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Review

Architectured Therapeutic and Diagnostic Nanoplatforms for Combating SARS-CoV-2: Role of Inorganic, Organic, and Radioactive Materials

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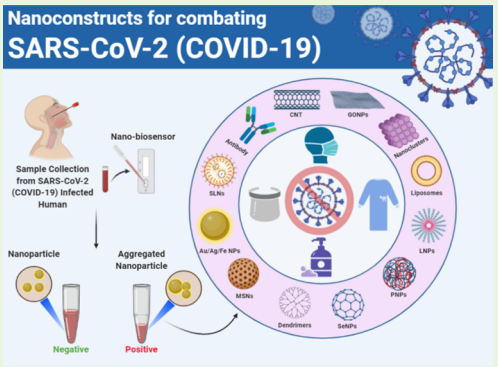
ABSTRACT: Although extensive research is being done to combat SARS-CoV-2, we are yet far away from a robust conclusion or strategy. With an increased amount of vaccine research, nanotechnology has found its way into vaccine technology. Researchers have explored the use of various nanostructures for delivering the vaccines for enhanced efficacy. Apart from acting as delivery platforms, multiple studies have shown the application of inorganic nanoparticles in suppressing the growth as well as transmission of the virus. The present review gives a detailed description of various inorganic nanomaterials which are being explored for combating SARS-CoV-2 along with their role in suppressing the transmission of the virus either through air or by contact with inanimate surfaces. The review further discusses the use of nanoparticles for development of an antiviral coating that may decrease adhesion of SARS-CoV-2. A separate section has been included describing the role of nanostructures in biosensing and diagnosis of SARS-CoV-2. The role of nanotechnology in providing an alternative therapeutic platform along with the role of radionuclides in SARS-CoV-2 has been described briefly. Based on ongoing research and commercialization of this nanoplatform for a viral disease, the nanomaterials show the potential in therapy, biosensing, and diagnosis of SARS-CoV-2.



KEYWORDS: *Nanostructures, Nanotechnology, COVID-19, Radioactive Materials, Organic Materials, Inorganic Materials, Therapeutic, Diagnostic*

1. INTRODUCTION

SARS-associated coronavirus-2 (SARS-CoV-2) is a causative agent of the present pandemic situation most of the nations are battling.[1] This virus belongs to the family *Coronaviridae* and genera β-coronavirus and is one of the largest RNA viruses known so far.[2,3] A global outbreak of SARS-CoV was first reported in 2003, which recorded around 800 deaths.[4] Extensive public health measurements such as isolation of infected patients, social distancing, and community containment measures, along with pharmaceutical intervention, aided in bringing down the virus spread in about 8 months. In the initial phases of the disease during December 2019, computed tomography (CT) revealing opacities in patients' lungs gave the notion of pneumonia, but polymerase chain reaction (PCR) based testing showed that the pathogen was of unknown origin. Around January 2020, from analysis of bronchoalveolar lavage (BAL) fluid of patients, it was discovered that the pathogen shares a similar genetic constitution with the betacoronavirus B lineage. It had 50% similarity with MERS-CoV and 96% similarity with the bat coronavirus RaTG13.[5] The novel virus named SARS-CoV-2 has a striking similarity with the SARS-CoV with regard to etiology and pathological features. It shows about 80% genetic homology with SARS-CoV[6] and, like its predecessor, interacts with the mammalian cell membrane associated angiotensin-converting enzyme-2 (ACE2) to infect humans. The virus primarily causes upper respiratory infection and manifests flu-like symptoms. However, recent reports suggest that it also infects the gastrointestinal tract, urogenital system, circulatory system, and central nervous system.[7−9]

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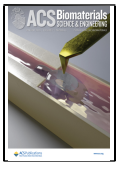

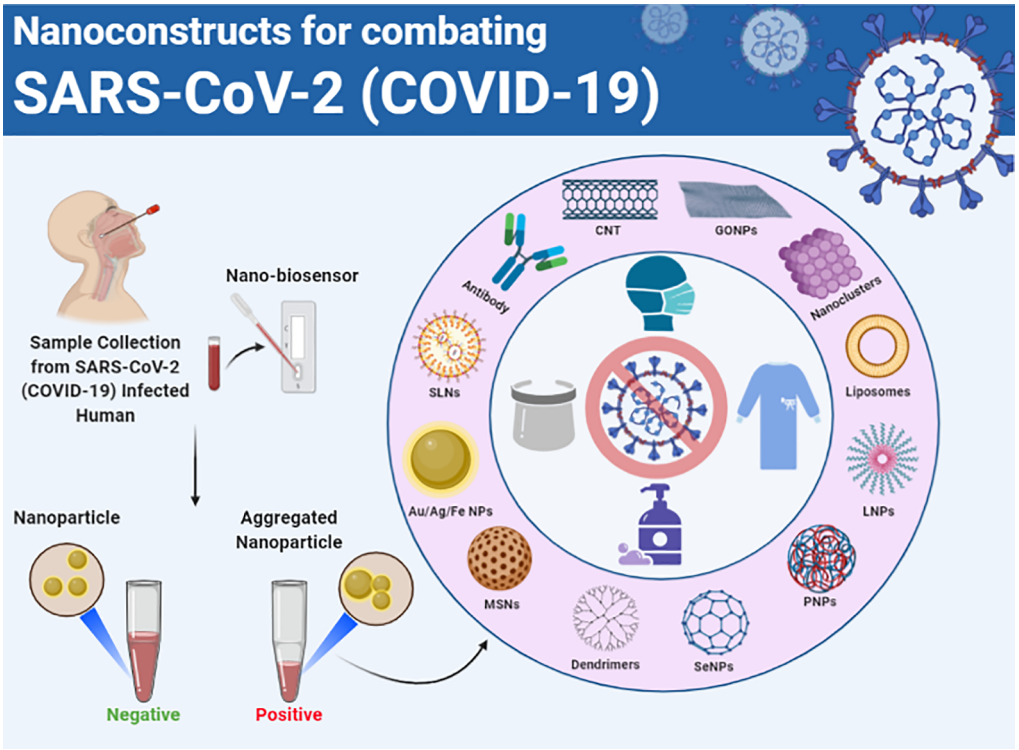

Figure 1. Functional nanomaterials in therapy and diagnosis of SARS-CoV-2.

Lack of fidelity of viral polymerases and frequent genetic recombination are possible contributors to natural selection and zoonotic transmission of the virus from bats to humans. RaTG13, a SARS-like coronavirus infecting bats, has ~96% overall homology to SARS-CoV-2. They diverge primarily in the receptor-binding domain (RBD) of spike protein, for which SARS CoV-2 shares similarity with pangolin coronaviruses. Therefore, bats are considered a primary host and pangolins an intermediate host for the virus.[10]

The human-to-human transmission of the disease is mainly through large droplets produced from sneezing and coughing, from an infected individual. Nevertheless, recently the World Health Organization (WHO) suggested possible airborne transmission.[11] Apart from respiratory droplets, the presence of the virus has also been confirmed in fecal samples of infected individuals.[12] Healthcare workers are more susceptible to human-to-human transmission due to their proximity to infected individuals with heavy viral load. Swab samples from inanimate surfaces in healthcare environments have also been found to bear viruses, which can increase the risk of transmission. Therefore, personal protective equipment (PPE) is essential to keep healthcare workers safe while executing their tasks. The consequent steep surge in PPE requirements for medical workers has led to their reuse and the problem of safe disposal.

While a large proportion of scientific resources are comprehensibly devoted to diagnosis and treatment, the importance of nanotechnology has not been sufficiently explored in the fight against viruses. One possible direction for investigation is the use of nanomaterials to combat viral resistance to conventional therapies; this resistance may be due to the exponential adaptation of viruses through mutation in the peripheral protein sequence, resulting in new viral strains.[13] Additional efforts can be made to limit the spread of the virus. Nanotechnology can offer great support in the design of contamination-safe equipment in this era of pandemic diseases. In our previous articles, we have discussed in detail potential therapeutic targets and drug repurposing to combat SARS-CoV-2.[1,14] Here, we elaborate on the role of nanotechnology in therapy as well as diagnosis of SARS-CoV-2, and also for suppressing its spread and transmission (Figure 1). Given that pandemics have become a recurring phenomenon in the world, our array of nanomaterials will bring many technical approaches to address existing and future public health emergencies.

2. NANOCONSTRUCTS FOR VIRUS-DISABLING AIR FILTRATION

Adequate and effective PPE is crucial for health professionals and the general public to prevent the spread of SARS-CoV-2.[15] The use of masks has formed an integral part of a full prevention and control package that can minimize the spread of respiratory viral conditions like COVID-19.[16] However, there is no inherent antimicrobial or antiviral intervention in the currently available PPE, thereby providing people with only passive barrier protection. The PPE limits the release of microbes/viruses into the air but does not inactivate or prevent the spread of microbes/viruses in the filter media.[17] HEPA filters can claim to trap the virus particle but not kill them. Hence, the development and rapid production of face masks and other protective materials that can destroy the microbe/virus along with immobilization of the aerosol droplets represents a big step forward to limit SARS-CoV-2 transmission. Several nanotechnology-based interventions using suitably designed materials for containment, diagnosis, and treatment of COVID-19 are currently being developed and implemented, e.g., deposition of Ag nanoparticles on the filter surface, use of photocatalytic materials, carbon materials, or

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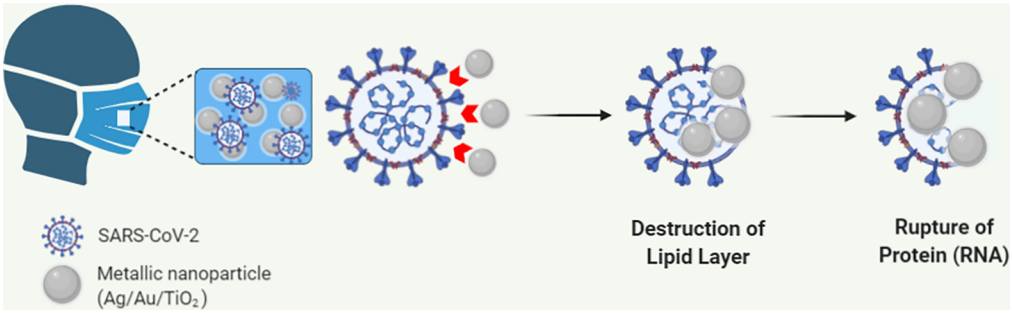

Figure 2. Schematic representation of virus inactivation due to coating with metallic nanomaterials.

catechin based filters can show virucidal activity. The general mechanism is shown in Figure 2.[18]

Graphene oxide has been used as a platform for inhibition of viral helicase. Studies with SARS-CoV and HCV NS3 helicase[19] have shown that viral helicase adhered to the surface of graphene oxide by $\pi-\pi$ stacking interactions between hexagonal units of graphene oxide and nucleotides.[20] This facilitates the use of graphene as a crafted material to boost barrier properties of the mask against bacteria and viruses.[21] Multifunctional "nanoflowers" of transition metal dichalcogenides can accommodate a high proportion of nanoparticles and molecules on their surfaces and edges, thereby inactivating pathogens by disrupting their cellular functions. Because of their unique properties, like high air stability and strong substrate adhering nature, the virus is quickly detected and inactivated by these nanoflowers, making them suitable for use in various formats—they may, for example, be sprayed as aerosols or deposited on masks.[22] MXenes are 2D carbides and nitrides of hydrophilic nature and bear a negative charge.[23] They act as a protein magnet by which the peplomers of the viral spikes (specific amino acids) can be adsorbed, immobilized, and deactivated. The inherent photocatalytic activity of MXenes helps to degrade the virus when adsorbed.[24,25] Research by Le et al. focused on the manufacture of a photocatalytic air filter made of TiO_2 nanoparticles deposited on the surface using a simple sol−gel technique. The nanomaterial was then deposited inside a quartz tube, which was placed in an air cleaner. Nano-Ag deposited on polypropylene was used as a prefilter, which showed antibacterial effects that could be further studied for virucidal effects, especially during the ongoing COVID 19 pandemic.[26] In India, studies are ongoing for N9 blue nano-Ag (highly potent antimicrobial agent) modified with Zn compounds to form nanocomplexes, which could work synergistically as an antiviral agent and be applied as coatings to face masks or other PPEs, thus increasing their efficiency and shelf life.[27] An active virus filter made of a thin carbon nanotube mat named TorStran has been developed, which shows good air permeability and filtration properties, enabling it to capture and instantly deactivate airborne/aerosolized droplet viruses.[28] Most filters lose their efficiency when exposed to water due to diminished electrostatic function, causing them to deform, making it nearly impossible to reuse them. Water-resistant reusable nanofibers can be designed and implemented. One study focused on optimizing the performance of nanofibers by using the insulation block's electrospinning process to create PVDF electret nanofibers that were charged using corona discharge, showing greater than 90% capture of facsimiles of airborne COVID-19 particles (simulated using 100 nm sodium chloride aerosols).[29,30] Another demonstrated the antiviral effect of Ag nanocluster/silica composite when coated directly onto the facial mask. They also stated that the coating can be used on different types of filter media as well as on metal, ceramic, glass, and polymer surfaces.[31] Hence, metal oxides or other organic metal frameworks must be encouraged, as they possess a strong virucidal effect, and would be useful in confined circumstances such as emergency wards, vehicles, hospitals, etc.

