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REVIEW

Exploring the Potential of Metal Nanoparticles as a Possible Therapeutic Adjunct for Covid-19 Infection

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Abstract The WHO has declared the Covid-19 outbreak as a global health emergency with a mortality rate of approximately 3%, across 200 countries. There has been a considerable risk involved with drug repurposing in Covid-19 treatment, particularly in patients with underlying chronic disorders. Intervention of appropriate adjunct to primary drug therapy at subclinical or clinical doses may help to reduce unintended consequences involved in Covid-19 therapy. Metal nanoparticles due to their intrinsic structural and functional properties, not only contribute to anti-viral properties but also help to reduce the risk for associated complications. Although, silver nanoparticles hold great promise as an effective biocidal agent, while other metal nanoparticles also fueled interest against virus infection. The present review discusses the important properties of selected metal nanoparticles, their antiviral principle with possible toxic consequences, provides invaluable information for scientists and clinicians about an appropriate metal nanoparticle as an adjunct for Covid-19 treatment.

Significant of statement: Present article focuses metal nanoparticles and their antiviral principle with possible toxic consequences, provides invaluable information for scientists and clinicians about an appropriate metal nanoparticle as an adjunct for Covid-19 treatment.

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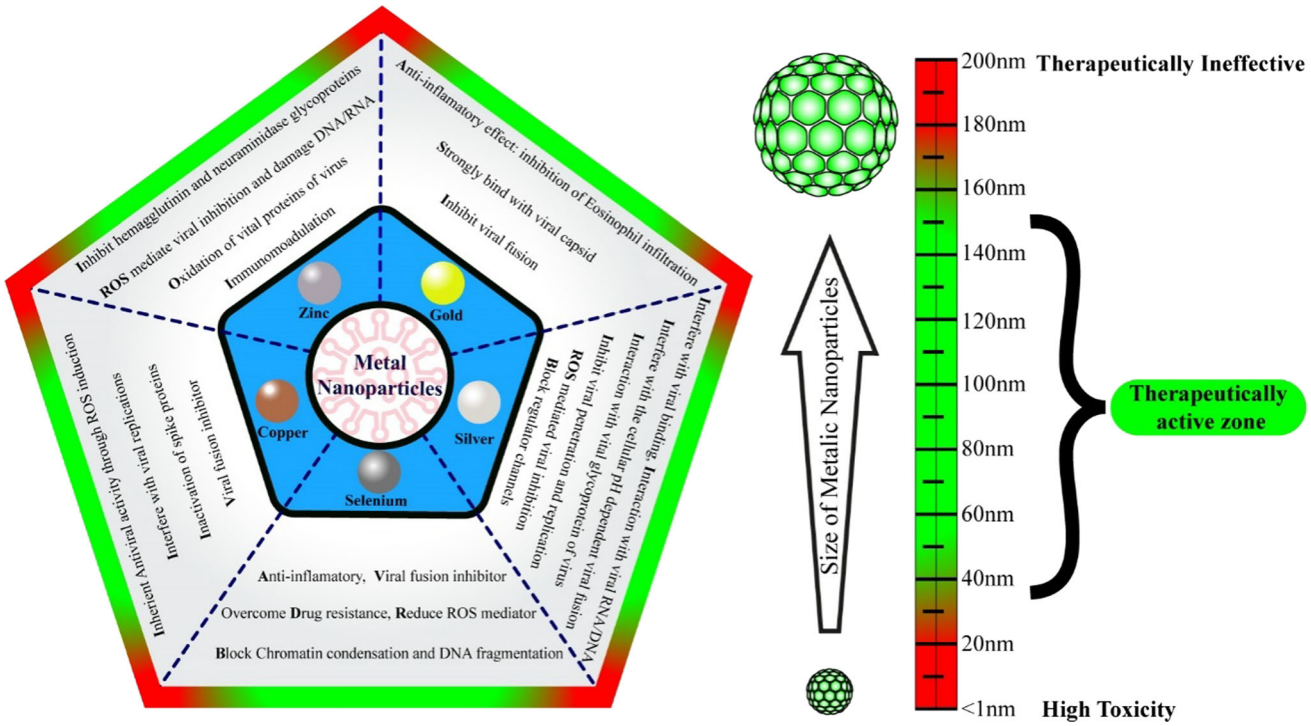
Graphical Abstract



Keywords Covid-19 · Metal nanoparticles · Functionalized nanometal · Anti-viral activities · Toxicity · Adjunctive therapy

