

## Review Article

# Recent Advances on Nanotechnology-Based Strategies for Prevention, Diagnosis, and Treatment of Coronavirus Infections

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is exponentially spreading across the world, leading to an outbreak of serious viral pneumonia. Antiviral therapies using chloroquine, hydroxychloroquine, and favipiravir have been approved by several countries to increase the quality of life of SARS-CoV-2-infected patients. Currently, several companies are intensively working on the production of coronavirus (CoV) vaccines, resulting in some specific vaccines that have been approved for CoV infections in humans. Nevertheless, efficient and specific prevention, treatment, and diagnosis are urgently required to combat the biological diversity and rapid mutation in CoV infections. Recently, significant attention has devoted to nanoformulation or nanoparticles (NPs) due to their specific features like high surface-to-volume ratio, drug encapsulation abilities, and specific optical properties to remove the complications of applied conventional therapeutic and diagnosis options. In this regard, NPs are increasingly used as new anti-CoV agents, vaccine carriers or adjuvants, and nanoscale biorecognition elements. The present review article provides a comprehensive discussion on the recent updates regarding the prevention, diagnosis, and treatment of different CoV infections with an emphasis on the application of NPs in vaccination, treatment, and diagnosis of CoV infections.

## 1. Introduction

Infections with coronaviruses (CoVs) have been on top of the list of leading mortality causes in recent decades. In late 2019, a pandemic outbreak of a new CoV infection in humans, known as severe acute respiratory syndrome CoV-2 (SARS-CoV-2) or COVID-19, has caused public anxiety [1]. Current antiviral therapies are fairly effective in the treatment of CoV infections [2, 3]. To date, some countries have approved some antiviral drugs as pharmacological treatment options for COVID-19. However, some approved COVID-19-specific vaccines are available. Several companies have developed various vaccine candidates for human CoV (HCoV) infections which are in the clinical trial stage [4]. Similar to other conventional therapeutic and diagnostic systems, CoV therapies and diagnostic systems also suffer from limitations in their efficient use in clinical situations to prevent, treat, and diagnose infections. The toxicity of antiviral drugs, low physicochemical stability of therapeutic agents, poor

pharmacokinetics and bioavailability, low sensitivity, and high-cost and time-consuming methods have hindered the advance of novel formulations [5].

The nanotechnology-based formulations are the promising developing formulations which are benefited from eminent features such as high surface to volume ratio, easy surface modification, enhanced physicochemical stability, specific optical properties, and targeted and controlled release capabilities that can lead to lower toxicity and higher efficacy, making them more favorable for the effective prevention, treatment, and diagnosis of viral infections, especially CoV infections [6]. Currently, different nanoparticle-based antiviral agents (especially gold and polymeric NPs) have drawn the attention of scientists due to their specific optical and encapsulation properties for prevention, diagnosis, and treatment of various viral diseases like Ebola, influenza, HSV, and HIV [7–12]. Given the extensive abilities of nanotechnology, it is probable that novelties in this field could substantially influence the advances in combat against

CoV-associated infections. In context, the current review is focused on the potential use of nanotechnology for the prevention, diagnosis, and treatment of CoV infections. However, most of these studies are at primary steps but their outcomes are promising.

## 2. Coronaviruses

CoVs are mostly spherically shaped viruses with a diameter of around 60-140 nm. They contain a single-stranded positive-sense RNA genome as one of the largest genomes among RNA viruses [13]. CoVs are split into four separate generations including  $\alpha$ -,  $\beta$ -,  $\gamma$ -, and  $\delta$ -CoV [14].  $\alpha$ - and  $\beta$ -CoVs only infect mammals, while  $\gamma$ - and  $\delta$ -CoVs can infect birds and some mammals. To date, seven CoVs such as CoV-OC43, CoV-229E, HCoV-OC43, CoV-HKU1, CoV-NL63, Middle East respiratory syndrome (MERS)-CoV, and severe acute respiratory syndrome (SARS)-CoV and SARS-CoV-2 or COVID-19 have been reported to cause infections in human [15, 16]. COVID-19 can result in severe upper respiratory infections similar to a common cold which can mostly lead to death in older people, mainly those with severe underlying health conditions compared to younger ones [17, 18]. The enveloped RNA genomes of CoVs encode three membrane proteins and nucleocapsid (N) protein associated with the RNA genome [19]. The membrane proteins consist of the large spike (S) glycoprotein which contains the receptor-binding domain (RBD) that has a significant role in receptor binding and virus entrance to cells. Since the M protein of SARS-CoV can induce neutralizing antibodies and N protein has T cell epitopes, they have attracted significant attention for vaccine developments [20–22].

## 3. Conventional Prevention, Diagnosis, and Treatment of Coronavirus Infections

Combating viral infection is an enormous challenge in healthcare systems, primarily due to the challenges associated with the spread of viral infections as well as the potential capability of the virus to survive through mutations [23]. Currently, the US Food and Drug Administration (FDA) and the National Medical Products Administration of several countries have approved limited emergency use of antiviral drugs as a remedy for COVID-19 [24]. As can be seen in Table 1, many companies and institutes all over the world are working to develop HCoV vaccines. However, some approved specific vaccine treatments have been licensed for COVID-19, yet prevention measures (e.g., blocking the transmission routes such as the mouth and nose by a napkin, frequent washing of hands, and hand disinfection after presence in public places) are important strategies to combat CoVs. Besides, public transport, as well as eating or touching animals in places struggling with epidemics, should be avoided. Moreover, people should boost their immune system by the well-adjusted diet, sufficient exercise and rest, and maintaining their emotional and mental health. Patients should be isolated in specified hospitals and receive supportive treatments including bed rest, oxygen, calorie, and enough electrolytes in combination with drug treatments

[16, 25]. The potential roles of nanotechnology in the prevention of CoV infections will be discussed in the succeeding sections.

On the other hand, given that the medication in the early stages of infection is closely linked to the effectiveness or success of treatment for CoV infections and the challenges in CoV infections detection from clinical symptoms, the production of rapid detection systems can significantly reduce the spread and morbidity of these infectious species [26]. Up to now, various diagnostic assays including protein microarray [27], enzyme-linked immunosorbent (ELISA), immunofluorescence [28], reverse transcription loop-mediated isothermal amplification (RT-LAMP) [29], and viral flow cytometry (FCM) [29] have been applied for fast and accurate diagnosis of coronavirus infections. Nevertheless, the determination of the genome sequences of coronaviruses, e.g., COVID-19, leads to the recognition of reverse transcription-polymerase chain reaction (RT-PCR) assays as a standard and highly sensitive technique for clinical diagnosis of COVID-19. The development of facile and quick assays is still a vital necessity [30, 31]. Since the RT-PCR method requires complicated machines, well-educated experts in molecular diagnostics, and specific laboratories, diagnostic kits have been designed by various research groups and companies to eliminate the RNA extraction and purification steps, resulting in rapid detection of CoV infections.

Currently, a broad range of pharmacological strategies, such as antivirals, and corticosteroid therapy, cell-based therapeutic options, and traditional Chinese medicine (TCM) have been applied to treat various CoV infections, as presented in Table 2. Recent antiretroviral therapy using HIV drugs has attracted increasing attention. Lopinavir/ritonavir, an HIV protease inhibitor, alone or in combination with other antiviral drugs or IFN $\alpha$  can contribute to the treatment of severe SARS-CoV or MERS-CoV patients [32–34]. IFN $\alpha$  promotes the immune responses of infected patients and also interferes with virus replication [35, 36]. In addition to protease inhibitors, nucleoside analogs have shown significant potentials for CoV infection therapy. For example, ribavirin or tribavirin can be used in the treatment of SARS-CoV and MERS-CoV infections by preventing inosine monophosphate dehydrogenase activity, which can prevent the guanosine triphosphate (GTP) synthesis required for RNA and DNA replication of virus [37, 38]. Another nucleoside analog, favipiravir, which has also shown anti-SARS-CoV-2 activity, is the first approved coronavirus drug in China's National Medical Products Administration [39]. The *in vivo* and *in vitro* anti-SARS and MERS activity of remdesivir, an Ebola drug, indicated that it can be used as a promising candidate for COVID-19 treatment [40]. Oseltamivir has been used for COVID-19 patients, but its efficacy should be further evaluated [16]. Altogether, despite the relative success of antiviral therapies in the treatment of CoV infections (especially in COVID-19), there are some concerns associated with their coadministration with other drugs as well as their potential side effects such as anemia, diarrhea, vomiting, and liver problems [41].

