i>	7	Spherical	[309]
<i>Nostoc linckia</i> (Algae)	5–60	Spherical	[310]
<i>Pterocladia capillacea</i>	7	Spherical	[309]
Raw algae (<i>Desmosus</i> sp.)	4–8	Spherical	[304]
<i>Sargassum Wightii Grevilli</i> (Marine Alga)	8–27	Spherical	[311]
<i>Spyridia fusiformis</i> (Marine red alga)	5–50	Spherical	[312]
<i>Turbinaria conoides</i> (Marine brown seaweed)	96	Spherical	[313]
<i>Ulvan Algae</i>	3–36	Spherical	[314]

H1N1 influenza A to foot and mouth disease of cattle and potato virus Y, and tomato mosaic virus of plants. Reduction in disease severity and viral infection with inhibitory action on localized effects on the host cell was promising to justify the selection of AgNPs as potential candidate for SARS-CoV. AgNPs have a greater enhanced virucidal effect against lettuce infecting tomato bushy stunt virus [TBSV] and also graphene-based silver nanocomposite contributes for absolute suppression of the disease against sun hemp rosetta virus [SHRV] in the plant culture system as potted plants exposed to the viral load sprayed [287, 393, 394].

Feline coronavirus (FCoV) and infectious bursal disease virus (IBDV) were systematically targeted using graphene oxide—silver nanocomposite and the inhibition route were found to be hydrophobic and electrostatic interaction

between the aromatic GO plane and lipids. Dipolar bonds between thiol residues and Ag⁺ ions were another assisting inhibitory route. For non-enveloped viruses, there will be the absence of the hydrophobic interaction, thereby the stronger dipolar (coordinate covalent) bond directs the extent of inhibition [395]. Other composites of silver nanoparticles includes tannic acid, poly vinyl chloride, chitosan as second constituent along with silver that were acted against herpes simplex virus type 2 (HSV-2), human immunodeficiency virus, and H1N1 influenza virus, respectively, follows interference with attachment, membrane receptor channel binding and interaction with the genetic material of the virus upon uncoating [396].

Different results show that the AgNPs' interaction with gp-120 was found to be size dependent and nanoparticles of



Table 10 Representative examples of other miscellaneous used for synthesis of silver nanoparticles

Name of the sources	Nanoparticle size (nm)	Nanoparticle shape	References
2,4-pentanedionate Ag (I)	15–36	Spherical	[315]
Arabic gum	10–30	Irregular shaped	[316]
Ascorbic acid	29–82	Spherical	[317]
Ascorbic acid and starch	17–30	Truncated triangle	[318]
Bacterial cellulose	50–70	Spherical	[319]
B-cyclodextrin grafted with poly acrylic acid [BCD-g-PAA]	3–22	Spherical	[320]
Casein hydrolytic peptides	5–15	Spherical	[321]
Chitosan	5–15	Spherical	[322]
Chitosan	20–75	Spherical	[323]
Chitosan/PEG	5–19	Spherical	[324]
Chondroitin 4-sulfate sodium salt	50–77	Spherical	[325]
<i>Cocos nucifera</i> coir extract (Coconut tree)	21–25	Spherical	[326]
Citrate	7	Spherical	[327]
Dextrose	4–23	Spherical	[328]
Gallic acid	12–21	Spherical	[329]
<i>Ganoderma applanatum</i> mushroom	133	Spherical	[330]
Gelatin	3–14	Spherical	[331]
Gelatin nanoshells	4.1–6.9	Spherical	[332]
Geraniol	1–10	Spherical	[333]
Glucose	30–80	Irregularly spherical	[334]
Glucose	10–20	Spherical	[335]
Glucose, gelatin	5–20	Spherical	[336]
Glutathione	5–10	Spherical	[337]
Graphene	14–17	Spherical	[338]
Honey	4–6	Spherical	[339]
Hyaluronan	5–20	Spherical	[340]
Hydroxypropyl- β -cyclodextrin	2–5	Spherical	[341]
<i>Lentinus edodes</i> (Edible mushroom)	50–100	Walnut	[342]
Local honey	16–25	Spherical	[343]
Maltose	53–72	Spherical	[344]
<i>Malva parviflora</i> (Cheeseweed)	19–25	Spherical	[345]
Mushroom <i>Pleurotus florida</i>	1–3	Spherical	[346]
Mushroom Extract of <i>Pleurotus giganteus</i>	2–20	Spherical	[347]
Mussel-inspired dopamine (GO-Dopa)	5–8	Irregularly spherical	[348]
<i>Panicum virgatum</i> (Switchgrass)	20–40	Spherical, rod-like, triangular, pentagonal, hexagonal	[349]
Pine honey	21–31	Spherical	[350]
Poly(acrylamide)	2–5	Cubical	[351]
rGO, MWCNT	30–50	Spherical	[352]
Ribose sugars, SDS	7–17	Spherical	[353]
<i>Salmalia malabarica</i> gum	5–9	Spherical	[354]
Seaweed <i>Urospora</i> sp.	20–30	Spherical	[355]
Sodium alginate	12–18	Spherical	[356]
Sodium citrate	20–25	Rhombical, hexagonal	[357]
Sodium tricitrate	15–24	Spherical	[358]
Spider cobweb	3–50	Spherical	[359]
Starch	20–50	Spherical	[360]
Sucrose	1–11	Spherical	[344]
Tannic acid	28–47	Spherical	[361]