Abbreviations

WHO	World Health Organization
TNF	Tumor necrosis factor
IL	Interleukin
iNOS	Inducible nitric oxide synthase
ACE 2	Angiotensin converting enzyme
COVID	Corona virus disease
VEGF	Vascular endothelial growth factor
IFN	Interferon
USFDA	U S Food and Drug Administration
MHLW	Ministry of Health, Labour and Welfare
RNA	Ribo nucleic acid
DNA	Deoxyribo nucleic acid
HA	Hemagglutin
MDCK	Madin–Darby Canine Kidney
NNRTIRV	Non-nucleoside retrotranscriptase inhibitor resistance virus
PIRV	Protease inhibitor resistance virus
HIV	Human immunodeficiency virus
TiO2	Titanium dioxide
CD4	Cluster of differentiation4
HSV	Herpes simplex virus
ROS	Reactive oxygen species
PEG	Poly ethylene glycol
RT-PCR	Reverse transcription polymerase chain reaction
PDGFB	Platelet derived growth factor subunit B
GCSF	Granulocyte colony-stimulating factor
VEGFA	Vascular endothelial growth factor A
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
LPS	Lipo-polysachharide
TGFβ	Transforming growth factor beta
MTT	3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
GPX	Glutathione peroxidase
CCl5	C–C Motif chemokine ligand 5
GAPDH	Glyceraldehyde-3-phosphate dehydrogenase
MDH	Malate dehydrogenase
SARS	Severe acute respiratory syndrome
MERS	Middle East respiratory syndrome

Introduction

The WHO has declared the coronavirus outbreak as a global health emergency with a mortality rate of approximately 3%, across 200 countries. Currently, there is no approved vaccine or medicines available for the treatment

of novel coronavirus [1]. Scientists are working on different drugs and their combinations relating to evidence-based pathology. In-depth understanding of coronavirus pathogenesis greatly helps physicians in designing future trials with minimum risk. The ability of coronavirus to modulate the levels of inflammatory mediators like TNF, IL-6, IL1-β, IL-15, IL-17, iNOS, etc., and subsequent dysfunction of vital organs incited by ischemia and inflammation encourage physicians for anti-inflammatory drugs like corticosteroids, chloroquine and hydroxychroquine to treat the infection. In addition to anti-inflammatory activity, hydroxychroquine is thought to exert virucidal activity through multiple mechanisms including glycosylation of ACE-2 (Angiotensin converting enzyme-2), preventing the fusion of virus to host cells and its ability to raise the cytoplasmic pH, inhibit endosomal fusion of viral particles, likely to reduce viral replication. Apart from some clinical benefits, recently it has been found that COVID-19 patients under hydroxychloroquine treatment were at increased risk of cardiovascular complications. Similarly, drugs like corticosteroids are potentially detrimental to host defense against viral infection. According to clinical evidence, corticosteroids due to its ability to inhibit of Janus kinase signaling pathway, suppress the production of anti-viral type-I interferon considered to be the first line of defense against inhaled pathogens. Further patients with coronavirus infection are reported to have systemic inflammation, usually associated with an increased level of free radicals. Elevated levels of free radicals involved in covid-19 infection disrupt the body's own antioxidant defense systems, trigger the oxidation of essential biomolecules, and continue to worsen the health conditions of patients. These conditions motivate physicians for antioxidant supplements to reduce the complications induced by free radicals. Recent clinical evidence suggests a high intravenous dose of vitamin C of about 1000 mg for 3 subsequent days significantly reduce flu and cold-like symptoms in patients with Covid-19 [2]. Enhanced levels of pro-inflammatory cytokines have been found to increase VEGF in the patient with Covid-19, accompanied by enhanced permeability of pulmonary epithelium leads to accumulation of fluid in lung alveoli results in respiratory failure. Macrolide antimicrobials like azithromycin, in addition to its ability to reduce bacterial co-infection, were also found to reduce pro-inflammatory responses in lungs usually detected in Covid-19. Moreover, Azithromycin also contributes to both passive and acquired immunity through its unique ability to modulate the expression of antiviral proteins including IFNβ, IFNλ1 and helicases. Similarly, recently Remdesivir, a nucleotide analogue is approved by USFDA and MHLW to treat patients with Covid-19. Earlier literatures suggest that the anti-viral principle of Remdesivir is related to its ability to inhibit RNA-dependent RNA polymerase. Remdesivir structurally resembles adenosine; as a result, virus RNA polymerase mistakenly recognizes Remdesivir as a correct base instead of adenosine, preventing viral replication. Recent clinical data related to Covid-19 patients suggest about 2–11% of patients show liver dysfunction with an increased level of aspartate aminotransferase and alanine aminotransferase. Since Remdesivir has already reports of hepatotoxicity, therefore, underlying liver conditions may worsen with Remdesivir administration [3]. Therefore, clinical pathology-based adjunct supplements may be advocated to minimize the risk of potential toxicities of standard drugs for better clinical outcomes in patients with Covid-19.

