



Role of Nanomedicine in Management and Prevention of COVID-19

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COVID-19, or the Coronavirus disease 2019, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a pandemic. At the time of writing this (July 28, 2020), more than 17 million people have become affected and 0.7 million people have died across the world. Remdesivir has shown glimpses of insight into how to fight the virus, but as of yet remain far from victory. Nanotechnology has proven its role in medicine to deliver the drug at the target site with minimal side effects, particularly in the anticancer domain. Most specifically, a range of nanotechnology-based products, such as nanosilver, are currently on the market because they have demonstrated the potential to combat viruses. This article provides an overview of the role of nanomedicine, including polymeric and inorganic materials, and its future capabilities in the management of the disease outbreak. Taking all this into account, an attempt has been made to educate readers in the simplest way of the role of nanomedicine, which can play a pivotal role in the management of diseases.

Keywords: COVID-19, pulmonary drug delivery, nanomedicine, nanotherapeutics, gold nano—particles

INTRODUCTION

The disastrous outbreak of COVID-19 originated in China, and its Wuhan province was the first epicenter of this pandemic (Wu et al., 2020). As of now, 17 million people worldwide have been infected and over 0.7 million people have lost their lives and still, this number is continuing to rise with many people losing their lives each day. This is one of the biggest catastrophes in human history since world war II, in which the whole world is affected by this frightening situation. The recent outbreak of COVID-19 has created a global emergency for the management of the crisis. COVID-19 is a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused by a novel coronavirus that has encountered humans for first time, and as a result humans lack the innate immunity to fight against this novel strain of the coronavirus which results in severe miscommunication among health care facilities (Al-Qahtani, 2020; Wu et al., 2020). Due to the pandemic situation, it was difficult to handle the enormous amounts of patients who required treatment, which placed a burden on the healthcare industry, and the death rate was higher than expected. The majority of the world experienced a complete lockdown situation to combat the outbreaks and limit the spreads of the virus (Liu et al., 2020). The term “Corona” is the Latin name for “crown” and has been assigned to the coronavirus due to its structure seen under electron transmission microscopy. It is a typical RNA virus family (**Figure 1**) that is divided into four

categories- α , β , γ , and δ which has a single-stranded RNA as a genetic material with capsid of the virus enclosed with a virus genome and club-shaped protein spikes on the surface. The β class of the coronavirus was known prior to this current pandemic, and it is the same class accountable for the previous outbreak, severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) (Al-Qahtani, 2020) SARS-CoV-2 is highly contagious and said to be spread with contact with an infected person, surfaces, and air droplets via the mouth, nose, and eye. It has a long incubation period of around 14 days and shows initial symptoms similar to typical seasonal virus infection like fever, dry cough, and fatigue with difficulty in breathing. However, as the infection spreads in the body, it can cause severe pneumonia with inflammation and fibrosis in the lungs and result in respiratory failure due to inefficient gas exchanges that lead to multiple vital organ (heart, kidney, liver, GIT, and brain) failure and a person can die if artificial oxygen is not provided on time (Al-Qahtani, 2020; Chauhan et al., 2020).

Nanotechnology could play a potential role in multi-disciplinary areas like as health, defense, agriculture, and many more. Currently in the available literature, nanotechnology will play a vital role in bringing multi-disciplinary ways of developing affordable, reliable, and powerful tools for the diagnosis and therapeutics of different serious diseases. Various metallic and non-metallic nanoparticles (NPs) like magnetic nanoparticles (Bohara et al., 2017), Zinc Oxide nanoparticles (Verma et al., 2017a,c; Das et al., 2019) (ZnONPs), Cuprous Oxide nanoparticles (Kumari et al., 2017) (CuONPs), Silver nanoparticles (Verma et al., 2017b, 2018b; Paul et al., 2018) (AgNPs), Nanosized Copper (I) Iodide particles (Kumari et al., 2018) (CuINPs), Gold nanoparticles on Silica nanoparticles (Verma et al., 2018a) (Au-SiO₂NPs) and some other organic nanoparticles (Arun et al., 2019) are very promising to inactivate the COVID-19 infection. This perspective review explains the current progression of nanotechnology for the detection and treatment of viral infections with a focus on coronaviruses especially regarding SARS-CoV-2.