3. INORGANIC NANOCONSTRUCTS FOR PERSONAL PROTECTIVE EQUIPMENT

During the 2002 SARS-CoV outbreak, infection through contaminated PPEs accounted for about 20% of all infections among healthcare workers.[32] Therefore, anti-adherent surface coating of these PPEs with antimicrobial substances, which can greatly reduce the spread of such infections, must be pursued.

Various metal-based nanoparticles are known to possess antibacterial and antiviral properties. The main mechanism involved in containing the spread of infectious pathogens is membrane disruption. Since nanoparticles have a high surface to volume ratio, they can have greater interaction with microbes. Thus, modifications of the structural properties of nanoparticles can also enhance the antimicrobial effect. An antiviral property exhibited by a coating of hybrid nanoparticles made up of Ag, Cu, and Zn on a glass surface demonstrated that not only post-exposure, metal nanoparticles can also be used as a barrier to restrict the virus spread.[33]

3.1. Copper Nanoparticles as Antiviral Coating. Copper metal nanoparticles have been studied for their antimicrobial effects. Hang et al. studied the inhibitory property of cuprous oxide nanoparticles (CO-NP) against Hepatitis C Virus (HCV) infection. Their work demonstrated that CO-NPs at nontoxic concentrations were able to significantly inhibit attachment and entry of HCV pseudoparticle (HCVpp).[34] Cu metal nanoparticles were also effective in inactivating the human coronavirus through an ROS-dependent mechanism.[35] Owing to these properties, Cu nanoparticles have been used as an antiviral coating material. A mask containing nanofibers embedded with CuO has been developed by the Respilon group and customized in shape to fit more appropriately. It can filter out viruses, and CuO present on the nanofibers is assumed to kill trapped viruses.[36]

3.2. Zinc Nanoparticles as Antiviral Coating. Similar to copper, Zn divalent metal ion is also effective as an antiviral agent. In a study conducted to understand the inhibitory effect of metal ions on viral replication, different metal ion conjugates such as Hg^{2+}, Zn^{2+}, and Cu^{2} were tested. Among all metal ions, Zn^{2+} exhibited more effective inhibitory properties.[37] Zn^{2+} ions and Zn^{2+} ionophores have been demonstrated to effectively

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inhibit replicase and RdRp enzymes of SARS at a molecular level.[38] PEGylated ZnO nanoparticles were effective in reducing the number of copies of herpes simplex virus-1 DNA.[39] In addition to the antiviral property at biomolecule interface, coating of surfaces with ZnO makes the surface water repellent and thus helps protect against contamination with any body fluids/droplets such as blood.[40] A team from IIT-Delhi, India has formulated an N9 blue nanosilver and Zn combined nanoparticle coating to make PPE surfaces virus-resistant.[41]

3.3. Graphene Oxide as Antiviral Coating. Several Coronavirus response researchers and firms are revisiting graphene oxide (GO) as a material with known antiviral potential. GO may provide a framework for combating a variety of viral infections such as SARS-CoV-2 and possibly as a coating, as its antiviral activity has been explored by many researchers.[42] A research study conducted in 2015 examined the antiviral properties of GO and concluded that GO and reduced GO (rGO) exhibit broad-spectrum antiviral activity against both DNA viruses (pseudorabies virus) and RNA viruses (porcine epidemic diarrhea virus) at a non-cytotoxic concentration, which may shed new light on the design of novel virucides.[43] In a study conducted in 2016, feline coronavirus (FCoV) and infectious bursal disease virus (IBDV) were picked as enveloped and nonenveloped viruses, respectively, to test the antiviral efficacy of GO-Ag (Silver) based nanocomposites. FCoV is a single-stranded RNA virus with a lipid envelope, belonging to the *Coronaviridae* family. IBDV is a double-stranded, nonenveloped RNA virus and belongs to the *Birnaviridae* family, genus *Avibirnavirus*. GO sheets with silver particles displayed antiviral activity both against enveloped viruses and nonenveloped viruses, while GO sheets alone could only constrain infection with non-cytotoxic concentrations of enveloped viruses. Another research study published in 2017 examined the possible role of cyclodextrin functionalized GO in combating respiratory syncytial virus (RSV), and concluded that the functional GO loaded with curcumin was confirmed to demonstrate highly efficient inhibition of RSV infection and high biocompatibility with host cells.[44] Similarly, researchers published a study in 2019 showing that GO/HY (hypericin) has antiviral activity against NDRV (novel duck reovirus), both *in vitro* and *in vivo*.[45] The inference we may draw from these works is that graphene oxide provides a suitable base for combating a variety of viral infections (such as the SARS-CoV-2), probably as some sort of coating, but further research is certainly required.

3.4. Functional Materials Impregnated as Nanofibers for Mask. Nanofiber frameworks are made of a thick spiderweb-like network, which has a large surface area. These membranes are integrated into respiratory masks, ensuring higher breathability and filtration efficiency. The most widely used face masks, called N95 masks, screen out up to 95% of fine pollutants with a diameter of at least 300 nm.[46] The researchers have designed and evaluated a highly breathable material based on nanofiber-based cellulose that is capable of removing nanoparticles of virus size. This new material which removes nanoparticles is developed to be used in biodegradable, antipollution masks as a disposable filter cartridge.[47] This is a significant factor especially for those for whom it is necessary to wear masks for long durations or those with existing respiratory conditions: the greater the breathability, the higher the comfort and the lower the fatigue.

3.5. Metal Nanoparticles for Antiviral Face Mask Products. Metal nanoparticles, especially silver nanoparticles (AgNPs), are well recognized for their antiviral activity. They act as inhibitors of viral replication and rely on the target virus for their viricidal action. For example, in the case of the HIV-1 virus, the AgNP capacity to inhibit viral entry in host cells was documented, showing that AgNPs can interact with cell receptors.[13] Concerning double-stranded RNA (dsRNA) viruses, AgNP was found to interact with a viral genome, inhibiting viral replication. Similarly, biocompatible polymer stable gold nanoparticles (AuNPs) demonstrated antiviral activity against HIV-1 and other influenza virus subtypes (e.g., H1N1, H3N2, H5N1). It has also been shown that gold nanoparticles coated with sulfated ligands, silver nanoparticles, and hybrid silver−copper nanoparticles can bind the HIV envelope glycoprotein gp120 and inhibit cellular HIV-1 infection *in vitro*.[48,49] Furthermore, a size-dependent HIV-1 infection (size 1−10 nm) was identified.[49] It has also been shown that functionalized AgNPs (e.g., with tannic acid and mercaptoethane-sulfonate) are capable of preventing HSV infection by specifically inhibiting virus binding, penetration, and spreading post-infection.[50,51] These antiviral metal nanoparticles could be of great help in enhancing a mask's efficacy. They can be used to modify surgical masks and respirators, crucial objectives in combating the spread of COVID-19.

4. NANOARCHITECTRONICS IN DIAGNOSIS AND DETECTION OF COVID-19

Currently, the RT-PCR or qRT-PCR method is consistently employed for diagnosis of SARS-CoV-2. Despite this being the gold standard method, it has been found in some cases to give false negative or false positive results. The reason for this discrepancy arises in patients with early stages of infection where the viral load is low. Other issues related to the method are that it is expensive, requires technical expertise, and is time-consuming. These reasons limit its use for widespread clinical diagnosis, and it is a huge public issue presently. Rapid and precise methods based on nanotechnology are underway to alleviate these drawbacks. Here, we discuss some recent developments in nanotechnology-based diagnosis and detection of the SARS-CoV-2.

4.1. Current Diagnostic and Detection Tests Involving Nanotechnology. Point-of-care testing methods are under development that have the advantage of testing patients in communities without laboratory infrastructure. One type of commercial lateral flow assay uses membrane strips coated with gold nanoparticle−antibody conjugates in one line and capture antibodies in another line. The test sample is placed on the membrane and capillary action causes the proteins in the sample to be drawn across the strip. When they pass through the first line, the antigens bind with the gold nanoparticle−antibody conjugates and the complex travels along the strip. When the second line is reached, capture antibodies cause the complex to be immobilized and a red or blue colored line is produced. Gold nanoparticles alone are red, but when they form a cluster, the blue color is seen due to plasmon band coupling. For IgM, a clinical sensitivity of 57%, a specificity of 100%, and 69% accuracy was obtained by this method. For IgG, 81% sensitivity, 100% specificity, and 86% accuracy were obtained. For a test detecting both IgM and IgG simultaneously, 82% clinical sensitivity was obtained. The sensitivity obtained by qRT-PCR was 51.9% indicating that there was a significant difference in the sensitivity of the two methods.[52]

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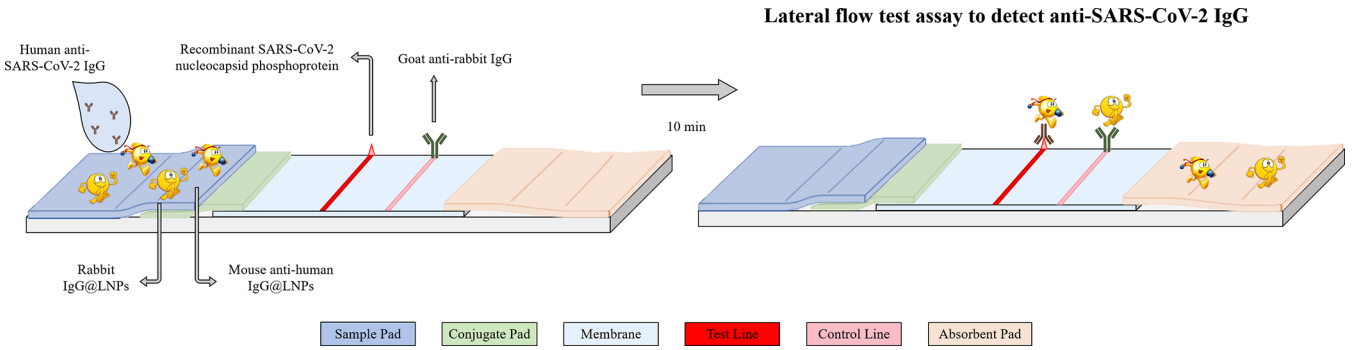

Figure 3. Lateral flow test assay to detect anti-SARS-CoV-2 IgG.