Metal nanoparticles, due to their intrinsic structural and functional properties, address most of the pathological conditions related to Covid-19. Transition metals like Zinc, Copper, Silver, Gold, Selenium, etc., due to their high primary electron energies interact with multiple targets of pathogens including thiol groups of important enzymes, intracellular RNA and DNA, electron transport components and membrane proteins, largely contribute to their antiviral activity (Fig. 1

Previous literature demonstrates broad-spectrum virucidal activities of metal nanoparticles against a wide range of viruses including HIV-1, influenza virus, hepatitis B virus, herpes simplex virus, etc. [4]. The molecular mechanism involved in the antiviral activities of transition metal includes multiple modes of action starting from inhibition of viral entry to inactivation of viral particles. Fusion inhibition considers being a potential therapeutic intervention against this novel virus. Researchers have found a novel coronavirus that uses spike glycoprotein to enter human cells through angiotensin-converting enzyme-2 receptor. The spike glycoprotein of novel corona virus has a structural similarity to HA protein of influenza A. Xiang and coworkers reported potential antiviral activity of AgNPs against H3N2 influenza virus confirmed through both in-vitro and in-vivo model. The antiviral activity of AgNPs can be explained by their ability to inhibit hemagglutination activity [5]. Metal nanoparticles with multiple binding interactions, have the potential to minimize the risk of multidrug resistance. Recently, Kim et al. established the superior target precision of surfactant-free porous gold nanoparticles for the conserved surface protein of the Influenza virus. Experimental findings indicate viability of virus-infected MDCK cells increased to 96.8% after gold nanoparticle treatment against 33.9% cell viability in control group [6]. Similarly, Lara et al. elucidated multiple antiviral mechanisms of silver nanoparticles against various viruses including some resistant strains like BCF01, NNRTIRV, PIRV, and 3TCRV. Their outcomes suggested that the antiviral activity of AgNPs against HIV is related to their ability to inhibit CD4-mediated virion

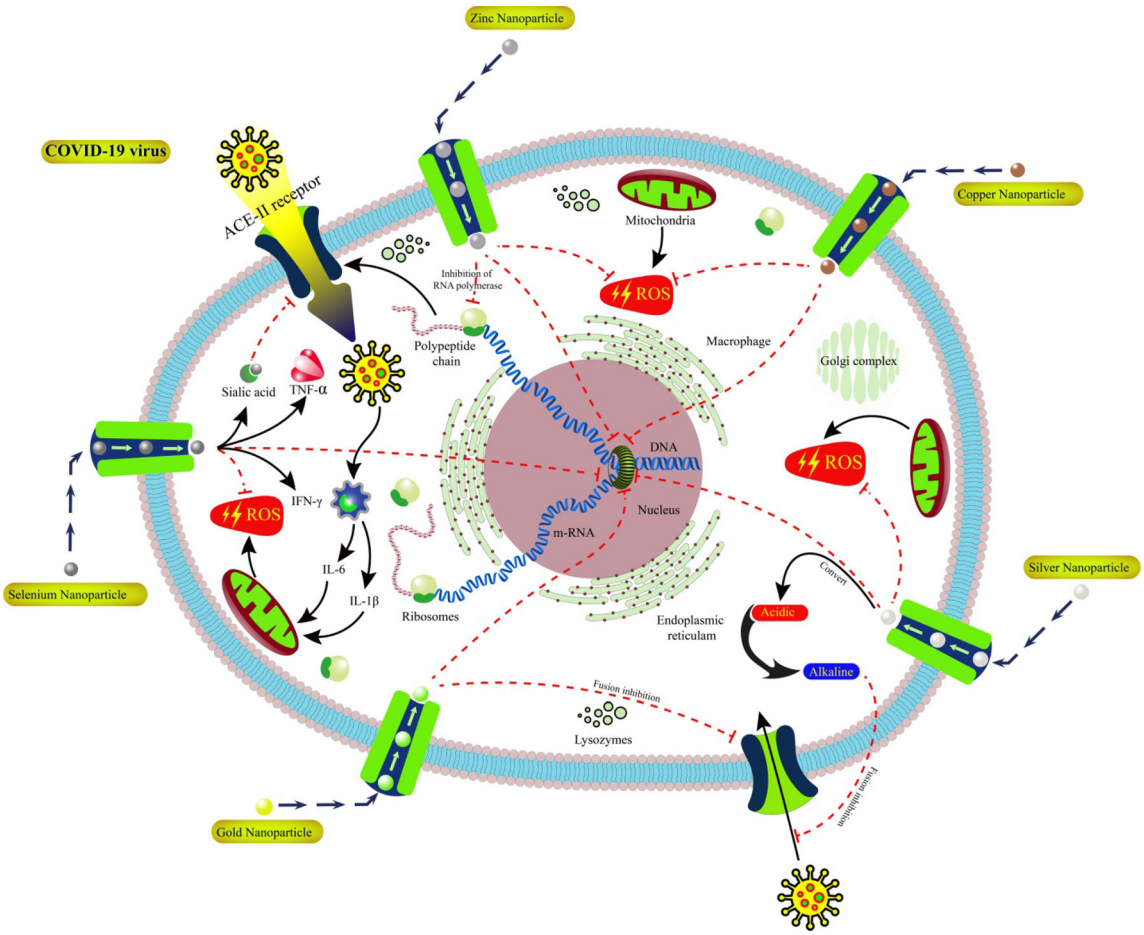


Fig. 1 The possible mechanism of action of antiviral properties of metal nanoparticles. AgNPs interacted strongly with respiratory enzymes, RNA and DNA, viral protein; AuNPs interacted strongly with viral capsid, led to virus destruction; ZnONPs inhibit hemagglutinin and neuraminidase glycopeptide resulted inhibition of virus replication process; SeNPs act by blocking chromatin condensation and DNA fragmentation of virus; CuNPs inactivates surface glycoprotein such as HA and NA by hydroxyl radials of virus

