



Environmental aspect and applications of nanotechnology to eliminate COVID-19 epidemiology risk

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Abstract

Herein, we discuss fast development of the new coronavirus disease COVID-19, emerged in late 2019 in Wuhan, Hubei Province, China, the ground zero of the coronavirus pandemic, and associated with relatively high mortality rate. COVID-19 risk originates from its ability to transmit easily from person to person through the respiratory droplets released during sneezing, breathing, talking, singing, or coughing within a range of nearly 1.5–2 m. The review begins with an overview of COVID-19 origin and symptoms that range from common cold to severe respiratory illnesses and death. Then, it sheds light on the role of nanotechnology as an effective tool for fighting COVID-19 via contributions in diagnosis, treatment, and manufacture of protective equipment for people and healthcare workers. Emergency-approved therapeutics for clinical trial and prospective vaccines are discussed. Additionally, the present work addresses the risk of severe acute respiratory syndrome coronavirus transmission via wastewater and means of wastewater treatment and disinfection via nanoscale materials. The review concludes with a brief assessment of the government's efforts and contemporary propositions to minimize COVID-19 hazard and spreading.

Keywords Severe acute respiratory syndrome coronavirus · Nanomaterials · Nanosensor · Nano-vaccine · COVID-19 · Wastewater

Introduction

The Coronaviridae family is classified into two subfamilies, *Coronavirinae* and *Torovirinae* [1]. *Coronavirinae* is subdivided according to phylogenetic studies and antigenic standards into alpha-, beta-, gamma-, and delta-coronaviruses (CoVs) [2]. CoVs are enveloped and non-segmented viruses with a positive single-stranded RNA genome [3]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

that causes coronavirus disease 19 (COVID-19) is a new member of the beta-CoVs genus [4] and has high homology to several bat CoVs [5]. The biochemical structure of coronavirus is included two main compartments, protein and non-protein. Coronavirus structural proteins consist of spike protein (S), envelope protein (E), membrane protein (M), and nucleocapsid phosphoprotein (N) [6]. However, the transcribed non-structural proteins are involved open-reading frames (ORFs), ORF1a, ORF1b, ORF3, ORF6, ORF7a, ORF7b ORF8, and ORF10 (Fig. 1) [7]. Briefly, the human infection with SARS-CoV-2 occurs via the virus entry to the epithelial cells of human lung through the S protein which interacted with the human receptor angiotensin-converting enzyme 2 receptor protein (ACE2) [8].

The spread of pandemic COVID-19 was started in December 2019 in Wuhan city when SARS-CoV-2 was rapidly spread all over the world as it has been circulating in some animals species like cats, camels, and bats [9]. Nowadays, SARS-CoV-2 can be transferred from animals to humans and from humans to humans causing respiratory diseases as the ribonucleic acid (RNA) of this pathogen is similar to that of SARS-CoV which appeared during 2002

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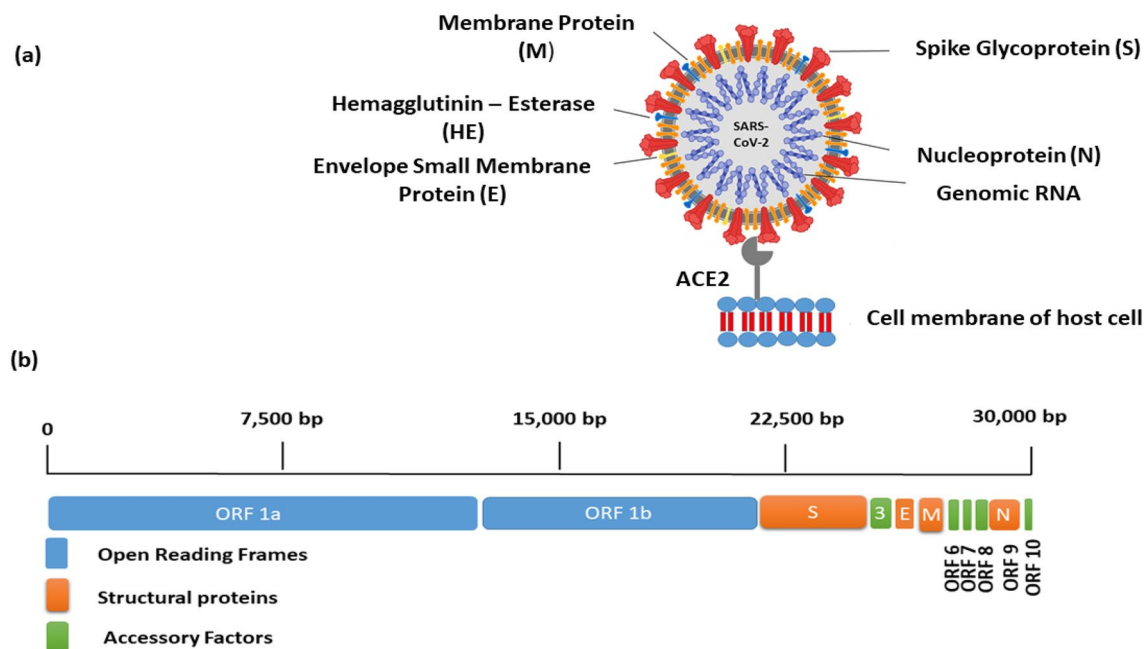


Fig. 1 a Schematic illustration of the SARS-CoV-2 virus structure and its interaction with its host cellular receptor, ACE2. b Design of the full-length genome of SARS-CoV-2 virus

in southern China [10]. According to the Centers for Disease Control and Prevention, most of the patients that have COVID-19 disease suffer from mild symptoms that included cough, fever, and shortness of breath; however, 20% of them have severe disease which is characterized by the incidence of pneumonia and respiratory failure, and in late cases, death may be occurred [11].

Laboratory diagnosis of COVID-19

Enormous laboratory diagnosis of COVID-19 is so crucial to fight transmission of the virus and diminish the time required to isolate and treat the infected cases [11]. There are three sorts of laboratory diagnosis: (i) molecular tests in which their target is the viral genome, (ii) antigen tests which concern with the viral proteins, and (iii) serological tests that detect the antibodies against the virus [12].

Molecular diagnosis via real-time quantitative reverse transcription polymerase chain reaction (RT-qPCR)

Sampling

Both upper and lower respiratory tract specimens can be considered samples of interest in case of COVID-19 infection [13]. In the early infection, both oropharyngeal and nasopharyngeal swabs are the best advised samples to

confirm the diagnosis [14], but under severe hygienic and controlled conditions, the swabs must remain 10 s and coiled three times. Based on previous studies, it was noted that in some cases nasopharyngeal swabs were more preferable than oropharyngeal to perform RT-qPCR technique [15]. On the other hand, in case of late infection, lower respiratory tract specimens such as sputum and bronchoalveolar lavage are used as they have produced the maximum viral loads and such samples gathering from patients must be carried out under intubation procedure [16]. Further rectal swabs can be used as another source of samples during late infection [17]. Regardless the kind of samples, all swabs should be gathered in non-toxic synthetic fibers and nylon handles, then put in universal viral transport media at 4 °C, and rapidly transported to the laboratory for investigation.

