



Metal Nanoparticles: a Promising Treatment for Viral and Arboviral Infections

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Abstract

Globally, viral diseases continue to pose a significant threat to public health. Recent outbreaks, such as influenza, coronavirus, Ebola, and dengue, have emphasized the urgent need for new antiviral therapeutics. Considerable efforts have focused on developing metal nanoparticles for the treatment of several pathogenic viruses. As a result of these efforts, metal nanoparticles are demonstrating promising antiviral activity against pathogenic surrogates and clinical isolates. This review summarizes the application of metal nanoparticles for the treatment of viral infections. It provides information on synthesis methods, size-related properties, nano-bio-interaction, and immunological effects of metal nanoparticles. This article also addresses critical criteria and considerations for developing clinically translatable nanosized metal particles to treat viral diseases.

Keywords Metal nanoparticle · Nanotherapeutics · Virus · Arbovirus · Treatment · Nanotechnology

Introduction

Nanotherapeutics has the potential to change the landscape of antiviral drug discovery and address issues related to resistance, emerging viruses, strain-specific targeting, and untreatable viral infections [1]. It uses nanoparticles (NPs) within the size range of 1–100 nm as a tool for drug delivery, diagnosis, and treatment of many infectious diseases [1–3]. Therapeutic NPs may be either inorganic (e.g., metal NPs) or organic (e.g., polymeric, liposomes, micelles, ferritin). Both types of NPs have been successful in pre-clinical studies and clinical settings for various medical conditions [4, 5]. Recently, progress in utilizing metal NPs as antiviral agents has advanced rapidly owing to the ability of metals having a multi-target “attack” on viruses, with minimal impact on the subsequent development of resistance [1, 6]. According to existing research, metal NPs have already proven to be active antiviral agents against human immunodeficiency virus (HIV), influenza virus, hepatitis virus, etc. [1, 6]. This review aims to discuss and highlight the synthesis, properties, reported antiviral activities, and immunological impact of metal NPs.

Synthesis of Metal Nanoparticles

There are wide arrays of physical, chemical, and biological methods to synthesize NPs [7]. In these methods, a three-component reaction of precursors, reducing agents, capping, or stabilizing agents is required [8]. Below is an overview of these methods.

Physical Method

The physical method for the synthesis of NPs include techniques such as ultraviolet (UV) radiation, microwave irradiation, sonochemical, thermal decomposition (thermolytic), photochemical, laser ablation, and radical induction [7, 9]. These techniques mainly utilize the top-down approach, prevent solvent contamination, and yield monodisperse NPs [9]. Synthesis proceeds from the evaporation of metal atoms to rapidly controlled condensation in which the metal atoms rearrange and aggregate to form small clusters of NPs [7]. Unfortunately, the abundant waste generated by physical methods for NP synthesis appears to be economically unfavorable [9].

Chemical Method

Chemical synthesis of metal NPs involves the bottom-up approach [7] with techniques such as the sol-gel method, microemulsion, hydrothermal synthesis, polyol synthesis,

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and chemical vapor synthesis [9]. Nanoparticles of well-defined size, dimension, composition, and structure are produced through chemical methods [10]. The synthesis mechanism entails reducing metal ions by chemical reductants or decomposition of metal precursors with extra energy in the presence of a stabilizer [7]. Inorganic and organic solvents are frequently used as reducing agents [11]. Stabilizing agents (i.e., organic solvents, synthetic, or natural polymers) are also used to prevent agglomeration of metal NPs. Alternatively, surfactants containing functionalities (e.g., thiols, amines, acids, and alcohols) may also act as a stabilizer and protect particles from sedimentation, agglomeration, or losing their surface properties [12]. Despite the appealing advantages of chemically synthesized NPs, there may be essential disadvantages such as environmental pollution, NP unsuitability for specific biomedical applications, and the use of toxic and non-biodegradable chemicals [7, 13].

Biological Method

Biological synthesis of metal NPs depends on the bottom-up approach that employs unicellular and multicellular biological organisms (e.g., actinomycetes, bacteria, viruses, fungus, yeast, algae, and plants) [7, 14, 15]. Biogenic NPs are eco-friendly, quickly produced in large quantities, biocompatible, and of well-defined size and morphology [7, 16]. Several controlling factors influence the size, morphology, nucleation, and stability of biogenic NPs. These factors include pH, temperature, reactant concentration, synthesis time, etc. [17]. Microorganisms can produce metal NPs through either intracellular or extracellular routes. For example, metal ions transported into the microbial cell and trapped on the cell surface are enzymatically reduced to intracellularly and extracellularly synthesized NPs, respectively [14, 18]. Plant-based viruses such as cowpea chlorotic mottle virus (CCMV), cowpea mosaic virus (CPMV), brome mosaic virus (BMV), and tobacco mosaic virus (TMV) are used as biological templates to fabricate nanomaterial. The advantages of using plant viruses for nanomaterial synthesis include their small size, symmetric structure, ease of functionalization, monodispersity, and ability to self-assemble. Plant viruses are also non-infectious to humans and animals [19, 20]. Biological extracts from leaves, flowers, stems, seeds, and roots of various plant species are also considered safe and environmental friendly for metal NP synthesis. In plant extracts, the existing metabolites (i.e., sugars, terpenoids, alkaloids, phenolic acids, proteins) are primarily responsible for the bioreduction of metal ions for the formation of stable NPs [7, 17]. In order to avoid environmental toxicity, cytotoxicity, and carcinogenicity, biological methods are preferred [7, 21].

Size-Related Properties and Nano-bio-interaction of Metal Nanoparticles

Metal NPs exhibit properties and catalytic activity that is size dependant and influenced by their metal ion [22]. These properties include physical [23], chemical, biological [24], mechanical [25], optical, magnetic [26], etc. The smaller the size of the NP, the higher the melting point, thermal conductivity performance, and viscosity [23]. Surface area and surface free energy are increased in smaller size NPs compared with the larger size, which results in changes in interatomic spacing [23]. The optical band gap energy increases with the decrease in particle size. Therefore, metal NPs in colloidal solution appear in a variety of colors that are size and shape related due to the surface plasmon resonance [23]. The presence of a higher specific surface area, heterogeneous catalysis [27–29], and metal ions, such as transitional [30, 31], in smaller sized NPs, is considered advantageous for catalytic support.

Furthermore, the biological activities (i.e., antibacterial, antiviral, antifungal, and anticancer) of NPs significantly increase with decreasing particle size [1]. Besides, the reduced particle size offers the possibility of intravenous administration of poorly soluble NPs without any blockade of the blood capillaries [23]. The biological activities of NPs also depend on their metal ions, shape, zeta potential, concentration, and method of preparation [1, 32]. In some instances, to stabilize and functionalize, metal NPs such as gold, silver, copper, palladium, and platinum ligands are used, due to their strong affinity towards the bare metal surfaces [33]. The binding affinity of ligands to cellular receptors increases proportionally with the size of the NPs because of the high protein content present on the surface of the NPs. The particle size is considered as the most crucial factor influencing cellular uptake and accumulation behaviors. Nanoparticles ranging from the size of 30–50 nm interact efficiently with cell membrane receptors and subsequently accumulate internally via receptor-mediated endocytosis. However, the optimal size for particle uptake is probably 50 nm since these sized particles offer a direct balance between the multivalent cross-linking of membrane receptors and the receptor-mediated endocytosis process [34]. In addition to size, the shape, composition, and surface charge of the NPs also influence cellular uptake and accumulation [32, 33]. Rod-shaped NPs tend to accumulate more than disc, spherical, cylinder, and cubed-shaped particles [32, 35]. Also, positively charged NPs achieve higher cellular uptake and accumulation internally by negatively charged cell membranes compared with neutral and negatively charged NPs [32].