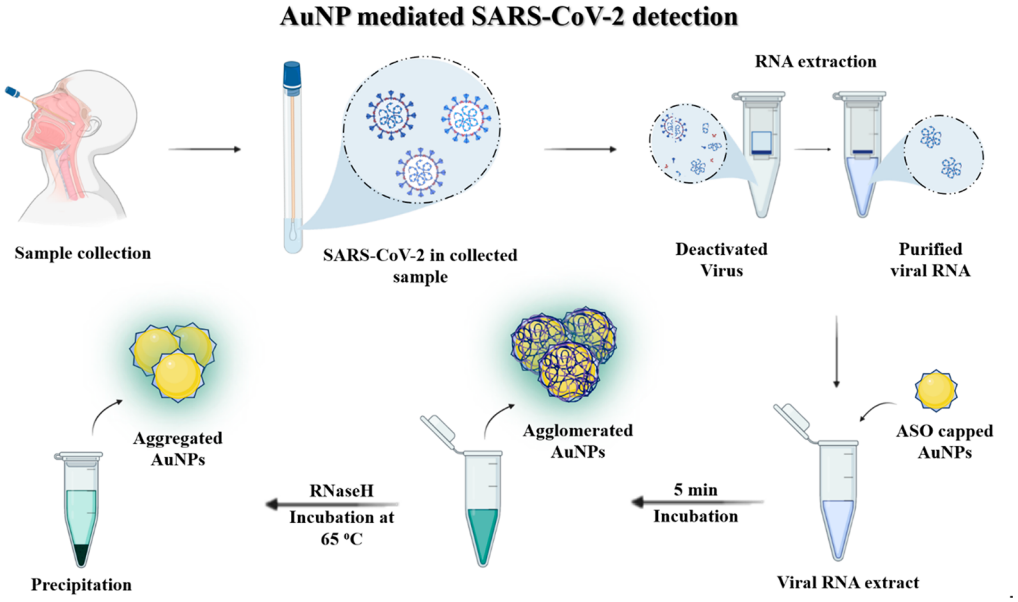

Figure 4. Illustration of the "naked-eye" detection method for SARS-CoV-2 RNA.

Mertens and a group from Coris BioConcept developed a "Respi-strip" immunochromatographic assay using a membrane with colloidal gold nanoparticles. The monoclonal antibodies used for the assay were against the nucleocapsid protein of the virus. This method provided results in approximately 15 min using nasopharyngeal specimens of symptomatic patients. Compared to qRT-PCR (gold standard), this assay had less diagnostic sensitivity, but it still serves as a complementary test to the current molecular techniques, because of its requirement of just 15 min testing time and a specificity of 99.5%. This kind of rapid diagnostic assay offers immediate positive confirmation of the suspicion of a COVID-19 infection so that the patient can be isolated and cared for at the earliest.[53] A lateral flow assay using lanthanide-doped polystyrene nanoparticles (LNPs) was developed by Chen et al. to detect anti-SARS-CoV-2 IgG present in human serum as illustrated in Figure 3. The nitrocellulose strip had a recombinant nucleocapsid phosphoprotein of the virus embedded onto it.

The fluorescent reporter used was mouse anti-human IgG antibody labeled with the self-assembled lanthanide-doped polystyrene nanoparticles. This assay could be completed in 10 min and showed consistent results for samples tested by RT-PCR, as well as clarifying suspicious results. The accuracy of the developed method was found comparable to that of RT-PCR.[54] However, serological or antibody-based detection assays are not appropriate for early-stage patients, as the incubation period of the virus is too short to elicit an immune response.

Another colorimetric assay has been developed using gold nanoparticles capped with antisense oligonucleotides suitably modified with thiol and targeting the nucleocapsid phosphoprotein (N-gene) of the SARS-CoV-2. This diagnostic test requires as little as 10 min to produce results. The detection is done through surface plasmon resonance (SPR), which demonstrates a change when the antisense oligonucleotide capped gold nanoparticles bind to their target sequence in the virus. The method is referred to as a "naked-eye" colorimetric method with the use of SPR and is depicted in Figure 4.[55]

Quantum dot barcode technology is under development for diagnosis of the SARS-CoV-2. This was initially clinically established by Kim et al. for the diagnosis of the Hepatitis B virus. Quantum dots to be used as barcodes have several advantages including better discrimination, identification, and capability of designing multiple barcode signals, as their properties can be tuned by modifying the chemical composition, size, and shape. Multiplexed quantum beads that can capture viral DNA and detect it have been employed.[5,56] Magnetic nanoparticles coated with poly(amino ester) with carboxyl groups were used to develop a sensitive

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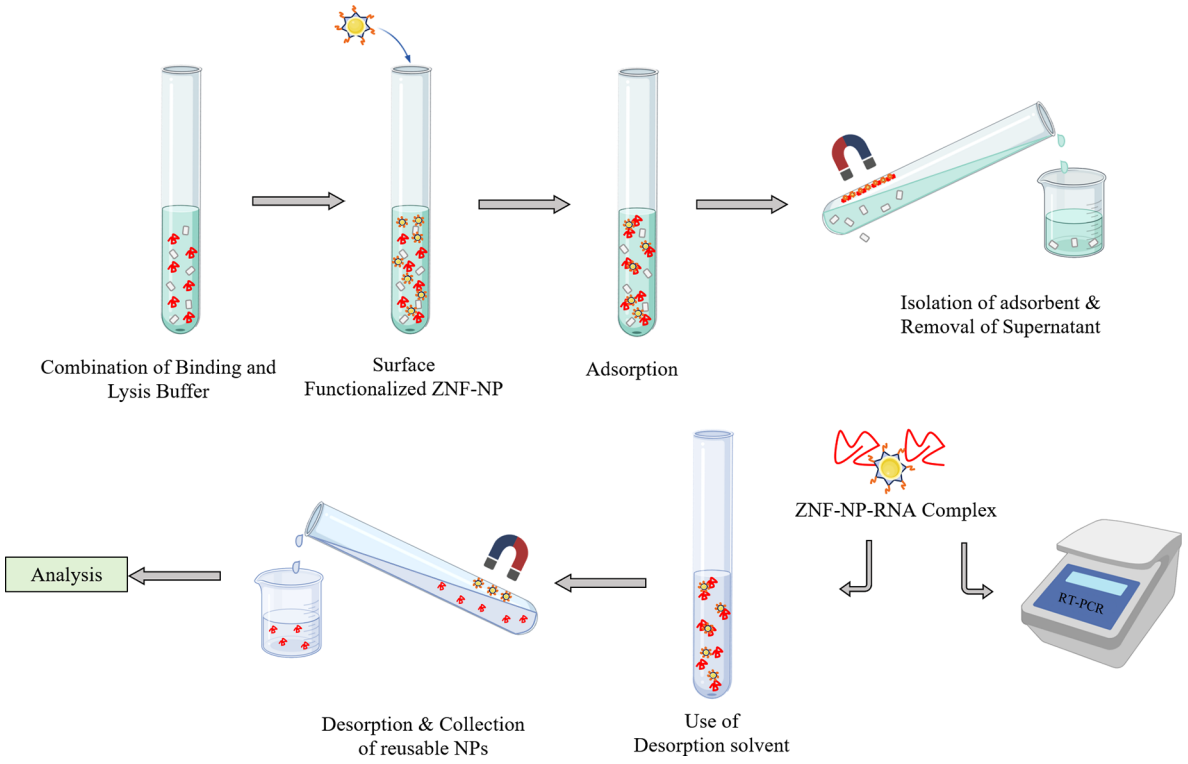

Figure 5. Schematic illustration of RNA-extraction aided by zinc ferrite nanoparticles.

detection method based on RNA extraction. This method provides an efficient extraction of the viral RNA bound to the nanoparticles which are then determined by RT-PCR. This process is simple, requires less time as lysis and binding steps are combined, works with both manual and high-throughput automated systems, and is also highly sensitive.[57] Reverse transcription loop-mediated isothermal amplification combined with a biosensor based on nanoparticles was developed for the diagnosis of COVID-19. The method uses F1ab and np gene amplification of the SARS-CoV-2 and its subsequent detection in a one-step single-tube reaction. The described method was sensitive, specific, rapid, and accurate, and no cross-reactivity was observed from clinical studies. Comparison with RT-PCR results showed that consistent results were obtained by the developed assay. The sensitivity and specificity of the proposed assay was found to be 100%.[58] Zinc ferrite (ZNF) based magnetic nanoparticles surface-functionalized with carboxyl containing polymers were used in the development of an RNA-extraction protocol for SARS-CoV-2. ZNF was the material of choice, because it is easy to prepare, has soft magnetic behavior and high chemical stability, and is biocompatible. Because of the carboxyl modifications on the nanoparticles, the viral RNA could be easily attracted and adsorbed. This was an automated process to extract viral RNA, which could subsequently be tested through RT-PCR as shown in Figure 5. Therefore, this method attenuated the cumbersome process of RT-PCR to provide ease of operation through automation, the requirement of less time, and high purity and productivity.[59] Gold nanoislands were designed as a plasmonic chip to detect the nucleic acid of SARS-CoV-2 by a combination of plasmonic photothermal effect and localized SPR. The two-dimensional gold nanoislands functionalized with DNA receptors complementary to the virus were able to generate local heat (when illuminated at their plasmonic frequency), which acted as the heat source for uniform and controllable hybridization for sensitive detection of the virus. Precise detection was achieved with a lower detection limit of up to 0.22 pM.[60]

Detection kits based on lateral flow assays using colloidal gold nanoparticles have been approved by WHO. These include test kits developed by companies such as Guangzhou Wondfo Biotech Co. Ltd. and Innovita (Tangshan) Biotech Co. Ltd.[61] Sree Chitra Tirunal Institute for Medical Sciences and Technology in conjunction with Agappe Diagnostics Ltd. has launched an RNA extraction kit based on nanotechnology. It uses magnetic nanoparticles to capture and extract the viral RNA from the sample. The kit is useful in obtaining concentrated, purified RNA at an affordable cost.[62]

Clustered regularly interspaced short palindromic repeats (CRISPR) associated (Cas) proteins or the CRISPR effectors are a vast group of proteins present in bacteria and archaea, and are known to have a role in their adaptive immunity. They have the ability to recognize and cleave specific nucleic acid sequences from foreign objects such as invading viruses. Some of these Cas proteins have been investigated for their role in a vast range of applications related to diagnostics. Two such methods are SHERLOCK ("specific high-sensitivity enzymatic reporter unlocking") and DETECTR ("DNA endonuclease targeted CRISPR trans reporter"). The former method makes use of Cas13a protein from the Cas13 family and the latter uses Cas12a from the Cas12 family. These two methods have found importance in the detection of a number of infectious diseases. Detection of both viruses and bacteria has been possible with the SHERLOCK assay. Single-stranded flaviviruses like Zika, West Nile, Dengue, and Yellow fever viruses and HIV could be detected by the SHERLOCK method, while DETECTR was initially developed as a detection tool for the human papillomavirus.[63−65] The SHERLOCK method is a

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versatile tool in the clinical scenario as it could be used for strain discrimination within viruses, detecting antibiotic resistance genes in bacteria, patient genotyping, and identifying cancer-related mutations in cell-free DNA.[66] A method based on CRISPR-Cas9 was developed by Koo et al. for detection of illnesses which are tick-borne, namely, scrub typhus and SFTS ("severe fever with thrombocytopenia syndrome"). The sensitivity of the assay was highly improved compared to that of traditional RT-PCR.[67] The detection limit of these methods could reach the attomole range, that is, even single molecules can be detected.

Colorimetric and visual methods using CRISPR-Cas have been reported for the detection of disease-causing viruses. Detection of African swine fever virus using the CRISPR system and magnetic bead bound quantum dots has been developed by Bao et al.[68] Gold nanoparticles and Cas12a have been used to develop a system for the detection of red-blotch viral infection from grapevines.[69] The SHERLOCK method has been evaluated for the detection of SARS-CoV-2 by using the CRISPR-Cas13a system together with a reporter group consisting of gold nanoparticles. Clinical samples were tested by the developed method showed 100% specificity and sensitivity when used in a fluorescent readout. The sensitivity in the case of the lateral-flow readout was 97%. The limit of detection per reaction was 42 RNA copies. The samples used were nasopharyngeal and throat swabs, and no cross-reactivity was observed. The method was proposed for the assessment of preoperative patients. Comparison with RT-PCR results showed that both were in complete agreement.[70] A simple and rapid assay called the "all in one dual CRISPR-Cas12a" has recently been developed for the detection of SARS-CoV-2 with high sensitivity and high detection specificity. It can be carried out as a single tube reaction and provides visual detection for which it could be used as a point-of-care test.[71] FELUDA ("FnCas9 editor linked uniform detection assay") was developed as an alternative tool for detection of SARS-CoV-2 and was able to distinguish between two different SARS-CoV sequences differing by a single nucleotide. It provides a rapid, accurate, and low-cost detection platform.[72]

Such alternative methods for detection of infectious viruses provide the possibility of conducting tests outside the laboratory without the need for sophisticated instrumentation and trained personnel. The use of these rapid and field-deployable tests would lessen the reliance on the existing RT-PCR tests and can be routinely used in locations outside proper diagnostic laboratories.