TABLE 1: Ongoing clinical trials for the treatment of CoV infections based on clinicaltrials.gov and chictr.orgdatabases.

Field	Title	Intervention/treatment	Phase	Status	Registration number*	Ref.
	Safety and immunogenicity study of 2019-nCoV vaccine (mRNA-1273) for prophylaxis of SARS-CoV-2 infection (COVID-19)	mRNA-1273 which targets the spike (S) protein of the coronavirus	Phase 1	Recruiting	NCT04283461	[53]
	A study of a candidate COVID-19 vaccine	Adenovirus vaccine vector	Phase 2	Recruiting	NCT04324606	[54]
	Safety, tolerability, and immunogenicity of INO-4800 for COVID-19 in healthy volunteers	INO-4800	Phase 1	Recruiting	NCT04336410	[55]
	Application of BCG vaccine for immune-prophylaxis among Egyptian healthcare workers during the pandemic of COVID-19	Intradermal injection of BCG vaccine	Phase 3	Not yet recruiting	NCT04350931	[56]
	BCG vaccination to protect healthcare workers against COVID-19 (BRACE)	BCG vaccine	Phase 3	Recruiting	NCT04327206	[57]
	BCG vaccine for healthcare workers as defense against COVID 19 (BADAS)	BCG vaccine	Phase 4	Recruiting	NCT04348370	[58]
	A clinical trial to determine the safety and immunogenicity of healthy candidate MERS-CoV vaccine (MERS002)	ChAdOx1 MERS	Phase 1	Recruiting	NCT04170829	[59]
	Safety and immunogenicity of a candidate MERS-CoV vaccine (MERS001)	ChAdOx1 MERS	Phase 1	Recruiting	NCT03399578	[60]
Vaccination	Safety and immunity of COVID-19 aAPC vaccine	Pathogen-specific artificial antigen presenting cells (aAPC)	Phase 1	Recruiting	NCT04299724	[61]
	Immunity and safety of COVID-19 synthetic minigene vaccine	Injection and infusion of lentiviral-SMENP-dendritic cells vaccine and antigen-specific cytotoxic T lymphocytes	Phase 2	Recruiting	NCT04276896	[62]
	A phase II clinical trial to evaluate the recombinant vaccine for COVID-19 (adenovirus vector) (CTII-nCoV)	Recombinant novel coronavirus vaccine (adenovirus type 5 vector)	Phase 1/2	Active, not recruiting	NCT04341389	[63]
	Phase Ib-II trial of dendritic cell vaccine to prevent COVID-19 in frontline healthcare workers and first responders	Autologous dendritic cells loaded with antigens from SARS-CoV-2, with or without granulocyte-macrophage colony-stimulating factor	Phase 1/2	Not yet recruiting	NCT04386252	[64]
	Study of safety and immunogenicity of BVRs-GamVac	Adenoviral-based vaccine against MERS-BVRs-GamVac	Phase 1/2	Recruiting	NCT04130594	[65]
	Randomized, double-blind, placebo-controlled phase Ib study to assess the safety and immunogenicity of MVA-MERS-S_DF-1	MVA-MERS-S_DF1-low and high doses	Phase 1	Not yet recruiting	NCT04119440	[66]
	Study of safety and immunogenicity of BVRs-GamVac-Combi	Heterologous adenoviral-based vaccine against MERS-BVRs-GamVac-Combi	Phase 1/2	Recruiting	NCT04128059	[67]
	Performance evaluation of BCG vaccination in healthcare personnel to reduce the severity of SARS-CoV-2 infection	BCG vaccine	Phase 3	Not yet recruiting	NCT04362124	[68]

TABLE 1: Continued.

Field	Title	Intervention/treatment	Phase	Status	Registration number*	Ref.
	A trial investigating the safety and effects of four BNT162 vaccines against COVID-2019 in healthy adults	Four prophylactic SARS-CoV-2 RNA vaccines: BNT162a1, BNT162b1, BNT162b2, and BNT162c2	Phase 1/2	Recruiting	NCT04380701	[69]
	Study to describe the safety, tolerability, immunogenicity, and potential efficacy of RNA vaccine candidates against COVID-19 in healthy adults	Four prophylactic SARS-CoV-2 RNA vaccine candidates against COVID-19: BNT162a1, BNT162b1, BNT162b2, and BNT162c2	Phase 1/2	Recruiting	NCT04368728	[70]
	Tableted COVID-19 therapeutic vaccine (COVID-19)	Once-daily pill of therapeutic vaccine made from heat-inactivated plasma from donors with COVID-19	Phase 1/2	Recruiting	NCT04380532	[71]
	Phase I study of a vaccine for severe acute respiratory syndrome (SARS)	A recombinant DNA vaccine, VRC-SRSDNA015-00-VP	Phase 1	Completed	NCT00099463	[72]
Cell therapy systems	Bone marrow-derived mesenchymal stem cell treatment for severe patients with coronavirus disease 2019 (COVID-19)	Bone marrow-derived mesenchymal stem cell	Phase 1/2	Not yet recruiting	NCT04346368	[73]
	Monocytes and NK cells activity in COVID-19 patients	Study of immune-mediated mechanisms in patients tested positive for SARS-CoV-2	—	Recruiting	NCT04375176	[74]
	Immune cells in inflammatory arthritis with coronaviruses, including COVID-19	SARS virus, 40 ml blood sample	—	Not yet recruiting	NCT04363047	[75]
	Safety and efficacy of intravenous Wharton's jelly-derived mesenchymal stem cells in acute respiratory distress syndrome due to COVID 19	Wharton's jelly-derived mesenchymal stem cells	Phase 1/2	Not yet recruiting	NCT04390152	[76]
Convalescent plasma therapy	Convalescent plasma compared to the best available therapy for the treatment of SARS-CoV-2 pneumonia (COP-COVID-19)	Plasma	Phase 2	Not yet recruiting	NCT04358783	[77]
	Anti-SARS-CoV-2 inactivated convalescent plasma in the treatment of COVID-19	—	—	Recruiting	NCT04292340	[78]
	Collection of anti-SARS-CoV-2 immune plasma (NIAID)	—	—	Recruiting	NCT04344977	[79]
	Inactivated convalescent plasma as a therapeutic alternative in patients COVID-19	Inactivated convalescent plasma	Phase 2	Not yet recruiting	NCT04385186	[80]
	Convalescent plasma for patients with COVID-19: a pilot study (CP-COVID-19)	Plasma	Phase 2	Not yet recruiting	NCT04332380	[81]
	Convalescent plasma for patients with COVID-19: a randomized, open-label, parallel, controlled clinical study (CP-COVID-19)	Plasma, hydroxychloroquine	Phase 2/3	Not yet recruiting	NCT04332835	[82]
Antibodies	Safety, tolerability, and pharmacokinetics of SAB-301 in healthy adults	SAB-301, an antibody produced in cows to fight MERS	Phase 1	Completed	NCT02788188	[83]
Antiviral drugs		Lopinavir/ritonavir	Phase 3	Recruiting	NCT04321174	[84]

TABLE 1: Continued.