RT-qPCR technique

The technique must be carried out in a safety cabinet under ice-cold conditions. Firstly, nucleic acid extraction is done by adding the collected samples to lysis buffer that contains guanidinium-based inactivating agent and non-denaturing detergent; this lysis buffer can sterilize the samples and inhibit RNA SARS-CoV-2 degradation so it indirectly hinders the false negative results [18]. After that, RNA virus is purified by column-based RNA purification kits or magnetic beads, and then, the RT-qPCR technique will be started. RT-qPCR technique is required mainly to forward primer for deoxy nucleic acid (DNA)

synthesis initiation, reverse primer, fluorescent probe, and reverse transcriptase and DNA polymerase enzymes. After the purification phase, the eluted purified RNA is amplified using single or two steps RT-PCR where RNA is converted first into complementary DNA, and then, each DNA single strand is amplified by RT-PCR (Fig. 2). Amplified products can be identified via TaqMan probe fluorescence where the probe has two dyes, a reporter and a quencher dye, that binds to a specific target sequence of SARS-CoV-2 which is found between the forward and reverse primers. In the extension phase of the PCR cycle, the polymerase enzyme destroys the bound probe, leading to the separation of the reporter dye from the quencher dye, which results in the elevation of the fluorescent signal. The fluorescence intensity is monitored at each amplification cycle. The threshold cycle of amplification is set to distinguish between positive and negative results. The threshold cycle is defined as the cycle number when the fluorescent signal exceeds the detection threshold. If the virus was not present in the sample, the fluorescence threshold is not reached, and the test result is then negative. The test result is considered positive if the amplification is noticed for two or more viral targets, while it is considered negative when such amplification is observed for only the control RNA sample, and it is not found in viral targets.

Advantages and limitations of RT-qPCR technique

RT-qPCR is a rapid, highly sensitive, and reliable technique for the detection of COVID-19 disease and not other CoVs even in the early infection, and this is attributed to its capability to (i) diagnose asymptomatic people at early phase, (ii) reduce the cycle times, (iii) use the fluorescent labels for virus detection, (iv) detect RNA-dependent RNA polymerase gene and virus that has an envelope protein (E) and target the Orf1b and N regions of the virus, and finally (v) allow the visualization of the amplification reaction, and also it permits the verification via a melting curve plot.

Though all the mentioned advantages, it has multiple limitations such as false negative and positive results which are represented a huge matter that affects its benefits and such may be attributed to (i) mutations in the used primer and probe that target the regions of SARS-CoV-2 gene [19] and (ii) low individual skills during the sampling, samples transportation and handling, and technique practice itself [20]. In addition, the presence of inadequate viruses or amplification inhibitors in the sample may be other hazard issues [21]. Further, RT-qPCR is an expensive technique and is not available to poor patients, and due to the high numbers of affected cases there is a big stress on the centralized labs all over the world and the results of the samples for the infected person may take 28 h. And, shortage of the used kits and reagents utilized in this diagnostic test may occur, especially with the increased number of infected people [22].

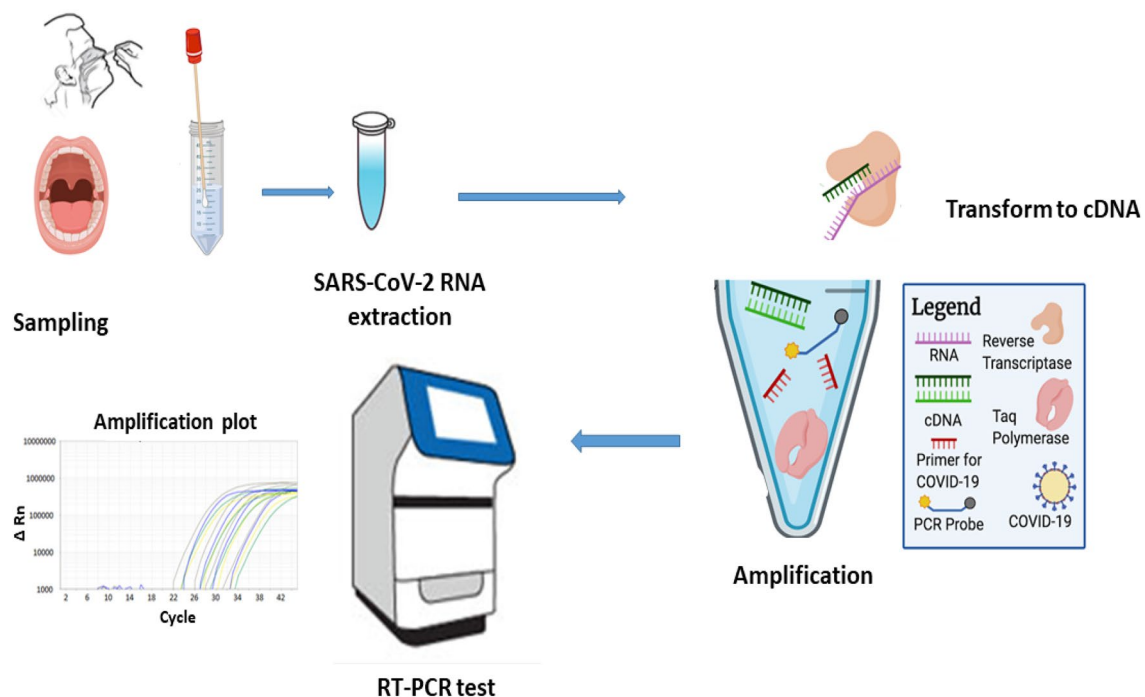


Fig. 2 Schematic representation of RT-qPCR technique for SARS-CoV-2 virus detection

Therefore, finding other techniques for diagnosing COVID-19 is crucial. Nowadays, nanotechnology has a vital potential role in the medical field and health problems involving viruses; hence, this review focuses on the role of nanoscience in diagnosing, treatment, filtration, and environmental protection against COVID-19 hazard.

Nanomaterial-based potential portable biosensors for COVID-19 detection

Biosensors, one of the analytical devices, have three main parts: (i) bioreceptor, (ii) transducer, and (iii) a signal detector. Briefly, the technique is based on bioreceptor interaction with the specific analytes and an electronic signal is produced via the transducer amplification. Biosensors are characterized by their sensitivity, specificity, rapid, and cost-effective methods for virus detection [23]. Additionally, the integration between nanotechnology and the biosensor provides the great capability to detect the pathogens [24, 25].

It was recorded different popular biosensors types that contribute to several viruses detection; among them are electrical (EC) biosensors, fluorescence-based biosensor, field-effect transistor (FET) biosensor devices, surface-enhanced Raman scattering (SERS), localized surface plasmon resonance (LSPR), quartz crystal microbalance (QCM), colorimetric biosensor, and piezoelectric microcantilever sensors (PEMS) [26–30]. These biosensors, especially smartphone-driven biosensors, can be used as a fast detection device either at home or the clinic [31].

Field-effect transistor (FET) biosensor devices

FET biosensors have a great potential for clinical diagnosis owing to their multiple efficacies in sensitive measurements through using small amounts of analytes [32]. And, they can be integrated with other devices like data analyzers and signal transducer. The source (S), the drain (D), and the gate (G) are the main parts of them. Their efficiency in biological sensing related to the replacing of the semiconductor metal of the gate with biological molecules such as DNA, enzyme, receptor, or antibody which are specific to the target analyte [33].