THE POTENTIAL ROLE OF NANOMEDICINE IN COVID-19

The sudden outbreak has created an urgent need for medicine to tackle the virus. To date, there is no standard therapy for the treatment and doctors have tried many methods to manage the symptoms with existing drug molecules such as Chloroquine, Hydroxychloroquine, Ribavirin, Favipiravir, Galidesivir, thalidomide, Emtricitabine, Tenofovir, Baricitinib, Remdesivir, Ruxolitinib, Darunavir, Camostat, Fingolimod, Umifenovir, Lopinavir, and Ritonavir. These drug molecules often suffer from poor solubility, permeability, and lack of targetability that leads to failure in exerting the desired therapeutic effect (Chauhan et al., 2020; Shah et al., 2020) Nanotechnology has proven its role in medicine to deliver the drug at the target site

with minimal side effects. Several nanotechnology-based products are currently on the market and are under clinical investigation.

Most common problems with drug molecules for COVID 19 like infection

1. BCS class II (high permeability and low solubility), III (High solubility and low permeability), IV (low solubility and low permeability)
 2. Non-specific drug distribution and high dose-related toxicity
 3. The short plasma half-life of the drug molecules.
-

Nanomedicine has many facets that can be precisely utilized to deliver the drug molecules to infected cells, and the targeted ligand conjugated nanoparticle specifically binds with epitopes of the virus that results in inactivation of the virus, causing it to fail to enter the cells. Thus, the infection can be neutralized with nanomedicine-based approaches as shown in **Figure 1**.

Several nanocarriers have been exploited for drug delivery to solve the problem associated with drug molecules. These can be divided into two categories, polymeric and inorganic nanocarriers.

In many research labs around the world, scientists are working on nanoparticle-based vaccine products which are still in consideration such as Novavax developing a protein subunit of a nanoparticle vaccine + matrix M (adjuvant) (based on recombinant SARS-CoV-2 glycoprotein). The University of Tokyo/ Daiichi-Sankyo is working on the RNA based lipid nanoparticles (LNP)-encapsulated mRNA for the SARS-CoV-2 infection-causing viruses. Similarly, The Scientific Research Institute of Vaccines and Sera, Saint Petersburg is working on a nanoparticle vaccine (recombinant protein) (S protein and other epitopes based) (Verma et al., 2017a,c; Das et al., 2019; Khalaj-Hedayati et al., 2020).

INORGANIC AND POLYMER-BASED NANOCARRIERS FOR COVID 19 TREATMENT

A polymer of natural or synthetic origin can form highly complex structures with varying parameters during synthesis. The size, composition and shape can be tailorable, which has a significant impact on the morphology and behavior of the polymeric nanocarrier. Natural, synthetic, and semi-synthetic materials can be used to fabricate the nanocarrier such as polymeric nanoparticles, liposome, cyclodextrin complexes etc.

POLYMERIC SOLID COLLOIDAL NANOPARTICLES

Polymeric nanoparticles enable the safe *in-vivo* administration of the drug molecules with its unique properties such as improved safety and efficacy, controlled drug release and targeted drug