Field	Title	Intervention/treatment	Phase	Status	Registration number*	Ref.
	COVID-19 ring-based prevention trial with lopinavir/ritonavir (CORIPREV-LR)					
	Evaluating the efficacy of artesunate in adults with mild symptoms of COVID-19	Artemisinin/artesunate	Phase 2	Not yet recruiting	NCT04387240	[85]
	Hydroxychloroquine as chemoprevention for COVID-19 for high-risk healthcare workers	Hydroxychloroquine sulfate (HCQ)	Phase 2	Enrolling by invitation	NCT04345653	[86]
	New antiviral drugs for treatment of COVID-19	Combination of nitazoxanide, ribavirin, and ivermectin	Phase 3	Not yet recruiting	NCT04392427	[87]
	Study to evaluate the safety and antiviral activity of remdesivir (GS-5734™) in participants with moderate coronavirus disease (COVID-19) compared to standard of care treatment	Remdesivir	Phase 3	Recruiting	NCT04292730	[88]
	Adaptive COVID-19 Treatment Trial (ACTT)	Remdesivir	Phase 3	Recruiting	NCT04280705	[89]
Traditional Chinese medicine	A real-world study for the efficacy and safety of large-dose Tanreqing injection in the treatment of patients with novel coronavirus pneumonia (COVID-19)	Large-dose Tanreqing injection	Phase 4	Not yet recruiting	ChiCTR2000029432	[90]
	Clinical study for Gubiaojieduling in preventing of novel coronavirus pneumonia (COVID-19) in children	Gubiaojieduling	—	Not yet recruiting	ChiCTR2000029487	[91]
	Clinical trial for Tanreqing capsules in the treatment of novel coronavirus pneumonia (COVID-19)	Tanreqing capsules	Phase 0	Recruiting	ChiCTR2000029813	[92]
	Shenfu injection in the treatment of severe novel coronavirus pneumonia (COVID-19): a multicenter, randomized, open-label, controlled trial	Shenfu injection	Phase 4	Not yet recruiting	ChiCTR2000030043	[93]
	A multicenter, randomized, open-label, controlled trial for the efficacy and safety of Shenqi Fuzheng injection in the treatment of novel coronavirus pneumonia (COVID-19)	Shenqi Fuzheng injection	Phase 4	Recruiting	ChiCTR2000029780	[94]
	A randomized, open-label, blank-controlled trial for Lianhua Qingwen capsule /granule in the treatment of novel coronavirus pneumonia (COVID-19)	Lianhua Qingwen capsule/granule	Phase 4	Completed	ChiCTR2000029434	[95]
	A randomized, open-label, blank-controlled, multicenter trial for Shuang-Huang-Lian oral solution in the treatment of novel coronavirus pneumonia (COVID-19)	Shuang-Huang-Lian oral solution	Phase 4	Recruiting	ChiCTR2000029605	[96]
	A randomized controlled trial for honeysuckle decoction in the	Honeysuckle soup	Phase 0	Recruiting	ChiCTR2000029822	[97]

TABLE 1: Continued.

Field	Title	Intervention/treatment	Phase	Status	Registration number*	Ref.
	treatment of patients with novel coronavirus (COVID-19) infection A multicenter, randomized, open-label, and controlled trial for the efficacy and safety of Kang-Bing-Du granules in the treatment of novel coronavirus pneumonia (COVID-19)	Kang-Bing-Du granules	Phase 4	Recruiting	ChiCTR2000029781	[98]
	Efficacy and safety of Jing-Yin granule in the treatment of novel coronavirus pneumonia (COVID-19) wind-heat syndrome	Jing-Yin granule	Phase 4	Not yet recruiting	ChiCTR2000030255	[99]
	A randomized, open-label, controlled trial for the safety and efficiency of Kesuting syrup and Keqing capsule in the treatment of mild and moderate novel coronavirus pneumonia (COVID-19)	Kesuting syrup and Keqing capsule	Phase 4	Recruiting	ChiCTR2000029991	[100]
	A multicenter, randomized, open-label, parallel, controlled trial for the evaluation of the effectiveness and safety of Xiyanping injection in the treatment of common type novel coronavirus pneumonia (COVID-19)	Xiyanping injection	Phase 4	Recruiting	ChiCTR2000030117	[101]
	Efficacy and safety of Xue-Bi-Jing injection in the treatment of severe cases of novel coronavirus pneumonia (COVID-19)	Xue-Bi-Jing injection	Phase 0	Recruiting	ChiCTR2000030388	[102]
Others	Clinical application of methylene blue for treatment of COVID-19 patients (COVID-19)	Methylene blue, vitamin C, N-acetyl cysteine (MCN)	Phase 1	Recruiting	NCT04370288	[103]
	NO prevention of COVID-19 for healthcare providers (NOpreventCOVID)	Inhaled nitric oxide gas	Phase 2	Not yet recruiting	NCT04312243	[104]
	Angiotensin-(1,7) treatment in COVID-19: The ATCO Trial (ATCO)	Angiotensin 1-7 (a peptide that is downregulated in COVID-19 patient and it may potentially improve respiratory function)	Phase 2/3	Not yet recruiting	NCT04332666	[105]
	Use of cSVF via IV deployment for residual lung damage after symptomatic COVID-19 infection (GARM-COVID19)	IV deployment of cellular stromal vascular fraction (cSVF) in sterile normal saline IV solution	Early phase 1	Enrolling by invitation	NCT04326036	[106]

\*NCT: National Clinical Trial; ChiCTR: Chinese Clinical Trial Register.

As pharmacological options, some medications used for the treatment of other diseases (e.g., malaria and arthritis) have recently gained increasing attention. Chloroquine and hydroxychloroquine have shown anti-SARS-CoV-2 activities and were recently approved by the FDA for limited emergency use against COVID-19 [42]. In fact, they inhibit the virus entry into the cells and hence blocking its transport into the cell organelles [43]. As another class of pharmacological options for treatment of CoV infections, corticosteroids have been applied to suppress cytokine production in SARS-CoV

and MERS-CoV patients; nevertheless, there is no compelling evidence for its effectivity on COVID-19 treatment and some recommended its use for a short time [16, 44, 45].

According to Tables 1 and 2, in addition to the above-mentioned therapeutic options, cell-mediated therapy based on immune and stem cell has been investigated as a promising option for the treatment of CoV infections. The convalescent plasma of the cured patients contains antiviral antibodies and can be exploited to reduce viral loading and mortality of patients [46, 47]. To date, in cell-based therapy

TABLE 2: Conventional drugs used in the treatment of CoV infections.

Type of treatments	Drugs	Mechanism of action	Ref.
Antivirals	Lopinavir/ritonavir	Protease inhibitor that interferes with the replication and synthesis of CoVs (bind to the endopeptidase C30 of SARS-CoV-2 protease as evaluated by molecular models)	[107, 108]
	Ribavirin or tribavirin	Prevention of RNA and DNA replication (interferes with RNA metabolism required for viral replication)	[15, 37]
	Favipiravir	RNA polymerase inhibitors; prevents replication of the viral genome	[109]
	Remdesivir	Prevention of RNA and DNA replication (interferes with RNA metabolism required for viral replication)	[110]
	Oseltamivir	Inhibiting the activity of the viral neuraminidase enzyme found on the surface of the virus which prevents budding from the host cell, viral replication, and infectivity	[111]
	Interferon alfa (multiferon)	IFN $\alpha$ suppresses viral infection by directly interfering with replication of the virus and by promoting both innate and adaptive immune responses	[41]
Antimalarials	Chloroquine	Interfering with viral particles binding to their cellular cell surface receptor	[40, 112]
Corticosteroids	Methylprednisolone	Binds to and activates specific nuclear receptors, resulting in altered gene expression and inhibition of proinflammatory cytokine production	[111, 113, 114]
Convalescent plasma	Convalescent plasma	Antiviral antibodies (IgG, IgA, IgM, IgE, and IgD) found in convalescent plasma from recovered patients	[115]

of CoV infections, natural killer (NK) cells and mesenchymal stem cells (MSCs) have shown bright potentials in the treatment of COVID-19 infection. NK cells can lyse antibody-coated virus-infected cells by mediating antibody-dependent cellular cytotoxicity (ADCC) against SARS-CoV [48, 49]. MSCs can improve the cytokine storm syndromes, acute respiratory distress syndrome, and lung injury by suppressing the infiltration of immune cells to pulmonary tissues and proinflammatory cytokine secretion which can be a valuable treatment to inhibit the COVID-19-associated lung damage [50, 51]. Also, TCM has been used as a complementary therapy for CoV-infected patients, declining the side effects of conventional therapeutics. TCM herb formulae can be used to inhibit the activity of CoV infections via different mechanisms especially inhibition of the enzymatic activities and cellular entry. Based on Table 1, several TCM formulations are now available in clinical trials [52]. Lately, in order to address the drawbacks of conventional prevention, diagnosis, and treatment of coronaviruses infections, the research community turned to nanotechnology to implement a new efficient nanotechnology-based approach to combat infections with coronaviruses which will be addressed in the next sections.