5. NANOCONSTRUCTS–MICROBIOME INTERFACE FOR COVID-19 THERAPY

Nanotechnology solutions could also potentially alleviate COVID-19 infection by their intrinsic reactivity with the "microbiome". Our body hosts trillions of microbes such as bacteria, fungi, and viruses colonized in different anatomical sites such as the skin, oral cavity, respiratory canal, and gastrointestinal tract. These tiny traders collectively referred to as the "microbiome" are commensals, and their distribution is spatially regulated. They form an intricate network by synergistic participation in a range of physiological processes of the host such as nutrition absorption, protection of host tissues, and regulation of immune responses.[73] Thus, the microbiota is regarded as the dynamic "hidden organ" of our body.[74] Healthy tissues are characterized by the presence of diverse microbial communities, and microbial populations dominating these varied host anatomical sites are also different. For instance, Firmicutes and Bacteroidetes are the major communities in the nasal microbiota, while lung tissue is dominated by Bacteroidetes. Gut tissue also hosts Bacteroidetes along with Firmicutes and Proteobacteria.[75,76] Impairment in the community composition termed "dysbiosis" has been associated with various diseases, from cancer to neurodegenerative diseases. Besides these multifactorial diseases, alterations in the microbiome are also observed during pathogenic microbial infections. Viruses are the common pathogen that our body often encounters, and these infections could alter the microbiome diversity. Lungs are the primary host site for SARS-CoV-2, with high expression levels of the ACE-2 receptor. SARS CoV-2 infection causes histological and functional damage to the lung tissue leading to pulmonary hypoxia. These tissue modifications caused during COVID-19 alter the native tissue condition leading to the growth of anaerobic bacteria, lung flora contamination by oral microbiota, and other opportunistic pathogens, thus causing lung microbiome dysbiosis, which could further worsen the lung inflammation and susceptibility to pneumonia.[77]

Viral infections are also are reported to alter the gut microbial community leading to variations in the intestinal metabolic profile and gut-mediated immune responses.[78,79] The intestinal epithelium also, similar to lung tissue, expresses the ACE-2 receptor, which increases its susceptibility for SARS CoV-2 infection. A detailed analysis of patient samples that tested positive for SARS CoV-2 demonstrated the infiltration of lymphocytes into the inner layer of the stomach, duodenum, and rectal tissues indicating infection and local inflammation. Immunohistological examinations demonstrated the presence of viral nucleocapsid protein and ACE-2 receptor in the epithelial cells of gastrointestinal tissues further confirming the intestinal SARS CoV-2 infection.[80] Besides respiratory symptoms, clinical case studies of the COVID 19 infected patients demonstrated the presence of SARS-CoV-2 viral load in stool samples even after seroconversion.[81] In some cases, the stool samples tested positive for the virus even longer than the oropharyngeal swabs and also in the absence of obvious respiratory signals associated with SARS CoV-2 infection.[82] These reports indicated hijacking of gut tissue by SARS CoV-2, which could result in longer-lasting infection of the gut than the lung tissue. As the gut microbiome plays a host protective role in such viral infections, a prolonged presence of viral load in fecal samples suggested that SARS CoV-2 infection disrupts the gut defending wall, viz., gut microbiota, by disturbing the commensal microbial populations.

A cross-sectional study with 16S rRNA gene sequencing confirmed that gut microbial diversity is compromised with a relative abundance of *Streptococcus* in COVID-19 infection.[83] A recent study analyzing stool samples of hospitalized patients indicated a depletion of anti-inflammatory microbes such as *Faecalibacterium prausnitzii* and other symbiotic bacterial species, while the samples were enriched in opportunistic pathogens such as Clostridium and Actinomyces which are known to cause bacteremia. This alteration was observed irrespective of antibiotic administration.[82] Thus, these reports indicating changes in microbial communities along with increasing evidence of the gastrointestinal symptoms associated with COVID-19 confirmed that SARS CoV-2 indeed caused the dysbiosis of gut microbiota.[84]

An interesting question to be raised here is whether changes in gut microbiota are post SARS CoV-2 infection in lungs, or

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due to concomitant infection in the gut itself. Although this is yet to be explored, previous reports with the infection models involving respiratory viruses such as Influenza A virus (IAV) and Respiratory Syncytial Virus (RSV) demonstrated disruption of the intestinal mucosal layer, altered gut microbial diversity, and elevated antimicrobial peptide levels,[85,86] indicating the involvement of the lung−gut axis during respiratory viral infections. During SARS CoV-2 infection, damage caused to the intestinal lining leads to elevated immune responses which can result in multiple organ failure, while infection from the lungs could reach the intestine through circulation. Cross-contamination of microbiota between lungs and gut has also been reported.[87] Although gut and lung are anatomically distinct, these experimental findings imply the involvement of the lung−gut axis and interactions of the microbiota of both these tissues in the pathological outcomes and immunological responses during viral infections.

With the understanding of the involvement of microbiota in SARS-CoV-2 infection, mitigating the microbiota could be an effective adjuvant in COVID-19 treatment. For this, a system with precise and tailorable properties is required. Since nanoparticles have intrinsic antiviral properties and can be easily modified for targeted applications, the nanotechnology aided approach would be an ideal method to target microbiota. Although fecal microbial transplantation has demonstrated promising results, there is an effort to understand if nanotechnology also could aid in the microbiota targeted therapy. Metal nanoparticles such as Ag NPs or Au NPs are recognized for their antimicrobial properties. In a murine model experiment, the animal was orally dosed with well-characterized AgNPs for 28 days to check their effect on gut microbiota. The results demonstrated that unlike broad-spectrum antibiotics, the administration of AgNPs did not affect the resident microbial diversity.[88] Similar to AgNPs, AuNPs also exhibit antimicrobial properties. Another report demonstrated that Au nanoparticles can form a complex with bacteria, and this interaction would influence their biological activity including the interaction with host cells, their uptake, and signaling. However, the interaction was reduced when the nanoparticles were coated with biomolecule corona.[89]

Through nanotechnology, one can also consider delivering the modified particles which could specifically interact with the pathogenic strains, or the nanoparticles can be designed to re-establish the strains which are normal residents, thereby balancing the dysbiosis. Though the nanotechnology and microbial interface is an emerging concept, it could be a more patient-friendly therapeutic approach. If the nanoconstructs successfully make peace with our microbiota, then it could be an important adjuvant therapy in infectious diseases such as COVID-19. Apart from therapy, nanotechnology can also be applied for the development of diagnostic tools for rapid detections of SARS CoV-2 infection such as breath analyzers and ingestible sensors.[90−92]

The microbiome by its host-protective nature demonstrates some important pathways and strategies to defend against pathogenic infections. Commensal microbes can trigger immune responses locally and also at distal sites during viral infections. One of the pathways the microbiome triggers as a protective mechanism is stimulating interferon production and activation of immune cells.[93] Interferon (INF) is an important member of the cytokine family secreted during viral infections for host defense. INFs trigger several cellular pathways such as JAK-STAT and MAP kinase pathways, thus conferring the protection against pathogen indirectly.[94] Type 1 INF, which includes INF-α and INF-β, is the primary antiviral agent, and many viruses evolve to evade INF I. Contradictory results have been observed with the levels of INF-1 and COVID-19 infections. A study from peripheral blood mononuclear cells (PBMCs) indicated low levels of INF-1 associated with severe COVID-19 infection. In a recent report, it was observed that SARS CoV-2 failing to counteract the STAT pathway of INF-1 is much more sensitive to INF-1 when compared to SARS CoV.[95] These findings indicate that INF therapy could help in mitigating the COVID-19 pandemic.[96]

6. THERAPEUTIC NANOCONSTRUCTS IN COVID-19 THERAPY

In terms of therapy, application of nanotechnology includes the use of various types of nanomaterials and nanoparticles (NP) like inorganic NPs, peptide-based NPs, polymeric and lipidic based NPs, quantum dots, and graphene oxide. The major advantages of nanotechnology over conventional drug delivery systems, namely, the nanosize range of the particles, targetability, biocompatibility, biodegradability, lower toxicity, and the ability for surface modification open a window for site-specific delivery of therapeutic agents, aid in the long circulation time, and provide stability to the drug molecule encapsulated inside the NP. Concerning virus-related diseases, nanotechnology has proven to be a promising technology in nanodrug design/production and vaccine design against viral infections. NPs are capable of interfering with the replication of the virus, thereby preventing its entry into the cell, and the large surface area of NPs facilitates the incorporation of large drug payloads;[97] NPs are known to enhance the bioavailability and stability of the antiviral drugs, and their surface modification enhances the versatility of the NPs, facilitating targeted delivery of the drug molecules across various cellular membranes;[98] NPs have biomimetic properties by virtue of which they are also known to have virucidal activity against a host of viruses;[99] NPs are engineered moieties which decrease the chances of drug resistance and protect drug molecules from possible degradation. Nanodrug therapy also opens the door for personalized therapy to treat viral infections.[100] These advantages have led to the development of innovative methods and approaches, including the development of multifunctional bioengineered nanomaterials, green nanomedicine, and biomimetic drug carrier systems.[100]

For addressing a respiratory virus like SARS-CoV-2, biocompatible NPs and polymers are being developed that can penetrate and overcome the barriers of the mucus membrane and act in the lung tissue to inactivate the virus and/or inhibit its interaction with host cells, with minimal toxic/adverse effects.[101,102]

Nanotechnology-based therapy to combat COVID-19 has been gaining a lot of attention currently. The three key aspects to be considered in developing nanobased therapeutics to treat SARS-CoV-2 infection are the nanoformulations developed should be capable of protecting the host cell, should be capable of inhibiting the attachment of the virus to the host cell receptors, and should be able to restrict the entry of the virus into the cell and prevent the spreading of the infection.[103] Metallic NPs (silver, gold, iron), inorganic NPs, lipidic and polymeric NPs, spike protein NPs, peptide-based NPs, graphene oxide-based NPs, and quantum dots are a few of the NPs that are currently being investigated for the treatment

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Table 1. Nanotherapeutics for the Treatment of Viral Infections[a]

