Potential nanoparticle applications for prevention, diagnosis, and treatment of COVID-19

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Abstract
The coronavirus disease 2019 (COVID-19) pandemic caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) poses an unprecedented challenge to establish effective methods of prevention and treatment. Nanotechnology has shown excellent potential in its ability to fight a variety of healthcare problems due to nanomaterials’ unique physicochemical properties and controlled nano-bio interactions. Expanding their application to a wide-range of upstream and downstream approaches is necessary to fight COVID-19. At different stages of this virus-caused disease, nanotechnology could offer promising solutions, including a way to combat the large number of fatalities caused by a late-stage cytokine storm. This mini-review provides an overview of the recent studies regarding nanoparticles’ applications in vaccines, personal protective equipment, sterilization of contaminated environments, diagnostic testing, and cytokine reduction treatment in combating COVID-19.

KEYWORDS
COVID-19, cytokine storm, diagnosis, nanoparticles, PPE, sterilization

1 | INTRODUCTION

Coronaviruses are responsible for two recent disease outbreaks, severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS).1,2 On December 29, 2019, four cases of acute respiratory syndrome were identified in Wuhan, China, which have been attributed to a novel strain of coronavirus.2 This disease was given the name coronavirus disease 2019 (COVID-19) and found to be caused by a virus later named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) due to high viral genome homology.1,2 The exact case fatality rate for
COVID-19 is difficult to determine, as it has been highly variable based on factors such as location, patient age, availability of intensive care, and access to and frequency of testing. Additionally, COVID-19 is highly contagious. In just a little over 3 months after the initial case in Wuhan, the World Health Organization (WHO) declared the outbreak to be a pandemic. Transmission of COVID-19 is mainly from person to person, typically through respiratory droplets from coughing, sneezing, or talking. Upon initially contracting SARS-CoV-2, the virus infects the epithelial cells of alveoli, trachea, and bronchi, attaching to the cells’ angiotensin-converting enzyme 2 (ACE2) receptors with a viral spike (S) protein. Virus uptake and proliferation in these cells will further spread the virus in the lung and to other people. Patients are typically asymptomatic during the virus’s 5-6 day incubation period. Following the incubation period, patients may experience a number of symptoms, the most common of which include fever, fatigue, cough, shortness of breath, and hypoxia. Death may occur between 6 and 41 days after the patient begins experiencing severe symptoms depending on various risk factors such as the patient’s age and immune system condition. Currently, the push to find an effective treatment regimen for COVID-19 has mainly focused on repurposing existing medication or developing a working vaccine. For the former, existing antiviral medications are being evaluated for their efficacy in reducing the ability of SARS-CoV-2 to infect host cells and to reproduce. One of these drugs includes Remdesivir (GS-5734), a nucleoside analogue prodrug originally purposed for the treatment of the Ebola virus. Later tests have demonstrated its inhibitory effects on pathogenic animal and human coronaviruses, including SARS-CoV-2 in vitro and MERS coronavirus (MERS-CoV), SARS-CoV-1, and SARS-CoV-2 replication in animal models. Clinical trials also showed that, among those who experienced coronavirus symptoms for 10 days or fewer, patients treated with Remdesivir could attain clinical improvement in a shorter time frame compared to those who received placebo treatments. Taking advantage of the mechanism by which SARS-CoV-2 infects host cells, there are other antivirals that target the ACE2 receptor, preventing uptake of the virus by the functional receptor with varying success rates. On the other hand, vaccines are a valuable preventative measure, as they can potentially eradicate the disease through the development of antiviral immunity. However, it may take months or even years to develop a vaccine that is both safe and efficacious. As of right now, the majority of the COVID-19 vaccine candidates are in the exploratory or preclinical stages. Therefore, while these two treatment regimens show great promise, we still do not have an effective treatment for the COVID-19 pandemic.