#### 4. Nanotechnology in Coronavirus Infections

Nanotechnology is referring to design, synthesis, and application of materials with at least nanoscale size (<100 nm) in one dimension. Owing to small size, large surface area, and high loading capacities, as well as specific optical properties of NPs, they have been widely explored in a variety of biological systems to attain the intended therapeutic or diagnostic performance [116–120]. Currently, a variety of NPs have been explored as nanopharmaceuticals, or nanosized pharmaceuticals, for prevention and treatment of various human diseases such as viral infections. Most of approved nanopro-

ducts in market have revealed lower toxicities and higher therapeutic efficacy compared to conventional formulations. Nonetheless, nanoformulations currently in clinical trials have demonstrated positive outcomes; thus, they are likely to be approved by the regulators in preceding years [121, 122]. Today, one important application in response to the increasing prevalence of viral infections especially coronavirus infections is the development of improved antiviral products. NPs applied in prevention, detection, and treatment of CoV infections are illustrated in Figure 1. Table 3 summarizes the description, pros and cons, and potential roles of NPs in coronavirus infections. In the next section, the application of NPs in prevention, diagnosis, and treatment of CoVs will be discussed.

*4.1. Nanotechnology in the Prevention of Coronavirus Infections.* The recent outbreak of CoV infection in the absence of effective conventional treatments highlights the importance of prevention and control of CoV transmission. Advances in nanotechnology have led to the development of nanotechnology-based vaccines, masks, and disinfectants for controlling CoV infections which are presented in the next sections.

*4.2. Nanotechnology-Based Vaccines for Coronavirus Infections.* Nowadays, vaccination has gained increasing attention owing to its promising results to combat various infections and to reduce the costs as well as deaths worldwide [128]. The recent rapid emergence of CoV infection has shown that vaccination can act as a significant function in managing the social safety and public health. Coronavirus vaccination may either preserve people against infection or have a therapeutic impact. However, development of CoV vaccines has encountered some limitations including inadequate protectivity, the absence of high-throughput animal models, scale-up and GMP production, and safety concerns. There are currently different types of vaccine formulations

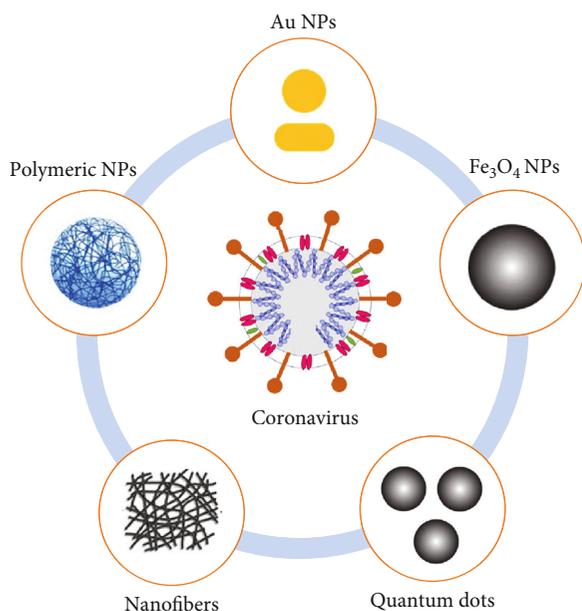


FIGURE 1: Applied NPs for prevention, detection, and diagnosis of CoV infections.

including attenuated viruses, viral proteins (subunits or virus-like particles), nucleic acids, or recombinant viral vectors that have been used to target diverse CoVs [19, 129, 130]. Nevertheless, they have been significantly correlated with the risk of the weak immune response, reversion to pathogenic virulence, and inadequate immunogenicity and induced partial protection. Hence, while improving safety and efficiency of candidate vaccines, alternative options should be considered in vaccine development to shorten the access time. Nowadays, nanotechnology-based vaccination systems have shown promising potentials in resolving the limitations of conventional vaccine formulations. They have several capabilities such as (i) delivery of different types of vaccines; (ii) vaccine administration through nasal or oral routes to stimulate mucosal immune reactions; (iii) targeted and controlled release of single or multiple antigens to antigen-presenting cells, leading to prolonged half-life and antigen presentation to the immune cells; (iv) boosted immunogenicity of vaccines and adjuvants; (v) decline in the potential antigen toxicity; (vi) protection of the encapsulated antigens under harsh conditions; and (vii) stimulation of the immune response as adjuvants [131, 132]. Such findings and observations have inspired material scientists to imitate viral infection for production of nanotechnology-based vaccination systems. Design of CoV vaccines adopts various strategies; however, most of them target the structural proteins including S or spike, N, envelope (E), and membrane (M) proteins that they might act as the most important inducers of neutralizing antibodies [19]. Following the identification of the SARS-CoV-2 structural proteins and promising results in development of the synthetic virus-like NPs [133, 134], Chen and coworkers recently developed a synthetic virus-like particle (sVLP) based on spontaneous protein corona formation using AuNPs and an avian CoV spike protein for vaccination in IBV-CoV infection, as presented in Figure 2

[135]. Developed sVLP formulation led to efficient lymphatic antigen delivery, stronger antibody titers, increased splenic T cell response, and reduced infection-associated symptoms in an avian model of CoV infection in comparison to vaccination with free proteins. Moreover, in comparison with a commercial whole inactivated virus vaccine, sVLPs offered superior antiviral protection. In addition to AuNPs, polymeric NPs have been recently applied as sVLPs for promoting immune cell engagement and antigen processing against CoV infections. For instance, Tasca and coworkers developed a viral capsid-like hollow poly(lactic-co-glycolic acid) (PLGA) NP for entrapment of cyclic diguanylate monophosphate (cdGMP), a canonical stimulator of interferon genes (STING) agonist. The cdGMP upregulates the proinflammatory cytokines to shape the adaptive immunity, as an adjuvant, and recombinant MERS-CoV RBD antigens as Th1 immune responses and cellular immunity promoters against the MERS-CoV infectious. The developed formulation showed significant antigen-specific cellular and humoral responses in immunized mice [136].

In addition to synthetic NPs, MERS-CoV spike protein NPs have been employed against MERS-CoV infection. In this strategy, MERS-CoV S protein NPs are combined with an appropriate adjuvant to promote sufficient immunization against CoV infections. Coleman et al. showed the applicability of MERS-CoV S protein NPs to prompt a robust neutralizing antibody response to MERS-CoV [137]. Following the mentioned research, they developed a formulation using MERS-CoV spike protein NPs and Matrix-M1 adjuvant to protect mice against MERS-CoV infection [138]. Their results indicated that adjuvant combination with MERS-CoV S protein NPs can neutralize antibody response in vaccinated mice as well as providing efficient MERS-CoV replication blocking in the lungs. Furthermore, Jung et al. developed vaccination formulation based on recombinant adenovirus serotype 5 delivering the MERS-CoV S protein gene (Ad5/MERS) and MERS S protein NPs with alum adjuvant to induce cellular and humoral immune responses with heterologous prime-boost vaccination strategy [139]. Results showed not only Ad5/MERS-induced-specific immunoglobulin G but also MERS S protein NP-induced-specific IgG. The results also revealed that just heterologous prime-boost immunization and homologous immunization with S protein NPs can induce MERS-CoV- neutralizing antibodies. Additionally, Ad5/MERS can induce Th1 cell activation, alone or in combination with S protein NPs. However, heterologous prime-boost vaccination Ad5/MERS regimens caused Th1 and Th2 responses, while homologous prime-boost vaccination did not exhibit any Th1 and Th2 responses indicating more usefulness of heterologous prime-boost for long-lasting immune responses against MERS-CoV. NPs could be also employed as adjuvants to prevent CoV infections. NPs have been administrated in combination with antigens as an adjuvant to enhance the immunization of vaccine systems. Sekimukai and colleagues developed two types of vaccine adjuvants based on AuNPs and Toll-like receptor (TLR) agonists to increase the efficacy of intranasally administered ultraviolet- (UV-) inactivated SARS-CoV vaccine [140]. Surface adsorbed recombinant CoV S protein AuNPs

TABLE 3: Definition, pros, cons, and potential use of applied NPs in prevention, treatment, and diagnosis of CoV infections.

