Nanotechnology Toolkit for Combating COVID-19 and Beyond

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Nano-Tools for tackling SARS-CoV-2

Diagnostics

Preventive Measure

Nanovaccine

Nanomedicine

Protein sub-unit vaccines

Vaccine loaded NPs

VLPs

Vaccination

High immunity

Inhibits Replication
Inhibits Protein synthesis

Virus cannot bind and infection is prevented

Host cell

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Abstract: The outbreak of SARS-CoV-2 is unlikely to be contained anytime soon with conventional medical technology. This beckons an urgent demand for novel and innovative interventions in clinical protocols, diagnostics, and therapeutics; to manage the current "disease X" and to be poised to counter its successor of like nature if one were to ever arise. To meet such a demand requires more attention to research on the viral-host interactions and on developing expeditious solutions, the kinds of which seem to spring from promising domains such as nanotechnology. Inducing activity at scales comparable to the viruses themselves, nanotechnology-based preventive measures, diagnostic tools and therapeutics for COVID-19 have been rapidly growing during the pandemic. This review covers the recent and promising nanomedicine-based solutions relating to COVID-19 and how some of these are possibly applicable to a wider range of viruses and pathogens. We also discuss the type, composition, and utility of nanostructures which play various roles specifically under prevention, diagnosis, and therapy. Further, we have highlighted the adoption and commercialization of some the solutions by large and small corporations alike, as well as providing herewith an exhaustive list on nanovaccines.

1. Introduction

On Feb 2021, Nature scientific journal released the results of a poll it conducted among one hundred immunologists, infectious-disease experts, and virologists to gain some insights on the future of the now globally notorious COVID-19 pandemic. In that poll, nearly 9 in 10 of the surveyed scientists believe that when COVID-19 ceases being a pandemic, it will most certainly become an endemic; 6 in 10 of them were a lot more certain of that too.\textsuperscript{1,2} And despite the global community having spent an estimated 12.6 trillion USD (in 2020 alone) on countering COVID-19, nations having curtailed socio-economic activity, and with the masses adhering to safety measures around the world, the pandemic still managed to infect nearly 170 million people and killed almost 3.5 million of them by May 2021 as per WHO; in fact these estimates maybe smaller than the true numbers due to the limitations associated with such unprecedented scales of testing and the ubiquity of asymptomatic cases.\textsuperscript{3–5} However, time and again throughout history, we have witnessed how the acquisition of new technology and knowledge often imbues us with capabilities previously inconceivable. Thus, notwithstanding the odds, there is good reason to be optimistic in that we may overcome this disease if we invest more resources into basic research (in fields such immunology, biomedicine, etc.) and emerging biomedical technologies.

And as terrible and terrifying as COVID-19 can be, it is still caused by a single external causative agent, the SARS-CoV-2 virus; this is unlike other major causes of mortality such as cardiovascular diseases or cancers which develop due to a multitude of contributing factors such as lifestyle, genetics, etc. Ergo, by targeting this virus and developing effective countermeasures against it, we can conquer this disease and may have in our hands a blueprint to neutralize pathogenic threats of similar nature if they should ever arise in future. One area of research that has a tremendous potential in providing us with the necessary solutions is nanotechnology. It is a revolutionary domain which has witnessed success in nurturing novel solutions for the management of complex diseases such as the intractable cancer; and by design it acts at incredibly small scales of things, at spatial dimensions comparable to that of viruses and consequently granting us potential avenues for enhanced spatial selectivity. Concordantly, in the following sections we shall expound on the existing nanotechnology-based solutions and research for the management of COVID-19 and its prospects.

This review has been categorized into three main sections, with each section dedicated to a specific aspect of COVID-19 management. It starts with the role of nanotechnology in designing and developing antibacterial/antiviral personal protective equipment (PPEs) to better control the spread and transmission of pathogens while concurrently providing information on PPEs developed in such manner. The succeeding section deals with the development of nanotechnology-based diagnostics for early detection of respiratory viruses such as SARS-CoV-2 and highlights the role of nanotechnology in overcoming the limitations associated with conventional detection techniques, which will be crucial during global health crises of this proportion. The final section is an overview on the potential applications of nanomedicine towards the development of COVID-19 therapeutics and details its role in nanovaccine development; starting with an overview of existing therapeutics against SARS-CoV-2 infection (including those which are still being tested), we move on to providing specific information about different classes of nanoparticles (NPs) that can emerge as nanomedicine candidates for the treatment of respiratory viral infections. Lastly, we provide a general outlook on the current situation, discuss the limitations associated with the current practices and comment on the future of nanotechnology in the management of disease outbreaks and pandemics. We believe that the systematic and categorical approach adopted by us in preparing this review, along with the compendious information provided herein will enrich and update a wide community of readers on the role of nanotechnology in the management of COVID-19.