Seo et al. [34] proposed FET biosensor based on graphene nanomaterials functionalized with SARS-CoV-2 spiked antibodies with a low detection limit (LOD) 1 fg/mL that equals 10^{-15} g/mL of SARS-CoV-2 spike protein, and this biosensor could differentiate between SARS-CoV-2 spike protein and that of Middle East Respiratory Syndrome Coronavirus MERS-CoV. The selection of graphene nanomaterials is attributed to its chemical structure as it is a single sheet of hexagonal-arranged carbon atoms; these atoms have a high surface area-to-volume ratio and high carrier mobility and

also been characterized by the biocompatibility that enables them for binding with the charged biomolecules [35].

Nano-plasmonic-based viral biosensors

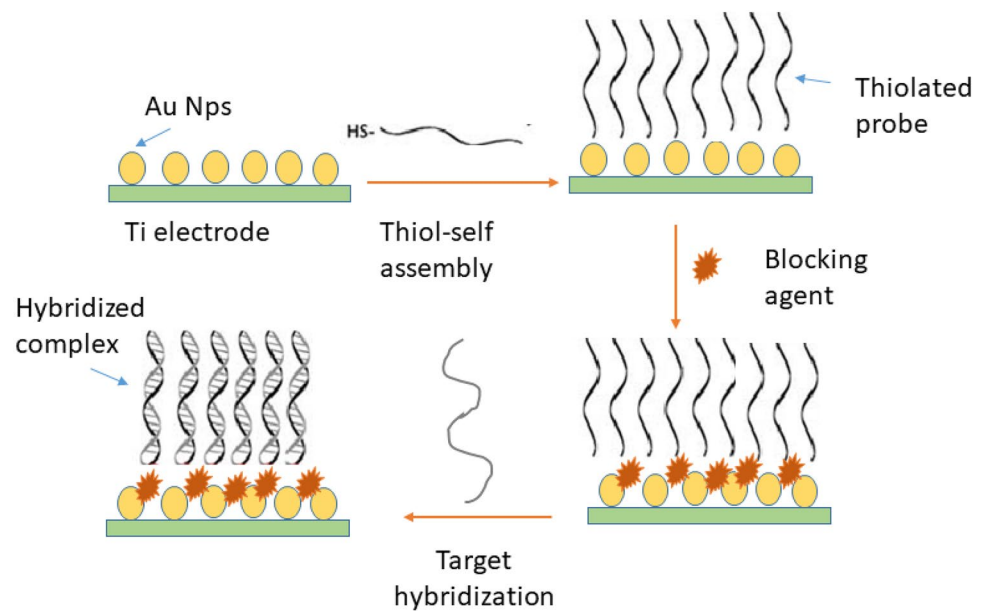
This group of biosensors is involved in surface plasmon resonance (SPR) and localized surface plasmon resonance (LSPR). They are characterized by their strong photon-driven coherent oscillation of the surface conduction electrons and high sensitivity to local variations such as the refractive index change and molecular binding. Therefore, they are suitable for real-time detection of microscale and nanoscale analyses, and they are also useful in sensitive medical detection and diagnosis of many viruses like human immunodeficiency virus (HIV), hepatitis B (HBV), and swine-origin influenza A (H1N1) [36]. Nanomaterials provide great interest in the plasmonic biosensors owing to their unique electrical, magnetic, and optical properties. Moreover, their high surface area enables the loading of biological agents in a wide manner. Various types of inorganic nanomaterials utilized in viral plasmonic biosensors like fullerenes, carbon nanotubes, otherwise metallic nanomaterials such as metal oxide and quantum dots provide great importance in plasmonic biosensor. Gold and silver nanoparticles are the most popular nanomaterials that are utilized in plasmonic biosensing, in particular LSPR, as they can transform LSPR spectra and harvest color variations, producing a signal response. LSPR based on gold nanoparticles (AuNPs) succeeds in clinical diagnosing and environmental monitoring [37].

Recently, Qiu et al. [38] developed new LSPR biosensing systems based on two-dimensional gold nanoislands (Au-NIs) functionalized with complementary DNA receptors to detect SARS-CoV-2 viral nucleic acid where Au-NIs can enhance the plasmonic photothermal heat energy. Moreover, using gold nanoparticles (Au-NPs) to target the sensing plate form SARS-CoV-2 RNA or the corresponding complementary DNA is achieved by [39]. It was noted that the presence of a noble element, Au, either in Au-Nis or Au-NPs, gives high stability, accuracy, and reproducibility for sensing the electrode; therefore, Au is desirable for biomolecules detections (Fig. 3).

Colorimetric-based biosensor

The colorimetric technique is the simplest procedure based on the detection of various biomolecules such as proteins and nucleic acids by the color changes which can be seen with naked eyes without complicated equipment. This technique is proper as a point-of-care (POC) diagnostic devices; however, there are some limitations in this technique as it lacks in some cases the sensitivity and needs a spectrophotometer for analysis [40]. Au-NPs are occupied great

Fig. 3 Schematic diagram showed the attachment of thiol-modified probe with Au-NP-modified sensing electrode, using standard blocking agent to block the non-specific sites on the sensing electrode, hybridization of genetic materials of SARS-CoV-2 virus with the complementary probe



attention in such types of biosensors as their reactivity and aggregation are responsible for the color change, owing to the unique optical properties of localized surface plasmon resonance, high extinction coefficient, and intrinsic photostability of Au-NPs [41]. Therefore, recently Moitra et al. [42] employed such technique for COVID-19 disease diagnosis by the naked eye where Au-NPs were capped with thiol-modified antisense oligonucleotides that are specific for N-gene of COVID-19, and this leads to agglomeration occurrence which subsequently makes alterations in its SPR, and the used Au-NPs could be detected within 10 min (Fig. 4). However, this method shows some limitations as

it is required single-stranded DNA probes preparation and extra intermediate steps like denaturation and annealing of the genetic material [43].

Nano-smart sensing devices and point-of-care testing

Nanoscience facilitated the fabrication of nano-smart sensing devices with microelectrodes which could detect low level of biomarkers with a wide range, and this is crucial for the diseases that are caused by viruses' diagnosis, especially in case of the pandemic conditions. Nano-sensing micro-electrode chips are the advanced approach for developing