Nanomaterials	Definition	Pros	Cons	Potential uses	Ref.
Polymeric NPs	Polymeric NPs, collectively named as spheres and capsules, are solid colloidal particles with submicron size, which are made from synthetic to natural polymers	They can be used to load multifunctional agents through encapsulation or covalent bonding They can be used to target special to cells and tissues by easily modifications with ligands Different route of administration Enhanced thermodynamic stability of loaded therapeutic agents	However, there are several challenges such as toxicity, remaining organic solvents from the manufacturing procedure, and the scaling-up problems for commercial production	Can be used to encapsulate antigens, adjuvants, and drugs for targeting, controlled release, and stimulate responsive delivery	[123]
AuNPs	AuNPs are nanosized gold particles with diameters ranging from 1–100 nm, which are dispersed in aqueous solution	Special optical properties including surface-enhanced Raman scattering (SERS), surface plasmon resonance (SPR), and fluorescence resonance energy transfer (FRET) Easily functionalization by thiol-bearing compounds Easy synthesis with tunable sizes and surface High cell permeability	Need to long-term cytotoxicity study High cost production Biodistribution, pharmacokinetics, and possible toxicity	Can be used as drug carriers, vaccine adjuvants, and electrochemical and colorimetric biosensors	[124]
Magnetic NPs	Magnetic NPs are nanosized particles made up of often iron, chromium, nickel, and cobalt, and a chemical compound that has functionality	Respond to external magnetic fields Good biocompatibility Easy surface modification Easy separation from media	Potential material toxicity Low colloidal stability and biocompatibility Might induce immunological or inflammatory response	Can be used for drug delivery, imaging, and RNA extraction	[125]
Quantum dots	QDs are nanosized luminescent semiconductors, 2–10 nm, with special optical and electrical properties that cause high brightness and photostability compared to traditional fluorescent dyes	Small size Good cellular and intracellular uptake and drug release Easy surface modification	Potential material toxicity	Can be used for drug delivery and biosensing	[126]
Nanofibers	Nanofibers are fiber-nanosized	Highly porous structure Large surface-to-volume ratio High scaling-up production rate and simplicity of the setup of electrospinning technique	Low yield, high operating voltage, and difficulty in attaining in situ deposition of nanofibers on different substrates	Can be used for nanofilter production	[127]

showed antigen-specific IgG response; however, it was unsuccessful to make a protective antibody and eosinophilic infiltration in the lungs in comparison to TLR agonists which effectively reduced the required extent of recombinant S protein for the vaccination and eosinophilic infiltration in the lungs after the SARS-CoV infection. Today, concerning the importance of CoV S protein in CoV vaccine development, Novavax, an American vaccine development company, has developed several recombinant NP-based vaccine candidates to target surface S protein of MERS infection which are in

animal models' testing stage [24]. The surface ligands of COVID-19 have also attracted the attention of NanoViricides company to develop a nanoformulation based on nanoviricide® technology [24]. In nanoviricides, polymeric micelles comprise a single-chain polymer conjugated to specific ligands that help in engulfing or coating the virus, resulting in virus neutralization and destabilization and may be viral genome attacking [141].

Currently, numerous antigens or adjuvants have been loaded into NPs to target antigen-presenting cells (APCs)

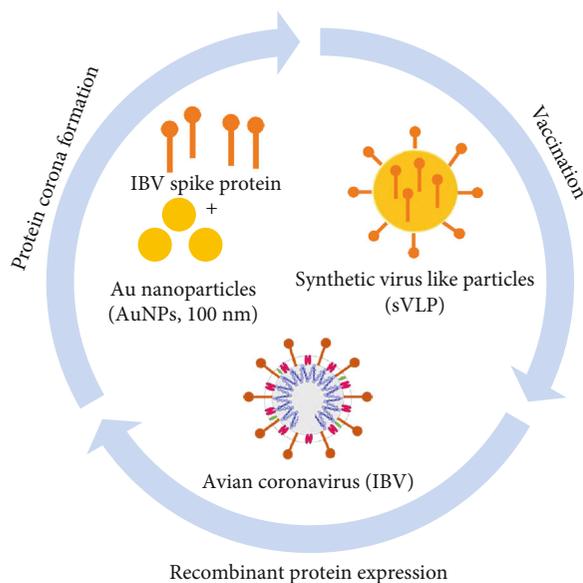


FIGURE 2: Preparation of avian CoV sVLPs through spontaneous protein corona formation strategy. Spike glycoprotein derived from an avian infectious bronchitis virus (IBV) was mixed with 100 nm AuNPs to prepare sVLPs for vaccination of an avian model of CoV infection [135].

resulting in efficient antigen recognition and presentation [142, 143]. Raghuwanshi and coworkers encapsulated plasmid DNA-encoding N protein (pVAXN) of SARS-CoV into biotinylated chitosan NPs for nasal immunization [144]. Biotinylated chitosan NPs were surface-functionalized with a recombinant bifunctional fusion protein (bfFp) which contains a single-chain variable fragment (scFv) to target DEC 205 receptors of DCs. The positively charged chitosan NPs can efficiently bind to negative sialic residues in the nasal mucus. The slow release of the formulation as well as the transient opening of the tight junctions can enhance paracellular transport across the nasal mucosa. Moreover, the binding of receptor-specific ligands to chitosan microspheres enables receptor-mediated endocytosis leading to cell-specific delivery vaccine formulations [145, 146]. The polymeric nanoformulation vaccines are resistant to DNase; thus, they can act as an *in vivo* efficient vaccination system. Intranasal administration of targeted polymeric nanoformulation in combination with anti-CD40 DC maturation stimuli can enhance the mucosal IgA and systemic content of IgG against N protein of SARS-CoV; however, no mucosal and systemic immune responses were observed for bare pDNA. Furthermore, results indicated higher systemic IgG responses for intramuscular injection of bare pVAXN or NP-loaded pVAXN as compared with the intranasal administration. Such a difference could be due to the low dosage of bare or nanoencapsulated DNA. In a study, Sun et al. showed that intramuscular administration of chitosan-encapsulated N protein of bovine CoV (BCV N) NPs can significantly enhance IgA and IgG levels as compared to Montanide ISA 206, an oil adjuvant, effectiveness of chitosan NPs to be used as an adjuvant for BCV N protein [147]. Altogether, nanotechnology-based vaccine formulations are promising

immune cell activators and antigen carriers for vaccination, but further studies are still required.