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1.1. SARS-CoV-2, the pathogen

SARS-CoV-2 belongs to a family of enveloped viruses having a single stranded (positive-sense) RNA as the genome. The SARS-CoV-2 virion has a genomic size of about 29.9 kb, which is packaged along with nucleocapsid (N) proteins inside a nucleocapsid. This is surrounded by a viral envelope composed of phospholipid bilayer and covered with three different types of proteins- envelope (E), spike (S), and membrane (M) proteins (Figure 1A)[6–8]. SARS-CoV-2 is a β-CoV measuring around 60 to100 nm in diameter and can be either round or oval in shape with protruding proteinaceous spikes on the outer surface (Figure 1A–B), which is a typical characteristic feature of coronaviruses such as SARS-CoV and MERS-CoV[9]. And just like SARS & MERS that have infected humans in the past, this COVID-19 virus has also been found to cause severe respiratory distress in humans followed by viral pneumonia and death. The virus infiltrates the host cells by adhering to the angiotensin converting enzyme-2 (ACE-2) receptor present on the cells of lungs, liver, heart, kidney and intestine using the spike (S) proteins.[8,9]

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SARS-CoV-2 is considered to be airborne and can easily transmit from one infected individual to another through close contact, respiratory droplets, aerosols, and feco-oral route or also via physical contact with surfaces of contaminated objects (with a mean incubation period of approximately 5 days, though it may range anywhere from 2–14 days). Recent studies show that it can remain airborne for hours\(^{[11,12]}\). The virus can be detected in the patient after even 20 to 37 days from the onset of infection. It is often the case wherein symptoms expressed by infected individuals are nonspecific and cannot be used for accurate diagnosis. Moreover, many infected individuals experience only mild upper airway symptoms and about 40% of the cases are asymptomatic\(^{[13]}\) despite being contagious,\(^{[14]}\) several others go on to develop severe symptoms such as pneumonia which may all further lead to incurable complications. Globally, the lack of decisive monitoring and the unavailability of any cure for SARS-CoV-2 currently poses us with an Augean challenge to manage its transmissibility and pathogenicity. Therefore, many countries have joined hands to adopt interdisciplinary approaches towards an attempt to successfully manage the current situation of COVID-19\(^{[15–17]}\).

1.2. Nanotechnology, the avant-garde

Decades of research on the application of nanotechnology in medicine and healthcare has undeniably demonstrated its trailblazing potential in preventing and managing various diseases; having been long established as an effective tool in detection, diagnosis, and monitoring, it has recently gained significant traction towards prevention and treatment\(^{[18,19]}\). The reason that nanotechnology has received such universal recognition in biological application is attributed to the unique properties inherent to nanomaterials; properties such as diverse surface chemistry, high surface area to volume ratio, edge effects, presence of fine structures at the nanoscale, enzymatic properties, quantum effects, photocatalytic behavior, free radical generation, etc. One apparent yet crucial advantage realized through the use of nanostructures is the ability to easily traverse the various biological barriers to reach the target sites such as the insides of microbes, cells or even nucleus. To this extent, nanomaterials and nanoparticles in the form of “nano-probes” have been utilized in detecting molecular target signals (proteins, nucleic acids, antigens etc.) of pathogens, in the form of “nano-bioimaging agents” for tracking live pathogenic microorganisms, and in the form of “nano-antimicrobials” to counter bacterial and fungal diseases\(^{[20]}\). However, within the context of managing COVID-19, the advent and application of “nano-antivirals” especially with respect to metal and metal oxide NPs, liposomes, polymeric NPs and nanogels will be of critical interest to us\(^{[21,22]}\).