Antiviral Activity of Metal Nanoparticles

The efficacy and antiviral activity of metal NPs depend on their size, shape, and metal ions. Notably, capped metal NPs present a significantly enhanced interaction with viruses and host cells than naked NPs [6]. The identified mechanisms of action for metal NPs can occur either inside or outside the host cells. These include the NP interacting with the gp120 proteins, competing with the virus for host cell-binding sites, interfering with the viral attachment, and blocking the virus-host binding or penetration. Other potential mechanisms of action involve inactivating the virus particles before cellular entry, interacting with the viral genome or binding to the viral particles. Furthermore, the intracellular compartment of an infected cell is abundant in virally encoded and host cellular factors required for viral replication and production of progeny virions. Therefore, the interaction of metal NPs with these replication factors is another antiviral mechanism of action [1, 6, 36].

Metal NPs, particularly silver and gold, have proven to exhibit antiviral activity against different viruses. The antiviral mechanism for gold NPs includes blocking of the gp120 attachment with CD4 to inhibit viral entry, whereas the antiviral mechanism of silver NPs involves inhibiting viral entry, attachment, or replication. For instance, silver NPs inhibit CD4-dependant virion binding, merging, and pathogenesis by interacting with the viral gp120 in the cell-free and cell-associated virus. In double-stranded RNA viruses, the silver NPs, after interaction with the viral genome, will inhibit viral replication [1, 6, 36]. Other metal NPs such as copper block the virus attachment, inhibit virus-cell binding, and viral entry into target cells. Copper NPs also destroy the viral genome and disrupt the capsid. Zinc NPs interfere with viral DNA polymerase activity resulting in viral replication inhibition. The inhibition of viral entry to the target cells depends on the ability of zinc NPs to bind to the virions. Iron NPs preferentially bind to the virus to inhibit it from binding to the cells. However, selenium NPs effectively protect the target cells from apoptosis caused by the infection of the virus [1, 6, 36].

Immunological Effects of Metal Nanoparticles

Metal NPs can interact with immune cells, such as macrophages, monocytes, dendritic cells, and lymphocytes, and potentially elicit modified immune responses [37]. However, the capacity of any metal NP to elicit an immune response depends on their physicochemical properties such as size, size distribution, surface area and reactivity, crystallinity, aggregation in a suitable medium, composition, surface coating, method of synthesis, and impurities [38, 39]. These immune responses include immunostimulation, immunosuppression, hypersensitivity, immunogenicity, and autoimmunity,

comprising of both innate and adaptive immune responses [38, 40]. Therefore, the unexpected interaction with the immune system and modulation of the immune function by NPs can be beneficial or detrimental. In the future, metal NPs can be designed to be immunomodulatory to serve specific functions (e.g., vaccine adjuvants, anti-inflammatory, pro-inflammatory drugs) and improve the nanotreatment of infectious diseases. However, engineered immunomodulatory or conventional metal NPs that modify the immune system must reconcile with concerns about biocompatibility and immunotoxicity of nanomaterial [40–42].

Elevated cytokine levels, particularly pro-inflammatory, upon treatment with NPs have been associated with immunotoxicity and low therapeutic efficacy. At times, the elevation of both pro-inflammatory (e.g., IL-6 and TNF- α) and anti-inflammatory (e.g., IL-10) cytokine levels because of an unregulated innate immune response (i.e., cytokine storm) has made it more difficult to understand the underlying mechanisms of immunotoxicity [40, 43]. Therefore, metal NP purification is essential for removing iron contaminants and endotoxins that contribute to stimulating cytokine storms and exaggeration of inflammatory reactions. Nanoparticles may also generate large quantities of ROS that can trigger TNF receptors, resulting in the release of pro-inflammatory cytokines through the activation of the NF- κ B transcription factor. In some cases, the inflammatory effect and release of cytokines can be inhibited by an enzyme, catalase, that protects against oxidative stress by catalyzing hydrogen peroxide decomposition into oxygen and water [43]. Nonetheless, a better understanding of the underlying interactions between metal NPs and the immune system is essential for the development of biocompatible, non-immunotoxic, and non-immunogenic nanomaterials for a variety of biomedical applications.

Antiviral Potential of Metal Nanoparticles Against Different Viruses

In recent years, there have been several reports on the antiviral activity of metal NPs, which are discussed below in detail and summarized in Table 1.

Adenoviruses

Human adenoviruses (HAdVs) are ubiquitous DNA viruses that possess a broad spectrum of pathogenicity. This virus is also associated with respiratory, gastrointestinal, urinary, and ocular illnesses in adults, infants, and immunocompromised individuals [44, 45]. Clinical treatment of HAdV infections focuses on alleviating the patient's symptoms or the use of antiviral drugs, such as ribavirin and cidofovir for HAdV severe infections in immunocompromised individuals [44, 45]. Despite the encouraging treatment outcomes of cidofovir,