type of NP	target virus	mechanism of action	refs
		Silver Nanoparticles (AgNP)	
Silver sulfide Nanoclusters (Ag_2S−NC)	PEDV	Inhibition of viral budding and negative RNA strand synthesis	116
Amantadine coated AgNP	H1N1	Inhibition of viral entry into the host by preventing DNA fragmentation and reversal of virus-induced apoptosis by decreasing the accumulation of ROS	117
Silver nanoparticles	SARS-CoV-2	Virucidal activity against SARS-CoV-2 by altering the pH of the respiratory epithelium	118
		Selenium Nanoparticles (Se NP)	
Amantadine − Se NP	H1N1	Inhibition of neuraminidase activity, thereby preventing the interaction of H1N1 virus with the host cell	173
Oseltamivir − Se NP (OTV-SeNP)	H1N1	OTV-SeNP inhibits the activity of hemagglutinin with low toxic effects and prevents the interaction of the virus with the host cell	174
		Graphene Oxide (GO)	
Curcumin−GO nanocomplex	RSV	Inhibits the viral replication by directly acting on the virus, thus providing synergistic antiviral activity against RSV	126
GO derivatives	HSV-1	Inhibits the viral entry and spreading mimicking the heparan sulfate receptor and competitively binding to HSV-1 virus	127
Curcumin − carbon dots	PEDV	Inhibition of proliferation and viral entry into the host cell by structurally altering the surface proteins of the virus	128
GO sheets	Feline coronavirus	GO sheets caused the aggregation and rupture of the viral envelope by attaching to the sulfhydryl group of the protein	175
Anti-retroviral drug conjugated − GO quantum dots (GOQDs)	HIV	Conjugation of the anti-retroviral drug with GOQD increased the targetability of the drug and inhibition of the viral replication cycle	176
Boronic acid conjugated quantum carbon dots	Human coronavirus −229E	Inhibits the viral replication cycle in a concentration-dependent manner	177
		Mesoporous Silica Nanoparticles (MSN)	
Glycosaminoglycan mimetic MSN	HSV-1/2	Inhibition of viral entry into the host cell by competitively binding to viral glycoproteins	129
Mesoporous silica nanoparticles (MSN)	HIV/RSV	MSN binds to the virions and suppresses the viral activity at a lower concentration	178
		Polymeric Nanoparticles (PNP)	
Diphyllin and Bafilomycin−PEG-PLGA NP	H1N1	Greater antiviral activity *in vitro* by increasing the therapeutic index of the drugs by 3−5 folds	136
Acyclovir−chitosan nanospheres	HSV-1 and 2	Inhibition of proliferation and higher antiviral activity	138
Lopinavir − ritonavir − efavirenz − PLGA NP	HIV	Provided sustained release of all three drugs for a prolonged period	139
		Solid Lipid Nanoparticles (SLNs)	
Efavirenz − SLN	HIV	To increase the bioavailability and to provide a controlled release of the drug in the treatment of HIV infection	179
Lopinavir − SLN	HIV	To increase the bioavailability of lopinavir and inhibit the viral load accumulating at the oral lymphatic region	180
		Dendrimers	
Efavirenz − dendrimers	HIV	Dendrimers increased the cellular uptake of the drug by macrophages and monocytes thereby enhancing the efficacy and decreasing the toxicity of the drug	146
Acyclovir thiolated dendrimers	HIV	To provide sustained release and enhanced mucoadhesion of the drug	147
Carboxylate polyanionic dendrimer	MERS-CoV	Effectively decreased the MERS-CoV plaque formation thereby reducing the viral infection	180
Peptide−polymer dendrimers	HSV	*In vitro* enhancement of the antiviral activity against HSV infection	181
		Lipidic Nanoparticles (LNP)	
Lopinavir − ritonavir − tenofovir − LNP	HIV	To provide sustained release of the drugs and to enhance the intracellular concentrations of the drugs in lymph and blood	182
		Liposomes (LP)	
Indinavir − LP	HIV	To provide enhanced delivery of the drug and to maintain a high concentration of the drug in the lymphoid tissue	151
Pulmonary proteoliposomes	SARS-CoV-2	The liposome complex competitively binds to ACE2 receptors and prevents the entry of the virus into the host cell	152
		Stem Cells (SC)	
Mesenchymal SCs	SARS-CoV-2	To reduce pulmonary inflammation and edema caused due to SARS-CoV-2 infection	183

[a]PEDV, Procaine Epidemic Diarrhea Virus; H1N1, Influenza A Virus Subtype H1N1; SARS-CoV-2, Severe Acute Respiratory Syndrome Corona Virus-2; HIV, Human Immune Deficiency Virus; RSV, Respiratory Syncytial Virus; MERS-CoV, Middle East Respiratory Syndrome Corona Virus.

of SARS-CoV-2 infection. These NPs can be prepared as a solution or emulsion and can be administered to infected patients either by delivering the antiviral/other therapeutic agents via encapsulation into a virus-like NP or by conjugating these therapeutic agents onto the NP surface.[104] Among the various nanotechnological platforms, metal nanoparticles are gaining wide attention for the treatment of viral infections. Silver (Ag), gold (Au), and iron (Fe) are some of the metals that are widely exploited for their applications in treating viral diseases. Detailed information on nanotherapeutics for the treatment of viral infections is given in Table 1 and depicted in Figure 6.

6.1. Silver Nanoparticles. Silver nanoparticles (AgNPs), because of their innate antiviral activity against a broad

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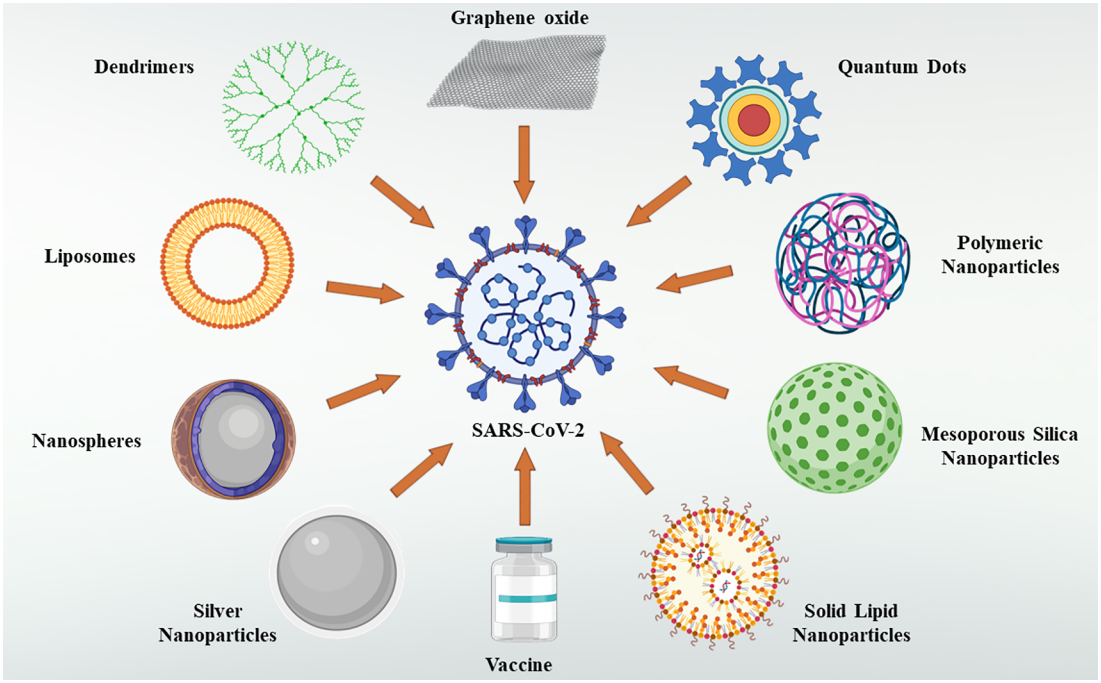

Figure 6. Nanotherapies for combating COVID-19.

spectrum of viruses, including HIV, HBV, HPV, MERS, SARS, H1N1, RSV, HSV, monkeypox virus, hantavirus, and tacaribe virus, have gained attention as a possible therapeutic approach for various viral infections.[105] The mechanism of action of AgNPs against a virus is not yet completely explored. In general, AgNPs act on different stages of viral replication. They inhibit the viral attachment to the host cell by interacting with the viral cell surface followed by interacting with the viral genome and inhibiting the replication and protein synthesis.[106] This observation was consistently backed by reports stating that AgNPs either affect the structural integrity of the virus by causing damage to the surface proteins or prevent the viral attachment thereby inhibiting infection in the early phase.[107,108] The antiviral activity of AgNPs largely depends on the target virus, and they generally act as viral reproduction inhibitors.[109] It was reported that the antiviral activity of AgNPs against HIV is mainly due to their interaction with the cell receptors, and in the case of double-stranded RNA virus, AgNPs inhibit the viral infection by interacting with the viral genome.[13] Few reports also suggest that silver reacts with amino, carboxyl, imidazole, and phosphate groups to denature the enzymes and thereby inactivates the virus.[110] AgNPs exert their antiviral activity at the early stage of infection which impacts on the rest of the viral replication cycle.[111]

AgNPs are also known to exert their antiviral activity by selectively binding to sulfhydryl group-rich proteins and destabilizing the protein by cleaving the disulfide bond, thus rendering the virus inactive.[112] The same antiviral action of AgNPs has been observed in the case of HIV infection, wherein the AgNPs inhibit the virus attachment to the CD4 binding domain of the gp120 surface protein by interfering with the disulfide bond.[105] Disulfide bonds play an important role in the binding of SARS-CoV-2 spike protein with the ACE-2 receptors, disrupting this viral binding by cleaving the disulfide bond will essentially render the virus inactive.[113] Thus, it can be presumed that AgNPs exert their antiviral effect on SARS-CoV-2 virus by disrupting the disulfide bond and impairing the viral attachment to the host cell. AgNPs also interact with viral nucleic acids and are known to exert intracellular antiviral activity.[114] Jeremiah et al.[115] reported a reduction in the viral load in VeroE6/TMPRSS2 cells which were pretreated with PVP-AgNPs. They attributed this partial antiviral activity to the destruction of the disulfide bond bridging the viral spike protein and ACE-2 receptors.[115]

There are many reports published on the use of AgNPs against viruses. Silver sulfide nanoclusters (Ag_2S−NC) for the inhibition of α-coronavirus and Procaine epidemic diarrhea virus (PEDV) were developed. The results suggested that Ag_2S inhibits the viral negative-strand RNA synthesis, preventing viral budding. The study also showed that the Ag_2S−NC successfully controlled IFN-stimulating gene proliferation and decreased the expression of pro-inflammatory cytokines, controlling the viral load on the host cell.[116] Amantadine, an antiviral drug used in the treatment of H1N1 and currently being considered for the treatment of SARS-CoV-2, has a major limitation of drug resistance. To overcome this, AgNPs were prepared to codeliver amantadine, wherein the AgNPs were surface decorated with amantadine. These modified AgNPs (AM-Ag NPs) prevented chromatin condensation and DNA fragmentation and inhibited the activity of caspase-3, blocking the entry of H1N1 virus into the host cell. The AM-AgNPs also reversed virus-induced apoptosis by preventing the accumulation of reactive oxygen species. Thus, the study concluded that AM−AgNPs have virucidal activity against H1N1 and can be used to prevent infection caused by related viruses.[117] A novel method for the treatment of SARS-CoV-2 has been developed which involves the delivery of water-dispersed AgNPs along with bronchodilators to the lungs by nebulization. The authors claim that AgNPs will kill the coronavirus over the respiratory epithelium by virtue of the antiviral and immunomodulatory effects of silver. Furthermore, the pH of the respiratory epithelium will be altered to alkaline by the silver ions leaching out of the NPs, making it a hostile environment for the survival of the virus. However, in this case,

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the dose of the AgNPs administered should be titerd in order to get better outcome in patients.[118]

6.2. Graphene Oxide. Graphene oxide (GO) is a two-dimensional, single-atom unique carbon material which is arranged in a hexagonal lattice.[119] GO, because of its unique properties like large surface area, optical transparency, high carrier mobility, biocompatibility, high thermal conductivity, high electron transport capacity at room temperature, and high mechanical strength is a promising next-generation nanomaterial for various biomedical applications, including the targeted delivery of the drugs.[120,121] The antiviral activity of GO is mainly due to its ability to interact with the virus and inhibit its entry and replication in the host cell.[122] The physicochemical interaction of GO with the virus is mainly ascribed to electrostatic interactions, hydrogen bonding and redox reactions.[123] GO acts against enveloped viruses like SARS-CoV-2 through binding between the opposite charges which lead to the association of the enveloped virus lipid tails with the aromatic plane of GO. This association leads to the aggregation of the virus followed by rupturing of the lipid membranes by GO.[124] Further, GO interacts with the host cell by controlling the orientation, protein adsorption, and conformation of the host cell.[125]

Curcumin-loaded cyclodextrin (β-CD) functionalized GO were developed to combat infection caused by RSV. The study aimed at increasing the bioavailability of curcumin by incorporating it in a GO−β-CD complex and thus providing a synergistic antiviral activity. The experimental data suggested that curcumin functionalized GO inhibits the virus from entering the target cell and inactivates the virus by directly interfering with the viral replication. The study concluded that GO can be successfully used as an antiviral therapy for RSV infection.[126] GO has also been used to inhibit HSV-1 infections. GO derivatives against HSV-1 infection were developed that mimic the cell surface receptor heparan sulfate, competitively binding to HSV-1 and thus decreasing cell-to-cell spreading.[127] Curcumin-loaded carbon dots (Cu-CD) were developed to study the antiviral activity of CDs using PEDV as a coronavirus model. The experimental data showed that Cu-CD complex inhibits the proliferation and entry of PEDV by structurally altering the surface proteins of the virus. Furthermore, the replication of the virus was suppressed by an increase in the production of proinflammatory cytokines and interferon stimulating genes, making a case for their use in treatment against PEDV and other coronavirus-related infections.[128]

