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Silver nanoparticles: synthesis, properties, and therapeutic applications

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Abstract

Silver nanoparticles (AgNPs) have been widely used in biomedical fields because of their intrinsic therapeutic properties. Here, we introduce methods of synthesizing AgNPs and discuss their physicochemical, localized surface plasmon resonance (LSPR) and toxicity properties. We also review the impact of AgNPs on human health and the environment along with the underlying mechanisms. More importantly, we highlight the newly emerging applications of AgNPs as antiviral agents, photosensitizers and/or radiosensitizers, and anticancer therapeutic agents in the treatment of leukemia, breast cancer, hepatocellular carcinoma, lung cancer, and skin and/or oral carcinoma.

Keywords

silver nanoparticles; physico-chemical properties; localized surface plasmon resonance; cytotoxicity; antiviral effect; photosensitizers/radiosensitizers; anticancer; assessment of the risks to humans and environment

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Teaser: By interacting with cells and mediating molecular processes to regulate cell functions, silver nanoparticles exhibit emerging biomedical applications as antiviral agents, photosensitizers and/or radiosensitizers, and anticancer therapeutic agents.

Introduction

AgNPs with unique optical, electronic, and antibacterial properties have been widely used in biosensing [1], photonics [2], electronics [3], and antimicrobial [4] applications, among others. The remarkably strong broad-spectrum antimicrobial activity of AgNPs is a major direction for the development of AgNP products, including textiles, food storage containers, antiseptic sprays, catheters, and bandages. The biocidal activity of AgNPs depends on their size, shape, and surface coatings. Therefore, the development of AgNPs with well-controlled morphological and physicochemical features for physiological application in humans is necessary to expand their biomedical applications. Recently, AgNPs have gained increased attention because of their therapeutic applications, such as their promising role as anticancer agents [5]. Positive outcomes have been achieved when incorporating AgNPs into cancer treatments [6]. Here, we focus mainly on the recently reported therapeutic applications of AgNPs as virucidal agents and anticancer agents, and on the safety issues relating to the use of AgNPs in humans and their effects on the environment. We conclude by discussing the prospects for additional uses of AgNPs in the clinic.

Synthesis methods

Many routes have been introduced for the synthesis of silver nanostructures, which can be categorized as: (i) chemical methods [7–10]; (ii) physical methods [11–14], and (iii) biological methods [15–17]. Chemical methods for the syntheses of silver nanostructures can be subdivided into chemical reduction [7], electrochemical techniques [8], irradiation-assisted chemical methods [9], and pyrolysis [10]. The synthesis of silver nanostructures in solution usually contains three main components: metal precursors, reducing agents, and stabilizing/capping agents. Widely used reducing agents include borohydride, sodium citrate, ascorbic acid, alcohol, and hydrazine compounds. It has been reported that AgNPs supported on nanostructured SiO_2 were obtained by flame aerosol technology, which enables close control of Ag content and size [9]. Similarly, Ag/silica nanoparticles with relatively narrow size distribution were made by flame spray pyrolysis (flame aerosol technology) [10]. By contrast, physical methods do not involve toxic chemicals and usually have fast processing times. Such methods include physical vapor condensation [11], Arc-discharge [12], energy ball milling method [13], and direct current (DC) magnetron sputtering [14]. Another advantage of physical methods is that the AgNPs formed have a narrow size distribution [14]; however, a major drawback is their high energy consumption. In the biological synthesis of AgNPs, the toxic reducing agents and stabilizers are replaced by nontoxic molecules (proteins, carbohydrates, antioxidants, etc.) produced by living organisms, including bacteria, fungi, yeasts, and plants. Biological methods based on microorganisms such as bacteria [15], fungi [16], and yeast [17], have been widely reported. The cheaper plant systems, such as lemongrass, *Aloe vera*, seaweed, alfalfa, tea, neem, mustard, safeda, lotus, and tulsi, have been explored for the synthesis of AgNP. The possible mechanisms of biological synthesis include enzymatic (e.g., NADPH reductase) and nonenzymatic reduction [18]. In general, AgNP synthesis using plant extracts is the most-used environmentally friendly method of production.