Table 1 Antiviral activity of metal nanoparticles

Virus	Type of metal nanoparticle	Average size of nanoparticle (nm)	Method of synthesis	Infected cell/animal model	Treatment strategy	Effective antiviral concentration	SI	References
Adenovirus	Silver	11.4	Chemical reduction	HeLa cells (cervical cancer)	3.125–400 µg/mL; 2 h	EC ₅₀ : 9.3 g/mL	-	[47]
	Gold coated with silicon dioxide shell	5	Sol-gel	MDBK (Madin-Darby bovine kidney) cells	200 µl (10-fold dilution); 3–7 days	IC ₅₀ : dilution 10 ⁻⁶	-	[48]
	Gold pitted with silicon dioxide shell	100	Grafting	Hep-2 (larynx epidermoid carcinoma) cells				
	Tungsten carbide	10–20 nm	Plasma atomization	A549 cells (human lung carcinoma)	100 mg/mL; 5–60 min	3.5 log reduction: 100 mg/mL	-	[49]
Coronavirus	Silver NP-graphene sheet	5–25 nm	Chemical	Fewf-4 cells (Felis catus whole fetus)	0.1, 1, 10, 100 mg/mL; 96 h	IC _{24,8} : 0.1 mg/mL	-	[57]
	Glutathione-capped silver sulfide	5.3 nm	Chemical	Vero cells (African green monkey; kidney epithelial)	46 µg/mL; 12 h	Reduced viral particles from 3.8 × 10 ⁵ to 2.5 × 10 ² PFU/mL; 46 µg/mL	-	[56]
	Gold nanorod-based HR1 peptide	54 nm (length) 18 nm (diameter)	Chemical Solid phase	293 T/MERS/EGFP cells and Huh-7 cells (human embryonic kidney and human liver)	0–20 µM; 0–12 h	IC ₁₀₀ : 1.171 µM	-	[55]
	Silver nanocluster with silica composite sputtered coating	Less than 200 nm	Radio frequency co-sputtering process with argon	Silver nanocluster/silica composite coating deposited on a facial FFP3 mask	Different silver concentrations; 72 h	100% inhibition	-	[58]
Coxsackievirus	Silver	57–146	Biological (plant extracts)	Vero cells	125, 250, and 500 µg/mL; 48 h	IC ₅₀ : 344–375 µg/mL	40	[62]
	Silver	8.91–27.89	Biological (plant extracts)	Vero cells	5.28–520.6 µg/mL; 48 h	IC ₅₀ : 12.74 µg/mL IC ₅₀ : 29.04 µg/mL	-	[63]
Enterovirus	Selenium (functionalized with oseltamivir)	10	Chemical	U251 cells (human astrocytoma)	9.8 µM of NPs (incl. 20 nM oseltamivir); 24–48 h	9.8 µM (incl. 20 nM oseltamivir)	-	[64]
	Selenium	100	Chemical	Vero cells	15.625 µM; 48 h	15.625 µM	-	[65]
Chikungunya	Silver	64–151	Biological (plant extract)	Vero cells	1000–31.25 µg/mL; 5 days	62.5 µg/mL	-	[75]
	Silver	50–120	Biological (plant extracts)	Vero cells	7.81–1000 µg/mL; 5 days	31.25, 125, and 250 µg/mL	-	[76]
	Zinc oxide	-	Precipitation method	MA104 cells (African green monkey fetal kidney)	0.5–6.5 pg/mL; 4 days	10-fold decrease in viral load: 2.5 pg/mL	-	[77]
Dengue	Gold-small interfering RNA	12.92–43.25 nm	Chemical	Vero cells	20–80 nM; 48–72 h	80 nM	-	[105]
	Silver	30–70 nm	Biological (plant extract)	Vero cells	10–100 µg/mL; 48 h	30 µg/mL	-	[108]
	Silver	35–65 nm	Biological (algae)	Vero cells	6.25–50 µg/mL; 48 h		-	[107]

Table 1 (continued)

Virus	Type of metal nanoparticle	Average size of nanoparticle (nm)	Method of synthesis	Infected cell/animal model	Treatment strategy	Effective antiviral concentration	SI	References
Herpes simplex	Silver	100 nm	Biological (seed extract)	Vero cells	10–40 µg/mL; 6, 24, 24 h	IC ₈₀ : 50 µg/mL IC ₅₀ : 12.5 µg/mL 20 µg/mL	-	[109]
	Gold	-	Biological (seaweed extract)	Vero cells	2.5, 5, 10, and 25 µL, 72 h	HSV-1: 10 µL HSV-2: 25 µL	-	[117]
	Silver	-	Biological (seaweed extract)	Vero cells	0.5, 1, 2.5, and 5 µL; 72 h	2.5 µL	-	[117]
	Silver-tannic acid	24 nm	Chemical reduction	C57BL/6 mice	100 µL; 10 days	100 µL	-	[120]
	Gold-3-mercaptopropylsulfonate (MES) and heparin	2.8 nm	Chemical reduction	Vero cells	0.1–100 µg/mL; 24 h (HSV-1) and 48 h (HSV-2)	HSV-1 EC ₅₀ : 10.9 µg/mL HSV-2 EC ₅₀ : 1.61 µg/mL CC ₅₀ : > 300 µg/mL	HSV-1 > 27- 52 HSV-2 >	[118]
Human immunodeficiency virus (HIV)	Zinc oxide-rich in hydroxyl group (H-ZNPs)	5–7 nm	H-ZNPs: co-precipitation OA-ZNPs: chemical C-ZNPs: chemical	Vero cells	0.1 and 0.24 mg/mL; 1, 2, 4, and 24 h	EC ₁₀₀ : 0.01 mg/mL (C-ZNPs; H-ZNP) EC ₈₅ : 0.01 mg/mL (OA-ZNPs)	-	[115]
	Chitosan (C-ZNPs)	40 nm	Commercially produced	Vero cells	20–100 µg/mL; 48 h	EC ₈₀ : 100 µg/mL	-	[113]
	Copper oxide	7.86 nm	Ultrasound induced rapid reduction of gallic acid (GA)	Vero cells	Different concentrations; 72 h	HSV-1 EC ₅₀ : 32.3 µM HSV-2	HSV-1 30.10 HSV-2	[119]
	Silver	30–40 nm	Commercially produced	Vero cells	6.25–200 µg/mL; 48 h	EC ₅₀ : 38.6 µM EC ₃₀ : 25 µg/mL	25.19 > 4	[121]
	Silver	24–53 nm	Biological (fungi)	Vero cells	0.1–10 µg/mL; 48 h	EC ₅₀ : 1–5 µg/mL	-	[122]
	Copper Oxide	45.4 nm	Chemical reduction	Huh7.5.1 cells (human hepatic)	0.5–8 g/mL; 72 h	1, 2, and 4 µg/mL	-	[114]
	Zinc Oxide-PEGylated	20–50 nm	Commercially produced	Vero cells	2.5–200 µg/mL; 48 h	2.5 log reduction: 200 µg	-	[116]
	Silver-sodium 2-mercaptoethane sulfonate (Ag-MES)	-	Sonochemical	HeLa cells	1–10 µg/mL; 72 h	EC ₅₀ : 5 µg/mL	-	[124]
	Silver-sodium 2-mercaptoethane sulfonate (Ag-MES)	-	Sonochemical	HeLa cells	1–10 µg/mL; 72 h	EC ₅₀ : 5 µg/mL	-	[124]
	Silver-dendrimer conjugates	70–90 nm	Chemical reduction	HEK293T cells	20, 40, 80, 120 µM; 72 h	IC ₅₀ : 40 µM	0.96	[132]
	46.8 nm	Micellar approach	HTHU cells (Microglial)	5 and 8 mg/mL; 48 h	8 mg/mL	-	[135]	

Table 1 (continued)