Nanoparticles (NPs) should be considered for applications in the fight against COVID-19. Their small size and unique properties lend them usefulness in medical applications and affords benefits not achievable by larger particles of the same substance. For instance, their large surface area to volume ratio and their ability to be specially designed and characterized with surface ligands gives NPs greater affinity and specificity in selective drug delivery. Furthermore, NPs can be administered through multiple routes of delivery, including but not limited to inhalation, intravenous injection, and topical application. Because of their utility and versatility in medicine, NPs are already being used in cancer drugs like Doxil and Abraxane, which have even been shown to result in fewer adverse side effects compared to other treatments. In addition, NPs have previously been formulated as vaccines to fight MERS-CoV. Some vaccines are designed and engineered to mimic the size, shape, and surface properties of the virus to enhance their immune boosting effects.

This mini-review explores the potential utility of NPs in both upstream prevention and downstream treatment of COVID-19. Specifically, we discuss applications of NPs in (a) vaccine formulation, (b) personal protective equipment (PPE) development, and (c) sterilization of contaminated environments before infection. We also consider the use of NPs after disease onset in (d) diagnosis and (e) treatment of infected individuals (Figure 1).

2 | VACCINES

Because of their unique properties and ability to be specifically engineered, NPs can be considered in the development of a COVID-19 vaccine. Already, polymeric, lipid-polymer hybrid, chitosan, and other types of NPs have been successfully used in vaccines for other coronaviruses, including MERS-CoV and SARS-CoV in avian and murine models. One method is to utilize virus-like particles (VLPs), engineered NPs that closely resemble the virus in physicochemical properties yet lack genetic material or the ability to replicate. Specifically, one of the main structural proteins of the coronavirus, the S protein, can be incorporated into the VLPs. These VLPs have been shown to elicit adaptive and innate immune responses and have been utilized in vaccines against the human papillomavirus and hepatitis B virus. A study conducted by Coleman et al revealed that gold-based NPs are especially useful in forming VLPs because of their high surface energy, a property that causes spontaneous adsorption of viral protein markers via protein corona formation (Figure 2A). While high surface energy contributed to the spontaneous formation of VLPs, NP shape was also manipulated to resemble actual viral particles. This method of
immunization can be made even more efficient by decorating the NP surface with other cell-targeting structures.\textsuperscript{7–9,18}

Replicating the strategy employed with antiviral medication treatment, vaccines are also being developed to target the S protein of SARS-Cov-2 to prevent the uptake of the virus by the ACE2 receptor.\textsuperscript{6} Specifically, NPs can potentially be designed to interact with and induce the unfolding of the S protein, rendering it unable to bind with its target.\textsuperscript{24} Deng et al showed the ability of negatively charged gold NPs to cause the unfolding of the fibrinogen protein.\textsuperscript{25} Further studies may reveal a way to utilize NPs to induce similar unfolding effects in the S protein.

3 | PERSONAL PROTECTIVE EQUIPMENT (PPE) AND NANOMATERIALS

Nanomaterials’ antiviral properties, nanoscale size, and ability to be chemically modified also motivate their implementation into PPE. A range of metal NPs have demonstrated useful antiviral properties against other deadly viruses. Silver (Ag) NPs, for example, not only present antibacterial mask opportunities in cost-efficient air filtration, but have also been shown to combat the human immunodeficiency virus (HIV) and herpes simplex virus (HSV).\textsuperscript{26,27} Various forms of iron oxide have demonstrated antiviral activity toward the Hepatitis C Virus (HCV) and HSV.\textsuperscript{27,28} When modified or conjugated with additional functional groups, gold NPs have been used effectively to curtail HIV, HSV, HCV, and influenza viruses.\textsuperscript{27–29} Titanium dioxide NPs have also exhibited inhibitory effects towards influenza viruses like H1N1, H5N1, H3N2, and H9N2 viruses.\textsuperscript{27}