2. Nanotechnology based preventive measures

The route of transmission of coronavirus mainly originates from liquid droplets which are discharged from the respiratory tract of infected individual while respiration, sneezing, or coughing. These droplets eventually get in contact with healthy individuals and thereby infects them. The discharged liquid droplets are individual hydrated accretions of the virus along with various other organic material which normally line the respiratory tract (epithelial cells, bacterial cells, and so on). And upon dispersion, the water in the droplets rapidly evaporate leaving behind solid residues which support the means of transmission of SARS-CoV-2 that may infect individuals coming in contact with these droplets\(^{[23,24]}\). Thus, the consistent use of personal protective equipment (PPEs) greatly abrogates exposure to virus particles. Indeed, with the emergence of the coronavirus pandemic, many nations have encouraged or even enforced the use face masks as the first line of defense to minimize the community transmission of the virus. The most commonly used N95 and other three-layer surgical masks are protective as long as the external surface layer is dry and hydrophobic. For instance, a pilot study from Singapore found that moistened masks (through sweat or respiratory droplets of the wearer) are vulnerable to microbial contamination as it is more permeable to infectious agents. Immediate replacement with fresh masks cannot always be
possible, especially during emergency procedures. Additionally, the healthcare workers can even contaminate themselves during removal of the mask. Hence, designing an antimicrobial coating for facemask is a need of the hour to reduce the risk of transmission of infectious agents through contaminated protective equipment. The first line of defense against the spread of COVID-19 and other aerosol driven infectious disease is often achieved through the use of physical barriers such as face masks and other protective wearables. Thus, incorporating antiviral and antibacterial properties to PPEs ensures a much higher degree of biosafety. It can be beneficial for healthcare professionals as they are the front-line workers and are most susceptible to infections. As per cryo-electron microscopic (cryo-EM) studies, the size of SARS-CoV-2 virus particles ranges between 70–90 nm. And PPEs are designed to filter out particles of these dimensions while ensuring breathability and comfort of the fabric. It is precisely for this reason that; nanotechnology-based solutions would be best suited in developing antimicrobial/antiviral personal protective textiles without decreasing the breathability or material flexibility of PPEs.

Excluding graphene-based and MoS$_2$-based nanomaterials, most others commercially utilized NPs under preventive measures are isotropic particles, this can be attributed to their ease/cost of manufacturing and ionization based antimicrobial activity; as in most cases it is observed that the increased surface area plays a crucial role in releasing metallic ions which subsequently engenders in the desired antimicrobial activity.

2.1. Nanomaterials in antimicrobial textiles

In developing PPEs with sustained antimicrobial properties, it is worth considering the economic feasibility and manufacturing ease of incorporating such properties. Inorganic metal and metal oxide-based NPs with antimicrobial activity are a good to start with since they can be easily incorporated into fabrics and are generally more robust and stable than organic ones. Herein, we enlist all the prospective NPs which can be incorporated into fabrics for the manufacturing of antimicrobial PPEs and have specifically been proven to restrict SARS-CoV-2.

2.1.1. Silver NPs

Silver and its compounds have long been recognized for their broad-spectrum antimicrobial activities. Silver nanoparticles (AgNPs) especially exhibit significantly enhanced antibacterial activity. This property of silver believed to be originated from the partial ionization to Ag$^+$ ion which inhibits the growth of the bacteria by penetrating bacterial cell walls and increasing cell membrane permeability, generating oxidative stress within the cells, denaturing ribosomes, and by interfering with ATP production and DNA replication. This partial ionization is enhanced with increase in surface area, thus explaining the incredible antibacterial property of 0-dimensional AgNPs. Jeremic et al. have shown that at concentrations ranging from 1 to 10 ppm, 10 nm AgNPs can effectively inhibit the entry of SARS-CoV-2 into cells by either extracellularly disrupting the structural integrity of the virus or interfering with binding of the virus to the cell surfaces. And indeed, AgNPs have been widely investigated as an antibacterial agent embeddable on various fabrics.

2.1.2. CuO NPs

In recent times, frequent use of AgNPs has been increasingly replaced with other inorganic metal oxide NPs for antimicrobial applications citing enhanced biocompatibility. Copper oxide nanoparticles (CuONPs) are more economical and physiochemically stable alternative to AgNPs. According to Applerot, the mechanistic route underlying the size based antibacterial activity of CuONPs was established. As per electron microscopic studies, CuONPs adhere to the surface of microbial cells and disrupt the membrane integrity to induce intracellular ROS generation, driven from the cellular response to the antibacterial treatment. From the results of this study, it delineates that CuONPs of smaller size releases superoxide anions in water and the overall detrimental cytotoxic effect towards microorganisms’ scales inversely with NP size. Recently, Cortes and Zuniga carried out a review on copper-based materials with relevance to their antiviral properties, especially for its ability to restrict respiratory pathogenic agents such as influenza, SARS-CoV-1, etc. Their findings concluded that various forms of copper including CuONPs are exceedingly capable of inhibiting, inactivating and irreversibly destroying many such viruses within minutes. Further, Doremalen et al. studied the stability of SARS-CoV-1 and SARS-CoV-2 on different surfaces and observed that no viable SARS-CoV-2 was found on copper surfaces after 4 hours. This contrasts with 8 hours by SARS-Cov-1 and over 48 hours and 72 hours on stainless steel and plastic respectively with some traces of infectious viruses still being detected. The incorporation of CuONPs onto fabrics have been well established. Indeed, Abramova et al. demonstrated that a coated CuONPs on textiles (using a sonochemical reactor) had great antibacterial activity and managed to eradicate more than 99.99% of MRSA and K. pneumoniae colonies.