#### 4.3. Nanotechnology in Prevention of Coronavirus Infections.

As previously mentioned in Section 3, blocking transmission routes especially the mouth and nose is an important strategy to combat CoVs. Hence, efficient personal protection devices against CoV nanoscale aerosols have attracted increasing attention. However, N95 and N98 masks protect people against aerosols with 300 nm, smaller aerosols, and airborne viruses might be transmitted to the respiratory system, resulting in infection. Concerning the nanoscale size of CoVs, many research groups are focused on the production of nanofilter masks to prevent the transmission of CoV aerosols smaller than 300 nm. Recently, Leung and Sun have designed a nanofiber filter based on a single or multiple layers of electrostatically charged polyvinylidene fluoride (PVDF) nanofibers (with size ranges of 84, 191, 349, and 525 nm) deposited on a mat substrate to capture airborne COVID-19 and nanoaerosols with less than 300 nm [148]. Results indicated that smaller nanofibers (84 nm) can offer higher mechanical capturing of neutral sodium chloride aerosols used as a virus model, which can be assigned to their large specific surface. In comparison to single-layer filters based on small nanofibers, small and large multilayer nanofiber filters were capable of capturing 90% of simulated 100 nm in size airborne COVID-19 which might be more hopeful for viruses with negative charges. In another research, they have developed a charged PVDF multilayer nanofiber filter to filter the simulated airborne COVID-19 using ambient nanoaerosols. Their results showed 6-layer charged nanofiber filter could be used to filter the nanoaerosols sizes of 50, 100, and 300 nm ambient aerosols with 88%, 88%, and 96% capture efficiency while the filtering efficiencies of 92%, 94%, and 98% could be achieved for the sodium chloride aerosols with the same size order [149]. Recently, a Korea Advanced Institute of Science and Technology developed a washable and ethanol-sterilizable nanofiber-based filter that can be easily fitted inside a conventional mask to filter 94% of contaminants [150].

#### 4.4. Nanotechnology-Based Surface Disinfectant in Coronavirus Infections.

As another exposure-reducing strategy toward CoVs and concerning the importance of the contaminated surfaces in the spread of the CoVs, specific attention has also paid to decontamination of surfaces using 70–85% ethanol, NaClO, and iodine-based disinfectants [151]. On the other hand, findings have approved the antiviral activity of NPs, resulting in their usage as surface disinfectants with cell membrane entrance virus replication inhibition as well as surface attachment interfere of the virus into cells [152]. Therefore, the Nanotech Surface Company has recently developed a self-sterilizing formulation based on titanium dioxide and silver ions to disinfect buildings in Milan [153]. Taken together, nanotechnology-based filters (face masks) and disinfectants are promising products for personal and public protections against CoVs which require further research.

**4.5. Nanotechnology in the Diagnosis of Coronavirus Infections.** Rapid and precise detection technique can reduce the spread and morbidity of CoV infections. There are numerous techniques being employed for the detection of CoV infections; however, most of them suffer from some limitations including low sensitivity, time-consuming procedures, high costs, and late detection [154]. The current standard technique for CoV detection, RT-PCR, is a highly time-consuming technique requiring expert users, and complex devices, highlighting the need for sensitive and early detection of CoV infection. Novel detection assays based on nanotechnology have gained increasing attention. The unique properties of NPs such as their high surface area, easy functionalization, and special optical properties have led to their application as rapid, sensitive, and cost-effective diagnostic systems with less sample volume and laboratory equipment [155, 156]. During the last decades, a great deal of effort has been dedicated to the use of NPs in the design of various nanobiosensors for the detection of infectious diseases [156]. In this section, different applications of NPs in design of colorimetric, optical, and electrochemical sensors for detection of CoV infections are presented.

**4.6. Nanotechnology in Colorimetric Detection of Coronavirus Infections.** Colorimetric biosensors are sensitive, selective, and low-cost detection tools capable of detecting analytes based on color changes that can be easily recognized by naked eyes or simple portable optical detectors [157–159]. Special physicochemical properties of NPs have led to emergence of new colorimetric diagnostic systems [160]. Among various NPs, AuNPs have gained increasing attention in the development of biosensors owing to their fascinating optical properties which are related to the strong surface plasmon resonance (SPR) absorption. SPR is generated by the incidence of light on a metal surface, causing collective coherent oscillation of conduction electrons. If frequency of the light source matches with that of the surface plasmon, amplitude of the electron oscillation increases which is known as SPR or localized SPR (LSPR) in NPs, resulting in strong absorption of the incident light which can be measured using a UV-Vis spectrometer [161]. The SPR can be affected by shape, size, and the dielectric constant of metal and the distance among the NPs [162]. Dispersed AuNPs, as one of the plasmonic NPs, have shown a specific color or LSPR band which may change into another color or LSPR band upon the addition of external materials such as biomolecules or ions [163, 164]. Recently, Kim and coworkers designed a colorimetric test based on AuNPs and thiol-modified probes for targeting partial genomic regions of MERS-CoV [165]. As shown in Figure 3, they designed thiol-modified probes linked to citrate-coated AuNPs via strong Au-S interactions to target the upstream of the E protein gene (upE) and open reading frames (ORF) 1a on MERS-CoV. A combination of thiol-modified probes and AuNPs at the presence of  $MgCl_2$  led to the aggregation of AuNPs with a reduction in intensity and an increase in bandwidth of LSPR band as well as the emergence of new bands at a longer wavelength. However, the presence of target DNA led to the formation of long assemblies of dsDNA on the surface of AuNPs and shielded

the disulfide bands leading to inhibition of the AuNP aggregation by  $MgCl_2$  which limited the color change for diagnosis of MERS-CoV.

AuNP can be also used in combination with other diagnostic systems such as fiber-optic biosensors to achieve sensitive virus detection. For example, Huang et al. developed a localized surface plasmon-coupled fluorescence (LSPCF) fiber-optic biosensor utilizing AuNPs for the identification of SARS-CoV N protein. Compared to the enzyme-linked immunosorbent assay (ELISA) toward the same monoclonal antibodies, the LSPCF fiber-optic biosensor exhibited a  $10^4$  time limit detection improvement [166].

**4.7. Nanotechnology in Electrochemical Sensing of Coronavirus Infections.** Another analytical methodology that has explored for detection of viral infections is the electrochemical sensing [167, 168]. Conventional electrochemical sensors include an electrolyte, a diffusion barrier, a sensing electrode (as transduction element), and a counter-reference electrode, resulting electrical signal from the interaction of target analyte and recognition layer of sensing electrode. Fascinating properties of NPs (especially metallic and semiconductor NPs) including high surface area, conductivity, and catalytic properties have led to their use in (i) surface immobilization of biomolecules, (ii) enrichment of electron transfer, (iii) effective catalysis, and (iv) labeling biomolecules [169]. The electrochemical immunosensors are comprised of an electrode surface immobilization with recognition component (i.e., antibody or antigen) and gained promising attention as reliable and efficient sensing platform for detection of viral infections [170, 171]. Layqah and Eissa developed a competitive electrochemical immunosensor for sensitive, cost-effective, and user-friendly sensing for the multiplexed detection of different CoVs, as depicted in Figure 4. AuNPs were electrodeposited on a carbon electrode (DEP) (AuNP/DEP) to increase the electron transfer efficiency and provide a higher surface area to improve the biosensor response signal due to presence of more immobilized biomolecules [154]. AuNP/DEP was modified with different antigens such as MERS-CoV, HCoV (Oc43 N), and bovine serum albumin (BSA) as a control electrode. The addition of constant concentration of antibody to the sample containing free virus and immobilized MERS-CoV protein, HCoV, and BSA changed the voltammetric response which can be measured via square wave voltammetry (SWV). Results indicated a linear correlation between the sensor responses and the concentrations as well as lower detection limits for artificial spiked nasal samples of MERS-CoV and HCoV.

In addition to AuNPs, QDs have been employed for the development of biosensors. Recently, Roh developed a biochip through modification by SARS-CoV N protein and QD-conjugated RNA oligonucleotide and tested the inhibitor screening of SARS-CoV N protein ability of fabricated biochip using several polyphenolic compounds (Figure 5). Among different polyphenolic compounds, galate and (-)-gallocatechin gallate with anti-HIV properties showed higher and equal half-maximal inhibitory concentration (IC<sub>50</sub>) values on a QDs-RNA oligonucleotide biochip in comparison with other polyphenolic compounds.