binding [7]. While the antiviral potential against HSV-2 is related to the affinity of silver for the thiol groups of viral capsids, that prevent viral internalization. Further nanometals due to their large surface area trigger the production of free radicals through intracellular signaling networks, eventually lead to the disruption of viral activity. The antimicrobial activity of TiO_2 is largely related to the production of ROS including hydrogen peroxide and hydroxyl radicals. However, literatures suggest TiO_2 possesses a weak anti-viral activity characterized by extremely low clearance of viral load after 2 h exposure of TiO_2 at a concentration of 1 g/L. However, silver doping significantly enhances the anti-viral potential of TiO_2 by increasing the formation of hydroxyl free radicals [8]. Ghaffari et al. demonstrate PEG-modified zinc NPs within a size range of 16–20 nm at a concentration of 75 µg/mL shows a significant reduction in the H1N1 influenza viral titer. Further author claims pre-exposure of nanoparticles did not produce any antiviral response, whereas post-exposure represents a substantial reduction in viral titer could be attributed to the ability of zinc nanoparticles to inhibit viral replication inside mammalian cells [9]. Kumar et al. reported the anti-viral potential of Zinc nanoparticles against chikungunya virus. Experimental outcomes supported by RT-PCR and adsorption studies revealed tenfold reduction in virus titer. Possible results could be attributed to the ability of zinc NPs to modulate virus transcription and change in membrane polarity induced by the negative charge of ZnO and positive charge of virus capsid [10].

In addition to direct antiviral intervention, nanometals also have potential characteristics to suppress the pathological complications associated with Covid-19 infection. The major clinical complications reported in Covid-19 are associated with hyperinflammation and respiratory dysfunction. Uncontrolled inflammation in Covid-19 is related to an explosive level of cytokines and chemokines including IL1-β, IL7, PDGFB, TNFα, GCSF, IL9, IL10, IFNγ, VEGFA, etc., by unregulated immune response.

Enhanced cytokines level contributes to systemic inflammation; eventually increasing the risk of sepsis and death. Further, high cytokines level trigger the activity of mitochondrial respiratory enzymes including xanthine oxidase, lipooxygenase, cyclooxygenase, etc., cause increase production of free radicals leading to further damage and progression of inflammatory disease. Literature revealed deficiency of zinc significantly influences the cytokines level that is particularly involved in the disease management of Covid-19 patients including IL-1β, IL-2, IL-6, and TNF-α. Experimental findings suggest zinc supplementation significantly modulates above-mentioned cytokines in a dose-dependent manner by inhibiting the activation of NF-κB [11]. Similarly, Yusuf et al. recently outlined the role of zinc on pro-inflammatory cytokines. Experimental work based on *E. coli*-LPS animal model suggests high zinc intake suppresses the level of pro-inflammatory cytokines (TNF-α, IL-1 and IL-6) [12]. However, there are some contradictory reports that suggest zinc- and copper-containing welding fume particles enhance the levels of pro-inflammatory mediators like IL-6, IL-8, TNFα, and IL-1β after 24 h of exposure. Patients with COVID-19 infection show lower levels of regulatory T cells, due to an imbalance profile of cytokine TGFβ. Regulatory T cells have a number of important functions to control the immune response including production of inhibitory cytokine (IL-35, IL-10 and TGFβ), immunosuppressive adenosine and indoleamine 2,3-dioxygenase, control IL-2 feedback loop, etc. Recent studies suggested that low level of regulatory T cells play an important role in cytokine storm pathology related to covid-19 patients. Rosenkranz et al. found that Zn supplementation significantly increases the number of CD4 and CD25 cells in both atopic and non-atopic subjects, characterized by an enhanced level of interferon (IFN)-γ/interleukin (IL)-10 ratio and a higher level of TNF-α [13]. Oxidative stress plays a pivotal role in the management of common pathological complications associated with Covid-19 including thrombotic complications, lymphopenia, ischemia, kidney dysfunction, and pulmonary oedema. Selenium plays a vital role in protection from oxidative stress. Tinggi and co-workers in his review presented selenoenzymes with excellent antioxidant activity including GPx, GPx1, GPx3, GPx4, GPx5, and GPx6. These selenoenzymes play an important role in host protection against all kinds of free radicals include superoxide, hydrogen peroxide, hydroxyl radicals, and nitric oxide [14].

Further, the properties of metalnanoparticles vary greatly depending on their size and surface properties (Table 1).