Properties of AgNPs

Major physicochemical properties of AgNPs

Some physicochemical properties of AgNPs, including size (surface area), shape, surface charge and coating, agglomeration, and dissolution rate, are particularly important for determining their biological interactions and impacts. Smaller particles have a larger surface area and, therefore, have greater toxic potential [19]. It is well known that the shape of silver nanostructures can dramatically affect their physical and chemical properties. Frequently utilized silver nanostructures in the biomedical field include silver spherical nanoparticles, nanowires, nanorods, nanoplates, and nanocubes [20]. Studies have found that the biological effects of AgNPs depend on the different surface charges of their coatings, which can affect the interaction of AgNPs with living systems [21]. Agglomeration is known to occur with most engineered nanoparticles. It was shown that agglomeration of AgNPs occurs in culture media and within the cytoplasm and nuclei of $HepG_2$ cells [22]. Dissolution of AgNPs as a result of surface oxidation leads to the production of ionic silver. The rate of dissolution depends on the chemical and surface properties of the particle as well as its size, and is further affected by the surrounding media [23].

Localized surface plasmon resonance of AgNPs

The remarkable optical properties of silver nanostructures result from their unique interaction with light, which causes the collective coherent oscillation of their free conduction band electrons, or LSPR. Oscillation of the free electrons results in either radiative decay with a strong visible scattering of light or nonradiative decay, which causes the conversion of photon energy into thermal energy. These two decay mechanisms have been readily utilized in biodiagnostic and imaging (both exploiting radiative SPR decay), and therapeutic (exploiting nonradiative SPR decay) applications [24].

LSPR of AgNPs depends on the size, shape, dielectric environment, and mutual electromagnetic interactions among particles in close proximity [25]. These parameters can be used to tune the plasmon peak of AgNPs in the range of 393–738 nm [26] and 500–1000 nm [27]. Therefore, LSPR of AgNPs results in strong visible and near-infrared (NIR) scattering and absorption, which enables the development of photothermal and thermolytic laser therapies [6,28,29]. Moreover, it was revealed that AgNPs could enhance the effect of cancer cell killing in radiation treatment [30].

Toxicity of AgNPs

Impact on human health—There are several possible ways in which patients can be exposed to AgNPs, such as dermal contact, oral administration, inhalation, and blood circulation. Macrophages are the first cells that AgNPs will encounter in the human body [31]. It is known that the size of the AgNP dictates its mode of cytotoxicity to murine macrophages (Ag^+ ion-specific and/or particle-specific). The toxicity of AgNPs (<10 nm) is mostly mediated by the released Ag^+ ions, with liver being the major target organ, followed by spleen, lungs, and kidney. One study showed that the effect of both 20 nm and 100 nm AgNPs on Wistar-derived WU rats treated at 6 mg/kg body weight doses was an increase in spleen weight; moreover, the clinical chemistry parameters also indicated liver damage [32].

A separate study on the inhalation toxicity of AgNPs showed that AgNPs had an influence on the neutral mucins in the respiratory mucosa of Sprague–Dawley (SD) rats exposed to AgNPs at concentrations of 0.5–61 μg/m^3, yet without toxicological significance [33]. Notably, another study showed that AgNPs had negligible impact on the nasal cavity and lungs [34]. Furthermore, it was reported that levels of silver reported from nanomaterial-manufacturing workers exposed to silver concentrations of 0.35–1.35 g/m^3 were only 0.0135–0.034 mg/m^3 for blood and 0.043 mg/m^3 for urine, and there were no significant findings on their health status [35].

Although many toxicological studies using AgNPs have been published, it is still difficult to draw a definite conclusion about their toxicity. We can conclude that AgNPs might have different toxicological properties owing to the different synthesis methods, their various sizes, the presence or absence of capping agents, different organisms, and/or culture cells. Hence, their risks should be assessed on a case-by-case basis.

Impact on the environment—The toxicity of AgNPs to the environment depends on their chemical form and the availability of free silver ions. Once released into the environment, AgNPs are dispersed in different ways, which modifies their properties and alters their transport, fate, and toxicity. According to a study by Blaser *et al.* [36], silver can release into solid waste, which is disposed of in solid waste landfills or incinerated in thermal waste treatment (TWT), and wastewater, which is either treated in a sewage treatment plant (STP) or directly discharged into natural waters. Sewage sludge is applied to agricultural soils, disposed of in solid waste landfills, or incinerated in TWT. Solid waste landfilling might allow silver to leach into subsoil and groundwater. Additionally, immediate release to the environment originates from STP effluents, untreated wastewater, and silver contained in sewage sludge that is spread out on agricultural fields. Furthermore, the release of silver incorporated into textiles and plastics used in all 25 European Union countries was found to be in the range 110–230 t/yr in the three different emission scenarios [36].