Table 10 (continued)

Name of the sources	Nanoparticle size (nm)	Nanoparticle shape	References
Tannic acid	3.3–22.1	Spherical	[362]
Tannic acid	7	Spherical	[327]
Thyme honey	21–31	Spherical	[350]
Trisodium citrate	32–53	Spherical	[363]

Table 11 Details of silver nanocomposites support material and their antibacterial activity

Name of the support material	Antimicrobial activity	MIC ($\mu\text{g/ml}$)	References
Graphene oxide	Multidrug-resistant <i>E. coli</i> strains	4	[367]
Chitosan	<i>Botrytis cinerea</i>	125	[368]
Silica	<i>Escherichia coli</i> ATCC 2732	62.5	[369]
Silica	<i>Klebsiella pneumoniae</i> ATCC 4352	62.5	[369]
Silica	<i>Pseudomonas fluorescens</i> LME 2333	62.5	[369]
Silica	<i>Salmonella enterica</i> serovar Enteritidis D1	62.5	[369]
Silica	<i>Salmonella enterica</i> serovar Typhimurium DB 7155	62.5	[369]
Silica	<i>Enterococcus faecalis</i> ATCC 19433	62.5	[369]
Silica	<i>Bacillus cereus</i> ATCC 14579	250	[369]
Silica	<i>Listeria monocytogenes</i> Scott A	500	[369]
Silica	<i>Staphylococcus aureus</i> ATCC 29213	250	[369]
Silica	<i>Candida albicans</i> ATCC 10259	125	[369]
Silica	<i>Aspergillus niger</i> ATCC 9642	2000	[369]
Silica	<i>Escherichia coli</i> ATCC25922	7.8	[370]
Silica	<i>Escherichia coli</i>	100	[371]
Silica	<i>Staphylococcus aureus</i>	150	[371]
Magnetic silica	<i>Escherichia coli</i>	15,625	[372]
Magnetic silica	<i>Staphylococcus aureus</i>	3125	[372]
Mesoporous silica particles	<i>Escherichia coli</i>	12.5	[373]
Mesoporous silica particles	<i>Staphylococcus aureus</i>	25	[373]
Mesoporous silica particles	<i>Escherichia coli</i>	75	[374]
Mesoporous silica particles	<i>Staphylococcus aureus</i>	75	[374]
TiO ₂	<i>Escherichia coli</i>	200–250	[375]
Chitosan	<i>Staphylococcus aureus</i>	50–100	[376]
Chitosan	<i>Escherichia coli</i> (CICC 21524)	32	[376]
Chitosan	<i>Salmonella choleraesuis</i> (CICC 21493)	64	[376]
Chitosan	<i>Staphylococcus aureus</i> (CICC 10384)	64	[376]
Chitosan	Vegetative cells of <i>Bacillus subtilis</i> (CGMCC 1.1377)	32	[376]
Carboxymethyl-cellulose	<i>Enterococcus faecalis</i>	60	[377]
Diatomite	<i>Staphylococcus aureus</i>	11.6	[378]
Diatomite	<i>Klebsiella pneumoniae</i>	232	[378]
SiO ₂	<i>Escherichia coli</i>	195	[379]
SiO ₂	<i>Staphylococcus aureus</i>	390	[379]
SiO ₂	<i>Escherichia coli</i>	10	[380]
SiO ₂	<i>Staphylococcus aureus</i>	4	[380]
SiO ₂	<i>Aspergillus niger</i>	0.13	[381]
SiO ₂ (irradiation)	<i>Aspergillus niger</i>	0.06	[381]