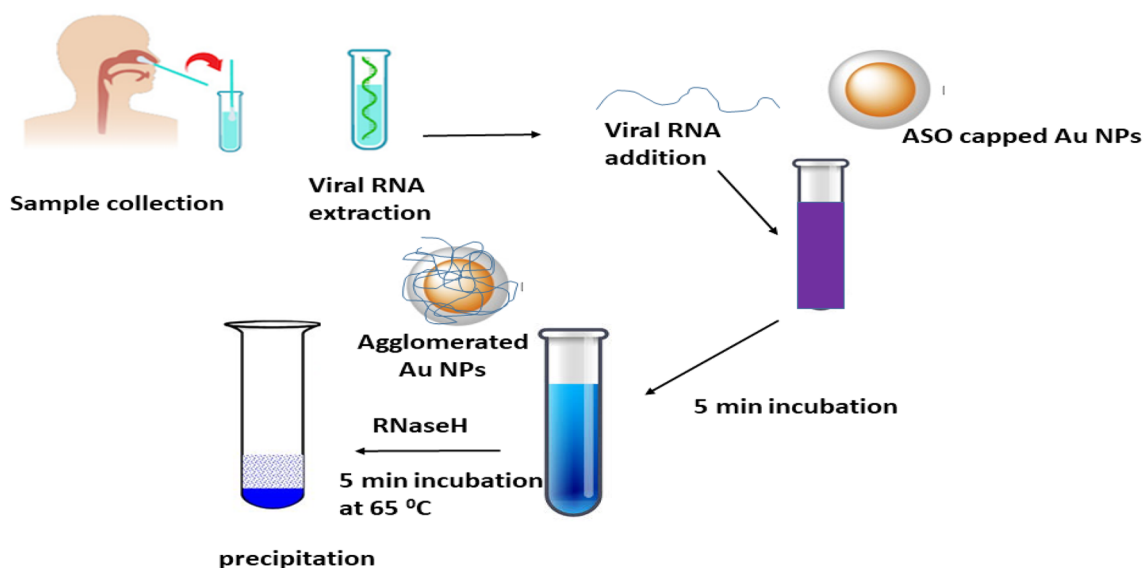


Fig. 4 Colorimetric assay based on ASO-capped Au-NPs for SARS-CoV-2 virus RNA detection

portable biosensors that affected the future of personalized POC devices which are used for pathogens detection through semi-skilled persons, and they are easy to be transported [44]. Zhuang et al. [45] developed the first microfluidic paper based on origami nanobiosensor to detect HIV through saliva antibodies, using zinc oxide (ZnO) nanowires which influence the binding capacity via increasing the surface area of electrodes, and it was found that this biosensor accomplished 60 fg/mL LOD and 99% sensitivity. Recently, Han et al. [46] established a microfluidic electrochemical immunosensor for sensing H1N1, H5N1, and H7N9 influenza viruses, through ZnO nanorods which are hydrothermally grown on the upper inner surface of the polydimethylsiloxane sensor region. The suggested immunosensors were evaluated using an amperometric technique with LOD 1 pg/mL that equals 10^{-12} g/mL, 10 pg/mL, 100 pg/mL, 1 ng/mL, and 10 ng/mL of H1N1, H5N1, and H7N9 antigens.

Further, cell phone-based healthcare and wearable sensing are other novel sensing techniques that enable rapid detection, data recording, and bioinformatics collection during the pandemic and determine the age, gender, and the environment of the infected person, and that is very important for pandemic management [45]. Kinnamon et al. [47] proposed a textile screen-printed biosensor based on graphene oxide (GO) to detect influenza A in biofluid analog buffer with a detection limit 10 ng/mL. More recently, Xia et al. [48] proposed a smartphone-based microfluidic system depending on Au-NPs to distinguish avian influenza virus with a LOD of 2.7×10^4 Egg Infective dose₅₀/mL (EID₅₀/mL). Hence, it is observed after decades of work that nanomaterial-based biosensors have made a break in the detection limit, time, and speed of virus discovery.

Therapeutics and COVID-19

Pharmaceutical drugs

Since the COVID-19 outbreak organizations and pharmaceutical companies are struggling to develop multiple drugs to fight the diseases, unfortunately at the same time, those drugs were questioned and strongly criticized nowadays [49]. This review will through the light on some of those developed drugs. The antiviral drugs are used as therapeutic agents for COVID-19 that act via inactivation of COVID-19 spike glycoprotein surface which is responsible for binding and entry of the virus into the host cells [50]. But till now such available antiviral drugs in most treatment protocols have limited activities which make them less effective, chiefly after confirming COVID-19 mutation [51]. Not only that but also, there is an erroneous prediction that using some of those antiviral drugs in high concentrations is effective, but that leads to multiple adverse effects and toxicity

to the patients. Further, some antiviral drugs were settled but didn't approved by US Food and Drug Administration (FDA); for example, in Japan, favilavir, one of the antiviral drugs used against the influenza virus, was permitted in China to treat COVID-19 [52]. Additionally, remdesivir, an antiviral drug, was intended to target Ebola through disruption of the capability of virus to reproduce by premature termination of RNA transcription and was used by China as a COVID-19 therapy [53]. But remdesivir had severe side effects as it leads to elevation of liver enzymes, hypotension, renal disorders, and gastrointestinal tract disturbance after treatment of patients [54].

Moreover, some anti-retroviral drugs as the combination between lopinavir and ritonavir were developed to be used against COVID-19 disease activity, but unfortunately till now they proved efficacy only when they blend with some drugs as ribavirin and interferon- β [55] and administration of ribavirin may lead to hemolytic anemia, and that is considered another side effect of such combination [56]. Also darunavir, another anti-retroviral and an HIV-1 protease inhibitor, was used in several trials of COVID-19 disease therapy [57]. Otherwise, the potential role of lopinavir toward COVID-19 is begun to be studied though it revealed hepatotoxic influence in previous studies [58].

Not only that but also chloroquine and hydroxychloroquine, specific drugs for malaria and arthritis therapy, respectively, were authorized by the National Health Commission of the People's Republic of China for COVID-19 cure [59, 60]. At the moment, chloroquine and hydroxychloroquine are under investigation by the FDA as a treatment for COVID-19 because multiple opposing effects were investigated including retinopathy, nausea, digestive illnesses, and in severe conditions heart failure may be occurred [61, 62]. At the same time, some anti-parasitic drugs were selected to decline the risk of COVID-19 between the affected people, such as ivermectin that was used in Australia for treatment of some COVID-19-affected patients [63].

Nanomaterials as a novel antiviral therapy

Antiviral activity

Nanomaterials have a great opportunity for new drugs development against the new viruses, whereas a broad range of metal nanostructure have antiviral activity and it can bind with biomaterials covers, causing direct inactivation of the virus, or may lead to blocking the virus entrance inside the host cell via the interaction with the receptors on the host cell surface [64]. The nanoscale gives nanomaterials high surface area which enables them to interact with the viral envelope proteins resulting in either inhibition or prevention the viral genome replication if it enters inside the host cells (Fig. 5) [65].