It is most likely that AgNPs would react with sulfide, chloride, or other natural substances, altering the original properties of the nanoparticles. Levard *et al.* found that even a very low degree of sulfidation of AgNPs can result in a significant decrease in their toxicity because of the lower solubility of silver sulfide [37]. Meanwhile, Tiede *et al.* [38] also revealed that >90% of AgNPs were removed during wastewater treatment. Although the dissolution of AgNPs in the presence of chloride in aqueous solution has not been thoroughly investigated, toxicity of Ag^+ in the presence of Cl^- among various species of fish has been studied [39].

Overall, little is known about the specific effects of AgNPs on the environment. Therefore, it is currently impossible to assess reliably the environmental risks associated with the production and use of AgNPs.

Mechanism of AgNP-induced toxicity—The interactions between nanomaterials and cells, the cellular uptake, and subsequent toxic response of the cell are among the most crucial issues relating to AgNP-induced toxicity. For most cells, uptake of AgNPs mainly through endocytosis depends on time, dose, and energy, and the major target organelles are

endosomes and lysosomes [40,41]. Nanoparticles can induce reactive oxygen species (ROS) production directly once they are exposed to the acidic environment of lysosomes [42]. Additionally, Singh *et al.* also demonstrated the accumulation of Ag^+ in lysosomes [43]. ROS contain superoxide anions (O^{2-}), hydroxyl radicals (·OH) and hydrogen peroxide (H_2O_2). Reactions between H_2O_2 and AgNPs are thought to be one of the factors leading to Ag^+ release *in vivo*. The possible chemical reaction involves: $2Ag + H_2O_2 + 2H^+ \rightarrow 2Ag^+ + 2H_2O$ $E^0 = 0.17$ V [41]. The reaction can occur upon contact with cell culture medium or proteins in the cytoplasm. Furthermore, ROS are highly reactive and result in oxidative damage to proteins and DNA, and induce mitochondrial dysfunction. AgNPs and Ag^+ ions can also escape from lysosomes, further inducing the increase of intracellular ROS. AgNPs and released Ag^+ ions prefer to interact with the thiol groups of molecules present in the cytoplasm, cell membrane, and inner membrane of mitochondria, which might release lipid peroxide and increase permeation of the cell membrane and mitochondrial systems [40,44]. Damage to the cell membrane results in leakage of cytoplasmic contents and eventual necrosis, whereas rupture of lysosomal membranes activates lysosome-mediated apoptosis. Furthermore, damage to mitochondria impairs electron transfer, thereby activating mitochondrion-dependent apoptosis [45]. In addition, it has been reported that AgNPs could readily diffuse into, and translocate to, the nucleus through nuclear pore complexes, thereby leading to the formation of ROS, which directly trigger DNA damage and chromosomal abnormalities [41]. Recent studies also indicated that Ag^+ can directly lead to DNA damage in addition to damaging mitochondria and inducing ROS production [46].

Few studies have investigated gene expression induced via AgNPs. RT-PCR analysis [47] indicated that the upregulation of metabolism and oxidative stress genes by AgNPs might have increased the production of ROS as a byproduct of oxidation. AgNPs also significantly upregulate the gene encoding Thioredoxin-interacting protein (*Txnip*), inducing the intrinsic mitochondrial pathway of apoptosis. It was also found that the *Atr* gene, which senses DNA damage, was significantly upregulated in the caudate nucleus of mice exposed to AgNPs.

In brief, exposure to AgNPs causes cytotoxicity by elevating ROS levels and increasing lipid peroxidation; it also leads to genotoxicity by inducing DNA and chromosomal damage (Figure 1).