2.1.3. TiO$_2$ NPs

Correspondingly, TiO$_2$ nanocomposites when subject to light excitation in the UV range reveals remarkable microbicidal and fungicidal properties. However, the exact mechanism of the observed microbicidal activity is yet to be elucidated. Though, it is postulated that the electron-hole pairs generated from excitation of light, react with water and oxygen to form superoxide hydroxyl radicals which eradicates bacteria, viruses, prions, and fungi. TiO$_2$ coated cotton fabrics exhibited antibacterial activity as well as self-cleaning property under the influence of fluorescence light. Recently, Khaiboullina and
coworkers experimentally demonstrated the complete disintegration of SARS-CoV-2 genome under UVC radiation (13 mW/cm² intensity) in less than half a minute. They also showed that the degradation of the virus is enhanced at higher relative humidity, which they attribute to the increase in photocatalytic activity of TiO₂. An additional advantage of TiO₂ is the extremely low toxicity which in fact permits its usage as a common food additive.

2.1.4. 2D Graphene oxide nanosheets

Deviating from the norm of incorporating metal or metal oxide-based NPs, two-dimensional graphene oxide nanosheets (GO-NSs) are excellent candidates which as of late has garnered much attention among the nano-biosciences and related technologies, due to their unique physio-chemical properties. The antibacterial properties of GO-NSs have already been well established and its low toxicity makes it a promising candidate for next generation antimicrobial agents.

The mechanism of the antibacterial effect of GO-NSs postulated in the literature suggests that when the GO-NSs interact with gram-positive or gram-negative bacteria, it disrupts the bacterial plasma membrane through single-layer structures and sharp edges of GO nanosheets. Due to this, oxidative stress is induced intracellularly with the generation of reactive oxygen species that leads to leakage of cytoplasmic contents into the surrounding with the complete death of the bacterial cell. GO-NSs have also been shown to inhibit herpes simplex virus type-1 (HSV-1) at non-cytotoxic concentrations. Recently, Unal et al. have demonstrated via in silico modelling and in vitro experiments that GO-NSs attach onto the spike proteins of SARS-CoV-2 which subsequently inhibits its infectivity even in cases of SARS-CoV-2 variants exhibiting mutated spike proteins. Further, it is well known that GO-NSs can be easily incorporated into fabric materials such as cotton.

2.2. Existing nano-based antimicrobial PPEs

Many researchers have understood the urgency and dire requirement of antiviral PPEs to counteract the ongoing pandemic and have thus already explored a few possibilities. For instance, in 2020 Zhong et al. developed a superhydrophobic antimicrobial mask by depositing a layer of graphene through laser induced forward transfer (LIFT) method on surgical masks’ surfaces. The addition of graphene incorporated photothermal properties such that when the mask was exposed to solar radiation for 15 mins, the surface temperature of the mask exceeded 80°C which was sufficient to sterilize SARS-CoV-2 which is normally inactivated at 56°C. The same group developed another superhydrophobic antibacterial mask by depositing two layers of NPs onto N95 respirators through laser-induced forward transfer method. The first layer was deposited with AgNPs and the other layer with graphene. This new mask outperformed the previous mask in that it reached 80°C within 1 min of exposure to sunlight. It is also believed that the synergetic effect of combining the photothermal activity of graphene with AgNPs would provide a long-term protection against SARS-CoV-2. Similarly, Kumar et al. developed a cost-effective antimicrobial mask made by introducing an additional layer of Molybdenum disulfide nanosheets (MoS₂ NSs) modified fabric to a commonly available 3-layer surgical mask. This repurposed facemask have similar photo...