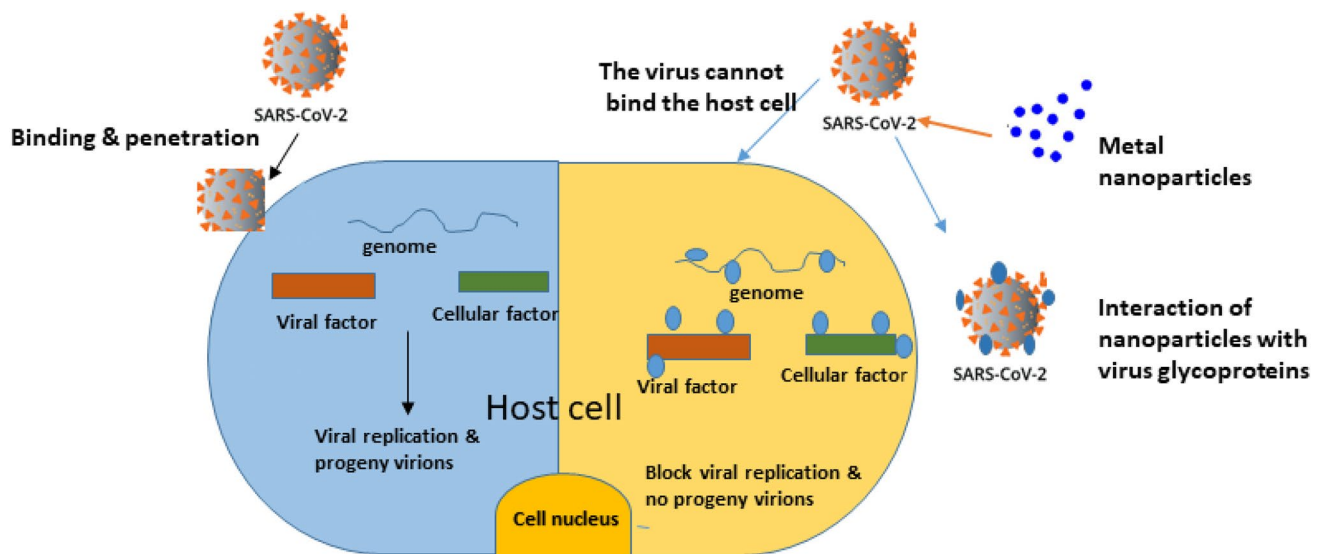


Fig. 5 Mechanism of antiviral activity of nanomaterials

Previous studies utilized silver NPs (Ag-NPs) in antiviral therapy against the H₁N₁ influenza virus [66, 67], HIV [68], HBV, and herpes simplex virus (HSV) [69]. Ag-NPs can bind with the viral envelope glycoproteins, block the penetration of the virus inside the host cell, and prevent their replications. According to Sarkar [70], Ag-NPs are considered an effective tool for COVID-19 treatment where low concentrations of Ag-NPs with bronchodilators were depressed in a simple nebulizer machine and spread it in the lungs of patients who suffer from COVID-19. It was noticed that Ag⁺ ions were released from the NPs and bounded with phosphorus or sulfur-containing bio-molecules of the virus [68], and so it was exhibited its antiviral effects. Further, Ag⁺ ions can alter the pH of the respiratory epithelium to alkaline and such media are not suitable for virus survival [71].

Furthermore, graphene nanomaterials are considered another nanomaterial that could be the first line that contributes to COVID-19 therapy, and it involves different chemical forms as GO and reduced graphene. Graphene nanomaterials exhibited antiviral activity due to their ability to bind with sulfated antiviral drugs and facilitated the conjugation of the drug with the positive-charged virions residue, and so virus replication will be blocked [72]. As mentioned by Palmieri, Papi [73] sulfated heparin which is an antiviral drug can interact with COVID-19 spike protein type-1 receptor and provide great impact for the virus treatment, and in the same hand graphene nanomaterials have a crucial role as a contact area for adsorption of the negative charge sulfated heparin derivatives owing to their large surface area. Otherwise, the functionalization of graphene sheets itself with sulfate derivatives leads to the antiviral effect in the case of HSV-type 1 (HSV-1) via conjugation of graphene nanosheet

with polyglycerol sulfate and fatty amine of the virus envelope, and that leads to its disruption (Fig. 6) [74]. Also, β -cyclodextrin-functionalized GO composite was developed and loaded with curcumin and provided an antiviral effect for respiratory syncytial virus infection therapy [75].

Nanocarrier-based drug delivery

Pandemic COVID-19 has a social and economic impact all over the world; therefore, developing new therapies that can treat and eliminate this pandemic is so critical and highly challenging task. The most challenges that face the new virus treatments are represented by the lack of therapeutic efficacy, imperfect aqueous solubility, bioavailability, short half-life, and toxicity [51].

To overcome these limitations, various nanocarrier-based drug delivery platforms have been designed to conjugate with antiviral drugs such as polymeric NPs, dendrimers, liposomes, and nanoemulsions [76]. Nanocarriers drug delivery system enhances the efficiency of the drug via facilitating targeting drug release, elevating the bioavailability, eradicating the side effect, diminishing the dose, reducing the drug cost, and finally protecting the drug from the enzymatic degradation [77]. Besides, modification of the nanocarrier surface with fitting linkers leads to an increase in the drug's ability to interact with the virus and enhance the elevation of the drug concentrations in the viral reservoirs. As shown in Fig. 7, the strategy of nanocarrier-based drug delivery is depending on development of antiviral drugs that are targeting either (i) SARS-CoV-2 life cycle through the site of action and that involve blocking the virus receptors in the host cells to prevent the enzyme binding with the cell membrane, (ii) the nasal mucosa which is the primary site of infection and it contains several antibodies and

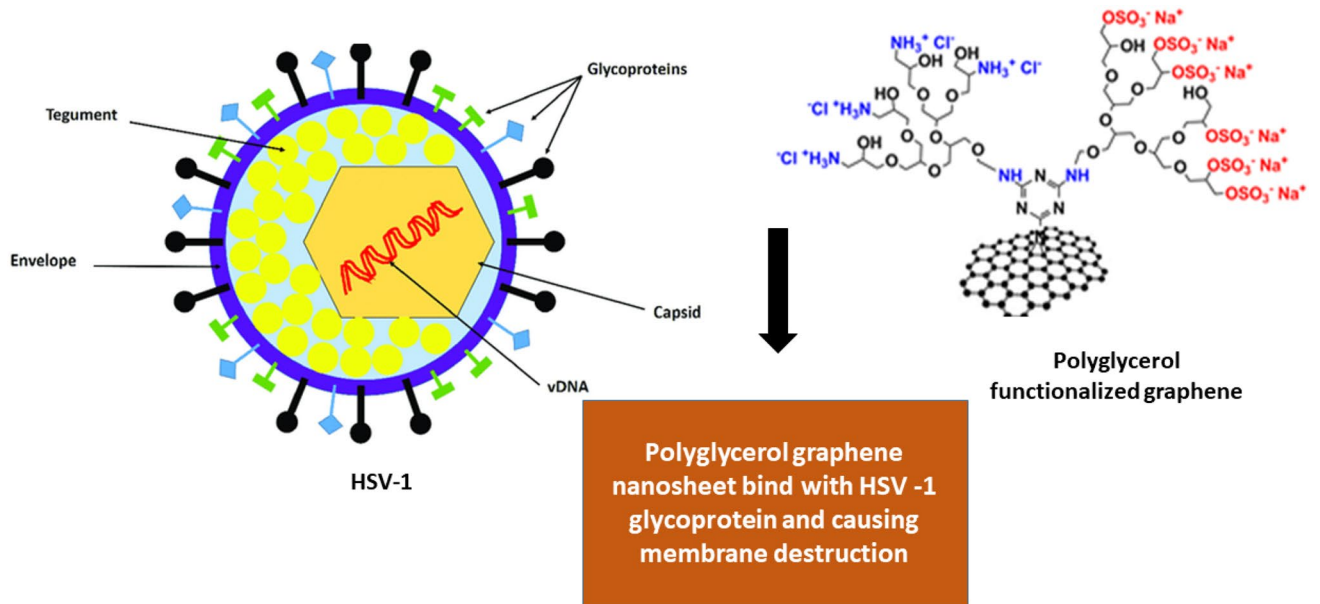


Fig. 6 Inhibition of HSV-1 by sulfated nanographene derivatives via binding with the glycoproteins on the virus envelope with alkyl on graphene derivatives leading to disruption for the virus envelope