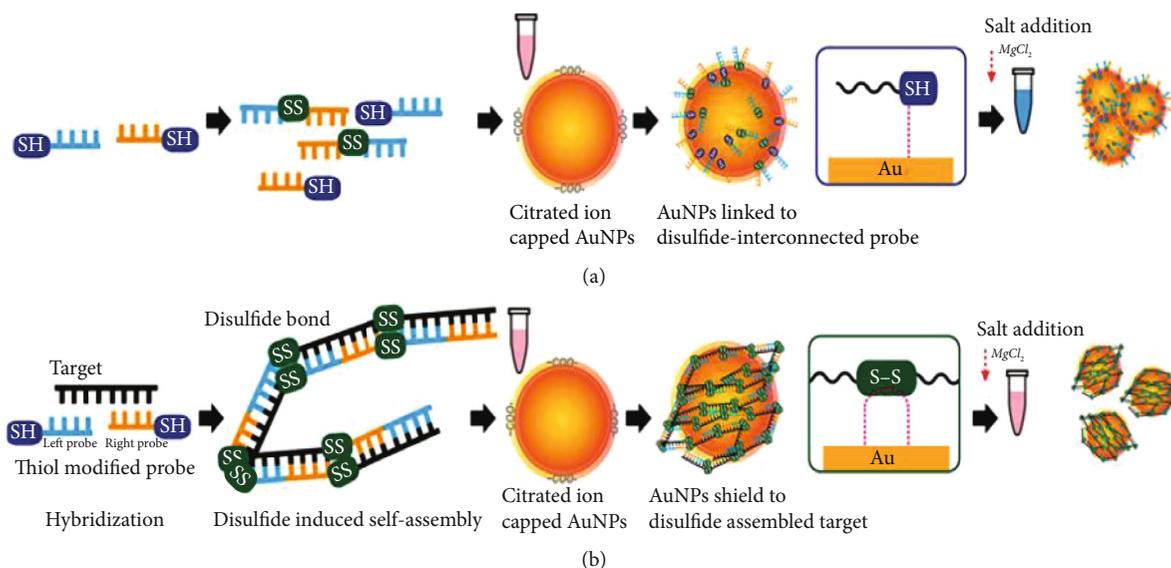


FIGURE 3: Schematic colorimetric method for diagnosis of MERS-CoV DNA. (a)  $MgCl_2$  led to self-assembly of AuNPs in the absence of target DNA and change in the color. (b) The presence of target DNA led to inhibition of disulfide self-assembly of AuNPs [165].

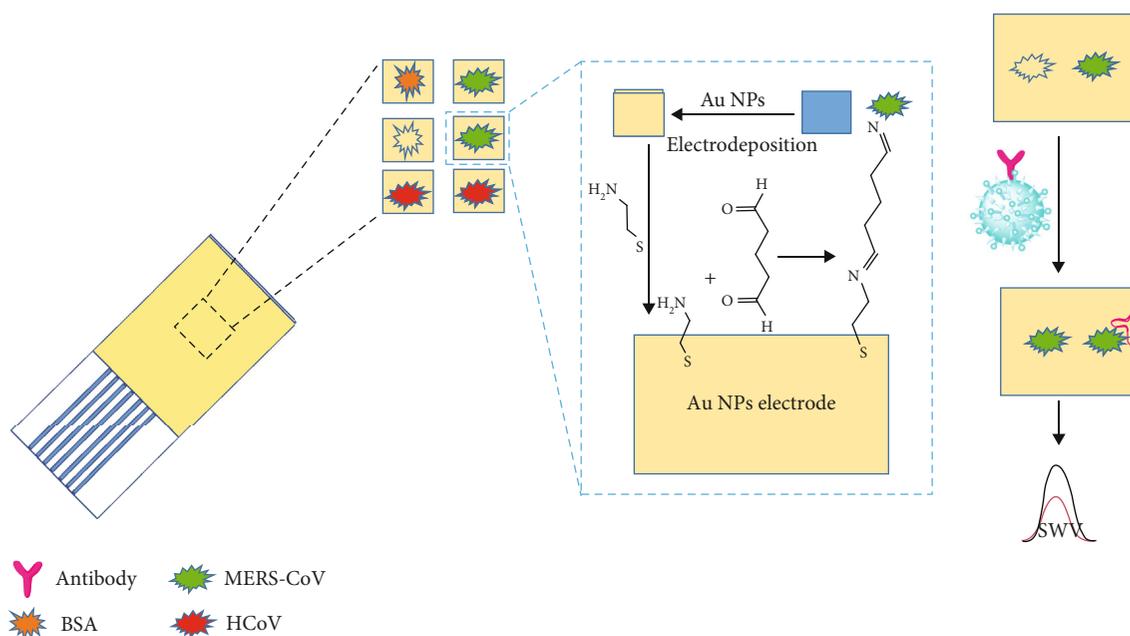


FIGURE 4: CoV immunosensor array chip was fabricated through deposition of AuNPs on electrodes to increase the surface area of electrodes. Increasing the surface area of electrodes can be led to improve the electron transfer and more numbers of immobilized CoV antigens for multiplexed detection of different CoVs via monitoring the change in the peak current [154].

The results revealed that biochips not only led to the specific detection of the SARS-CoV N protein but also could be used for inhibitor screening of SARS-CoV N protein [172]. Moreover, Zhu and coworkers coupled NP-based biosensors (NBS) with reverse transcription loop-mediated isothermal amplification (RT-LAMP) for the diagnosis of COVID-19 which resulted in the selective and sensitive detection of SARS-CoV-2 [6]. Taken together, electrochemical sensing might be promising technique for the rapid detection of CoV infections. For more

detailed information, interested reader is referred to excellent review on this topic by Kaushik and coworkers [173].

4.8. *Nanotechnology in RT-PCR-Based Detection of Coronavirus Infections.* As mentioned earlier, RT-PCR is the main conventional diagnostic method for CoV infections. This method requires the extraction of high-purity nucleic acids to produce strong signals and low false negative results [174, 175]. Regarding that present methods for the extraction of nucleic acids using filtration or centrifugation are very

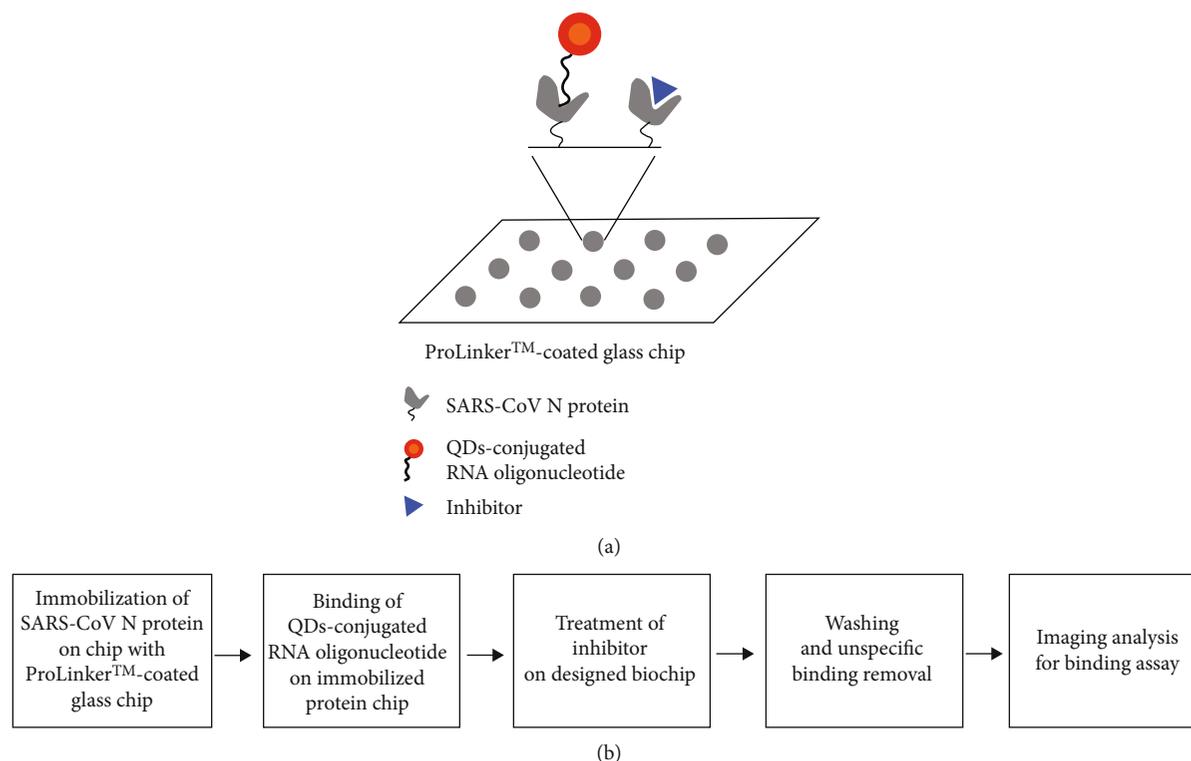


FIGURE 5: Schematic preparation of the inhibitor screening of SARS-CoV N protein biochip based on quantum dot- (QD-) conjugated RNA oligonucleotide and polyphenol compounds as inhibitors for facile inhibitor screening of SARS-CoV N protein [172].