6.3. Mesoporous Silica Nanoparticles. Mesoporous silica nanoparticles (MSNs) are biocompatible and less cytotoxic compared to other NPs, and because of their multiple porous structures, both hydrophilic and lipophilic drugs can be easily encapsulated when compared with other nanostructures. There are many reports available of MSNs used to deliver antiviral drugs. As an example, glycosaminoglycan (GAG) mimetic functionalized MSNs were developed to prevent the entry of HSV-1 and -2 viruses into the host cell. The study showed that GAG−MSN acts as an antiviral agent. GAG−MSN competes with heparan sulfate to bind to the viral glycoproteins and thereby inhibits the viral entry into the host cell and its subsequent proliferation and replication.[129]

6.4. Polymeric Nanoparticles. Polymeric nanoparticles (PNPs) are solid colloidal particles made up of biodegradable polymers like polylactide−polyglycolide copolymers, poly(lactic-*co*-glycolic acid) (PLGA), polylactides (PLA), polycaprolactones (PCL), and polyacrylates (PCA).[130−133] PNPs are more stable than any other nanoparticles in biological fluids and under different storage conditions owing to their polymeric composition. The drugs can either be covalently bonded, entrapped, or adsorbed on to the polymeric matrix.[134] PNPs are widely explored for their application in antiviral drug therapy because of the following advantages: PNPs effectively protect the drugs (protein, peptides, small molecules) that are prone to degradation and have a short half-life, and simultaneously enhance their solubility and bioavailability. PEGylation of PNPs promotes even longer circulation times of drugs in biological systems. PNPs effectively bypass the recognition of the particles by the reticuloendothelial system (RES) and decrease the chances of immune responses.[135]

A research group developed PEG−PLGA NPs encapsulating antiviral drugs diphyllin and bafilomycin for the treatment of infection caused by the influenza virus. The results showed that the NPs have greater antiviral activity and are less cytotoxic *in vitro* in comparison with the free drugs thereby increasing the therapeutic index of both diphylline and bafilomycin 3−5-fold.[136] Thermoresponsive polymer (TRP) nanoscaffolds for the codelivery of RSV fusion (F) protein trimers with Toll-like receptor 7 and 8 agonists (TLR 7/8a) were developed to neutralize RSV infection. The conjugation resulted in increased immunogenicity and enhanced binding capacity of F trimers to TRP platform in delivering TLF 7/8a to more than 3-fold.[137] Acyclovir chitosan nanosphere-based topical formulations were developed for the treatment of infections caused by HSV-1 and -2. These nanospheres showed better permeation of the acyclovir in the skin and higher antiviral activity in comparison to the plain drug.[138] In another study, PLGA-based NPs encapsulating a combination of three drugs—lopinavir, ritonavir, and efavirenz (AR-NP)—were fabricated for the treatment of HIV infection. The experimental data suggested that the intraperitoneal administration of the AR-NPs showed a sustained release of all three drugs from the AR-NPs over 28 days and significant inhibition of viral entry into the host cell in comparison with the free drugs.[139]

6.5. Dendrimers. Dendrimers are well-defined, nanosized, monodispersed radially symmetrical molecules. These are highly branched nanostructures which are polyvalent and have a globular structure.[140−142] The dendrimers are mainly composed of an outer shell, an inner shell, and a symmetric core.[143] They have the unique ability to encapsulate hydrophobic drugs in their core and can be functionalized by attaching different functional groups onto their surface.[144] Dendrimers showed antiviral activity by interacting with both extracellular and intracellular stages of the viral replication cycle.[145] For example, Efavirenz (EFV) encapsulated in fifth generation dendrimers separately conjugated with mannose and t-Boc-glycine. This dendrimer conjugate demonstrated a prolonged release of the drug from the dendrimer form. The cellular uptake of EFV by monocytes/macrophages from mannose conjugated dendrimer was significantly higher when compared with t-Boc-glycine conjugated dendrimer or the free drug. This fact was mainly attributed to its targeting the lectin receptors, while phagocytosis was the root cause for the uptake of EFV from t-Boc-glycine conjugated dendrimer. The study concluded that dendrimers can be used as a carrier to increase the efficacy and reduce the toxicity of anti-retroviral therapy.[146] In another study, thiolated cysteamine conjugated PAMAM dendrimers were developed as a mucoadhesive drug delivery system for the antiviral drug acyclovir. The results suggested a

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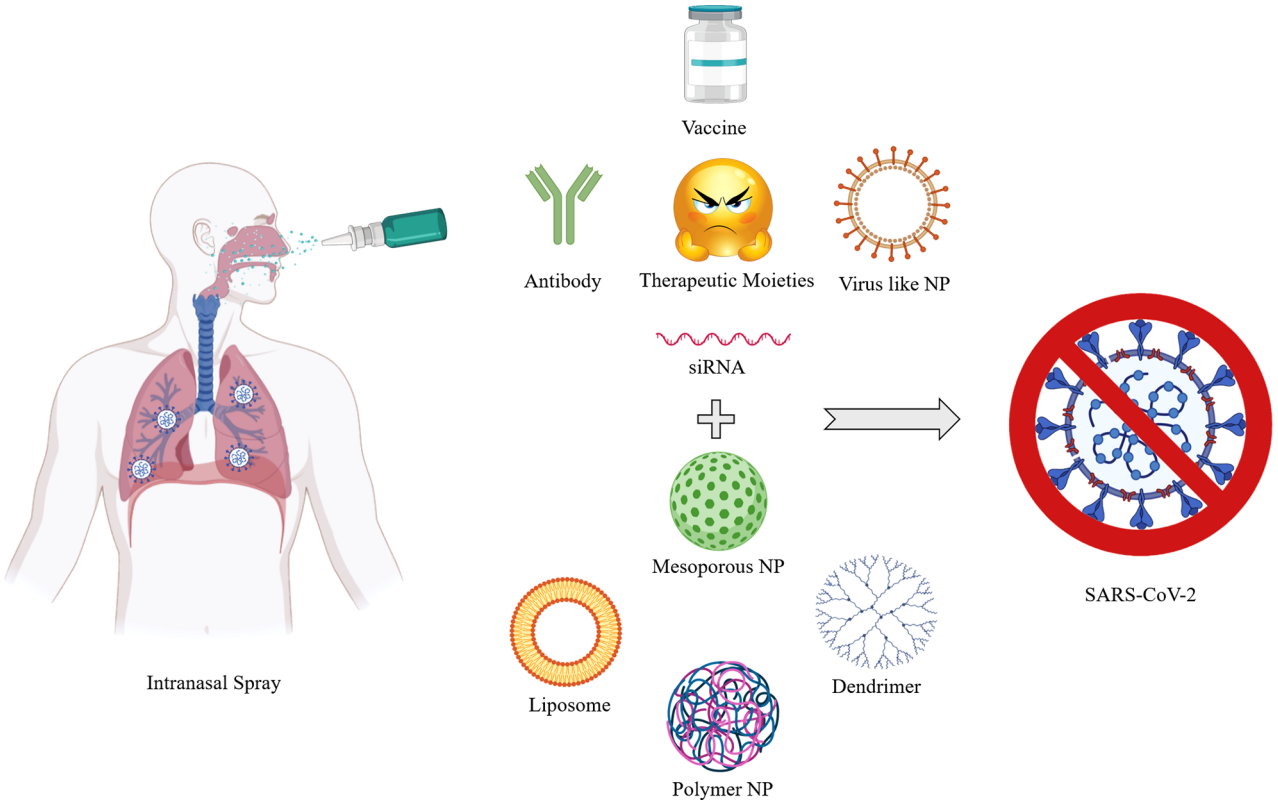

Figure 7. Nanoparticles-based therapeutic strategies for intranasal delivery of bioactives.

sustained release of the drug from the thiolated dendrimers. Thiolated dendrimers proved to be a useful mucoadhesive carrier for acyclovir as the bioadhesion of the thiolated dendrimers was enhanced. The enhancement in mucoadhesion was mainly attributed to the interaction of the thiol groups of the conjugates with the cysteine-rich glycoproteins of mucin present in the intestine by forming inter-disulfide bonds. The loading of acyclovir was also enhanced concluding that thiolated dendrimers can be successfully used as a carrier for antiviral drug therapy.[147]

6.6. Liposomes. Liposomes are spherical nanostructures made up of an outer phospholipid bilayer and an inner hydrophilic core. Liposomes have the unique ability to encapsulate both lipophilic and hydrophilic drugs and are biocompatible and biodegradable.[148−150] There are many reports available on the liposomal formulations of various antiviral drugs for the treatment of viral infections. As an example, indinavir-loaded immunoliposomes were developed for the treatment of HIV for enhanced delivery of the drug to lymphoid organs. The *in vitro* study suggested that indinavir immunoliposomes successfully delivered high concentrations of indinavir to lymphoid tissues increasing drug accumulation up to 126 times in lymph nodes.[151] A new strategy for the treatment of COVID-19 was pursued by another research group. They designed pulmonary proteoliposome complexes, using a combination of ACE2-like membrane proteins and liposomes. These proteoliposomes compete with the virus in binding to ACE-2 receptors, helping to reduce the spread of the infection. The lumen of these proteoliposomes can be filled with drugs, which will further help in reducing the viral load in lung tissues.[152]

6.7. Nanovaccines for COVID-19. Vaccines are sterile biological preparations used as a prophylactic treatment method to provide acquired immunity to particular viral infectious disease. A vaccine should have the following characteristics to induce immune responses in the host: it should not cause any infections, it should induce cellular and humoral immune responses, it should produce long-lasting immunity, and it should be readily adaptable to different pathogens and viruses.[103] The problems associated with conventional vaccine therapy can be counteracted by nanotechnology. Various nanocarriers including inorganic nanomaterials, liposomes, dendrimers, micelles, and polymeric nanoparticles have been widely exploited for application in vaccine development. They aid in improving the stability, pharmacokinetics, solubility, and permeability of the vaccines.[153] They also facilitate the controlled or targeted delivery of immunogens to antigen-presenting cells.[154]

Vaccination is an affordable, cost-effective strategy to control and prevent viral infections. In current times, a greater emphasis is being put on developing a suitable vaccine against SARS-CoV-2 virus. Currently, vaccine development in the area of COVID virus (CoV) is focused on the transmembrane spike (S) glycoprotein which serves as an entry point to the virus into the host cell.[155] A recent study showed that CoV spike protein nanoparticles (S NP) induce anti-MERS and SARS-CoV antibody response in mice.[156] Another study reported the use of alum as an adjuvant in a SARS-CoV virus-like particle (VLP) proved to be highly immunogenic and elicited neutralizing antibodies against the lethal infection.[157] A ferritin-NP based RNA mediated vaccine against MERS-CoV was developed, which showed a generation of interferons and TNF-α upon antigen stimulation.[158] A research group developed a vaccine strategy of lipid nanoparticle encapsulating a SARS-CoV-2 spike protein-encoding self-amplifying RNA (saRNA−LNP). The results suggested that saRNA−LNP

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induced high SARS-CoV-2 specific IgG antibodies in mice and produced a higher cellular response and viral neutralization, suggesting that these data can be translated into a robust vaccine for preventing SARS-CoV-2 infection.[159]

Drug-loaded nanoparticles are delivered to the target organs/tissues via different routes of administration like oral, ophthalmic, dermal, transdermal, parenteral, nasal, pulmonary, and rectal routes.[160] The oral route is the most preferred route of administration because of its high patient compliance, the convenience of administering the dosage form, and the ease of application. The oral route is suitable for high drug absorption, as the gastrointestinal tract has a large absorption area with excellent blood supply, providing a higher residence time to the dosage form.[161] The transdermal route is widely explored for the delivery of nanoparticles as it offers advantages like bypassing the first pass hepatic metabolism,[162] providing controlled release of the drug over a prolonged period of time and decreasing the need of multiple dosing.[163] Delivering nanoparticles via the nasal route helps in bypassing the blood-brain barrier, provides faster onset of action due to higher permeation and drug absorption, provides precise drug targeting, and protects the drug from enzymatic destruction.[164]