Virus	Type of metal nanoparticle	Average size of nanoparticle (nm)	Method of synthesis	Infected cell/animal model	Treatment strategy	Effective antiviral concentration	SI	References
	Mesoporous curcumin encapsulated in iron-phenanthroline Gallium	-	Commercially produced	THP-1 macrophages	25–300 μ M; 15 days	300 μ M	-	[131]
	Glucon particle encapsulated gallium NP	< 30 nm	Low desorption	PBMC (primary peripheral blood mononuclear)	26, 108, 150, and 355 μ g Ga/mg glucan particle; 7 days	EC ₅₀ : 108–355 μ g Ga/mg glucan particle	-	[130]
	Silver	12–28 nm	Biological (leave extract)	-	0.25, 0.5, 0.75, and 1 μ g/mL	IC ₅₀ : 0.4 μ g/mL	-	[178]
	Gold-synthetic (oligo) mannosides (Te-10 and Te-50)	100 nm	Chemical	TZM-bl cells (HeLa cell derivative)	2, 4, 5.5, 11 μ M	Te-10: 11 and 5.5 μ M Te-50: 4 and 2 μ M	-	[129]
	Gold	17 nm	Modified method of Turkevich	HeLa-CD4-LTR-B-gal	0.01–0.8 mg/mL; 48 h	IC ₅₀ : 1.12 mg/mL	-	[128]
	Silver-curcumin	45 nm	Biological	ACH-2 cells (acute lymphoblastic leukemic T cell)	20–200 μ l; 24–48 h	100 μ L	-	[134]
Hepatitis	Silver	8.91–27.89 nm	Biological (plant extracts)	Vero cells	5.28–520.6 μ g/mL; 48 h	IC ₅₀ : 520.6 μ g/mL IC ₅₀ : 36.36 μ g/mL	-	[63]
Influenza	Cuprous oxide	45.4 nm	Solution phase	Huh 7.5.1 cells	2 μ g/mL; 7 days	> 0.2 μ g/mL	-	[114]
	Selenium	200 nm	Chemical reduction and dialysis	MDCK cells	15.6 μ M; 48 h	15.6 μ M	-	[144]
	Selenium-ribavirin	< 100 nm	NPs-commercially produced	MDCK cells	0.001–1 nM with 0.03–5% FluPep ligand; 48 h	Gold-FluPep IC ₅₀ : 0.03% and 0.073 nM	-	[146]
	Gold-FluPep	10 nm	conjugate-mixed matrix ligands	MDCK cells	31.25–500 μ g/mL; 48 h	Silver-FluPep IC ₅₀ : 0.03% and 0.14 nM	-	[147]
	Silver-FluPep	25–55 nm	Biological (bark extract)	Vero cells	6.25–200 μ g/mL; 48–96 h	IC ₅₀ : 12.5 μ g/mL	-	[148]
	Silver	10 nm	-	MDCK cells (Madin-Darby canine kidney)	12.5, 25, and 50 μ g/mL; 48 h	IC ₇₈ : 12.5 μ g/mL	-	[149]
	Silver	9.5 nm	Oxidation-reduction method	MDCK cells	2.5 μ g/mL; 24 h	2.5 μ g/mL	-	[145]
	Silver	3–2 nm	Chemical reduction and dialysis	MDCK cells	0.005–0.25 M; 24 h	0.25 M	-	[150]
	Silver-oseltamivir	5–15 nm	Ultra-sonication-assisted method (plant extract)	MDCK cells	0.5–6.5 pg; 4 days	IC ₅₀ : 1.1 pg	-	[143]
	Silver	10–15 nm	Chemical reduction and magnetic separation	MA104 cells (embryonic rhesus monkey kidney)	0.0083–1.66 μ M	IC ₅₀ : 0.083 μ M	-	[154]
Norovirus	Iron oxide	10–15 nm	Chemical reduction and magnetic separation	MA104 cells (embryonic rhesus monkey kidney)	0.5–6.5 pg; 4 days	IC ₅₀ : 1.1 pg	-	[143]
	Gold-core	2–5 nm	Chemical reduction and magnetic separation	MA104 cells (embryonic rhesus monkey kidney)	0.0083–1.66 μ M	IC ₅₀ : 0.083 μ M	-	[154]

Table 1 (continued)

Virus	Type of metal nanoparticle	Average size of nanoparticle (nm)	Method of synthesis	Infected cell/animal model	Treatment strategy	Effective antiviral concentration	SI	References
	Copper sulfide		Seeded growth method and core coating with CuS nanoshell	Norovirus GI.1 (Norwalk) virus-like particles as a model viral system				
	Silver	10, 75, 110 nm	Chemical reduction	CRFK cells (Crandell-Rees feline kidney)	25, 50, and 100 µg/mL; 15 and 30 min; and 1, 2, and 4 h	50 and 100 µg/mL (10 nm)	-	[156]
	Silver NP films	1.1 µm	Chemical reduction, coating, electrospinning technique	RAW 264.7 cells (mouse leukemic macrophage)	2.1 and 21 mg/L; 24 h	0.86 log reduction	-	[158]
	Anatase titanium dioxide	0.5–45 nm	Sol-gel	RAW 264.7 cells	2 and 20 µg/mL; 24 and 48 h	IC ₅₀ : 20 µg/mL	-	[155]
	Tungsten carbide	10–20 nm	Plasma atomization	RAW 264.7 cells	100 mg/mL; 5–60 min	3.5 log reduction: 100 mg/mL	-	[49]
	Silver NPs on magnetic hybrid colloid (MHC)	500 nm (silver NPs: 7, 15, 30 nm)	Chemical and magnetic separation	RAW 264.7 cells	4.6×10^7 , 4.6×10^8 and 4.6×10^9 particles/mL of MHC; 1–6 h	2 log reduction: 4.6×10^9 particles/mL	-	[157]
Poliovirus	Silver	7.1 nm	Electrochemical	RD cells (Human rhabdomyosarcoma)	3.13–50 ppm; 30 and 60 min	3.13 ppm	-	[162]
	Tungsten carbide	10–20 nm	Plasma atomization	BGM cells (buffalo green monkey kidney)	4.6×10^7 , 4.6×10^8 and 4.6×10^9 particles/mL of MHC; 1–6 h	3.5 log reduction	-	[49]
Respiratory syncytial virus infection (RSV)	Silver NPs coated with polyvinylpyrrolidone	10 nm	Commercially produced	A549 cells	10, 25, and 50 µg/mL; 24 h	Decreased viral replication by 79% (A549) and 78% (HEp-2); 50 µg/mL	-	[168]
	Silver NPs-curcumin	13.69 nm	Biological (curcumin)	HEp-2 cells	0.008–0.24 nM; 24–72 h	0.008–0.12 nM	-	[167]
Rift Valley fever virus	Silver	35 nm	Commercially produced	Vero cells	4.8–12 µg/mL; 24–72 h	Reduced 98% of infectivity: 12 µg/mL	-	[174]
Rubeola virus	Gold	6 nm	Biological (garlic extract)	Vero cells	0.03–10 µg/mL; 72 h	EC ₅₀ : 8.829 µg/mL	16.05	[177]

therapeutic use is limited due to its low bioavailability and nephrotoxic effects [44, 46].

Silver, gold, and tungsten carbide NPs have been evaluated as potential therapeutics for the treatment of human adenovirus infections. Chen et al. [47] reported that silver NPs exhibited dose-dependent inhibitory activity on adenovirus in vitro. The half-maximal effective concentration (EC_{50}) of the studied silver NPs against virally infected cells after 2 h of incubation was 9.3 g/mL, and this concentration was not toxic to uninfected cells [47]. Lysenko et al. [48] synthesized two types of gold NPs as antiviral agents against adenovirus. Gold NPs coated with silicon dioxide shells and gold-silicon dioxide carrier NPs reduces the associated toxicity effects of gold ions. Both types of NPs showed to be effective against adenovirus with 96% and 100% inhibition. Pfaff et al. [49] showed that tungsten carbide NPs could reduce the infectivity of adenovirus type 5 by 50% in 15 min. These NPs also displayed significant antiviral activity against other types of viruses such as modified vaccinia virus Ankara (MVA), poliovirus, and norovirus. In this regard, these NPs might be utilized as an effective nanotechnology-based disinfectant [49].