In recent antiviral research specifically for COVID-19, Doremalen et al showed copper is more effective in curtailing SARS-CoV-2 viability than plastics or stainless steel.\textsuperscript{30} The redox cycling between copper ions catalyzes the production of highly reactive hydroxyl radicals, which subsequently damages viral RNA and other biomolecules.\textsuperscript{31} Further research is required to determine the specific SARS-CoV-2 antiviral effects of copper and other metal NPs. Based on these findings, incorporation of metal NPs such as copper oxide NPs into masks, face shields, or nursing gowns may assist in killing SARS-CoV-2 or damaging cellular components residing on PPE surfaces. However, because inhalation of metal NPs such as copper oxide have shown adverse toxic responses, their (bio)reactivity must also be heavily considered and further investigated when integrated into PPE.\textsuperscript{32–35}

Masks are of specific interest in reducing the respiratory transmittance and exposure to viral particles. Although
FIGURE 2 Possible mechanisms of application for NPs. (A) Protein corona formation occurs when NPs spontaneously take up viral protein markers. The resulting VLP can be used for vaccination against future coronavirus infections. (B) Various antimicrobial mechanisms of NPs. (C) Mechanism used by nanosensor to detect SARS-CoV-2 virus. (D) Cytokine storm syndrome following SARS-CoV-2 infection. Following infection, MΦs secrete large amounts of IL-6 and TNF-α cytokines, leading also to downregulation of CD4+ and CD8+ T-cells. NPs with specific surface functionalizations can neutralize these pro-inflammatory cytokines.

touted as the most efficient masks thus far, N95s have only an 85% filtration efficiency for particles smaller than 300 nm.36 The COVID-19 virus, however, has been shown to have a diameter range of 60-140 nm, illustrating an unmet need for more efficient filtration masks.37 The development of nanofibers, commonly produced by electrospinning, offers many potential materials to target this goal.38 Li et al presented an alumina nanofiber filter with an aerosol removal efficiency of 94.35% for particles in the range of 10-400 nm.39 A set of positively charged polyvinylidene fluoride (PVDF) nanofibers were also shown to capture a target set of 100 nm aerosols at pressure drops less than 30 Pa with >90% efficiency.40 Therefore, the use of NPs by molecular size filtration may provide useful in masks, upon proven safety concerns.

Purification of molecules according to their biological function and structure rather than their molecular size is another possible route to enhance PPE. A wide range of electrospun nanofibrous materials (including polyvinyl alcohol [PVA], polyglycolide [PGA], and polylactic acid [PLA]) have been shown to immobilize specific proteins, molecules, and ligands.41,42 As discussed earlier, the SARS-CoV-2 virus binds to the ACE2 receptor in human lung cells. Masks and face shields coated with
this receptor can therefore absorb the virus, removing it from the inhaled air that remains a crucial route of transmission. Nanoflowers, flower-shaped NPs with multiple layers of petals for enhancing enzymatic activity, are one such structure that can be coated with the ACE2 receptor.  

Nanosponges, sourced from human cell membranes that are natural targets of SARS-CoV-2, have also been designed to competitively bind to the virus. By displaying receptors that the virus uses for cell entry, these nanosponges have been shown to neutralize SARS-CoV-2 binding to host cells in a concentration-dependent and potentially viral-mutation-independent manner. Although these approaches may be used to further fortify PPE against viral transmission, the integration of ACE2 receptors on masks may be economically prohibitive.

A more cost-effective route may be synthetic sulfated-derivatives of graphene oxide (GO). Antivirals such as sulfate-rich particles and heparan-sulfate can mimic cell surface receptor sugars that viruses bind for attachment. Recent unpublished and preprinted research has specifically suggested an interaction between SARS-CoV-2 S1 protein receptor and heparin that initiates a conformational change in the protein. Thus, the conjugation of heparin and other repurposed sulfates onto GO NPs, a popular substrate for its high ligand conjugation of heparin and other repurposed sulfates onto GO NPs, a popular substrate for its high ligand contact, may present SARS-CoV-2 adsorption properties. The integration of these NPs into fabrics present another option in fortifying PPE against viral transmission.