time-consuming and labor-intensive, the application magnetic NPs in sample preparation have fascinated more attention. Magnetic NPs can be easily separated from the media using an external magnetic field during the sample preparation, also called pre-enrichment [176]. In recent years, magnetic NPs have gained promising attention as solid-phase adsorbents of various biomacromolecules; this method is superior over conventional procedures due to shorter processing times, decreased chemical consumption, and simpler procedure via automation [177]. For this purpose, Zhao and coworkers developed poly(amino ester) with carboxyl group-(PC-) coated magnetic NPs (pcMNPs) for the extraction of SARS-CoV-2 RNA, resulting in the sensitive detection of COVID-19 via RT-PCR [178]. In comparison to column-based nucleic acid extraction methods, pcMNPs showed a rapid simple extraction with high purity and productivity with the assistance of an external magnet, resulting in time-consuming RNA extraction for the diagnosis of COVID-19. Taken together, as presented in Table 3, NPs might be promising materials for the detection and extraction of CoV infections. Further experiments are still necessary to assess their safety and efficacy.

**4.9. Nanotechnology in the Treatment of Coronavirus Infections.** The absence of specific anti-CoV drugs and also the continuous advent of new CoV infections rise the demand for specific antiviral therapies. As mentioned before, current COVID-19 therapies are deduced from MERS-CoV, SARS-CoV, and H1N1 influenza which are a combination of different antiviral agents including protease inhibitors, nucle-

oside analogs, and corticosteroids. Nowadays, with the advancement of nanotechnology, a growing focus has been devoted to nanoscale antiviral materials as efficient modulating process platforms for viral infections [179]. Nanoscale antiviral materials can be used for (i) targeted delivery of pharmacological agents to the sites of CoV infections, (ii) prolonged drug release for efficient treatment, (iii) decreasing the drug toxicity and associated side effects, (iv) improving the drug efficacy and potency, (v) delivery of gene and/or immune-based therapies, and (vi) targeting the virus entrance mechanism. Numerous nanoscale antiviral materials have been designed to interfere with the virus and cell receptor interactions. In fact, the high surface-to-volume ratio of NPs led to their efficient attachment to the healthy or noncontaminated cells which result in blocking virus entrance into cells [180].

Recently, the ability of carbon quantum dots (CQDs) to interfere with the HIV-1 and herpes simplex virus type 1 cell entrance has led to the use of boronic acid-functionalized CQDs for the treatment of HCoV-229E infection [181–183]. Łoczechin et al. synthesized seven CQD derivatives which had dose-dependent anti-HCoV-229E activity [184]. Among the CQDs, just boronic acid-functionalized CQDs exhibited anti-HCoV-229E activity; but the low content boronic acid derivatives of CQDs showed lower  $EC_{50}$  in comparison to the higher content of boronic acid derivatives. Results also revealed that the boronic acid derivatives of CQDs not only caused an interaction with cell entry factors but also affect the genomic replication of the HCoV-229E virus. Consequently, boronic acid-functionalized CQDs

might be regarded as a therapeutic agent for COVID-19. Moreover, in the functionalization of nanomaterials to improve their antiviral activities, their shape plays an effective role in their antiviral activity. However, most of the reported antiviral nanomaterials are spherical; nonspherical nanomaterials may display higher antiviral effects compared to their spherical peers [185]. Recently, Zhou et al. reported that mercaptoethane sulfonate-functionalized bovine serum albumin- (BSA-) coated tellurium star-shaped NPs (Te/BSA NPs) are able to suppress the internalization process of porcine epidemic diarrhoea virus (PEDV), a model of CoV, more than the spherical Te/BSA NPs, which might be due to its more interactions with viruses. Moreover, free mercaptoethane sulfonate did not show any significant antiviral effect on PRRSV probably because of its free rotation which may lead to its weak binding affinity to viral proteins. The star-shaped Te/BSA NPs showed higher distribution in the cytoplasm leading to a decline in reactive oxygen species (ROS) content of porcine reproductive and respiratory syndrome virus- (PRRSV-) infected MARC-145 cells, hence resulting in cell apoptosis or even necrosis [186]. Apart from interfering with protein S-receptor interaction, NPs have been applied to target vacuolar ATPase (V-ATPase) activity, which pumps protons into endosomal compartments. Recently, Hu and coworkers prepared poly(ethylene glycol)-block-poly(lactide-co-glycolide) (PEG-PLGA) NPs to target feline CoV (FCoV) infection [187]. They encapsulated diphyllin, a natural V-ATPase inhibitor into PEG-PLGA NPs to reduce its off-target effect and increase its antiviral activity. PEG-PLGA NPs showed dose-dependent endosomal acidification inhibition activity in (felis catus whole fetus-4) cell line as well as in vitro prominent antiviral effect against the feline infectious peritonitis virus (FIPV), a biotype of FCoV.

Recently, the combination of nanotechnology and human natural stem cell-based therapies has led to emergence of new strategies in treatment of various diseases. For example, “LIFNano” (leukemia inhibitory factor nanoformulation), a synthetic stem cell product with the current indication in multiple sclerosis (MS) and rheumatoid arthritis, has attracted much interest in the management of COVID-19 pneumonia [188, 189]. The surface ligands of COVID-19 have also attracted the attention of NanoViricides company to develop a nanoformulation based on nanoviricide® technology [24]. Nanoviricide®, an antiviral polymeric nanomicelle-based formulation for influenza, HIV, herpes, etc., comprises a single-chain polymer conjugated to specific ligands that help in engulfing or coating the virus, resulting in virus neutralization and destabilization and may be viral genome attacking [141]. Taken together, nanotechnology-based antiviral materials might be promising options for the treatment of CoV infections. Further experiments are, however, necessary to assess their safety and efficacy.

## 5. Conclusion

Combating CoV infections is an enormous challenge for healthcare systems, primarily due to its high transmittance rate, and the virus potential to survive through multiple

mutations. Up to now, few drugs have been approved for CoV infections (especially COVID-19); however, the development and design of old and new drugs are still urgently necessary for humans. Currently, there are some authorized vaccines for COVID-19 protection, but it is highly important to prevent its spread by various techniques, such as the isolation of infected patients, the use of personal protective devices and disinfectants, and rapid and early detection systems. As new systems, the benefits of nanotechnology result in the design and development of different nanoscale systems for the prevention, treatment, and diagnosis of CoV infections. Nanotechnology-based formulations can offer controlled and sustained release of antigens and therapeutic agents, as well as interfering with the entry of the virus into cells to enhance the prevention and treatment measures toward CoV infections. Moreover, nanotechnology can help in the development of rapid, cost-effective, and high-sensitive diagnostics systems for CoV infections. However, the majority of studies in the field of CoV nanotechnology continues in the preliminary drug development phases, and problems remain until these systems can progress into clinical use. The efficacy, stability, and safety of nanoscale-based prevention and therapeutic and diagnosis systems must be evaluated by relevant clinical endpoints. Ongoing studies to address these issues must continue. Ultimately, nanotechnology provides several interesting systems to promote the fields of CoV prevention, treatment, and diagnosis.

## Conflicts of Interest

The authors declare that they have no conflict of interest.

## Acknowledgments

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