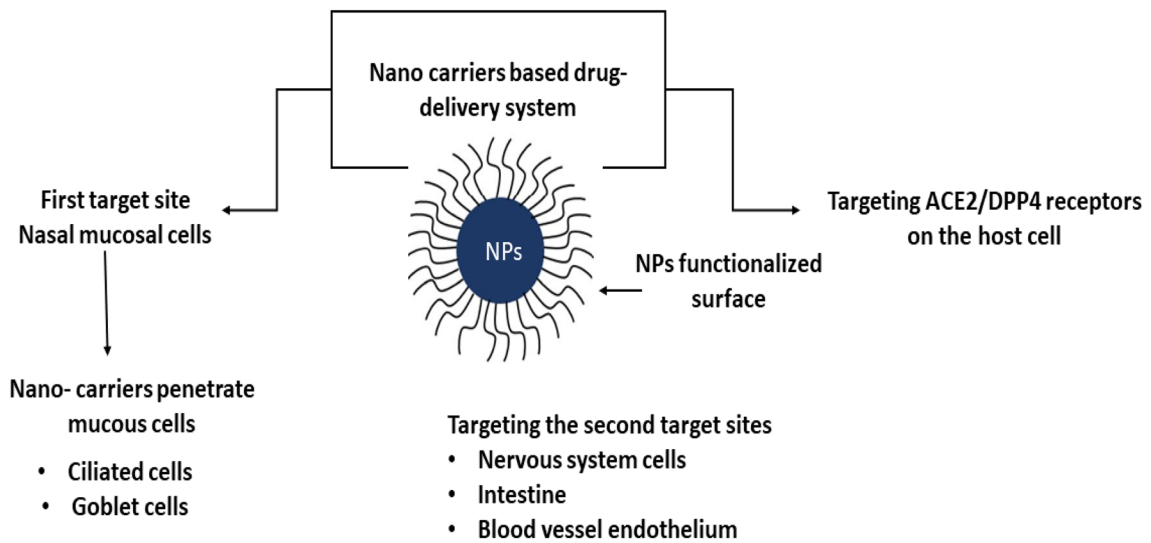


Fig. 7 Strategy of nanocarrier-based drug delivery system to targeting the sites of infection

it is considered the first line of defense, or even iii: the immune system of patients to inhibit the inflammatory response caused by the virus [78].

Vaccines and COVID-19

Vaccine development

Vaccines are the most effective strategy for preventing and controlling virus infection. They are believed to be the best hope for curtailing the pandemic and returning society to normality. The major two components of vaccines are the antigens that are targets of immune response and the adjuvants which are responsible for immune response enhancement toward the antigens. There are various formulations used for the immunological responses which involved weak viruses, inactivated pathogens, or subunit protein antigens [79]. Some limitations that related to the current vaccine generations were observed such as (i) the use of whole inactivated pathogens, (ii) use of non-pathogenic vaccines based on synthetic peptides or recombinant subunit protein that have poor immunogenicity, (iii) poor adjuvants that are required to enhance the immune response, and (iv) degradation of the antigens in the host cell environment [50].

Until the present, no appropriate vaccine is approved for COVID-19 treatment, but many promising vaccines that displayed over 90% in clinical trials were developed such as (i) Symvivo Corporation established a formalin

inactivating whole virus particles combined with an alum adjuvant, (ii) Moderna industrialized a prefusion stabilized S protein mRNA vaccine, (iii) BioNTech SE/Pfizer settled lipid nanoparticle mRNA vaccines, (iv) University of Oxford, Jenner Institute, and Astra Zeneca established a Chimpanzee adenovirus vaccine vector (ChAdOx1), (v) Sinovac Biotech manufactured a formalin inactivating whole virus particles combined with an alum adjuvant, and (vi) Novavax developed a stable, pre-fusion S protein given with adjuvant, Matrix-M [80]. Further, some trials for new vaccines were performed by other developers like CureVac, Clover biopharmaceuticals, University of Queensland, Sanofi and GSK, CanSino Biologics, Johnson and Johnson (Janssen), Institut Pasteur (Themis/Merck), and University of Hong Kong [81].

Nano-vaccine

NPs are an alternative approach as antigen carriers instead of traditional vaccines; in many cases, they serve as a carrier for the antigen or perform as an adjuvant. Moreover, they prevent antigens degradation and enhance the stability of them. And, NPs increase the antigens uptaking via antigen-presenting cells (APCs) [82]. The size of selected NPs for the immune system must be put in the considerations where NPs within the range 20–200 nm enter the APCs via the endocytosis and induce T-cell response while the large size of NPs (0.5–5 μm) enters via phagocytosis and enhances the humoral immune response [83]. The mechanism of the nano-vaccine depends mainly on the ability of

Table 1 Examples of vaccines based on NPs for respiratory viruses

Nanomaterials	Size (nm)	Advantages	Virus	Antigens	References
<i>Inorganic nanoparticles</i>					
Au-NPs	10–100	It is biocompatible and inert	Influenza	Swine transmissible gastroenteritis coronavirus	[84]
			SARS-CoV	SARS-CoV antigens	[85]
<i>Liposomes</i>					
DLPC liposomes	30–100	They have high biocompatibility and antigen protection and low immunogenicity	Influenza (H ₁ N ₁)	Mitochondrial 2, hemagglutinin A and nucleoprotein	[86]
<i>Polymer NPs</i>					
Chitosan	100–200	They are highly variant in size and aspect ratio, and they are potential for high drug/antigen loading	Influenza (H ₁ N ₁)	H ₁ N ₁ antigen	[87]
Poly-glutamic acid (γ -PGA)			Influenza (H ₁ N ₁)	Hemagglutinin	[88]
Hollow polymeric NPs			Middle East Respiratory Syndrome Coronavirus (MERS-CoV)	RBD	[89]
<i>Self-assembling proteins</i>					
N nucleocapsid protein of respiratory syncytial virus (RSV)	10–100	They have small size that helps in tissue penetration	RSV	RSV phosphoprotein	[90]
Spike protein NPs			MERS-CoV	–	[91]

the nanomaterials to penetrate the cell membrane targeting specific subcellular materials, and the antigens may be conjugated with the surface of the nanomaterials or they can be captured inside them; then, antigens are directed with the adjuvant to the specific target and enhance the immune response [82]. Many NPs act as antigens carriers like lipid NPs, polymeric NPs, liposomes, emulsions, and inorganic NPs as shown in Table 1.

In the past few years, NPs have a potential role in delivering the antigens of viruses, especially that of respiratory viruses; however, there is a big challenge to make NPs mimic the respiratory viruses in their size, shape, and surface to be able to deliver the antigens to the target tissues. Moreover, the NPs charge exhibits another challenge as the immune response and entrapping of antigens is affected by the type of charge, where it is supposed that NPs with a positive charge are more desirable than those with a negative charge surface [83].