1–10 nm size were able to bind with extra-ordinary activity of inhibition and also involved with reduction of reverse transcription inhibition, so that the transformation of the viral RNA into cDNA gets inhibited and thus the viral load replicative steps and infectivity [397].

Respiratory syncytial infections of viral origin are a peril to humankind by making the infected individuals vulnerable to other range of infections, i.e., serving as a comorbidity to different other diseases. Silver nanoparticles and also its composite exploration as an antiviral agent to such respiratory infections are promising with past to recent present. Silver nanoparticles reduced using ascorbic acid with different weight percentages, capping of graphene oxide (GO) over the silver nanospheres, and silver nanoparticles bound to thiol-group functionalized GO were tested in vivo against coronavirus OC43 and Influenza A virus resulted with mild infectivity inhibition under certain conditions in ascorbic acid reduced AgNP and inhibition only at undiluted level in thiolated samples. Rapid viability and infectivity reduction in intact GO-capped Ag nanospheres observed were promoted by stabilization of bonds with steric hindrance of the composite. Interestingly, the plaque forming ability inhibition of the viruses was found with undiluted (100% concentrated) to diluted to 1% concentration of GO-capped-Ag-nanospheres as there is a synergistic effect between GO-AgNP against enveloped viruses that is independent of carrier solvent in the experiment. Five minute treatment to the viral load in prior infecting to the cell lines rapidly reduces the infectivity. Similar synergistic effect was also observed with the AgNPs–chitosan composites which is higher than the individual activities of them against the infection. Various assays that are useful to find the antiviral activity of the silver nanoparticles include proliferation assay, plaque forming unit assay, cell viability assay, real-time quantification polymerase chain reaction, western blot, cytotoxicity assays and pseudo virus entry assay, indirect immuno fluorescent assay, etc. [398–401].

Silver nanoparticles with their incredible antiviral attributes on monosystem also possess the property of agglomeration due to their tremendous surface energy when present as a single entity in the colloidal solution. Once after the agglomeration the increased grain size diminishes the properties of silver nanoparticles, i.e., reduced stability and activity. Various methodologies have been developed to address the agglomeration of colloidal AgNPs through the process of capping from green components to different inert molecules. The capping agent usually interacts with the external surface of the mono-nanoparticles and thereby reduces the aggregation. Polymers, inert macromolecules, resins and gums, plant extracts, and other capping agents influence the steric and electrostatic stabilization and enhance the activity. The following table (Table 12) comprises representative examples

of capping agents with silver nanoparticles and their mode of action against various families of virus [402–405].

Silver nanoparticles in SARS-CoV-2 therapy

Silver nanoparticles have their application in a very broader spectrum among which the latest utilization is against the destructive core global pandemic of this millennium, novel coronavirus, severe acute respiratory syndrome-coronavirus 2 (SARS-CoV2), the seventh coronavirus till date from the first virus identified in 1960, which is the one with highest infectivity rate and the fatality rate among the others from the same class [401]. Coronavirinae the subfamily of coronaviridae viral family which is been composed of four genera of viruses such as α -genera, β -genera, γ -genera, and δ -genera among which the alpha and beta genera are so far reported to be infectious to highly infectious against humans, whereas the gamma and delta are targeted to avian species. Around 79% of the similarity with gene sequence of SARS-CoV2 are conserved with SARS-CoV reported earlier and 50% identical sequence with middle-east respiratory syndrome related coronavirus (MERS-CoV). The MERS and SARS-CoV2 binding to cell surface is a remarkable feature of difference among which earlier one binds to dipeptidyl peptidase receptor-4 and the later one to angiotensin-converting enzyme-2 receptor. Such unique non-conserved region and properties make the novel SARS-CoV2 more infectious than any other coronaviridae viruses and thus given the name ‘novel’ coronavirus [414–417].