Bekele and co-workers investigate the antiviral potential of silver nanoparticles of different sizes (10, 75, and 110 nm) against feline calici virus. Experimental findings supported by antiviral study and western blot analysis suggest 10 nm particles at a concentration of 50 and 100 μg/mL show significantly higher anti-viral activities compared to 75 and 110 nm AgNPs [15]. Further the surface properties of nanoparticle including surface charge, surface hydrophobicity, etc., plays an important role in their antiviral activity. Meléndez and coworkers investigate the antiviral activity of nano-gold prepared by garlic extract against Measles virus using Quantitative Real-Time PCR and virucidal assay using Vero cells (ATCC® CCL-81™). Experimental findings suggest an antiviral activity of 57.07% with modified gold nanoparticles at a concentration of 10 μg/mL against 46.43% and 6.96%, respectively for the selected precursors, i.e. auric chloride and garlic extract [16]. Similarly, Alghrair et al. investigate the anti-influenza potential of Flu-Pep modified silver and gold nanoparticles in canine MDCK cells. Results indicate both functionalized nano-systems show good antiviral potential characterized by an IC50 value of 2.1 nM but were less potent compared to Flu-Pep itself with an IC50 value of140 pM [17].

Regardless of some positive outcomes, metal nanoparticles have been reported to cause toxicity. In general, the key pathways involved in metal nanoparticles toxicity are oxidative stress, increased expression of proinflammatory mediators, influencing enzymatic activities, and inhibition of detoxification pathways. Recently, Bao et al. based on their extensive investigation about the toxicity of silver nanoparticle of varying size on Zebra fish, concluded that long-term exposure to silver nanoparticles particularly particles with less than 20 nm might cause sex-dependent and organ-specific toxicity to adult zebrafish [18]. Therefore, understanding the antiviral activity of metal nanoparticles with realistic toxic profiles helps to increase the clarity and clinical relevance of metal nanoparticles for improving clinical outcomes. The section presents the important properties of selected metal nanoparticles, their antiviral principle with possible toxic consequences, guides for selecting an appropriate metal nanoparticle as an adjunct for Covid-19 treatment.

Metal Nanoparticle and Their Possible Antiviral Action

Silver Nanoparticle

Silver nanoparticles (AgNPs) are known for its broad-spectrum antimicrobial activity against a variety of microorganisms including fungus, bacteria (gram + ve and gram −ve,) and viruses (respiratory syncytial virus, hepatitis B, simplex virus, HIV-1, and retrovirus) [7]. The antimicrobial potential of AgNPs is related to its ability to

Table 1 Size dependent antiviral approach of metal nanoparticle

Sl no.	Name of Nanoparticle	Size (nm)	Virus	Cell line model	IC_{50}/Expt. Conc	Target site for virus inhibition
1	Ag NPs	30–50	HIV-1	HeLa cell	0.44 μg/mL (IC_{50})	Prevent virus entry
2	Ag NPs	10	Feline calcivirus	CRFK cells	50 and 100 μg/mL achieved 5.7 and 6.5 $\log_{10}$ TCID50	Viral inactivation
3	Ag NPs	8–12	Respiratory syncytial virus	A549 epithelial cell	1 mg/mL (Expt. Conc.)	Binding to the surface of glycoprotein of virus over respiratory epithelium
4	Ag NPs	25	Monkeypox virus	Vero cells	25 μg/mL	Inhibit early steps of binding and penetration by blocking virus-host cell
5	AgNP-MHC	30	Bacteriophage ϕX174, murine norovirus, and adenovirus serotype 2	MS2, RAW 264.7 cells, A549 cells	$2\log_{10}$ after exposure to 4.6×10^9	Damaging the viral coat protein
6	Ag NPs	50	Hepatitis B virus	HepAD38 cell line	$K_b = 8.8$	Inhibit the extracellular virion formation
7	FluPep-Ag NPs	10	Influenza virus	MDCK cells	$IC_{50} = 2.1$ nM	Block its binding to host cells and prevent viral fusion
8	PVP-coated Ag NPs	69 ± 3 nm	Respiratory syncytial virus	HEp-2 cells	–	Interference with viral attachment
9	Au NPs using garlic extract	6	Measles virus	Vero cells	$EC_{50} = 8.8$ μg/ml	Inhibit viral infection by blocking viral particles directly
10	Au NPs	30	Influenza virus	MDCK cell lines	–	Interact with virus caspid
11	Au NPs	10	HIV-1	HeLa-CD4-LTR-B-gal cell	57–78 μg/mL	Inhibit HIV-1 fusion
12	Au NPs	8–17	Peptide-Food-and-mouth disease virus	BALB/c mice	–	Immunogenic property
13	ZnO NPs	20–50	H1N1 influenza virus	MDCK- $SIAT_1$ cell	Viability ≥ 90% @ 75 μg/mL	Inhibit progeny release
14	ZnO NPs	10–15	Chikungunya virus	MA104 cell line	50% cell viability was observed with ZnO NPs at 5.15 pg	Changes of viral RNA transcription
15	ZnO-PEG-NPs	16–20	H1N1 influenza virus	MDCK- $SIAT_1$ cell	Cell viability ≥ 90% @ 200 μg/mL	Inhibit progeny release
16	Se NPs	100	H1N1 influenza virus	MDCK cells	Cell viability -65.2%	Prevent apoptosis induced by virus
17	CuI NPs	160	Influenza A virus	MDCK cells	50% reduction of virus titer@17 μg/ml	Inactivation of viral protein
18	CuO NPs	40	Herpes simplex 1	Vero cell	83% of viral load	Interfere the viral replication

attract electrons from the surrounding, as a result; silver interacts with a wide variety of biomolecules including respiratory enzymes, RNA and DNA, viral protein,. etc., leads to cellular dysfunction and eventually causes microbial death. The particle size of AgNPs plays a significant role in determining their antiviral potential. Smaller particles owing to their high-free surface energy, show an increased dissolution and transport activity eventually lead to greater antimicrobial activity. Literature evidence suggested that particle size less than 10 nm exhibited significant antiviral activity against HIV-1 virus [19]. Lara and coworker reported that AgNPs with a size range between 30 and 50 nm shows IC50 value of 0.44 to 0.91 mg/ml against different strains of HIV-1 virus generated from luciferase-based antiviral assays [7].