Au-NPs are the most common NPs utilized for vaccination because they can be easily recognized by dendritic cells and macrophages and then promote their activations [92]. Moreover, the great affinity between the thiol group and Au-NPs provides them with antiviral properties and facilitates their conjugation with antigens [93]. Recently, Staroverov et al. [94] exhibited that the conjugation of Au-NPs with swine transmissible gastroenteritis virus which is a type of coronavirus in immunized mice and rabbits leads to rising both T-cell proliferation 10-folds and activation of respiratory macrophage. Additionally, Sekimukai et al. [85] designed two types of vaccines for recombinant S protein of coronaviruses, and these vaccines structure was involved Au-NPs and acted at several sides, immunization, an antigen carrier, and an adjuvant, where IgG response was induced by Au-NPs adjuvant protein, but

both vaccines were failed to reduce eosinophilic infiltration which appeared in the lung.

Nanotechnology approach for environmental management of utilizing personal protective equipment (PPE) during COVID-19 pandemic

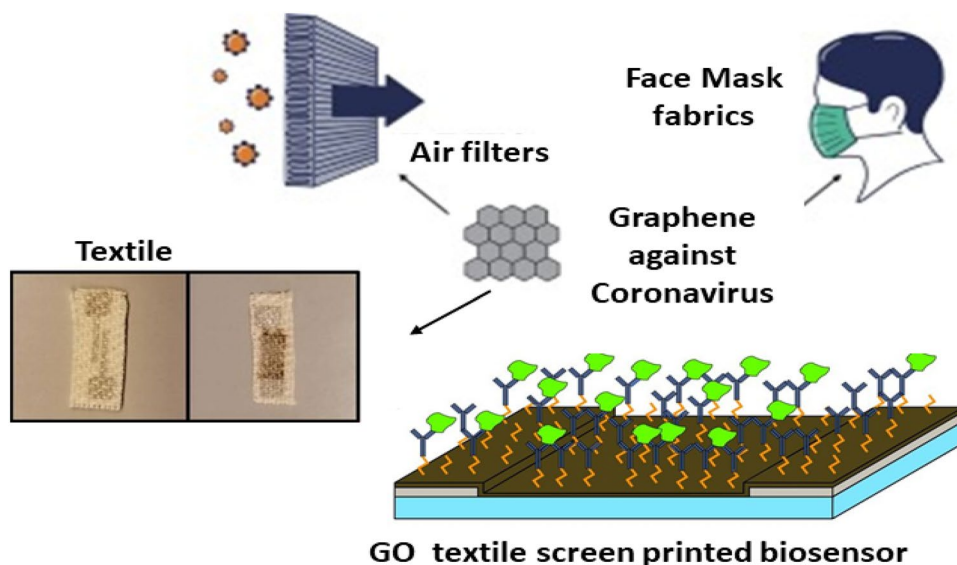
In the case of pandemics, using appropriate PPE such as face masks, face shields, gloves, goggles, gowns, and aprons is vital matters to protect the individuals, in particular health-care workers from the infection. However, the contamination of the PPE is an acquisition environment to spread the infection [95]. Many workers in the health field died during the Ebola outbreak in West Africa in 2014 as a result of insufficient or unsuitable PPE.

On the other hand, through epidemic conditions, the demand for single-use PPE elevates leading to the accumulation of solid waste all over the world, and the management of PPE waste is one of the most challenges that face the communities nowadays. As improper landfilling, incineration, or even recycling these disposable PPE threatens the environment and health, consequently sustainable and safe recovery and treatment of PPE are very crucial. Based on the nanoscale, new research was developed to reusing the medical PPE to eliminate the waste that generates from the medical PPE.

PPE based on graphene nanomaterials

Graphene and their derivatives like GO have a prospective role in PPE treatment [96], they contribute in the manufacturing of an effective protective face masks and air filtration, as they can capture the particles and bacteria (Fig. 8) [97].

Fig. 8 Role of graphene in manufacturing PPE



Moreover, a new research provides the solution of reusing and recycling of the surgical mask via deposition of few layers of graphene into low molten temperature masks by using a dual-mode laser-induced forward transfer technique, this method increases the hydrophobic properties of the mask, and it can be sterilized by sunlight; besides, it can be recycled to use in solar desalination outlet [98]. On the other hand, coating of GO with metals like Ag-NPs provides antimicrobial and disinfection capability as reported by [99] who investigated the antiviral activity of GO with Ag-NPs against enveloped and non-enveloped viruses.

The hydrophilic nature of GO improves their interaction with polymer matrix and fibers which enables the GO to integrate with textiles for protective clothes manufacturing. Kinnamon et al. [47] developed a screen-printed GO textile biosensor to detect the influenza virus through conjugation with specific protein antibodies for influenza virus, as similar for that the researcher could develop smart protective clothes with COVID-19 sensor for controlling the virus spread.

PPE based on Ag-NPs

Ag-containing substance shows wide antibacterial and antiviral activity, and that owing to the interaction of Ag^+ ions with thiol groups of bacterial protein-membrane causes induction of oxidation stress, lysis, and killing of the cell.

Hence, Ag substances, especially their nanomaterials, are added value to reduce the infection risk between health-care workers. Nakamura et al. [100] developed an Ag-NPs chitin nanofiber sheet (CNFS) to resist *E-Coli* bacteria and H1N1, so these materials could be useful in manufacturing protective clothes, masks, and gloves. Besides, V. et al. [101] incorporate Ag-nitrate NPs with polyvinylidene fluoride (PVDF) nanofibers using the electrospinning method for air filtration applications and the results showed that the bacterial filtration efficiency for the synthesized PVDF-Ag nanofibers reaches to 99.86%.

PPE based on copper oxide (CuO) nanomaterials

The biocidal properties and antiviral activity of CuO lead to the impregnation of CuO-NPs into respiratory mask N95 by Borkow et al. [102], to reduce the risk of influenza viruses without a change in the filtration efficiency for the mask. Moreover, Ungur, Hruža [103] developed CuO-polyurethane nanofibers for air filtrations, and the results have proved that CuO is suitable for polyurethane modification for air filtrations.