Nanoparticle-based drug delivery can be a potential way to deliver vaccines or to stimulate an immune response in the infected cells in the treatment of SARS-CoV-2 infections, as these nanocarriers can be tailored by altering surface characteristics, charge, size, and shape. Furthermore, these nanocarriers are capable of penetrating into mucosal surfaces and capillaries when administered through different routes like intranasal and oral, and as subcutaneous and muscular injections.[165] Recent studies suggest that the nasal cavity serves as the major route for SARS-CoV-2 to enter into the body. Ciliated cells and the mucus producing goblet cells present in the mucosal epithelial cells of the nasal cavity are the main target sites for inducing corona infections.[166] Nasal associated lymphoid tissue (NALT) is considered a promising target for the delivery of drugs and vaccines against respiratory virus, specifically CoVs.[165] NALT comprises dendritic cells, lymphoid follicles, and macrophages, which upon activation by the production of antigen specific antibody or by killer cells, leads to the clearance of infection causing agents from the mucus layer.[167] Via emulsion or suspension of NPs conjugated with therapeutic agents like antibodies, siRNAs can be formulated into nasal sprays as described in Figure 7 and can be administered intranasally as a mode of efficient therapy against SARS-CoV-2 infection.[104] ACE-2 receptors are widely expressed on type II lung alveolar cells, and SARS-CoV-2 virus attaches to these ACE-2 receptors to gain entry into the airway and lung epithelia.[168] Upon infecting the lung epithelial cells, SARS-CoV-2 virus causes pulmonary hyper inflammation.[169] This makes the pulmonary route of drug delivery an excellent option in the treatment of SARS-CoV-2 infections. In the pulmonary route, the drugs are directly carried to the airway and alveolar epithelia in higher concentrations, and the drug come into direct contact with the pathological lung epithelia, thus providing a rapid onset of action which leads in the reduction of respiratory distress symptoms and lung occlusions.[170] Nanoformulations of systemic antivirals, anti-inflammatory drugs, and glucocorticoids can be administered via the pulmonary route for the efficient treatment of SARS-CoV-2 infections. NPs can also be delivered intravenously (IV). The IV route is suitable for the drugs that cannot be injected into muscles or other tissues and for the drugs that are not absorbed by the GIT. The IV route protects the drugs from getting degraded by proteolytic enzymes.[171]

The main advantage of IV route is that it provides 100% bioavailability of the drugs and it bypasses first-pass metabolism.[172] Owing to these advantages of the IV route, nanoformulations of antivirals, IgG, and vaccines can be delivered intravenously for combating SARS-CoV-2 infections.

7. NANOCONSTRUCTS, INANIMATE SURFACES AND COVID-19 TRANSMISSION

SARS-CoV-2 spreads in a manner similar to that of Rhinoviruses, via direct contact with an infected aerosol droplet. It is estimated that approximately 108 viral copies might be present per mL of sputum.[184] A superspreader is an extremely infectious individual infected with a disease that is more likely to infect others (when infected, secrete a higher number of the pathogen) and follows the 80/20 rule which denotes that 20% of infected individuals are responsible for 80% of disease transmissions.[185] The superspreaders may either have immune suppression, lack of herd immunity, and/or coinfection with other pathogens, or conversely, their immune system may be highly active, rendering the individual asymptomatic. In comparison to other disease outbreaks like tuberculosis, measles, smallpox, Ebola, SARS, and MERS, the latest COVID-19 pandemic appears to have a higher number of superspreaders, as detected by contact tracing.[186] Lock-downs and extreme social distancing are the only possible ways to prevent superspreader contact with other individuals. Coronavirus can spread through contaminated surfaces, so it is necessary to be able to sterilize high-contamination surfaces, such as door buttons, elevator buttons, or handrails, in general, in public areas, hospitals, and clinics.[187] However, several studies have reported that these viruses can survive from hours to days on inanimate surfaces. For instance, this virus is capable of residing for up to 6 days on the surface of metals, cloth, and plastics. It was found that the virus prevails better at room temperature and higher relative humidity environments. In addition, infectious respiratory secretions and other body fluids (urine, saliva) may also contribute to the spread of SARS-CoV-2. Moreover, undocumented infection exacerbates the rapid spread of SARS-CoV-2. Therefore, the first containment barrier to preventing the virus from spreading would be efficient disinfection measures.[188] The WHO recommends that surfaces be thoroughly washed with water, detergents, and commonly used disinfectants to clean the environment.[189] Kampf et al. through their study showed that ethanol (62−71%), sodium hypochlorite (0.1%), and hydrogen peroxide (0.5%) were the most potent disinfectants among others, reducing virus infectivity within a minute.[190,191] In this section, we describe the role of nanotechnology in suppressing the spread of the virus.

Although coronavirus can be killed easily and quickly by breaking the fragile envelope around it by using the aforementioned disinfectants,[192] surface sanitization is, however, impractical at all times and does not ensure that the surface is not contaminated again. In such a scenario, it is much wiser to render the inanimate surface capable of repelling the pathogens, thus enabling it to self-sanitize. To overcome these challenges, researchers are designing new long-term surface coatings containing nanoparticles of metal ions embedded onto the polymers with a virucidal and antimicrobial activity that could be sprayed or painted on surfaces. Since metal ions will be released very slowly in a controlled manner,

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the coating could be effective for several weeks or months. Literature surveys reveal that nanoparticles (NP) of different metals and metal oxides (ZnO NPs,[193] CuO NPs,[194] Ag-NPs,[195] and others) are promising candidates proven to inactivate the virus. For instance, Ag-NPs are reported to inhibit virus nucleotide replication, which is primarily responsible for its virulence. They bind with electron donors such as nitrogen, sulfur, and oxygen, which are commonly found in microbe enzymes and, thus, denature vital enzymes, causing the death of the microbe. In the case of SARS-CoV-2, cationic silver might work by interacting with spike protein (S) as it functions in HIV.[195]

In this context, Nova Surface-Care Centre, developed Nanova Hygiene+, is a nanoactive surface coating to function as an antimicrobial coating solution for all surfaces. It works as an omniphobic surface (repelling both water and oil) and exhibits low surface energy. The test reports of this coating complied with the global JIS Z2801 standard to protect against bacteria up to 99.9%. Researchers at Hong Kong University have developed an antiviral coating (MAP-1) containing nanocapsules of disinfectant that could last 90 days.[196] A scientific team at the University of Pittsburgh have developed an antiviral coating containing nanoparticles of polytetrafluoroethylene that are suspended in solvents and drop-casted onto the fabric by the application of heat.[197] Similarly, the results of initial antiviral testing performed on Poliovirus (MS2 Bacteriophage), showed a 99.9% antiviral efficacy in just 2 h of surface contact (in compliance with AATCC 100−2012 global standard). Tests to establish its efficacy against SARS-CoV-2 on different surfaces are currently in progress. If the product succeeds, it can serve as a potential coating to prevent the spread of the virus to the living body cells from inanimate objects and could save lives.[198]

8. NANOTECHNOLOGY-BASED ALTERNATIVE STRATEGIES TO COMBAT COVID-19

Although theoretically, several drug molecules have the potency to destroy SARS-CoV-2, most of them are under clinical trials. Thus, it is wiser to be safe than sorry. Use of alternatives like disinfection chambers, UV radiation, ventilation, and opening of windows and increasing exposure to sunlight should be considered to reduce the viral load, taking account of the likely spread of the virus through inanimate surfaces and its possible evolution within cave environments.[199]

The disinfection chamber is an enclosed space where spray devices are used for disinfection. Features such as temperature scanners, lighting, chemical atomizers, and audio/video options can additionally be found. Commonly used agents in disinfectant chambers include chlorine-based chemicals, benzalkonium chloride, and chloroxylenol.[200] In this context, IIT Kanpur developed a low-cost disinfection chamber that can be used in public places like malls, markets, and offices. This device uses two chambers, one for atomization and the other for thermal shock. This combination provides an economical and rapid disinfection process (80% disinfection in 2 min) and is safe for human beings.[201] Similarly, the DRDO, Government of India has developed COVSACK, a sample collection kiosk with integrated disinfection facility that helps the health care workers to collect the swabs from suspect carriers without the need for PPE kits.[202] WeInnovate BioSolutions, a Pune based start-up, has developed a silver nanoparticle solution as a sanitizer to prevent viral RNA synthesis. This nonalcoholic silver solution is nonflammable and free of harmful chemicals and can effectively disinfect the hands and surfaces to prevent the spread of the virus.[203] Ag-NPs have been proved to be effective against viruses like HIV, HBV, influenza, and others, and can prevent healthcare workers from being exposed to the virus.[108]

Nanotechnology plays a pivotal role in preventing and combating many of the diseases. In this perspective, a team of researchers from Pune developed a water-based nanomaterial disinfectant, which is nontoxic and eco-friendly and can be used to disinfect even toys and edible items. It serves as an alternative in overcoming the efficacy problems of handwashing soaps and the flammability of alcohol-based sanitizers. This formulation is a combination of aromatic medicinal herbs and a potent nanometal compound having antiviral activity.[204] Likewise, the Defense Institute of Advanced Technology in Pune developed Ananya, a nanobased disinfectant spray, which can disinfect all types of surfaces. The formulation contains Ag-NPs and ampicillin, which aid in neutralizing the external protein of the virus and also in destroying the virus membrane, thus making it ineffective. It is a water-based spray that adheres very well to metallic objects, plastic, and fabric, and is of negligible toxicity for humans. Once sprayed, it remains effective for 24 h, and its shelf life is estimated to be more than 6 months.[205]

Another group of researchers from the Ben-Gurion University of the Negev are developing antiviral nanoparticle coatings based on polymers containing copper and other metals. Studies demonstrate that these nanoparticles exhibit strong antiviral activities and enable the controlled release of ions rendering it effective for a longer period of time (weeks to months).[206] MACOMA Environmental Technologies has developed FN-NANO, a titanium dioxide based photocatalytic nanocoating for walls, and ceilings to prevent the spread of the virus. Several studies support the photocatalytic activity of titanium dioxide in decomposing the bacteria and viruses. MLK Hospital in Southern California and Las Vegas International Airport have already used this coating to prevent the spread of virus.[207]

Mobile phones are omnipresent and are touch-operated making them an absolute Petri dish retaining the virus. It is estimated that the virus remains viable for up to 96 h on the surface of the phone, contributing potentially to the spread of the virus. Nanoveu Ltd. has come up with 12 prototypes of antiviral protective cases and screens for mobile phones. The company is testing the prototypes in independent laboratories in Singapore and the US for coronavirus OC43, which has the same genus of SARS-CoV-2 and is aiming to submit its innovation as a Class I Medical Device under the Australian TGA regulatory body.[208]

Over the past decade, the notion of superhydrophobicity has been commonly used in developing self-cleaning coatings. A surface is said to superhydrophobic if the contact angle is more than 150° along with a sliding angle less than 10°. In this context, natural rubber surfaces were coated with silica nanoparticle-based superhydrophobic coatings and characterized. The results of imaging techniques proved the presence of nanoparticle coating on the surface of gloves, and further, the coated gloves exhibited better alcohol resistivity.[209] This concept could be used in developing a coating which renders the surface of gloves hydrophobic and, thus, prevents the spread of the virus.

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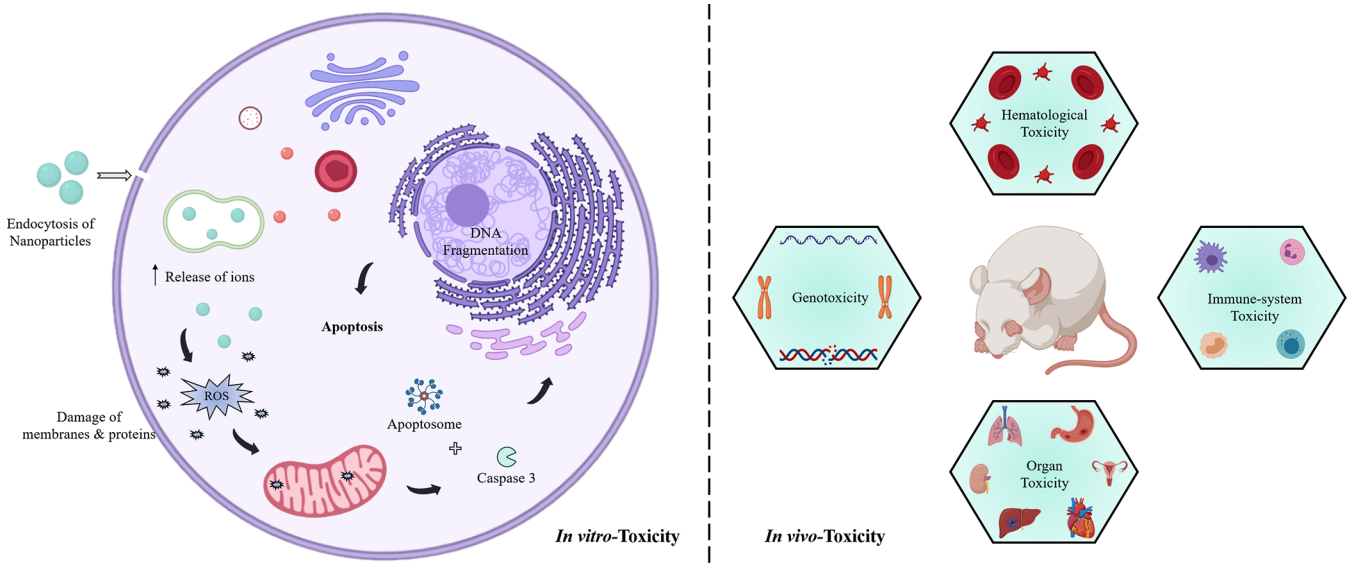

Figure 8. Schematic representation of the *in vitro* and *in vivo* toxicity of nanoparticles.