Coronavirus

Coronavirus (CoV) is an enveloped positive-sense RNA zoonotic virus [50]. In humans, it consists of a wide range of viruses contributing to the common cold and severe respiratory diseases such as the Middle East respiratory syndrome (MERS), severe acute respiratory syndrome (SARS), and novel coronavirus [51]. Epidemics of coronavirus emerge unexpectedly and spread quickly, causing an unusually high death toll, threatening human health and daily activities. These include the SARS-CoV and MERS-CoV epidemic in 2003 and 2012, respectively [51]. To date, the coronavirus disease 2019, (COVID-19) pandemic, is accelerating in infection and mortality rates worldwide [51]. The causative agent is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), with no specific treatment or vaccine found to be successful in treating infected individuals [51].

Nanotechnology has received considerable attention from scientific communities as a vaccine [52], treatment, diagnostic, and protective source to combat coronavirus [51, 53, 54]. A recent study by Huang et al. [55] validated a new gold nanorod-based HR1 peptide inhibitor (PIH-gold NRs) for MERS. At a concentration of 1.171 μ M, PIH-gold NRs exhibited a 10-fold higher inhibitory activity than treatment with the peptide inhibitor only. Besides, at the same concentration, PIH-gold NRs completely inhibited cell fusion. This study further concluded that their newly developed PIH-gold NRs are biocompatible, biostable, and a highly effective anti-MERS agent [55]. Du et al. [56] validated that glutathione-capped silver sulfide nanoclusters, 5.3 nm in size, are active against porcine epidemic diarrhea virus (PEDV), a

coronavirus model. Treatment with a concentration of 46 μ g/mL for 12 h reduced plaque formation unit (PFU) from 3.8×10^5 to 2.5×10^2 per mL. This study also proposed that treatment with the studied nanoclusters inhibited PEDV infection by activating the production of IFN-stimulating genes (ISGs) and pro-inflammatory cytokines. These nanoclusters also prevented viral replication and budding [56]. Therefore, these results have paved the way for further research on other metal NPs (i.e., copper, zinc) to combat coronaviruses infections, such as COVID-19.

Researchers have also investigated the application of silver NPs to decrease the transmission of viruses in personal protection equipment. Graphene-silver nanocomposites, at a concentration of 0.1 mg/mL, inhibited 24.8% of infection by 4.7×10^4 TCID₅₀ (tissue culture infective dose required to kill 50% of the infected host) per mL of feline coronavirus [57]. Silver nanocluster silica composite sputtered coating applied to the facial FFP3 mask, ultimately reduced the titer of SARS-CoV-2 to zero [58]. Therefore, applications of NPs for personal protection equipment to decrease the transmission of coronaviruses and other viruses require further consideration.

Coxsackievirus and Other Enteroviruses

Coxsackievirus is an enterovirus, associated with the hand, foot, and mouth disease (HFMD), acute febrile illness in children, acute localized exanthema, myocarditis, hepatitis, and pancreatitis. Intrauterine infection and fetal demise are also coxsackievirus-related infections during pregnancy [59, 60]. There are no specific antiviral therapies available. Therefore, the preferred treatment regimen includes medication to reduce symptoms and manage pain [59, 61]. Salem et al. [62] found that silver NPs with aqueous leave and fruit extracts from *Ricinus communis* inhibited Coxsackievirus at half-maximal inhibitory concentrations (IC_{50}) of 344 to 375 μ g/mL, possibly by acting as a fusion inhibitor. Haggag et al. [63] found that silver NPs with extracts from *Lampranthus coccineus* showed significant antiviral activity against Coxsackievirus at an IC_{50} of 12.74 μ g/mL. Furthermore, molecular docking findings predicted that an existing interaction between the biosynthesized NPs and Coxsackievirus 3c protease was responsible for the antiviral activity [63].

Selenium NPs were found to be active against enterovirus. Also, selenium NPs conjugated with oseltamivir inhibited enterovirus activity by reducing the production of ROS in human astrocytoma cells [64]. Li et al. [65] reported that selenium NPs inhibited the Jun amino-terminal kinase (JNK) signaling pathway, p38 kinase, and ROS production, resulting in reducing the viral protein synthesis and viral yield [66] and controlling ROS [67], which promoted antiviral activity against enterovirus.

Chikungunya Virus

Chikungunya is a febrile disease caused by positive-sense single-stranded RNA alphavirus in the *Togaviridae* family. The virus is transmitted primarily by the mosquito belonging to the *Aedes* genus [68, 69]. The common symptoms include muscle pain, headache, nausea, fatigue, and rash. The virus can cause acute, subacute, or chronic disease. Complications such as eye, heart, neurological, and gastrointestinal are commonly seen in infants, adults with comorbidities, and elderly patients [70–72]. Occasionally, co-infections with other mosquito-borne viral infections such as dengue and Zika present an additional challenge during differential diagnosis and treatment [73]. There are no specific antivirals or vaccines available for chikungunya, except for symptomatic treatment [70]. Alternatively, control of the mosquito vector becomes the primary target for the effective management of chikungunya [74].

Metal NPs have also been reported to have potential antiviral and larvicidal activity against vector-borne diseases such as chikungunya. For example, Kaushik et al. [75] investigated silver NPs capped with plant extracts (*Carica papaya*), as an antiviral agent for chikungunya infection using Vero cells. The reported maximum non-toxic dose (MNTD) and $\frac{1}{2}$ MNTD of silver NPs were 125 $\mu\text{g/mL}$ and 62.5 $\mu\text{g/mL}$, respectively. A concentration of 62.5 $\mu\text{g/mL}$ of NPs induced 52% inhibition against chikungunya virus [75]. Similarly, the anti-chikungunya activity of silver NPs capped with extracts from *Andrographis paniculata* was reported, with a concentration of 31.25 $\mu\text{g/mL}$ (MNTD) and 15.63 $\mu\text{g/mL}$ ($\frac{1}{2}$ MNTD) exhibiting 75–100% and 25–49% inhibition of cytopathogenic effects (CPE) respectively [76]. Treatment with low concentrations of zinc oxide (2.5 $\mu\text{g/mL}$) displayed anti-chikungunya activity by decreasing levels of viral RNA transcripts within 24 h of infection as revealed by RT-PCR [77]. Another study reported that copper oxide NPs synthesized using leaf extracts from *Tridax procumbens* displayed larvicidal activity against the chikungunya vector at a median lethal dose (LD_{50}) of 4.209 mg/L [78]. Silver NPs capped with plants extracts from *Ambrosia arborescens*, paddy straw, *Rhazya stricta*, *Daemia extensa*, *Solanum mammosum* L. *pilaquinga*, and *Hymenodictyon orixense* demonstrated larvicidal activity against the chikungunya vector at a LD_{50} of 0.28 ppm [79], 13.625 ppm [80], 30.66 $\mu\text{g/mL}$ [81], 3.842 ppm [82], 0.06 ppm [83], and 17.10–20.08 mg/mL [84] respectively.

Dengue Virus

Dengue is a mosquito-borne endemic infectious disease of tropical and subtropical countries, rapidly becoming a global burden [85]. The dengue virus causes symptoms of varying degrees, ranging from mild asymptomatic dengue fever to severe dengue hemorrhagic fever and dengue

shock syndrome, which may be fatal. To date, there are no effective antiviral drugs and vaccine candidates for dengue. Therefore, clinical management focuses on supportive treatment [85–87].