One among the promising candidatures for the preventive recommendations, treatment has unique position for AgNPs. As AgNPs have been previously reported counter activity against wide spectrum of pneumonia-like zoonotic, acute respiratory viruses, they shall be utilized along the drugs or therapy in combination as well as the single bioactive compound with the therapeutic compound.

The exact sequential mechanism of virus and AgNP interaction have different conceptual hypothesis (Fig. 1) from mimicking as cell-surface receptor to innate immunity activation. Intervention with cell-surface receptor binding and thereby inhibiting the attachment of the virus to the ACE receptor cells. By the attachment of AgNPs to the viral genome inhibits the viral replication inside the host like paramyxoviridae viruses, influenza viruses, retroviridae viruses, and hepatitis B virus. The pH of airway epithelium might become more acidic due the decrease in pH by the release of silver ions, which makes the environment more difficult for the virus to sustain. Ag^+ ions have the ability to interact and inhibit the respiratory enzymes of the virus and their potential interference with the viral nucleic acid was already demonstrated against wider spectrum of viruses in the past [394, 396, 418]. The In vitro study on Vero E6 cells infected with a fixed amount of SARS-CoV-2 virus revealed that the



Table 12 Representative example of different capping agents and spectra of virus treated with silver nanoparticles:

S.No	Type of virus	Family	Capping agent	Size (nm)	Concentration of AgNP	Time of study	Mode of action	References
1	Human immunodeficiency virus—1	Retroviridae	Polyvinyl pyrrolidone	30–50	0.44 mg/ml (± 0.3)	48 h	Inhibition through impeding with gp120-CD4 interaction	[385]
2	Human Immunodeficiency Virus—1	Retroviridae	Polyurethane	30–60	Ag-NPs-coated PUC (1 cm ²)	72 h	Direct transfer of silver ions from oxidized NPs to viral membrane proteins gp120 and gp41	[406]
3	Herpes simplex virus—1 (HSV-1 and HSV-2)	Herpesviridae	–	4–23	10 mg/ml	48 h	Irreversible inactivation of virions	[407]
4	Herpes simplex virus—1 (HSV-1 and HSV-2)	Herpesviridae	–	4–23	10 mg/ml	72 h	Irreversible inactivation of virions	[407]
5	Human parainfluenza virus (HPIV-3)	Paramyxoviridae	–	–	5 mg/ml	48 h	–	–
6	H1N1 Influenza A virus	Orthomyxoviridae	Chitosan	3.5–12.9	100 μ g /mg of chitosan	7 days	Spatial restriction of binding between virions and AgNP/Ch Matrix	[408]
7	Transmissible gastroenteritis coronavirus	Coronaviridae	Polyoxyethylene Glycerol Trioleate	10–20	3.125–12.5 (μ g/ml)	48 h	Depolarization of host cell's mitochondrial membrane protein and induction of apoptosis cascade	[409]
8	Tomato Bushy Stunt Virus	Tombusviridae	Graphene oxide	30–50	–	–	spatial distribution of the interacting ligand/receptor molecules between coat proteins of the virus and infected cell receptors	[393]
9	Respiratory Syncytial Virus	Pneumovirinae	Curcumin	11–12	0.008, 0.015, 0.03, 0.06, 0.12 nM	–	Reduction of cytopathic effects and inactivation of RSV before its entry into the host cell	[410]
10	Feline coronavirus	Coronaviridae	Graphene oxide	1–25	0.1 mg/ml	96 h	Negatively charged GO adsorbs to the positively charged lipid membrane and disrupts its integrity	[411]
11	Infectious bursal disease virus	Birnaviridae	Graphene oxide	–	1–0.125 mg/ml	96 h	Conjugation between the sulfur group of viral protein and silver nanoparticle on GO surface	–
12	Severe acquired respiratory syndrome—Coronavirus 2	Coronaviridae	Silicon dioxide	65	Approximately 50 ppm	2–10 min	High oxidizing ROS production led damage to the virus	[412]
13	Feline calicivirus	Coronaviridae	Poly(tannic acid)	10.61 \pm 1.54	20 mm \times 20 mm	72 h	Direct binding of the silver nanoparticles to viral envelope glycoproteins, thereby inhibiting viral penetration into the host cell	[413]
14	Influenza virus	Orthomyxoviridae	–	–	–	–	–	–