4 | STERILIZATION

Given the infectious nature of SARS-CoV-2, limiting the spread of the virus is a priority. Studies have shown that SARS-CoV-2 can remain active on various surfaces for up to 72 h. Thus, disinfection of hospital surfaces that have been directly exposed to COVID-19 patients may be an effective preventative strategy to combat this pandemic. Additionally, secondary infections have been found to be quite prevalent among critically ill COVID-19 patients in pandemic hotbeds of Wuhan, China and New York, USA. Therefore, proper sanitation is a necessity in protecting both medical workers and patients. Currently, the Centers for Diseases Control and Prevention (CDC) recommends disinfecting exposed surfaces with bleach containing 5-6% sodium hypochlorite or alcohol with a concentration >70%. However, NPs, namely silver, gold, iron oxide, and titanium dioxide, may serve as an equally effective, if not more effective, disinfectant compared to the aforementioned biocides.

The antibacterial nature of NPs has already been heavily documented (Figure 2B). Out of all metal oxides, silver has the most compelling case for being an effective antibacterial with a multitude of studies demonstrating successful treatment of bacteria like Escherichia coli (E. coli), Staphylococcus aureus (S. aureus), and Mycobacterium tuberculosis. Iron oxide NPs have demonstrated effective antibacterial activity against E. coli, Proteus vulgaris, and S. aureus as well as inhibition of growth in Pseudomonas aeruginosa (P. aeruginosa) and Serratia marcescens. While standalone gold NPs have produced largely mixed results, studies have shown that gold NPs have been able to bolster the effects of antibiotics against bacteria like E. coli, P. aeruginosa, and S. aureus when conjugated with these drugs. Titanium dioxide has been used effectively alone and used to an even greater effect when light-activated against such bacteria as S. aureus, Streptococcus mutans, and E. coli. These NPs could be useful to combat secondary bacterial infections caused by COVID-19.

NPs have also been successfully used as antivirals. Similar antiviral properties as those that have potential to be implemented into PPE may also be used for sterilization, including silver, iron oxide, gold, and titanium dioxide NPs. Although there is currently limited literature on the effects of NPs against coronaviruses, specifically SARS-CoV-2, the available documentation sheds light on their promising antiviral therapeutic effects.

With the current widespread use of antibacterials and antivirals during the outbreak, the problem of drug resistant bacteria and viruses has become an even more pressing issue. For this reason, NPs’ ability to prevent drug resistance is an advantage as an antimicrobial and disinfectant. While bacteria and viruses may be able to develop a limited number of mutations in response to the typical antimicrobial, the probability of bacteria and viruses being able to simultaneously develop multiple resistance mutations that directly counter the multiple mechanisms of an NP is slim. Different NPs could attack microbes through diverse mechanisms such as oxidative stress, enzyme disruption, and membrane damage. Additionally, NP applications often maximize the strengths and minimize the weaknesses of various NPs by utilizing multiple types of NPs in combination or by equipping a single NP with multiple functional groups. Finally, some NPs can effectively inhibit the production of biofilms, the assembly of microorganisms into a composite structure that promotes antibody resistance by shielding microorganisms within its interior.

Further research must be conducted on the effects of NPs on SARS-CoV-2 before NPs can be widely used as a disinfectant during this pandemic. However, because of their unique antimicrobial and potential antiviral nature, NPs warrant serious consideration for potential application in sanitation products.
5 | DIAGNOSTIC TESTS

In regards to viral diagnosis in the human body, the CDC-recommended test is a nasopharyngeal swab that detects the presence of the genomic sequence of the SARS-CoV-2 virus after reverse transcription and amplification of the cDNA.\(^5\) However, this method requires sending patient samples to a lab for testing and therefore takes multiple days to determine the result.