Studies have investigated the larvicidal activity of copper [78, 88], selenium [89], gold [90–92], and silver [93–102] NPs, and demonstrated their potential for inactivating the significant mosquito vectors (genus *Aedes*) of dengue [103, 104]. Paul et al. [105] analyzed the antiviral activity of gold NPs conjugated with small interfering RNA against the dengue virus. These NPs were able to enter the infected Vero cells and significantly reduce dengue virus serotype 2 (DENV-2) replication and infectious virion release under both pre- and post-infection conditions [105]. Quach et al. [106] reported on a novel subunit vaccine with a hybrid containing gold NPs and domain III of the viral envelope protein (EDIII) for dengue virus. In this study, anti-EDIII antibodies were induced into mice immunized with the hybrid gold NPs in a size and concentration-dependent manner [106]. Also, biosynthesized silver NPs using algae (*Centroceras clavulatum*), plant (*Bruguiera cylindrical*), and seed (*Moringa oleifera*) extracts showed anti-dengue activity at concentrations of 12.5–50, 30, and 20 $\mu\text{g/mL}$, respectively [107–109].

Herpes Simplex Virus

Infection with herpes simplex virus, known as herpes, can be due to either herpes simplex virus type 1 (HSV-1) or herpes simplex virus type 2 (HSV-2). Both types are highly prevalent within the human population [110]. HSV-1 is mainly transmitted orally (oral herpes), whereas HSV-2 through oral-genital contact (genital herpes) [111]. Herpes virus infections are recurrent, lifelong, and incurable. Current antiherpes therapies (i.e., pharmacological, topical, systemic, or laser therapy) are known to prevent or shorten outbreaks and reduce the risk of transmission [112]. However, individuals with immunosuppression (due to human immunodeficiency virus (HIV) malignancies or transplantation) may develop HSV-1 and HSV-2 variants that are resistant to the current antiherpetic therapies [110].

Various nanomaterials, e.g., copper [113, 114], zinc [115, 116], gold [117–119], and silver [117, 120–122], have proven to be effective against herpes. Silver NPs tend to block herpesvirus entry into the host cell by competing for binding to cellular heparin sulfate via the sulfonate end group [123, 124], whereas zinc NPs inhibit viral DNA polymerase activity [116]. Copper NPs generate ROS to inactivate the HSV by oxidation of viral proteins or degradation of the viral genome [113]. Mercapto-ethyl sulfonate gold NPs (with or without surfactant) inhibited HSV-1 and HSV-2 in cell culture [117–119].

Human Immunodeficiency Virus

Incurable infectious diseases such as HIV are among the leading causes of death worldwide [125, 126]. There are currently more than 30 approved antiretroviral drugs for the treatment of HIV infection, which includes 13 single-tablet drug combinations of two or more antiretroviral drugs. Antiretroviral therapies (ART) can suppress HIV replication to undetectable levels, provided that patients adhere to treatment regimens [127]. However, globally, HIV remains a challenge despite significant progress in decreasing its incidence and mortality rate [126].

Various metal NPs such as iron, silver, gallium, and gold have shown to be active against HIV, resulting in decreased viral growth and replication [1]. Silver NPs bind to gp120 protein to inhibit CD4-dependant virion binding, fusion, and infectivity. Gallium NPs interact with the CD4 membrane, thereby inhibiting HIV infection in macrophages. Gold NPs inhibit virus entry and are virus-neutralizing agents [1]. Vijayakumar and Ganesan (2012) [128] reported that stabilized gold NPs were effective against the M-tropic, T-tropic, dual tropic, and resistant HIV isolates with a 50% inhibition concentration of 1.12 ± 0.05 mg/mL. Marradi et al. [129] synthesized gold NPs coated with synthetic oligomannosides (Te-50 and Te-10), present in gp120, to stimulate 2G12-mediated neutralization of HIV infection in TZM-bl reporter cells. The NP formulations at concentrations of 2 μ M (Te-50) and 5.5 μ M (Te-10) neutralized 50% of the HIV-1-infected cells [129]. Glucan conjugated with gallium NPs inhibited HIV in macrophages (> 80% inhibition with formulations containing 108–355 μ g gallium/mg glucan particles) [130]. Another study has revealed that gallium NPs suppress the co-infection of HIV and tuberculosis [131]. Silver NPs (12–28 nm) with leaf extracts from mangrove *Rhizophora lamarckii* also inhibited HIV-1 reverse transcriptase activity with the IC₅₀ value of 0.4 μ g/mL [178]. Individually, silver NPs conjugated with either anionic linear globular dendrimer [132] or sodium 2-mercaptoethane sulfonate (Ag-MES) [124] inhibited HIV replication efficiently.

Curcumin has been known to have many therapeutic benefits that now includes antiviral activity [133–135]. Curcumin-stabilized silver NPs with a diameter of 45 nm, demonstrated non-toxic antiretroviral and immunomodulatory effects on ACH-2 cells latently infected with HIV-1 [134]. Another study determined that multi-functional mesoporous curcumin encapsulated in iron-phenanthroline nanoclusters, with a particle size of 46.8 nm, significantly decreased the expression of HIV-p24, TNF- α factors, IL-8, and nitric oxide by 41%, 61.2%, 41%, and 50.2%, respectively [135].

Hepatitis

Globally, viral hepatitis has been confirmed as one of the leading causes of death, liver diseases, and disability. These liver diseases include cirrhosis, hepatocellular cancer, decompensated disease, and extrahepatic manifestations [136, 137]. Currently, hepatitis C is curable if detected early with the aid of direct-acting antiviral therapies. Hepatitis B is often manageable through oral nucleos(t)ide therapies with high-resistance barriers. Significant advances in the management of hepatitis D infection are occurring [136]. However, a cure for viral hepatitis remains elusive, in the setting of viral genetic persistence within the hepatocyte nucleus, even with suppressive antiviral therapy [136]. Therefore, a possible cure and future therapeutic options must consider the targeting of multiple viral replication pathways in order to eliminate viral hepatitis as a public health threat [136].

Silver NPs have shown renewed promise in their ability to inhibit hepatitis replication. In a study by Lu et al. [138], different size silver NPs (10, 50, and 80 nm) were evaluated as an antiviral agent against hepatitis B. In this study, the silver NPs, 10 nm in size, produced 38% and 80% viral inhibition with a concentration of 5 μ M and 50 μ M respectively, while the silver NPs of 50 nm were slightly more potent with 53% and 92% inhibition at a concentration of 5 μ M and 50 μ M, respectively [138]. Haggag et al. [63] have recently analyzed biosynthesized silver NPs with extracts from *Lampranthus coccineus* and *Malephora lutea* against hepatitis A. This study reported that these NPs exhibit antiviral activity against hepatitis A and protect the host cell from viral infectivity [63]. Hang et al. [114] also indicated that copper NPs blocked hepatitis infection at the entry and attachment stages. Therefore, these findings suggest that silver and copper NPs may have novel roles in treating chronic hepatitis patients.