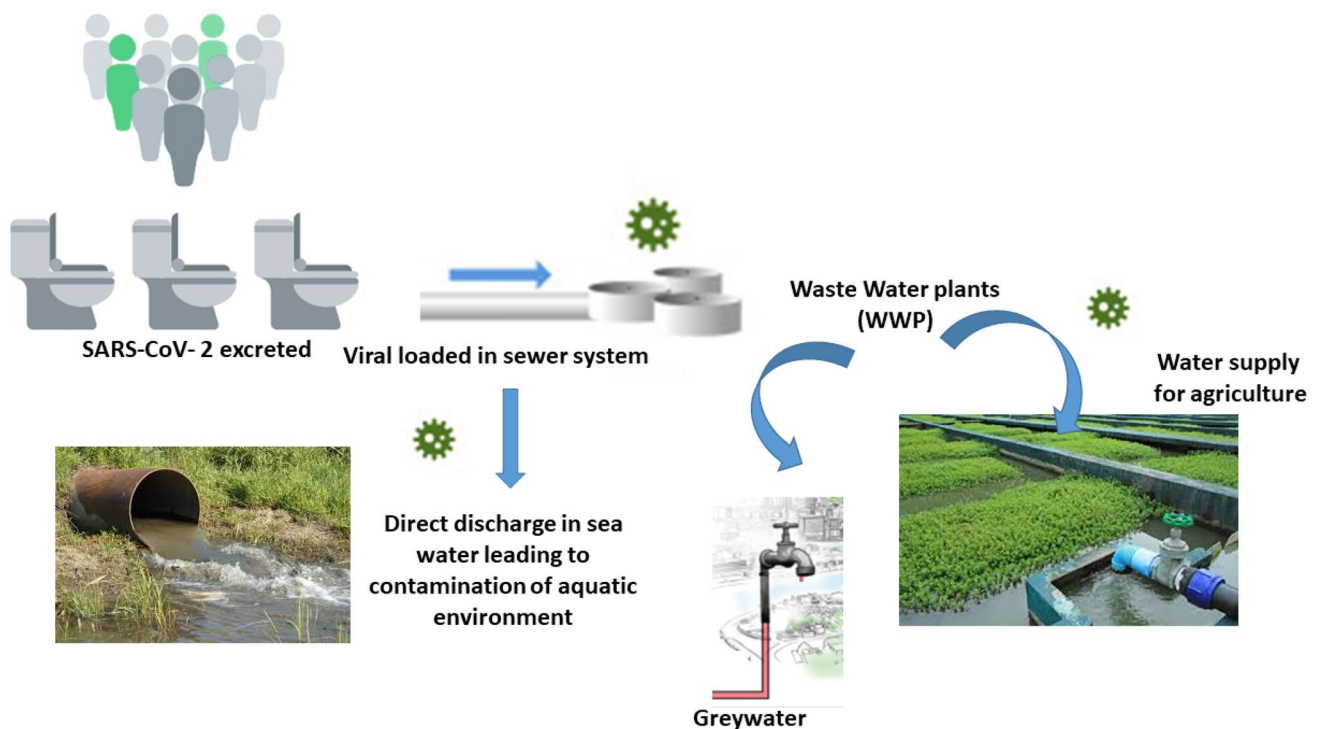


Fig. 9 Transmission of SARS-CoV-2 virus via waste water in sewer system

COVID-19 pandemic and wastewater

SARS-CoV-2 is infected and replicated inside the human gastrointestinal tract via mucosa proteases which enhance the penetration of the virus inside the enterocytes [104], and it is reported that SARS-CoV-2 RNA is found in human feces which excreted into the wastewater; therefore, the insufficient treatment of wastewater may lead to fecal–oral transmission of COVID-19 [105]. It should take into account that the presence of SARS-CoV-2 in the sewer system results in the spreading of the pandemic through various pathways as shown in Fig. 9; the collection of sewer wastewater for treatment and reuse in agriculture and in some times for drinking water lead to increase the possibility of the virus transmission. On the other hand, the direct discharge of sewage water into aquatic environments like seas and oceans elevates the infection rate [106]. The collected samples from some patients of Zhejiang Province hospital displayed that SARS-CoV-2 can survive in stool samples within a range from 4 to 22 days while it remains in respiratory samples till 18 days and in serum samples till 16 days [107]. Therefore, it is of great importance to develop safe wastewater management to ensure harmless recycled water and eliminate the infection rate.

Many techniques are used nowadays for water disinfection and treatment like UV inactivation, ozone treatment, and reverse osmosis [108]. Recently, using nanomaterials to deactivate viruses in wastewater has a great potential and it becomes a wide approach; several types of nanomaterials remove viruses in the wastewater such as metal ions, fullerenes, photocatalysts, and membranes integrated with nanomaterials [109]. The metal ion in nanoscale has an antibacterial capacity and can disinfect the water, and there are many types of them such as (i) titanium oxide-NPs (TiO_2 -NPs) which are photocatalysts with optical and electrical properties and can remove the bacteria and harmful pathogens from water [110], (ii) Ag oxide-NPs (Ag_2O -NPs) that have a particular size and shape enable them to inactivate waterborne pathogens and they can damage the bacterial membrane resulting in enzymes denaturation [111], and (iii) carbon nanotubes such as fullerenes which possess antimicrobial characteristic owing to their unique properties of size, surface functionalization, and the length and layers of the tubes [112].

From previous information, it is expected that nanotechnology has a potential role in struggling the viruses, but we need further studies that recover all the fields of nanotechnology that serve to fight COVID-19 as well as their limitations and challenges.

Limitations and challenges of nanomaterials

Nanomaterials have significant potential in the medical field. They are used broadly in bio-applications; however, there is certain toxicity associated with these materials as they could produce reactive oxygen species (ROS) and genotoxicity to the organism during inhalation and ingestion, besides they have an adverse effect on the respiratory system when they consumed with high concentrations. Further, nanomaterials are translocated through the body and bound with proteins leading to a loss of enzyme activity, fibrillation, unfolding, and thiol crosslinking [73].

Yang et al. [113] studied the cytotoxicity, genotoxicity, and oxidative effects of four types of nanomaterials involving single-wall carbon nanotubes, carbon black, silicon dioxide, and ZnO through methyl thiazolyl tetrazolium and water-soluble tetrazolium assays, and the results showed that ZnO produces much greater cytotoxicity than non-metal NPs and that attributed to the oxidative stress which may be caused by NPs, while Jia et al. [114] highlighted *in vitro* and *in vivo* toxicity of different sizes of graphene and GO and the study revealed that the exposure to them generated ROS and induced DNA damage and the degree of toxicity was depended on the size of these nanomaterials and the oxidation states. Another study investigated variance in the cytotoxicity and genotoxicity of ZnO-NPs on HepG2 cell lines where the cytotoxicity and DNA damage were based on the NPs concentrations and the exposure time to the HepG2 cells [115]. Moreover, Park, Neigh [116] examined the effect of different concentrations of Ag-NPs on developing inflammations, cytotoxicity, and genotoxicity via *in vitro* assays, and the results indicated that 20 nm of Ag-NPs was more toxic than the larger NPs and the effect of NPs on the cell damages was more than the Ag ions.

From the previously collected data, it is found that there are breakthroughs in utilizing nanomaterials in medical fields, but it is important to manage their safety to eliminate their toxicity and maximize their bio-applications.

Conclusion and future prospects

Collaborative networks should be established between the governments, research academies, and the industries for the pandemic preparedness and prevention of infection spreading, and cooperation between different communities should be based on developing new techniques for diagnosing and increasing the mass production of the COVID-19 tests. Nanobiotechnology may have a vital role in the struggle of the pandemic through emerging new biosensing techniques that are portable, easy to use by the infected persons, with

reliable mass production, and with minimum cost and time consumptions.

Several attempts to produce a safe and an effective vaccine for SARS-CoV-2 are proceeding and become the promising hope so further studies are recommended to carry out on the nano-based vaccine in animal models, and developing antiviral drug delivery systems based on nanomaterials may be effective to fight that virus.

Numerous studies were proved the capacity of nanomaterials to solve the problems of the production of safe protective clothes and masks for healthcare worker protection and so the integration between the scientific community and the industry should be established to face the challenge and the shortage in the PPEs all over the countries.

Not only that but also, further studies and investigations should be performed on wastewater as it is a potential source for virus transmission. Wastewater treatment and disinfection are other challenges during COVID-19 epidemic, and extensive research should be developed for SARS-CoV-2 removals from the wastewater to eliminate the risk of fecal–oral transmission and maximize the reusing and recycling of wastewater via the epidemic period.

Overall, recently nanoscience achieved progress in medical applications, diagnosis, and treatments; however, more facilities and effort should be carried out to improve the current technologies to face sudden infectious diseases.

Declarations

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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