The magnetic properties of nanomaterials contribute to the potential use of NPs as a biosensor for SARS-CoV-2 virus detection. Gold NPs have magnetic properties that could allow them to rapidly detect the virus.\(^6\) The use of magnetic nanosensors has been extensively studied in regards to the HSV and adenovirus, and functions by detecting magnetic NP clusters, which form after coming into contact with the virus (Figure 2C).\(^5\) COVID-19 diagnostic tests are currently in development utilizing this property in lateral flow antigen detection. In these assays, a membrane strip is coated with two lines: one line presents the gold NP-antibody conjugates and the other captures the antibodies. The patient's sample is added to the membrane, and the proteins are drawn across the strip through capillary action. As antigens pass through the first line, they bind to the gold NP-antibody conjugates, and the complex flows together through the membrane. Upon reaching the second line, the complex is immobilized by capturing the antibodies, and a red or blue line becomes visible. The red line indicates the presence of individual gold NPs, while the blue line signals the presence of clustered gold NPs, thus indicating the presence of the virus.\(^5\)

This diagnostic test allows for rapid detection by allowing tests to be run on-site and thus eliminates the current waiting period. Considering the time-sensitive nature and importance of coronavirus testing, this implementation of NPs to create point-of-care diagnostic tests may prove to be beneficial.

6 | NPS FOR NEUTRALIZING CYTOKINE RELEASE SYNDROME

As there is still no proven treatment for COVID-19, it may be beneficial to turn attention to a less investigated direction, namely toward the cytokine storm or cytokine release syndrome (CRS) phenomenon. This systemic inflammatory response syndrome is a complication found in many severe COVID-19 cases and may be a major factor contributing to the deadliness of the disease.\(^5\) Normally, cytokines are released following the recognition of a pathogen in order to recruit and modulate the immune response. However certain cases of COVID-19 results in CRS, a condition where the immune system uncontrollably releases pro-inflammatory cytokines.\(^3,58,59,60\) In COVID-19 patients with CRS, the two major pro-inflammatory cytokines found at elevated levels are interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-\(\alpha\)) (Figure 2D).\(^58\)–\(^60\) These cytokines are not only inducers of apoptosis but are also known down-regulators of various T-cells, which explains the marked decrease in CD4\(^+\) and CD8\(^+\) T-cell counts in patients experiencing CRS.\(^60\) The increase of cytokines also explains the symptom of lymphopenia present in many severe COVID-19 patients.\(^59,60\) However, more importantly, the elevation of IL-6 and TNF-\(\alpha\) causes toxicity that may lead to tissue degradation, organ failure, acute respiratory distress syndrome, and, eventually, death.\(^3,60\) With the ability to compromise organ systems and the immune system, CRS is a life-threatening medical condition that must be addressed in order to improve health outcomes in treating COVID-19 patients. Therefore, current studies suggest that developing antagonists for IL-6 and TNF-\(\alpha\) may be a promising plan for effectively treating CRS and, more broadly, COVID-19.\(^56,57\)

In order to reduce the excessive immunogenic response of CRS, novel therapeutic agents that directly capture and neutralize cytokines are of particular interest. A number of monoclonal antibodies are currently undergoing clinical trials for treating COVID-19-induced cytokine storm and systemic inflammation issues. Tocilizumab, an anti-IL-6 drug currently in phase III of clinical trials, and Adalimumab, an anti-TNF-\(\alpha\) drug investigated by the Chinese Trial Clinic Registry, have both been proposed as treatments against CRS.\(^61\) Conjugating such cytokine-neutralizing antibodies onto NPs have been shown to enhance their stability, specific targeting, and prolonging retention after local injection.\(^52\) For example, the conjugation of anti-IL-6 antibodies onto an NP of crosslinked chitosan and hyaluronic acid (HA) have been shown to neutralize cytokine activity in arthritic joints. The potent macrophage (M\(\Phi\)) inhibition resulting from the immobilization of IL-6 onto these NPs drives the potential therapeutic use of NPs for CRS in COVID-19 patients.\(^63\)