Influenza

Influenza, commonly known as the flu, consists of three types of viruses (A, B, and C) that belong to the Orthomyxoviridae family. These are enveloped and negative-strand RNA viruses [139]. Influenza occurs globally as local outbreaks or seasonal epidemics [140]. In the past 100 years, four influenza pandemics have occurred: H1N1 Spanish influenza in 1918, H2N2 Asian influenza in 1957, H3N2 Hong Kong influenza in 1968, and H1N1 swine influenza in 2009. In 1977, the H1N1 virus re-emerged but did not cause a pandemic [140]. However, since 1918, a novel influenza virus emerged from each pandemic, either directly from an avian host (1918), by reassortment between an avian virus and a circulating human strain (1957 and 1968), or through influenza virus reassortment in pigs (2009) and spread to the human population, causing considerable morbidity and mortality [140–142].

Annual vaccination remains the critical mode of prevention against seasonal influenza; however, the vaccines are effective only if the antigenic matching of the vaccine strains corresponds with the circulating virus strains [142]. The antiviral drugs currently available against influenza viruses are amantadine, rimantadine, zanamivir, oseltamivir, peramivir, and baloxavir marboxil. Antiviral resistance, influenza A virus infections, and control of future influenza pandemics are still an ongoing global concern [142].

Several studies have demonstrated the efficacy of metal NPs as potential antiviral agents against the influenza virus [143]. Iron oxide NPs showed *in vitro* inhibition (50%) against the H1N1 influenza A virus strain using a low concentration of 1.1 μg [143]. Lin et al. [144] analyzed the anti-influenza effects of selenium NPs and their conjugate with a broad-spectrum antiviral drug, ribavirin (RBV). Influenza infected Madin-Darby canine kidney (MDCK) cells exposed to no treatment, RBV only, selenium NPs, and selenium NPs with RBV achieved a cell viability of 48.4%, 68.5%, 65.2%, and 80.6%, respectively [144]. In a study by Li et al. [145], silver NPs were used to co-deliver oseltamivir to inhibit the H1N1 influenza virus activity through ROS-mediated signaling pathways. Infected MDCK cells exposed to no treatment, oseltamivir, silver NPs, and oseltamivir delivered by silver NPs achieved a cell viability of 39%, 59%, 65%, and 90%, respectively. These results indicate that the antiviral activity of currently prescribed antiviral drugs is effectively strengthened when conjugated with metal NPs. Each of these studies also revealed that the antiviral drugs conjugated with NPs used blocking of the H1N1 from infecting MDCK cells, preventing caspase-3 activity and inhibiting viral accumulation of ROS as antiviral mechanisms of action [144, 145].

“FluPep” is an established peptide inhibitor of influenza type-A virus; however, silver and gold peptide (FluPep) NPs were synthesized and tested for enhanced antiviral activity [146]. Silver and gold NPs functionalized with FluPep ligand (0.03%) showed inhibition (50%) against the influenza A virus strain at concentrations of 0.14 nM and 0.073 nM, respectively. Most importantly, the study demonstrated that conjugation of FluPep to silver and gold NPs enhanced its antiviral potency compared with the free peptides and are capable of targeting both influenza and bacterial co-infections [146]. Although these results suggest that functionalized NPs are useful antiviral agents against influenza, researchers have also found that non-functionalized metal NPs (i.e., silver) can be effective as well [147–150].

Silver NPs synthesized with Panax ginseng root extract using the sonication method exhibited antiviral activity against the influenza A virus (strain A/PR/8) [150]. Low anti-influenza activity was identified at NP concentrations of 0.005, 0.01, and 0.15 M, with inhibitory rates of 5.31%, 4.18%, and 5.97%, respectively. However, the anti-influenza effects improved by 7.10% and 15.12%, with concentrations

of 0.02 and 0.25 M, respectively [150]. Silver NPs with extracts from cinnamon (bark) demonstrated antiviral activity against the highly pathogenic avian influenza virus subtype H7N3. The NP concentration that inhibited 50% of infectivity was 125 $\mu\text{g}/\text{mL}$. Additional findings revealed that active constituents in the cinnamon bark extract interacted with the virus to interfere with viral replication and inhibit viral entry into the host cell [147].

Xiang et al. [148] confirmed that silver NPs at 50 $\mu\text{g}/\text{mL}$ exerted maximum anti-H1N1 influenza A virus activity. Additional findings revealed that the silver ions from the NPs inhibited viral growth by DNA interference, suppression of respiratory enzymes, and electron transport components [148]. Xiang et al. [149] also reported that silver NPs at a concentration of 50 $\mu\text{g}/\text{mL}$ demonstrated significant antiviral activity against the H3N2 influenza virus (A/Human/Hubei/3/2005 strain). These results indicate that functionalized and green synthesized silver NPs could be promising anti-influenza therapeutics.

Norovirus

Noroviruses are positive-strand RNA viruses and highly contagious. Globally, it is an established etiological agent in acute gastroenteritis outbreaks affecting all age groups. The infection causes a sudden onset of vomiting, diarrhea, abdominal pain, and cramps after contact with contaminated food or infected individuals [151]. Norovirus can be life-threatening to children, especially undernourished children from developing countries [152], infants, older adults, and immunocompromised individuals [151]. There are no clinically approved antivirals and vaccines for norovirus infections [153] since the challenge is that the virus presents with a vast genetic diversity, with over thirty different genotypes infecting humans [151].

Metal NPs have been reported to exhibit antiviral activity against surrogate models for human norovirus. Broglie et al. [154] produced gold NPs as cores and coated them with copper sulfide nanoshell to inactivate human norovirus-like particles. These NPs at concentrations of 0.083 μM and 1.66 μM inactivated 50% and 100% of the human norovirus virus-like particles, respectively, within a treatment period of 10 min. In this paper, direct binding of the NPs to the virus and damaging of the capsid were mechanisms used by the NPs to inactivate the viral particles [154]. Agnihothram et al. [155] showed that anatase titanium dioxide NPs (20 $\mu\text{g}/\text{mL}$) reduced cell viability of murine norovirus (MNV)-infected RAW 264.7 macrophages by 50% and 75%, at 24 h and 48 h post-infection respectively. Pfaff et al. [49] reported that exposure to tungsten carbide NPs caused a four-log reduction of MNV within 15 min. Ultimately, their findings also suggested that tungsten carbide NPs may be a promising antiviral agent against norovirus, other non-enveloped, and enveloped viruses [49].

Silver NPs are also considered as promising antiviral agents against human norovirus. Bekele et al. [156] revealed that silver NPs of 10 nm, at concentrations of 50 µg/mL and 100 µg/mL, effectively reduced the titer of feline calicivirus (FCV), a surrogate for human norovirus, beyond the limit of detection. In this paper, the results also showed that the silver NPs of 75 nm and 110 nm presented no significant antiviral effects. Furthermore, treatment with the 10 nm silver NPs reduced FCV capsid protein by 73% compared with the 75 nm and 110 nm silver NPs [156]. Park et al. [157] observed that a novel magnetic hybrid colloid (MHC) conjugated with silver NPs (AgNP-MHCs) caused a two-log reduction in MNV after treatment for 1 h [157]. The study also found that these particles damaged the viral coat proteins and nucleic acids [157]. Castro-Mayorga et al. [158] evaluated the efficacy of silver NP-based films for inactivating the FCV and MNV. Results revealed that exposing the FCV to the silver NP films for 24 h, produced 100% virus inactivation [158]. These evidence-based studies show that metal NPs and their composites can be considered as promising antiviral agents against the human norovirus and agents for disinfectants, food packaging, and contact surface industries.