Morris and his team reported improved antiviral and immunomodulatory performance of smaller AgNPs (10–12 nm) against the respiratory syncytial virus through the suitable animal model. The virucidal activity of synthesized AgNPs may be due to its ability to interact with surface glycoprotein of virus over respiratory epithelium, while the immunomodulatory effect of AgNPs is associated with the down-regulation of pro-inflammatory cytokines like IL-6, IFN and CCL5. Authors further reported that AgNPs at the dose of 50 μg/ml do not exhibit any cytotoxicity against A549 epithelial cells. These outcomes encourage scientists to use AgNPs as an adjunct for COVID-19 treatment [12].

Similarly, Park et al. demonstrated the antiviral activity of AgNPs against bacteriophages, adenovirus accessed by a plaque assay and real-time TaqMan PCR. Experimental findings revealed silver nanoparticles (30 nm) displayed the maximum efficacy for inactivating the viruses. The mechanism of antiviral activity involves the interaction between silver ion and cystine rich domain of essential transmembrane component of virus, releases reactive oxygen species causing inactivation of virus. In addition, it was reported that Ag + ion causes shift in intracellular pH of respiratory epithelium from acid to alkaline region, prevents the acid-dependent fusion activation of virus, and is the key features of AgNPs, indeed be exploited for the treatment of Covid-19 [20]. Furthermore, AgNPs reported to inhibit the VEGF-induced angiogenesis, which may help to attenuate secondary complications associated with Covid-19 including cardiovascular diseases, inflammation, acute lung injury syndromes, and carcinogenesis.

Moreover, appropriate surface functionalization of AgNPs improves membrane permeability, stability and catalytic potency for higher bioactivity. Recently, Lee and co-workers investigate the catalytic function of polyvinylpyrrolidone (PVP) coated AgNPs (100 nm) against thiol-containing enzymes including GAPDH and MDH [21, 22]. Results indicated that AgNPs strongly bind to the thiol group, cause a sharp decrease in their activity. Reduction in reaction rate appears to be highly dependent on the concentration of silver ions. Interestingly, spike glycoprotein of SARS-CoV-2 have many cysteine residues, supporting the possible application of AgNPs to treat Covid-19. Secondary complications associated with inflammation of the breathing tract in Covid-19 causes more damage to host. Pulmonary administration of colloidal AgNPs with sizes 3 to 7 nm produces potential antiviral and suppression of inflammation characterized by marked reduction in the viral load in the respiratory mucosa of airway, hence could find application as a potential therapeutic intervention of Covid-19 infection. In addition to its antiviral action further, these properties of AgNPs can be employed to manage viral and bacterial pneumonia often registered in Covid-19. Recently, the antiviral activity of AgNPs against monkeypox virus was established. Experimental outcomes indicated that AgNPs prevent the entry of *tacaribe* virus into the host cell through multiple mechanisms including interfering with virus RNA-dependent RNA polymerase, inhibition of host gene expression, inhibition of viral glycoprotein, and inhibition of intracellular replication of virus [23].

Although the AgNPs show good antimicrobial potential but have unacceptable toxicity, which limits its application for the treatment of lungs infection. Surface functionalization appears to be an important approach to reduce nano-metal toxicity. Sun and coworker reported that saturated surface capping with bovine serum albumin (BSA) and poly (*N*-vinyl-2-pyrrolidone) (PVP) significantly reduce cytotoxicity of AgNPs at a concentration of 100 μg/ml [24]. These findings suggest that surface capping using an appropriate substance acts as a potential strategy to reduce the toxicity without affecting the efficacy of nanoparticle.

Gold Nanoparticle

Gold nanoparticles (AuNPs) owing to its distinct structural and functional properties offer a multiplex platform for antimicrobial application. Literature evidence reveals AuNPs exhibit broad-spectrum antimicrobial performance against a wide variety of microorganisms including both gram-positive and negative bacteria and viruses such as HIV-1, influenza virus, hepatitis B virus, herpes simplex virus, etc. The antiviral properties of gold nanoparticle are related to size-dependent response and local-field interaction between AuNPs with the cell wall of virus. Literature suggests size (7–70 nm) dependent antiviral activity of AuNPs against influenza virus A/FM/1/47 (H1N1) in MDCK cell line. Experimental finding reveals gold-nanoparticle up to 30 nm shows optimum antiviral activity, whereas larger particles (> 30 nm) shows negligible or no antiviral activity, suggesting smaller size nanoparticles (≤ 30 nm) interacted strongly with viral capsid, led to virus destruction [25].