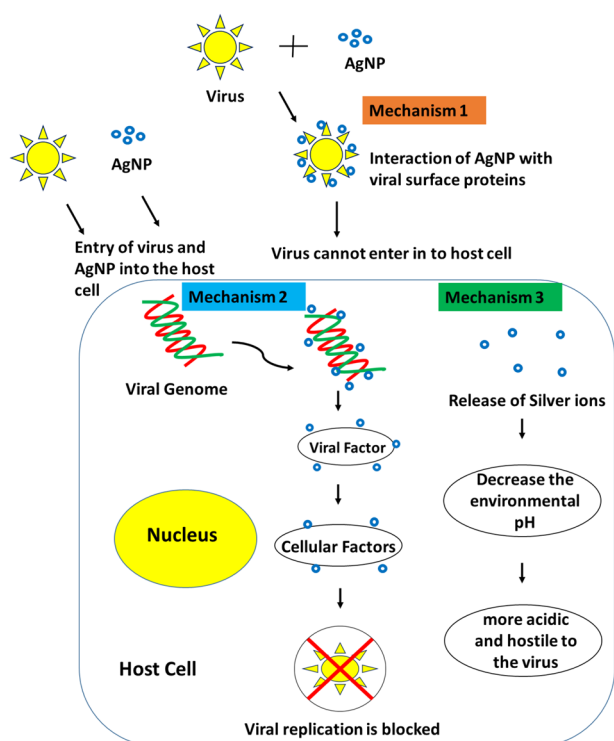


Fig. 1 Possible antiviral mechanism of silver nanoparticles

concentration of AgNPs between 1 and 10 ppm inhibited the SARS-CoV-2 viral infection by inhibiting the viral entry by disrupting viral integrity [400]. In another *In vitro* study on SARS-CoV-2 infection in cultured cells showed that a reduction of about 80% cells at a concentration of 0.03% [419]. Nanoparticle composite hybrids of silver, zinc, and copper exhibited vast antiviral property against HIV and other similar enveloped viruses. Capped silver nanoparticles are found to inhibit the negative riboxy nucleic acid strand synthesis of PEDV, another member of the corona virus family. Moreover, the innate immune response induction by the nanocomposites focuses on elimination of the probability of viral progeny development [420].

Formulations on the way to store

A provisional patent filed formulation of Quickgun Lifesciences, India has cepharanthine (CEP), a potent inhibitor drug against the virus in screening, loaded in combinatorial with biosilver. This CEP-biosilver oral spray formulation is about to direct a double-targeting of glycoproteins present in the pathogenic virus among which the phyto-derived inhibitor CEP inhibits the replication through targeting the corona virus glycoprotein and AgNPs usually targets the glycoprotein knobs of viruses. In PEGylated form as dry powder, the silver nanoparticles are formulated to deliver in either single dose or multiple dose

inhalers. With further research, this drug therapy shall be proven and considered as a potentially safe drug, as AgNPs are with extra-ordinary biocompatible characteristics, but are cytotoxic and apoptotic to cancer and other abnormal cells [421].

Imbed biosciences Inc., a Madison, Wisconsin-based pain killer and wound-healing formulation firm, is working on the integration of the pre-approved microlyte matrix wound-healing complex with the antiviral silver nanoparticles. They are bound with the viral particles and found to interact and freeze the mechanism through which viral particles and human cells interact. In a preliminary research carried out by the Virology Research Institute, London, the AgNPs synthesized by the company, is found to be either -cidic (kill) or -static (inactivate) with 99.9% of the SARS-CoV2. These controlled lab results are really hopeful to take on into the preliminary clinical trials and follow-of-human trials. The product is planned to be delivered in a nasal spray formulation once it clears the levels of pharmaceutical trials [422].