Poliovirus

Poliovirus, the causative agent of poliomyelitis (polio), consists of a single-stranded positive-sense RNA genome with 7500 nucleotides. There are three serotypes of the wild poliovirus: serotypes 2 and 3, which were eradicated in 2015 and 2019, respectively, while, serotype 1 remains endemic. The clinical features range from mild cases of respiratory illness, gastroenteritis, and malaise to severe forms of paralysis [159, 160]. It can affect different age groups but common in children under 5 years old who have not received the vaccination. There is no cure for polio infection. However, vaccination is recommended for all infants, children, and adults to establish lifelong immunity against the disease [159, 161].

Silver and tungsten carbide NPs have been investigated for antiviral activity against poliovirus. Electrochemical-synthesized 7.1 nm silver NPs of quasi-spherical shape with high purity exhibited anti-poliovirus activity. A concentration of 3.13 ppm reduced the poliovirus infectivity by 50% within 30 min [162]. Huy et al. [162] also stated that the size of the synthesized NPs was smaller than that of poliovirus particles (20–30 nm). Therefore, the NPs could easily interact with the viral particles to inhibit viral binding to the host cells and replication. Pfaff et al. [49] also reported that exposure to tungsten carbide NPs caused a 3.5-log reduction in poliovirus infectivity within 15 min. However, it is unfortunate that research on the use of metal NPs for poliovirus treatment is scanty and warrants further investigation.

Respiratory Syncytial Virus Infection

Respiratory syncytial virus (RSV), a ubiquitous RNA virus [163], is the leading cause of lower respiratory tract infections in infants and adults [164, 165]. Severe RSV infections can exist among premature babies, older adults, infants, adults with the chronic pulmonary or circulatory disease, and immunocompromised individuals [166]. RSV is increasingly recognized as a global health priority because it remains a significant cause of death [165]. It is worth mentioning that except for ribavirin, there is no other treatment and licensed vaccines for RSV [164, 165].

Emerging evidence suggests that silver NPs could potentially be a therapeutic application for RSV infections. In a study by Yang et al. [167], curcumin modified silver NPs exhibited significant antiviral activity against the RSV, at concentrations ranging from 0.008 to 0.12 nM. Based on mechanistic findings, this study further revealed that the curcumin modified silver NPs attached to the viral envelope glycoproteins directly and interfered with the infectivity of RSV [167]. In another cell culture analysis, Morris et al. [168] found that polyvinylpyrrolidone (PVP)-coated silver NPs at a dose of 50 µg/mL decreased RSV replication by 79% and 78% in A549 and HEp-2 cells respectively. Similar antiviral mechanisms of action were noted by Morris et al. [168]. Hence, metal NPs, particularly silver, as antiviral agents for RSV, embrace great potential for future research.

Rift Valley Fever Virus

Rift Valley fever (RVF) virus is a zoonotic mosquito-borne virus, consisting of a three-segment genome of single-stranded RNA [169, 170]. It is associated with periodic epidemics of perinatal deaths and abortions in livestock (i.e., cattle, sheep, and goats), an acute febrile illness, encephalitis, retinitis, blindness, neurological disorders, and hemorrhagic syndrome in humans [171, 172]. RVF is endemic in sub-Saharan African countries, including South Africa [173]. Vaccines that are essential for the containment of RVF outbreaks and antiviral drugs for the effective treatment of RVF are currently unavailable [170]. Thus, research has advanced into investigating the potential application of silver NPs to control RVF infection. Borrego et al. [174] demonstrated that metallic silver NPs at a concentration of 12 µg/mL eradicated viral propagation, resulting in a 98% reduction of viral infectivity. This study also reported that the interaction of silver NPs with the RVF virus affects its infectivity, perhaps by interfering with the virus-cell attachment and viral entry [174]. Further investigations on the application of silver NPs and other metal NPs against RVF infectivity will help combat infection.

Rubeola Virus

Rubeola virus is known as the causative agent of measles. This virus is enveloped with a single-stranded negative-sense RNA and spreads through the respiratory route. Measles is highly contagious with clinical symptoms, including skin rash, fever, cough, coryza, and conjunctivitis [175]. A safe and cost-effective vaccine is available. However, measles is still associated with high mortality rates worldwide, particularly in developing countries with inadequate vaccination and health care facilities. No specific antiviral exists for the treatment of measles. Therefore, HIV-infected children, unvaccinated children, pregnant women, and a vaccinated individual who did not develop immunity are at the highest risk of measles and its complications [176]. A study by Meléndez-Villanueva et al. [177] reported that gold NPs synthesized with garlic extract from *Allium sativa* exhibited antiviral activity against the measles virus at an EC₅₀ concentration of 8.829 µg/mL. This study also proposed that the gold NPs displayed virucidal effects by directly blocking viral receptors. Gold NPs may be a promising strategy for the treatment of measles, therefore warrants further investigation.

Future Perspectives

Over fifty nanopharmaceuticals have received FDA approval since 1995 that is currently available for clinical use. These include polymeric, liposomal, nanocrystal formulations, micelles, and inorganic (metal) NPs. The first FDA-approved nanoformulation drug was Doxia (doxorubicin hydrochloride, Janssen) to treat Kaposi's sarcoma in HIV patients [179–181].

Metal NPs have significant potential to increase the pharmaceutical market growth and improve health benefits for viral diseases. However, the current scientific research, pre-clinical and clinical translation, and regulatory gap for nanomedicines are vast and challenging. Notably, from the outset of metal NP design, it is critical to consider the physicochemical features of different metal NPs, disease pathophysiology, and heterogeneity. Researchers considering these abovementioned factors can assist in tailoring metal NPs with optimal therapeutic benefits. These considerations will also help overcome biological barriers, such as improved targeting and reduced accumulation in non-targeted cells, tissues, and organs. Pre-clinical evaluation for therapeutic efficacy, safety, biodistribution, and pharmacokinetics in appropriate animal models of the disease, relevant to the human condition, is necessary. Before pre-clinical evaluation, extensive in vitro assays for therapeutic efficacy and nanotoxicity screening is essential. After that, pre-clinical toxicology studies in animal models can predict both short-term and long-term toxicity, as circulation half-lives and drug retention times vary with the type of metal ions used for NP synthesis or encapsulation.

Monitoring the absorption, distribution, metabolism, and excretion of emerging metal NPs in vivo is also essential to predicting their toxicological safety profile. Additionally, screening of NPs for immunotoxicological and immunomodulation potential is essential since these functional outcomes correlate with tissue uptake and clearance mechanisms [181]. Hence, addressing these issues is critical to safeguard the clinical application of metal NP-based therapeutics for viral infections.

Conclusion

Therapeutically, metal NPs, as antiviral agents, are proving to be a promising candidate to tackle current treatment challenges in clinical settings for a broad spectrum of viruses. However, translating the large number of in vitro studies displaying the antiviral activity of metal NPs against different viral infections to pre-clinical and clinical applications is scanty or non-existent. Therefore, scientific evidence gained through research addressing these priority areas can help tailor and synthesize clinically translatable nanosized metal particles to treat viral diseases.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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