Key factors mediating toxicity of AgNPs—Toxicological investigations of AgNPs imply that, in addition to time, dose, and temperature, other factors, including particle size, shape, surface coatings, and cell type, could also influence the toxicity of AgNPs. In general, the toxicity of nanomaterials is related to their reactivity, which in turn depends on the nanoparticle size [48]. As reported elsewhere, the effect of AgNP size on macrophages was seen to affect cell viability, induction of oxidative stress, and release of cytokines [49]. To achieve stable AgNPs and reduce the potential risks of AgNPs on human cells and the environment, chemical modification of the AgNP surface with biological ligands has been investigated. It was shown that three organocoated AgNPs have different toxicity against two model organisms, *Escherichia coli* and *Daphnia magna*, that is dependent on the particle size, surface charge, and concentration [50]. Interestingly, Sotiriou *et al.* reported that coating AgNPs with a thin SiO_2 layer preserves their plasmonic performance and minimizes their toxicity by blocking ion release and bacteria and/or cell contact [51]. The

shape of AgNPs also has an important role in their toxic and immunological effects. Recently, George *et al.* [52] reported that plate-shaped AgNPs are comparatively more toxic against a fish gill epithelial cell line (RT-W1) and zebrafish embryos compared with sphere- or wire-shaped AgNPs because of the presence of surface defects. In addition, it was demonstrated that the human sperm cells exhibit a lower cytotoxic response to 8–10 nm AgNPs compared with human lymphocytes [53].

Generally, the smaller the size of AgNPs, the stronger cytotoxic effects they could have. Moreover, different surface coatings of AgNPs can trigger different events depending on the cell type.

Therapeutic applications of AgNPs

The function of AgNPs as antibacterial and antifungal agents has been well documented [54,55] and is not discussed here. Moreover, applications of AgNPs have been expanded to emerging fields, such as drug delivery and diagnosis. Here, we focus on their therapeutic applications as antiviral, photosensitizer and/or radiosensitizer, and anticancer agents.

AgNPs as virucidal agents

AgNPs have been shown to inhibit HIV-1, Tacaribe virus (TCRV), hepatitis B virus (HBV), recombinant respiratory syncytial virus (RSV), monkey pox virus, murine norovirus (MNV)-1, and influenza A/H1N1 virus. Table 1 summarizes the antiviral effects of AgNPs reported in recent publications. Park *et al.* [56] recently developed and evaluated a novel micrometer-sized magnetic hybrid colloid (MHC) decorated with variously sized AgNPs that could be used to inactivate viral pathogens ΦX174 and MNV with minimum chance of potential release into the environment. In addition, Xiang *et al.* [57] showed that AgNPs have beneficial effects in preventing A/Human/Hubei/3/2005 (H3N2) influenza virus infection both *in vitro* and *in vivo*. Another study [58] observed that AgNPs had better antiviral activity (80–90% inhibition) against Herpes simplex virus (HSV)-1 and human parainfluenza virus (hPIV)-3 and were less cytotoxic to Vero cells. In addition, it was found that AgNPs can inhibit the replication of Vaccinia virus (VACV) [59].

AgNPs as photosensitizers and/or radiosensitizers

LSPR of nanoparticles enables the use of AgNPs in nonionizing radiation and ionizing radiation. In a report by the Cai group, it was revealed that aptamer–Ag–Au shell–core nanostructures have a high ability to absorb NIR irradiation and are able to perform photothermal therapy of the A549 cells at a low irradiation power density (0.20 W cm^{-2}) without destroying the healthy cells and the surrounding normal tissues [28]. Moreover, it was reported that grapheneoxide@Ag-doxorubicin-DSPE-PEG2000-NGR (GO@Ag-DOX-NGR) showed excellent chemophotothermal therapeutic efficacy, tumor-targeting properties, NIR laser-controlled drug-releasing functions, and X-ray imaging ability in an *in vivo* murine tumor model [29]. Furthermore, it was revealed that hollow Au–Ag nanoshells (HGNS) showed potential for photothermal therapy because of their stability when PEGylated under laser illumination [6]. In addition, Zhao *et al.* [30] reported that Fe_3O_4/Ag/

C225 (epidermal growth factor receptor) combined with X-ray treatment could increase the sensitivity of human nasopharyngeal carcinoma cell lines (CNEs) to irradiation.