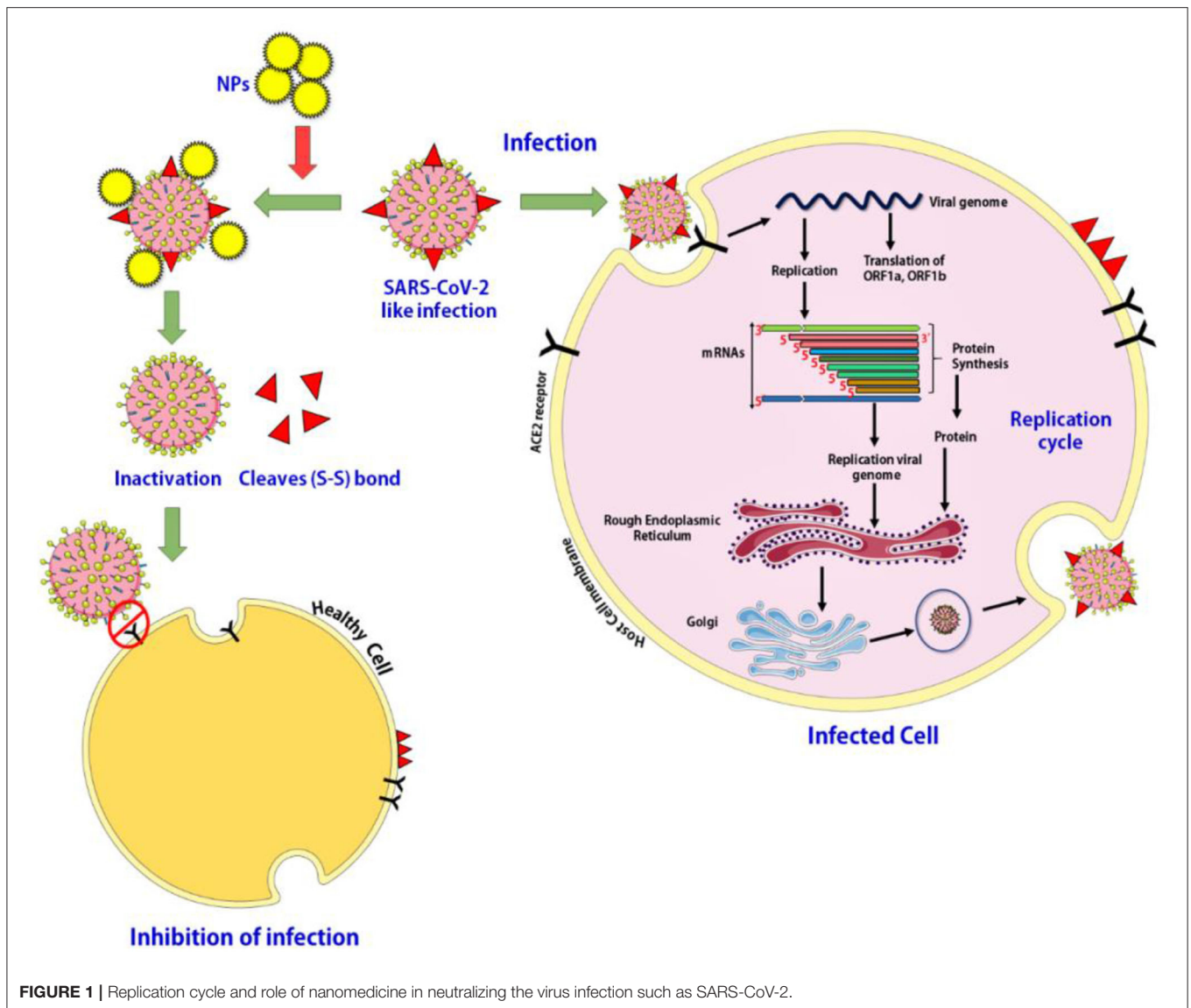


FIGURE 1 | Replication cycle and role of nanomedicine in neutralizing the virus infection such as SARS-CoV-2.

delivery (Kumari et al., 2017; Verma et al., 2017b, 2018b; Paul et al., 2018). It also reduces the high dose-related side effects and permeability across the cellular membrane due to its nano-size properties. This beneficial effect of the polymeric nanoparticle can be utilized for drug delivery to revive the existing drug to treat the SARS-CoV-2 infection. Zhang et al. (2020), have developed the poly (lactic-co-glycolic acid) (PLGA) polymer-based nanosponge to tackle SARS-CoV-2 Infectivity. Mainly, human lung epithelial type II cells and human macrophages membrane-coated nanosponge was fabricated with PLGA as the inner core material which shares the same cellular physiology required for the entry of SARS-CoV-2 into host cells. This artificial cellular nanosponge acts as a receiving target for SARS-CoV-2 during incubation where it becomes neutralized and unable to infect the host cells (Kumari et al., 2018). In this way, the polymeric nanoparticle is a potential nanocarrier system to deliver drugs to treat SARS-CoV-2 infection.