Recently, the global pandemic caused by SARS virus, contributed a major threat to human population and continuously increase the fatality rate. It was found that the SARS-CoV-2 is capable of infecting the human through spike proteinS1 and S2, where S1 help to bind cell through dipeptidyl peptidase-4 receptor and S2 binds to cell membrane through heptad repeat 1 (HR1) and heptad repeat 2 (HR2) leading to endocytosis. Huang and coworker reported that the complex between natriuretic peptide and gold nanorods was shown to inhibit HR1/HR2 mediated membrane fusion between MERS-CoV and host. These findings encourage the researcher to use AuNPs in

the management of Covid-19 infection since both MERS-CoV and SARS-CoV utilizes a common entry platform to enter into host cells.

Successful immunization looks to be an effective choice to fight against infections caused by influenza and coronavirus. It was reported that intranasal administration of antigen (r-trimetric influenza A/Aichi/2/68(H3N2) HA) conjugated AuNPs exhibits strong cellular and humoral immune response. Since influenza virus and SARS-CoV-2 shares ~ 80% identity including surface glycoprotein hemagglutinin, therefore AuNPs may be used as an effective adjunct for efficient vaccine design against Covid-19. In addition, Sekimukai et al. also reported immunization potential of recombinant S-protein with or without AuNPs. Results suggest the immunization with AuNPs at low dose (0.5 μg) shows improved immunological performance characterized higher immunoglobin G titer and reduced eosinophilic infiltration in lungs. These observations further elucidate the potential of AuNPs as an antigen carrier and adjuvant against severe pneumonia-associated coronaviruses [26].

Kim and coworkers reported the antiviral activity of gold nanoparticles is partially related to their affinity for thiolated domain of hemagglutinin, represents a highly conserved fusion protein of influenza virus. Results indicate the viability of virus-infected MDCK cells increased to 96.8% after Au NPs treatment against 33.9% cell viability in the control group [6]. The possible mechanism of anti-influenza action of AuNPs is attributed to its increased affinity for disulfide bond with HA leads to inhibition of viral membrane fusion, confirmed by real-time RT-PCR. Like influenza virus, SARS-CoV-2 also contains HA, therefore these thoughtful evidences encourage scientists for the use of AuNPs as an adjunct for Covid-19 treatment. AuNPs are usually considered as nontoxic, however small AuNPs (1.4 nm) capped with triphenylphosphine monosulfonate shows cytotoxicity due to up-regulation of stress-related gene following 6 and 12 h of incubation with IC_{50} concentration. Pretreatment with antioxidant or reducing agents like N-acetyl cysteine can lead to depletion of cytotoxicity of AuNPs. Recent literature evidence suggests AuNPs owing to its distinct optical properties successfully used as a diagnostic agent for Covid-19 diagnosis. Experimental results indicate AuNPs following 10 min of incubation with SARS-CoV-2, changes its color from purple to blue indicating a confirmed case of Covid-19.

Zinc Oxide Nanoparticle

Zinc oxide nanoparticles (ZnO NPs) because of its strong reducing ability and excellent biocompatibility have been extensively investigated for different medical conditions, especially in the field of antimicrobial, cancer and anti-inflammatory. The antimicrobial activity of ZnO NPs is connected with their high surface to volume ratio, ensures strong electrostatic interactions between nanoparticle and cell wall of pathogen, produces reactive oxygen species and subsequent cell death. Ghaffari and coworkers reported the antiviral activity of ZnO NPs against H1N1 influenza virus using MDCK-SIAT1 cell lines in MTT and RT-PCR assay. Experimental finding indicates the antiviral activity of 52.2 percentage with post-exposure of ZnO NPs at a concentration of 75 μg/ml could be attributed to the ability to inhibit hemagglutinin and neuraminidase glycopeptide led to inhibition of virus replication process in the cell [9]. Kumar et al. reported the antiviral effect of ZnO NPs against chikungunya virus using MA104 cell line by MTT and RT-PCR assay. Results suggest ZnO NPs at a concentration of 5.15 pg and 3.10 pg experience cell viability of 50% and 90%, respectively. The possible mechanism involved could be related to the capacity of ZnO NPs to inhibit viral RNA transcription and change in charge conformation of capsid protein of chikungunya virus [10]. These mechanism of ZnO NPs can be exploited for controlled inactivation of SARS-CoV-2 virus. Further the size and morphology of zinc nanoparticles affect the antiviral properties. A 3-D form of zinc oxide tetrapods block the entry of herpes simplex virus into the cells, which could be attributed to the ability of oxygen vacancy of tetrapods to engage viral fusion glycol-protein (haparan sulfate) as an attachment receptor to prevent the entry of virus. Recent development suggests human coronavirus NL63 utilizes heparan sulfate as an attachment factor with host cell, therefore above findings may provide a new insight to scientist or clinician as a treatment strategy for Covid-19.