A consortium of companies that include ApIfilm, Braskem, Nanox, and the UFSCar (Brazil) and Jaume I of Castellón (Spain) universities developed and licensed technology of PVC polymer films used in food packaging, coated with silver and silica nanoparticles, is successfully found to inactivate the novel coronavirus. Different time bound direct exposure of novel SARS-CoV2 virus upon the film was carried out and after which the viral particles were made to infect African monkey kidney cell lines, called as vero cells. The infection, virulence and replication rate before and after exposure to films and films without silver and silica coatings were carried out and comparison studies were done. The amplification of viral materials by PCR shows about 99.84% and almost 100% reduction in the viral genetic materials, after exposure time of 2 and 15 min, respectively. A highly satisfactory performance of stretch-wrap wrapping material for perishable food and other grocery items is more about to explore and the exact mechanism studies shall open up more avenues of improvised strategies to tackle the novel SARS-CoV2 [423].

Recent research includes incorporative application of the AgNPs' coating and dispersion in train cargos, air filters, handles of subways, handrails of elevators and to surgical face masks, medical devices like personal protection equipment kits, and the list of consumables extends.

Pros and cons of faster human trials of silver nanoparticles

Several advantages of utilizing AgNPs as candidature to SARS-CoV2 newer virus variants with faster clinical trials than usual include greater probability of effective virucidal

properties to similar respiratory syncytial disease causing viruses, rapid activation of the host's innate immunity response and cascade system, greater stability, biocompatibility and easy to control over coating process, diverse choice of conjugation and hybrid therapy as they are encapsulated nanocarrier themselves, synergistic property with improved efficacy and reduced level of resistance, and availability of valid, standard, optimized, controlled, and commendable property engineering technologies [424–426].

Concerns range from availability of nanoparticle precursor, activity variation with respect to the source of nanoparticle synthesized, non-optimized and unstandardized procedure of surface coatings, pharmacodynamics and pharmacokinetic studies of the antiviral candidatures, and no application restrictions framework—MRI exposure to metallic nanoparticle-coated mask leads to face burn that WHO advised lately. Lack of a proper standard disposal protocol of silver incorporated products shall be an eco-system pressure created on the natural microbiota of the environment [400]. The selection of the capping agent that provides prolonged stability to the silver nanoparticles coating from a wide range of such preceding successful components should be appropriately chosen with the trials. However, eventual addressing of all such cons and standardizing the protocols for prolonged activity retainment on the coated surfaces shall take the integrated research to tackle SARS-CoV2 for the very next level.

Conclusion

Silver nanoparticles, the prominent aspiring and promising candidate against the multitude of applications, have been narrowed toward its antiviral spectra attributes with the review. Green synthesis of silver nanoparticles through phyto-mediated route is found to be more promising due to its simplicity of conduction and presence of versatile natural plant-based compounds such as polyphenols to alkaloids, etc., provides the combined arena for synthesis that covers nanoparticles of varying sizes and morphologies as the outcome. Tailoring and scale-up of the plant-mediated route has a higher edge and ease of convenience compared to the microbe-mediated and other macromolecule-mediated methods of synthesis.

Silver nanoparticles' activity against the virus is dependent on various factors such as the size and concentration of the nanoparticles, enveloped and non-enveloped coat of virus, nature of genetic material (DNA /RNA), sensing of strand (positive/negative sense strands), agglomeration, etc. Binding with the glycoproteins to formation of affinity interactions and denaturation of the bonds of viral surface, there are conglomerated routes through which the inactivation and the disintegration of viral strain takes place at different targeting points such as during entry and post-entry.

Several SARS-CoV2 formulations utilize silver as a core targeting compound or with combinatorial drugs as hybrids. The proven antiviral property strongly suggests the usage of silver nanoparticles with appropriate capping agent coatings and also with composites in surface sterilization to therapeutic targeting. A newer avenue of being a composite component of targeted drug delivery system emulsions to being the core component of drug composite, multiple actions of silver nanoparticles against existing and still evolving viruses would be a more fascinating research and development area of the near to far future.

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Declarations

Conflict of interest The authors declare no conflict of interest in preparing this article.

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Authors and Affiliations

C. Karthik¹  · K. A. Punnaivalavan¹ · S. Pandi Prabha² · D. G. Caroline¹

¹ Department of Biotechnology, St. Joseph's College of Engineering, Old Mamallapuram Road, Chennai 600119, Tamil Nadu, India

² Department of Biotechnology, Sri Venkateswara College of Engineering, Sriperumbudur Taluk, Chennai 602117, Tamil Nadu, India