LIPOSOMAL TARGETED DELIVERY TO TREAT COVID-19 DISEASE

The liposome is a lipid bilayer vesicle and has been widely utilized for the delivery of hydrophobic and hydrophilic drugs. The liposome can functionalize as a “stealth liposome” that shows long systemic circulation, targeted and stimulus-responsive drug delivery. Due to its biocompatible and biodegradable nature, it is one of the preferred carriers for drug formulation and can be a potential platform for developing the novel formulation to treat COVID-19 infection. Ohno et al. (2009), have studied the synthetic peptides-based liposomes to treat SARS coronavirus infection. The chemically conjugated peptide-liposome is effective for the induction of cytotoxic T lymphocytes that clears the virus load and can be a potential treatment strategy against SERS (Verma et al., 2018a). Tai et al. (2020), Investigated the liposome-based novel formulation of hydroxychloroquine

in Sprague-Dawley (SD) rats as a potential treatment for COVID-19. This inhalable formulation has found a higher drug concentration in the lungs (~30-fold) with a longer half-life in lung and lower exposure to another organ such as the heart compared to intravenous injection (Arun et al., 2019). Thus, the liposome as a carrier system may impart distinctive advantages for drug delivery to treat the COVID-19 infection.

CYCLODEXTRIN COMPLEXES PREVENT INFECTION AND PROGRESSION OF COVID-19

Cyclodextrin is a natural cyclic polysaccharide containing α , β , and γ as a basic unit. It has been widely explored as a pharmaceutical solubilizer to developed formulation via host-guest complexation to dissolve the hydrophobic and hydrophilic drug molecules (Shah et al., 2020). Currently, cyclodextrin nanoparticles have gained attention due to the presence of multiple units of cyclodextrin that dissolved a higher quantity of drug compared to native cyclodextrin (Khalaj-Hedayati et al., 2020). It is one of the generally recognized as safe (GRAS) materials for human administration and has been proved safe for many decades and has many established formulations on the

market. Recently, the FDA has approved the cyclodextrin-based formulation of Remdesivir for the treatment of COVID-19 (Jones et al., 2020), and it has shown promising effects in a clinical scenario against several other viruses such as Nipah virus (Li C. et al., 2020) and MERS-CoV infection (de Wit et al., 2020; Sheahan et al., 2020). Cyclodextrin not only acts a pharmaceutical solubilizer for the mainly hydrophobic drug but it also has anti-infective properties against several viruses (Kumari et al., 2017; Jones et al., 2020) Hence, cyclodextrin may be considered as a potential delivery vehicle for the pulmonary aerosol for localized drug delivery to the lungs.

INORGANIC AND METALLIC BASED NANOCARRIER FOR COVID 19 TREATMENT

Various metal nanoparticles such as gold, silver, platinum, gadolinium, silica, and its hybrid nanostructure can be used to synthesize inorganic nanocarrier for drug delivery (Jadhav et al., 2018; Chaturvedi et al., 2020). The silver nanoparticle is known for its broad-spectrum antimicrobial activity and is an active component in pharmaceutical products such as silver-sulfasalazine where silver ion enhances the antimicrobial property of sulfasalazine drug. It has been used in the treatment

TABLE 1 | Inorganic nanocarriers' roles in the treatment of viruses like SARS-CoV-2.

S.No.	Name of Nanomaterials	Strategies used	COVID like respiratory viruses	Animal model (Host)	Dose	References
1	Ag ₂ S nanoclusters	Inhibition of viral proliferation <i>in vitro</i> cells	Porcine epidemic diarrhea virus (PEDV)	Pig	46 μ g/ml	(Du et al., 2018)
2	Bio polymeric nano/microspheres N-(2-hydroxypropyl)-3-trimethyl chitosan-nano/microsphere (HTCC-NS/MS)	Capable of adsorbing coronaviruses	Human coronavirus NL63 (HCoV-NL63)	Human	10 mg/500 μ l	(Ciejka et al., 2017)
3	GO-Ag nanocomposite	Antiviral activity against enveloped viruses	Feline coronavirus (FCoV)	Cat	0.1 mg/ml	(Chen et al., 2016)
4	Diphyllin nanoparticles	Inhibition of endosomal acidification responsible for virus uncoating and cytoplasmic entry	Feline Infectious Peritonitis Virus (FIPV)	Cat	2 μ M	(Hu et al., 2017)
5	Ag NPs, Ag NW	Inhibition of cell apoptosis induced by the virus	Transmissible gastroenteritis virus (TGEV)	Pig	3.125–12.5 μ g/ml	(Lv et al., 2014)
6	Composites with silver colloid and titanium dioxide nanoparticles	Inhibited the growth of the viruses	Transmissible gastroenteritis virus (TGEV) and porcine epidemic diarrhea virus (PEDV)	Pig	1,000-fold diluted from original	(Cho et al., 2014)
8	PLGA nanoparticles (PLGA-KAg)	Induced cross-protective cell-mediated immune response	Bovine parainfluenza 3 virus (BPI3V) Swine influenza virus (H1N2)	Pig	2 μ g/ml	(Dhakal et al., 2017)