9. RADIONUCLIDES AND COVID-19

One of the less explored fields having the potential to tackle COVID-19 is the use of radiation. Although very few reports have been published so far, the results discussed therein suggest that radioactivity can play a vital role in combating COVID-19. It was hypothesized that radiotherapy can be explored for deactivating the COVID-19 virus.[210] In recent research, the Monte Carlo simulation method was used to study the impact of radiation on SARS-CoV, influenza, and SARS-CoV-2 GlycoProtein 6VSB. The results demonstrated that SARS-CoV-2 and influenza virus models showed lower radiation resistance than the original SARS-CoV.[211]

It has been proposed to treat pneumonia in COVID-19 patients using a low dose of linear energy transfer radiation (less than 100 cGy), citing that pneumonia has been treated with X-rays with success in reducing the mortality rate. Rapid symptom relief, acute phase reduction, and anti-inflammatory cytokine production have been observed earlier in pneumonia treatment with low-dose radiation. The authors thus recommend investigating the potential of low dose radiation therapy in clinical trials, which could help in downstaging patient criticality and decrease the stress on intensive healthcare.[212] Whole lung low dose radiation therapy has been investigated in COVID-19 patients under clinical trial named "RESCUE 1-19". The study is designed primarily to investigate clinical, radiographic, and immune outcomes in patients with pneumonia or severe acute respiratory syndrome associated with coronavirus disease 2019 (COVID-19) following whole-lung, low-dose radiation therapy (LDRT).[213] The trials are still ongoing and their clinical inference is awaited. A similar clinical trial based on low dose radiation therapy sponsored by the All India Institute of Medical Sciences (AIIMS), New Delhi, India has been started in June 2020. The study is a single-arm study designed to assess the feasibility and clinical efficacy of low dose radiation therapy (70 cGy in single fraction) in patients with COVID-19 pneumonia.[214] National Early Warning Score (NEWS) score will be used to assess the response based on the symptomatic improvement or deterioration in COVID-19 patients.

Radiopharmaceuticals are pharmaceutical formulations containing radionuclides. The gamma emitting radionuclide such as ^{99m}Tc and ^{18}F with a few hours half-life are used for diagnosis, whereas particulate emitters (beta, gamma, or Auger electron emitters) which can deposit their energy in nanometer to few millimeters range are used for therapy. Various ligands such as antibiotics, antimicrobial peptides, vitamins, etc., labeled with radionuclides are used for detection of microbial infections, as reviewed by Ebru et al.[215] Radiolabeling of white blood cells with suitable agents such as ^{99m}TcHMPAO or ^{111}In-Oxinate is considered the gold standard for infection imaging. Whereas antimicrobial peptides labeled with ^{99m}Tc and ^{68}Ga are finding more applications recently.[216] Efforts are underway to develop specific radiopharmaceutical for imaging virus infections and now including COVID-19 virus. Monoclonal antibodies (MAbs) are specific carrier molecules used for radiopharmaceuticals; the MAb specific against Glyoprotein S1 of SARS-CoV-2 is now labeled with ^{131}I and being evaluated for its therapeutic efficacy against COVID-19.[217] However, mutagenicity observed with the virus poses current challenges of specificity for use of monoclonal antibodies, and extensive studies are warranted.[218] However, considering the current developments in the field of radiopharmaceuticals, it is worth the effort and research is underway for development of diagnostic/theranostic agent.

10. NANOCONSTRUCTS AND TOXICITY

Toxicity is a major concern in nanoparticle-based drug delivery. The molecular mechanism by which NPs exhibit their toxicity includes the following: (1) NPs interact with cellular DNA and impair important enzyme function due to the release of toxic ions, impacting the organism. (2) NPs trigger the internal signaling pathway that damages the cells or they damage the cell membrane by directly associating with the cell surface of the organism.[219] (3) NPs create oxidative stress on an organism by generating reactive oxygen species which will subsequently damage the organism's genetic material or impair important enzyme functions.[220] Figure 8 describes the *in vitro* and *in vivo* toxicity of nanoparticles. Toxicity of NPs can mainly arise due to particle size and composition.[221]

Biodegradable NPs accumulate within the cells and causes toxicity by inducing alteration in the genetic material or by damaging the integrity of the organelles. Reports suggest that

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AgNPs can cause physiological and structural alterations of vital organs. AgNPs upon inhalation accumulate in the alveolar region resulting in lung injury, and they also produce significant alterations to liver and kidney tissues.[222] The toxicity of AgNPs is mainly attributed to their interaction with the biological macromolecules, the release of silver ions, and surface oxidation occurring due to their transformation under specific environmental and biological conditions.[223] The *in vitro* results suggest that AgNPs are capable of inducing genotoxicity, apoptosis, and oxidative stress.[224] AgNPs, when administered in non-cytotoxic doses, result in mutagenicity, chromosomal abnormality, and DNA damage.[225]

In the case of GO shape, surface chemistry, dose, purity, lateral dimension, and route of exposure plays a vital role in inducing toxicity.[226] GO induces time- and dose-dependent cytotoxicity by entering into the nucleus and reducing cell adhesion, resulting in apoptosis.[227] GO also enters cell organelles like endoplasm, lysosomes, and mitochondria, inducing injury.[228] It also increases intracellular ROS levels by accumulating in the cytosol.[229] Furthermore, GO interferes with the normal physiological functions of the vital organs and causes chronic injury and acute inflammatory responses.[230] The mechanism through which MSNs exert their cytotoxicity includes glutathione depletion, membrane peroxidation, followed by mitochondrial dysfunction and DNA damage eventually leading to cell death.[231] In most of the cases, MSNs elicit ROS generation and proinflammatory responses leading to autophagy.[232] Studies have reported that the size of MSNs plays an important role in inducing hemolysis. Toxicity varies inversely with size, as smaller particles are better taken up by the cells, making the silanol groups of MSNs more available for cell contact leading to hemolysis.[233] Dendrimer toxicity is mainly due to the presence of terminal amine groups and multiple cationic charges. The electrostatic interactions between the amino surface groups of the dendrimers and the negatively charged cell membrane increases the permeability of the lipidic bilayer of the cell membrane and decreases the integrity of the cell membrane.[234] The interaction of the dendrimers with the cell membrane results in the leakage of cytosolic proteins like lactate dehydrogenase and luciferase finally resulting in the disruption and cell death.[235] Dendrimers are also reported to show generation and concentration-dependent cytotoxicity and hemolysis effect.[236] Nanotechnology for drug delivery has a plethora of beneficial applications, but the toxicity with respect to nanocarriers is a major concern. In deep studies, toxicity of NPs is still limited, and in general, one should consider the toxicity aspect while selecting them for a particular application.

The above discussion suggests that although various nanoplatforms can be beneficial for combating COVID-19, the inherent toxic effect of some inorganic nanoconstructs needs to be paid attention to. Based on the route of administration, the toxicity of these nanoconstructs can be nullified or suppressed. Various surface modification such as using biopolymers, proteins, or lipid might be helpful in enhancing the biocompatibility of the nanoconstructs.

11. CONCLUSION AND FUTURE PROSPECTIVE

While the COVID-19 pandemic is an alarming challenge to human societies across the world, it should be considered as an opportunity to remind our global community that multi- and interdisciplinary approaches, encouraging diversity in the formation of problem-solving groups and the exchange of expertise between countries would all be central to achieving new and vital scientific solutions.[237] Nanotechnology is expected to play a vital role in the battle against COVID-19 by designing biosensors to detect the virus at the early stages of infection, preventing its transmission using nanocomposites which can also be used to disinfect public medical devices, and eventually leveraging vaccines to provide immunity against transmission.[238] While additional research is required, antiviral nanomaterials are an option to minimize COVID-19 spread, because they have been effective against other viruses. Based on present understanding, nanomaterials with strong antimicrobial activity can be effective sanitizers, that can improve safety in healthcare-related institutions and public spaces, particularly in developed countries. Nanotechnology can also enhance the antiviral potency of some drugs, making them an important alternative to combat secondary infections and to treat multidrug-resistant microorganisms for future treatments. Overall, protocols that favor the simple, quick, and cost-effective synthesis of antimicrobial and antiviral nanomaterials produce powerful nanomaterials that might reduce viral spread. In countries which lack access to advanced technologies, this innovative nanotechnology may help in fighting COVID-19. Easy-to-synthesize nanomaterials can be made available for use in front-line situations, such as mobile medical units, rural health centers, public spaces, and military medical posts on the field.[239]

NPs can be introduced to different types of methods for detecting viruses. Due to the exclusive optical properties of QDs and metal NPs, there is an increased sensitivity for optical biosensing. Meanwhile, because of their magnetic properties, MNPs are especially added to the virus extraction process. In addition, the nanocomposites integrate the benefits of each NP type to enhance the effectiveness of virus detection. Virus detection by means of NP has recently been identified as an auspicious tool for detecting the recently identified SARS-CoV-2 that induces COVID-19. NPs will certainly play a crucial role in enhancing the efficacy of coronavirus identification as well as other biological pathogen diagnosis.[240] Overall, the findings discussed in this part indicate that different NPs can be used to develop drugs to inhibit SARS-CoV-2 binding to the ACE2 receptor and block the mechanism of cellular uptake while remaining relatively nontoxic to the host cells. In order to avoid viral replication that is long enough for an immune response to react against the virus, in order to reduce cellular disruption caused by the viral intrusion, and also to mitigate genetic mutations associated with a high incidence of the proliferation of the virus, which could contribute to therapeutic resistance, successful antiviral therapies, particularly in the early stages of infection, are important. NPs of different structures, conjugations, and formulations have been manufactured and tested as highly efficient modifications or replacements to many current antiviral therapies consistent with growing drug tolerance in various circumstances.[240]

Various human-infecting viruses varying from members of the coronavirus family to other viruses with near structural resemblance to SARS-CoV-2 itself have been rigorously investigated for antiviral efficiency, stability, and biocompatibility of these NPs. Many NPs have already been shown to be successful against a wide range of viruses with limited cytotoxicity using innovative antiviral methods with versatile combinations, indicating that these NPs are ideal candidates for NP-based antiviral therapies to combat the COVID-19

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pandemic. Thus, in the battle against COVID-19, NPs are predicted to play a significant role. For developing diagnostic test kits, the optical and magnetic properties of different NPs may be used. SARS-CoV-2's stark anatomical and physicochemical similarity with conventional NPs also allow NPs an effective intervention technique. In order to execute unique inhibitory roles while still acting as excellent delivery vehicles, NPs may be extensively functionalized with different polymers, proteins, and functional groups. Using subunit proteins instead of entire viruses, NPs give possibilities for quick and secure vaccine production. In fact, NPs can also be used to develop broad-spectrum pulmonary medicines and vaccines which can shield us from common viruses too and prepare us for potential pandemics.[240] Overall, the review discussed in this section provides the useful insight required for the development of COVID-19 vaccines. More now than ever, nanotechnology is needed to counteract this current global threat to public health, plan for potential new threats, and devise a more sustainable science-based future.

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