Potential therapeutic applications of AgNPs in cancer

AgNPs have proven promising antitumor effects. It was reported that a low concentration of AgNPs can cause DNA damage and chromosomal aberrations (genotoxicity), although no significant cytotoxicity was recorded [40]. However, Lima *et al.* showed that no genotoxicity effects were observed for different human culture cells treated with up to 10 mg/mL of capped AgNPs (diameter 6–80 nm) [60]. The generation of many toxicological data concerning nanoparticles sometimes creates a negative perception of their use. However, toxicity itself can be useful for cancer therapies because it is highly sought. Positive outcomes have been achieved when incorporating AgNPs into cancer treatments. They can not only passively interact with cells, but also actively mediate molecular processes to regulate cell functions. Table 2 summarizes the potential therapeutic applications of AgNPs in cancer reported in recent publications.

AgNPs as antiangiogenic agents—It is well established that angiogenesis has a central role in several diseases including cancer. Eom's group [61] reported AgNPs and a natural antiangiogenic molecule, PEDF, almost contributed equally to the inhibitory effects of vascular endothelial growth factor (VEGF)-induced angiogenesis by blocking PI3K/Akt phosphorylation at Ser-473 in bovine retinal epithelial cells (BREC) *in vitro*. In addition, it was revealed that the formation of new blood vessels is inhibited by AgNPs *in vivo*. Another study [62] by the same group also revealed that AgNPs showed cytotoxicity against Dalton's lymphoma ascites (DLA) cells *in vitro* and *in vivo* and significantly increased the survival time in the tumor mouse model by approximately 50% compared with tumor controls.

Application in leukemia—Leukemia is a group of cancers that usually begins in bone marrow and results in high numbers of abnormal white blood cells. Several investigators have reported that AgNPs induced a cytotoxic effect against leukemic cells, such as THP-1, Jurkat, and K562 cells. Recently, Guo *et al.* [46] found that poly(*N*-vinyl-2-pyrrolidone (PVP)-coated AgNPs could inhibit the viability of acute myeloid leukemia (AML) cells, including isolates from patients with AML at low concentrations, suggesting a novel approach for the treatment of AML in the future. Another study by the same group [63] demonstrated that AgNPs were able to enter K562 cells in a dose-dependent manner and localize within the endosomes.

Application in breast cancer—It has also been observed that AgNPs have dose-dependent cytotoxic effects in MCF-7 breast cancer cells through induction of apoptosis, with a concentration of 50% cell growth inhibition (LD_{50}) of 3.5 ng/mL and LD_{100} of 14 ng/mL [64]. More recently, Gurunathan *et al.* [65] found that AgNPs induced MDA-MB-231 cell death through ROS generation, activation of caspase 3, and DNA fragmentation. Further work by this group also indicated that single-crystalline AgNPs have cytotoxic effects with apoptotic features [66].

Application in hepatocellular carcinoma—An *in vitro* cytotoxic study conducted by Kim *et al.* [22] demonstrated that the cytotoxicity of AgNPs against human liver HepG2 cells is primarily the result of oxidative stress. Recently, Sahu *et al.* [67] revealed a significant concentration-dependent cytotoxicity of AgNPs in HepG2 cells and that a different mechanism of AgNPs-induced mitochondrial injury leads to the cytotoxicity. Notably, Faedmaleki *et al.* [68] showed that AgNPs had a 44-times stronger inhibitory effect on HepG2 cells compared with normal cells (primary liver cells of mice).

Application in lung cancer—AgNPs have also been shown to display cytotoxicity to lung cancer cells. Foldbjerg *et al.* [69] observed a dose-dependent reduction in mitochondrial function of human alveolar cell line A549 cells. It was shown that AgNPs are taken up by the cells, leading to increased production of ROS and ultimately apoptotic and necrotic cell death. Moreover, Nazir *et al.* [70] showed that AgNPs have effective anticancer properties against the H157 (squamous cell lung carcinoma) cell line with an IC_{50} of 3.6μM.

Application in skin and/or oral carcinoma—Work by the Nazir group showed that AgNPs have effective anticancer properties with an IC_{50} of 0.36μM against HT144 melanoma cell lines [70]. Recently, Austin *et al.* [71] demonstrated that the nuclear-targeting peptide-conjugated AgNPs cause DNA double-strand (ds) breaks and a subsequent increase in the sub-G1 (apoptotic) population in the HSC-3 cancer cell model at lower concentrations compared with nuclear-targeting gold nanoparticles (AuNPs).