of wound dressing and burn care products. Moreover, silver has recorded anti-cancer, anti-inflammatory, antiplatelet, anti-angiogenesis antifungal, and antibacterial activities. Additionally, silver nanoparticles are under investigation for viricidal effects. Coronavirus has been found to adhere to surfaces and remains there for around 12 h where the silver-based anti-infective coating can neutralize the virus (Rai et al., 2009; Balagna et al., 2020), studied the anti-infective property of silver by developing the Silver nanocluster-silica composite coated facial mask that exerts a viricidal effect against SARS-CoV-2. This coating can be applied to metallic, glass and ceramic surfaces, so it has vast importance and beneficial application for safety in crowded places like supermarkets, hospitals, and schools to limit the spread of SARS-CoV-2 (Balagna et al., 2020). There are several multifunctional metal nanoparticle/hybrid structures that were explored to limit the range of SARS-CoV-2 through their anti-infective properties as shown in **Table 1**.

NANOMEDICINE AS A PROMISING APPROACH FOR COVID 19 DIAGNOSTICS

During the COVID-19 crisis, there was the urgency to develop the diagnostic kits for the early detection of SARS-CoV-2 infection to restrict the movement of the infectious person. Several laboratory-based tests like chest computed tomography, RT-PCR and point of care tests like detection of antibodies against SARS-CoV19 have been developed. This test can be utilized by medical professionals based on the acute and chronic phase of the viral infection. The efficacy of the test depends on various factors like the invasive nature of the infection, and the development of antibodies against antigens presented by the virus in the human body (Li C. et al., 2020). Nanotechnology has played a significant role in the fabrication of the diagnostic tools at various levels such as lateral flow assay (Panda et al., 2020). Surface-enhanced Raman spectroscopy-based detection where metallic nanoparticles have a fundamental role in improving the signal of analytes and its discovery by optical, electrical and immunofluorescent approaches (Kumar et al., 2020; Mujawar et al., 2020). Li C. et al. (2020), have developed a point-of-care, lateral flow immunoassay-based test for the simple and rapid detection of the antibodies (immunoglobulin M (IgM) and IgG antibodies) against SARS-CoV-2 virus in a human blood sample

in 15 min where the antigen was coated in gold nanoparticles, which further detect the antibodies by the colorimetric reaction. This test can be utilized for the rapid testing of SARS-CoV-2 carriers, symptomatic or asymptomatic, in hospitals, clinics, and test laboratories (Li Z. et al., 2020). Recently, Li C. et al. (2020) has demonstrated in-depth information about the COVID 19 diagnosis that readers can refer to for a more detailed insight.

CONCLUSION

Nanomedicine is one of the most important fields of science that has played a substantial role in the development of the novel technology to tackle the problems associated with disease treatment and diagnosis. Several nanocarriers are under investigation to improve the conventional drug delivery systems to effectively target drug releases, low dose, reduced toxicity, improved permeability, and controlled release of the drug. Moreover, nanomedicine has also performed significant parts in creating point-of-care testing to tackle infectious diseases like COVID 19. Cyclodextrin-based Remdesivir formulation is one of the great success of nanomedicine in the treatment of COVID 19 infection. Additionally, plasmonic nanoparticle (Gold, silver, and its hybrid nanostructure) exert anti-infective activity against COVID 19 and has played a vital role in the development of point-of-care diagnostic tests for its detection. Hence, nanomedicine has provided crucial support to manage the COVID 19 pandemic crisis.

AUTHOR CONTRIBUTIONS

RB: conceived the idea, writing, and data collection. CB: data collection. VC: figure and table. JW: drafting. MS: proofreading and guidelines figure and table. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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