Extracellular matrix glycosaminoglycan (GAG), such as heparin and heparan sulfate, have also been shown to bind a diverse range of cytokines.\(^62\) By mimicking the intracellular matrix, the electrostatic interaction between the negatively charged sulfate groups of GAG and the positively charged amino acid residues of the cytokines have been shown to effectively modulate cytokine transport and activity.\(^64\) Such dynamic binding interactions have been integrated into NP formulations for cytokine neutralization. For example, a series of NPs with heparin and GAG derivatives have been shown to suppress the production of...
inflammatory cytokines, such as IL-6, TNF-α, and IL-1β, in lipopolysaccharides-stimulated MΦs.65,66

Another treatment that could potentially reduce the severity of the CRS systemic effects are cell-membrane-coated NPs. MΦ-membrane-coated NPs possess a similar antigenic morphology to MΦs that can capture and neutralize pro-inflammatory cytokines, including IL-6 and TNF-α. One study sonicates the cell membrane from E. coli-treated mouse MΦs to form membrane vesicles, which are then fused with polyactic-glycoylic-acid (PLGA) NPs to make the MΦ-membrane-coated NPs. The therapeutic potential of this treatment was evaluated in E. coli-treated mice that had bacterial sepsis and proved to achieve a significant increase in survivals.67 It is important to note that COVID-19 has the potential to cause sepsis in patients affected by the CRS, and thus this treatment could enable effective sepsis management.68–70 Similar to MΦ-membrane-coated NPs, neutrophil-membrane-coated NPs have shown anti-inflammatory effects by neutralizing TNF-α and IL-1β.71 Thus, the current capabilities to engineer NPs via chemical conjugation and target cell membranes mimicry position NPs as a possible treatment opportunity for the deadly CRS phenomenon.

7 | CONCLUSION

The physicochemical properties of NPs allow it to be a highly versatile agent in the prevention and treatment of COVID-19. The various areas of application explored in this mini-review include vaccines, PPE, sterilization, diagnostic tests, and late-stage treatment of COVID-19-induced CRS.

One way NPs can aid vaccine development is through synthesis of VLPs by altering the NP surface to incorporate coronavirus spike proteins.16,21 This allows NPs to mimic the coronavirus structure while mitigating the risk of viral replication due to lack of the viral genome.19,22,23 NPs, especially metal and metal oxide NPs, can also be used in developing PPE due to their antimicrobial and antiviral properties.26–29 This same property renders it useful in sterilizing contaminated surfaces, especially because usage of a variety of different NPs in tandem can maximize effectiveness and prevent drug resistance.48,49–51,54 NPs have beneficial applications even after an individual is infected with COVID-19. Namely, magnetic NPs can be functionalized as diagnostic tests to detect the virus more efficiently than traditional methods.36,57 Since NPs are able to elicit anti-inflammatory effects, they should be considered in the treatment of CRS, a main cause of COVID-19-related mortality.58,63

While certain limitations exist, such as the complexity and time required for the design and creation of NPs in meeting current demands created by COVID-19, NPs possess vast potential to combat the virus. However, the biosafety of NPs must be considered. Past studies have demonstrated NPs’ toxicological effects through inhalation or other pathways of NP introduction to the human body, including vaccination. Though NPs’ cytotoxic effects are currently being studied, it is important to actively consider these properties in future studies and clinical trials.72,73 Additionally, certain NPs may not be degradable in the body, causing adverse effects. As such, producing safe-by-design NPs ensures biodegradability, optimizes the clearance time in the body, and should be used in future studies.74 Due to their versatility and effectiveness, NPs will help scientists and healthcare professionals to mitigate or cure COVID-19.

CONFlict OF INTEREST

The authors declare no conflict of interest.

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