Concluding remarks and future perspectives

In summary, silver nanoparticles exhibit particularly unique physical, chemical, optical, and biological properties that different from other biomedical nanomaterials and, thus, can serve as therapeutic platforms in many biomedical applications, including but not limited to: (i) antiviral agents; (ii) photosensitizers and/or radiosensitizers; and (iii) anticancer therapeutic agents in leukemia, breast cancer, hepatocellular carcinoma, lung carcinoma, and skin and/or oral carcinoma. However, despite their promising potential in medical applications, the impact of AgNPs on human health (both positive and negative) needs to be fully understood before their wider use. The successful translation of silver nanotechnology to the clinic requires the development of simple, safe, cost-effective, and eco-friendly preparations of AgNPs, and a fuller understanding of the safety control mechanisms as well as the biodistribution and pharmacokinetics of AgNPs in clinical applications.

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Highlights

1. AgNPs possess intrinsic therapeutic properties for biomedical applications.
2. AgNPs are employed in newly emerging applications as photosensitizers/radiosensitizers, antiviral and anticancer agents.
3. Treatment of a variety of cancers with AgNPs have been documented. with AgNPs.
4. The underlying anticancer mechanisms of AgNPs include (1) disruption of cell membranes, and (2) production of reactive oxygen species and Ag^+ to damage protein or DNA.
5. The photosensitizing mechanism of AgNPs is based on nonradiative decay converting photo energy to thermal energy.

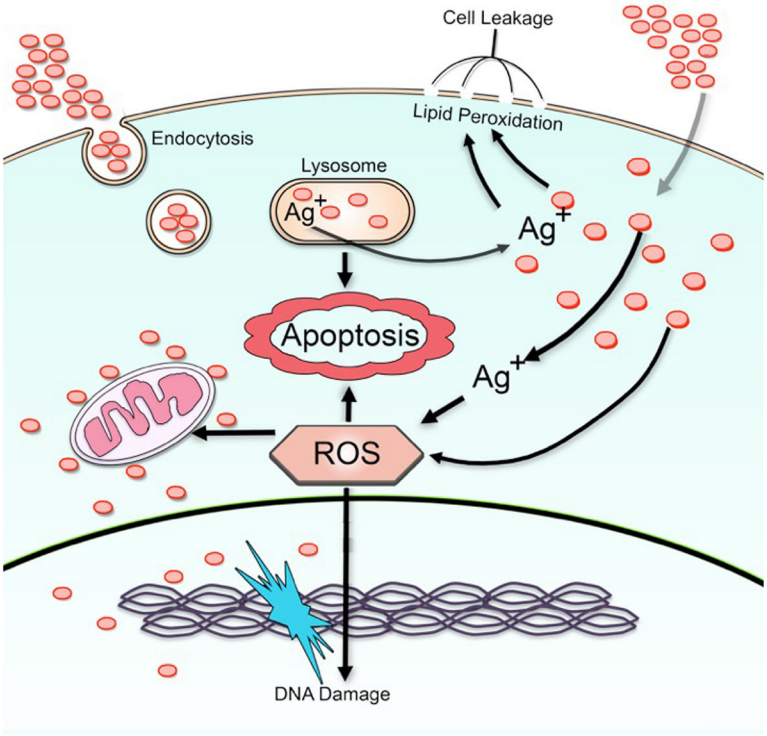

Figure 1.
Schematic representation of possible mechanisms for silver nanoparticle (AgNP)-induced cytotoxicity. The red circles denote AgNPs. Abbreviation: ROS, reactive oxygen species.