Selenium Nanoparticle

Selenium nanoparticles (Se NPs) because of its unique anti-oxidant properties, protect host against oxidative stress and combat a wide range of disease condition such as bacterial and viral infection, inflammation, drug-induced toxicity, cancer, diabetes, and nephropathy. In addition, it is also used as drug carrier in various disease conditions. A recent study indicates ribavirin-loaded Se NPs exhibit improved protection of Madin-Darby Canine Kidney cells against H1N1 influenza virus. Moreover, it aids in reducing the toxicity of encapsulated drugs confirmed via MTT assay. Further the surface properties of nanoparticle including surface charge play an important role in their antiviral activity. Li and coworker investigated the therapeutic performance of oseltamivir-surface modified Se NPs (Se-OTV) directed against H1N1influenza virus-infected MDCK cells. Experimental outcomes indicate Se-OTV successfully protects the cells from H1N1 influenza virus infection by blocking chromatin condensation and DNA

fragmentation. Further antioxidant potential of Se-OTV protect cells from ROS, indicated by higher cell viability (Li et al.) [27]. In addition, Se-OTV appears to inhibit the glycoproteins HA and NA, which plays an important role in viral infection by combining sialic acid-containing receptors on host cells and mediating the entry and fusion of the virus.

The novel coronavirus uses spike glycoprotein (HA and NA) to enter human cell which have structural similarities with glycoprotein of H1N1 influenza virus. Therefore, above-mentioned information gives a novel thought to the clinicians that Se NPs may be used as an adjunct against Covid-19. The antioxidant properties of selenium are particularly useful in reducing complications in Covid patients with associated comorbidities such as arthritis, tumor, heart and brain diseases.

Researcher also found that deficiency of selenium increases the risk of viral infection. Interestingly the administration of Se NPs at the dose of 0.5 mg per kg, improves the protective response by increasing the level of TNF-α and IFN-γ [28], which suggests Se NPs may be an efficient approach for improving immunity during Covid-19 infection. Moreover, literature evidence suggests multiple binding interactions of Se NPs help to reduce the risk of drug resistance. Aligning the above-mentioned statement, surface modified Se NPs by amantadine (SeNPs-AM), were found to be effective at preventing MDCK cell line against H1N1 influenza by suppressing the neuraminidase activity and enhancing cell apoptosis. Metal nanoparticles because of their multifaceted mechanism not only helps to trigger drug activity but also prevent drug resistance. These outcomes suggest metal nanoparticles may have the potential as an adjunct for Covid-19 treatment.

Copper Nanoparticle

The oxidized copper nanoparticle (CuO NPs) is a well-known catalyst, have the capacity to reduce the bacterial and virus population. The study report suggests that Cu^{2+} ion because of increased oxidative stress shows antiviral potential against all types of virus such as HIV-1, influenza, herpes simplex virus. Fujimori et al. demonstrate the antiviral activity of copper (I) iodide (CuI) nanoparticle (160 nm) against H1N1 influenza confirmed through plaque titration assay. Experimental results indicate nanoparticles at a concentration of 17 μg per ml over an incubation period of 1 h produces dose-dependent reduction of virus titer. The possible mechanism of virus inactivation is related to inactivation of surface glycoprotein such as HA and NA by hydroxyl radials [29]. Similarly, another study on vero cell line demonstrate CuO NPs of 40 nm size reveals excellent antiviral potential against Herpes simplex virus characterized by an 83.3% reduction of virus load, attributed to the ability of CuO NPs to inhibit the viral fusion in host cells and inhibition of viral replication. In addition to antiviral effect, copper nanoparticle could be useful in the preparation of safe and effective personal protective equipment (PPE) such as face mask, respirators, hair cups, etc.

Regardless of its positive outcomes, copper nanoparticles have been reported to cause toxicity. Literature revealed CuO NPs shows size-dependent cytotoxicity and genotoxicity in C57BL/6 mice cell line. Further in-vivo toxicological findings suggest inhalation of CuO NPs induces pulmonary inflammation and fibrosis in a dose-dependent manner [30]. In another study, it was found that intratracheal instillation CuO NPs (33 nm) induces acute toxicity, inflammation and edema in F344 male rats. Irrespective of size-dependent toxicity, distinctive advantages of copper nanoparticles against respiratory pathogens could make a significant impact in the management of Covid-19.

Conclusion

Currently, there is no approved treatment available for COVID-19, creating an unprecedented threat for the entire world. Development of nano-based technology, especially using the intrinsic properties of the metal nanoparticle provide a viable approach to combat viral infection. There are many established scientific reports that claimed the potential benefits and antiviral activities of different metal nanoparticles against a wide range of viruses including HIV-1, influenza virus, hepatitis B virus, herpes simplex virus, etc. Recent evidence suggests structural and functional characteristics of metal nanoparticles such as size, surface charge and surface area are the most likely factors determining their biodistribution and subsequent anti-viral efficacy. Silver and gold nanoparticles show great potential against a wide range of respiratory viruses. However, their prospective application against coronavirus is not properly elucidated. Irrespective of several advantages, metal nanoparticle possesses substantial risk of serious toxicity, therefore it requires extensive toxicological evaluation before making their recommendations as a safe adjuvant for Covid-19 treatment.

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