Table 1

Antiviral effect of AgNPs

Type	Size (nm)	Surface stability	Microbial strains	Function	Refs
AgNPs	1–10	Carbon, PVP and BSA	HIV-1	Size-dependent interaction with HIV-1; inhibits virus from binding to host cells	[55]
	10 and 25	None and polysaccharide	TCRV	Inhibits viral replication	[55]
	10, 50, and 800	None	HBV	Only 10-nm AgNPs inhibit replication of HBV	[55]
	N/A	PVP- AgNPs, recombinant RSV fusion (F) protein and BSA	RSV	44% inhibition of syncytial virus	[54]
	10–80	None or polysaccharide-coated	(MPV)	AgNPs of approximately 10 nm inhibit MPV infection *in vitro*	[55]
	11.2	biogenic Ag^0	MNV-1	Addition of 31.25 mg biogenic Ag^0 m^{-2} on the filter caused 3.8-log decline of the virus compared with 1.5-log decrease by original filter	[55]
	10	None	H1N1 influenza A virus	Rapidly inhibits H1N1 influenza A virus hemagglutination of chicken RBCs	[55]
AgNP@MHCs	7, 15, and 30	None	ΦX174, MNV, and AdV2	Inactivates viral pathogens with minimum chance of potential release into environment	[56]
AgNPs	9.5 nm	None	H3N2 influenza virus	Prevents H3N2 influenza virus infection both *in vitro* and *in vivo*	[57]
	4–13, 5–23, and 7–20	None	HSV-1, HSV-2, and HPIV-3	AgNPs with a size of 4–13 nm and 5–23 nm, had better antiviral activity against HSV-1 and HPIV-3 viruses	[58]
	25	None	VACV	Inhibits vaccinia virus replication by preventing viral entry	[59]

[a] Abbreviations: BSA: bovine serum albumin; N/A: not available..

Table 2

Anticancer effect of AgNPs[a]

Application	Cells and/or organisms	Size (nm)	Surface stability	Dose	Exposure time	Function	Refs
Antiangiogenesis	BREC/female C57BL/6 mice	40–50	None	IC_{50}: 500 nM; injection: AgNPs (500 nM)	24 h for cell assay; injection for 7 days	Inhibits formation of new blood vessels	[61]
	DLA/female Swiss albino mice	50	N/A	IC_{50}: 500 nM; intraperitoneal injection: AgNPs (500 nM)	24 h for MTT assay; injection of AgNPs for 15 days	Increased survival time, decreased volume of ascitic fluid in tumor-bearing mice by 65%, returning body weight to normal	[62]
Antileukemia	AML cells	3,11, and 30	PVP-AgNPs	0–10 μg/mL	24 h	11-nm AgNPs have significant inhibition effect with low IC_{50} (0.90 – 3.43 μg/mL) on six AML cells	[46]
	K562 cells	---	PVP-AgNPs	-----	---	Enters K562 cells in a dose-dependent manner and locates in endosomes	[63]
Antibreast cancer	MCF-7	NA	Grenetine-stabilized colloidal silver	LD50: 3.5 ng/mL	5 h	Dose-dependent cytotoxic effect in MCF-7 cells	[64]
	MDAMB-231	5	None	IC_{50}: 6.0 μg/mL	24h	Inhibits cell viability and induces membrane leakage	[65]
	MDAMB-231	2–10	N/A	IC_{50}: 8.7 μg/mL	24h	Inhibit the growth of cells in a dose-dependent manner	[66]
Antihepatoma	HepG2	5–10	None	IC_{50}: 3.38 μg/mL	28 h	AgNPs exhibited cytotoxicity with a potency comparable with that of Ag^+ ions	[22]
	HepG2	20	None	1–20 μg/mL	24 h	Oxidative stress did not have major role in observed cytotoxicity of AgNPs in HepG2	[67]
	HepG2 and primary liver cells of mice	20–40	None	IC_{50} 2.764 μg/mL for HepG2 cell line and IC_{50} 121.7 μg/mL for primary liver cells of mice	24 h	44 times stronger inhibitory effect on growth of HepG2 cell line compared with normal cells	[68]
Antilung caner	A549	30–50	PVP-AgNPs	0–20 μg/mL	24 h	Reduction in mitochondrial function	[69]
	H157	10–20	AgNPs capped with table sugar	IC_{50}: 3.6 μM	48 h	Remarkable inhibition on H157	[70]

Application	Cells and/or organisms	Size (nm)	Surface stability	Dose	Exposure time	Function	Refs
Antiskin/oral cancer	HT144	10–20	AgNPs capped with table sugar	IC_{50}: 0.36 μM	48 h	Remarkable inhibition on HT144	[70]
	HSC-3 and HaCat	35	Peptide–AgNP	0.1 nM	24 h	DNA ds breaks and a subsequent increase in the sub-G1 (apoptotic) population	[71]

[a] Abbbreviations: IC_{50}, the drug concentration that inhibited cell survival by 50%; LD_{50}, the concentration of 50% cell growth inhibition; N/A: not available.