Figure 2. (A) Figures related to AgNPs-graphene coated mask (a) 405 nm laser decontamination via plasmonic heating of embedded nanosilver. (b) A comparative profile of photothermal temperature elevation between the nanocoated mask and pristine N95 mask under the same laser intensity. (c) FESEM images after 100 cycles of laser exposure. (d) Superhydrophobic features are revealed via contact angle measurement on the nanocoated samples which has undergone 100 cycles of laser decontamination. With permission this image has been reproduced. Copyright 2020, American Chemical Society. (B) Figures relating to MoS₂ modified fabric mask: (a) Illustration of the 4 layers of mask consisting of the MoS₂ embedded fabric. (b) Digital photograph of all four layers. (c) Digital photograph of a person wearing the mask. With permission this image has been reproduced. Copyright 2021, American Chemical Society.
thermal properties where the surface temperature of the MoS$_2$ NS modified fabric reached up to 77°C within 3 minutes of exposure to sunlight.$^{[56]}$ Huang et al. synthesized laser induced graphene (LIG) substrates and compared the antibacterial efficiency with melt-blown fabric (MBF) and activated carbon fiber (ACF) which are commonly used materials in masks. When the LIG fabrics were irradiated with 0.75 kW/m$^2$ of sunlight for 10 min, it exhibited 99.99% inhibition, whereas, ACF and MBF attained 67.24% and 85.3% inhibition respectively.$^{[51]}$ Horvath et al., in 2020 developed TiO$_2$ nanowire-based air filter and used it in PPEs including masks, utilizing the photocatalytic properties of TiO$_2$ under UV.$^{[52]}$ And in early 2021, Karagoz et al., developed a multifunctional material by electrospinning a solution consisting of AgNPs, ZnO-NPs and PMMA (poly-methyl methacrylate) into 450 nm thick fibers onto a non-woven fabric. It was found that the material had antibacterial, antiviral, and photocatalytic properties, it was employable in SERS (surface-enhanced Raman scattering) imaging in quantifying pollutants on the nano-fibers on the surface. They proposed that the PMMA/AG-Zn NF material has high utility in PPEs due to its antimicrobial and sensing properties.$^{[53]}$

Meanwhile, many companies and textile industries have launched various types of nanomaterial-based masks for protection against COVID 19. For example SilverNanofacemasks Ltd. started manufacturing washable, reusable masks with silver ions that show antimicrobial properties which are wearable for 8 hours a day.$^{[54]}$ Similarly Anson nanobiotechnology,$^{[55]}$ Nanoshel Ltd.$^{[56]}$ also developed silver based face mask that protected against microbial infections even after several washes. Further, graphene-based bacteria-resistant facemasks have been developed by various companies such as the leading global producer of advanced graphene products IDEATI’s Ltd. and planar TECH Ltd.$^{[57]}$ a Chinese company AECC Beijing Institute of Aeronautical Materials (BIAM),$^{[58]}$ LIGC Applications.$^{[59]}$ Copper3D developed a face mask, NanoHack, where CuO NPs are impregnated between the three layers of the non-woven polypropylene filtration system for better antimicrobial and antiviral properties.$^{[60]}$ Hieq viroblock, a Zurich based company, launched a combination of silver and vesicle technology to produce antibacterial and antiviral textile named HeiQ Viroblock NPJ03, which happens to be one of the first textiles with proven efficacy against SARS-CoV-2 (up to 99.9% reduction in virus) in a lab setting conducted in partnership with Peter Doherty Institute for Infection and Immunity in Melbourne; Australia (Doherty Institute). The HeiQ vesicle technology works by targeting the lipid-enveloped viruses, such as coronavirus, and deactivates them. The growth and spread of various microbes (including enveloped viruses) on textile surfaces can be inhibited by HeiQ Viroblock NPJ03.$^{[61]}$ ZEN Graphene Solutions Ltd. and Graphene Composites Ltd. (GC) developed a potential virucidal graphene-based composite ink which can be applied onto fabrics including N95 masks and other personal protective equipment (PPE) to reduce the risk of transmission.$^{[62]}$ An extensive list of NP-based PPE developed by various companies in the recent past have been presented in Table 1.

### 2.3. Nanotechnology focused disinfectants

Till date, WHO acknowledged wearing a medical mask as a crucial first-step preventive measures (among many others) to limit the spread and ubiquity of SARS-CoV-2 and other respiratory disease-causing agents. Every certified mask has a technical standard protocol to dispose of after use, but this has and could lead to masks shortages during the pandemic crisis. Moreover, masks alone cannot provide adequate protection against the disease, virus particles can be found on various surfaces that we come into contact regularly (doorknobs, railings, etc.). Therefore, many governments and several agencies around the world have adopted various measures to promote reuse, cleaning, sterilization, and disinfection of masks, PPEs, and surfaces of commonly used objects.

Kampf et al., carried out studies and analyzed the duration of human coronaviruses persisting on a specified surface. It was

| PPE type | Metal-based Nanoparticles | Textile type | Manufacture/organization name | Country | Reference |
|----------|---------------------------|--------------|--------------------------------|---------|-----------|
| Mask     | Silver                    | Nonwoven     | Hieq viroblock                 | Switzerland | [61]     |
| Mask     | Silver                    | Yarn         | SilverNanofacemasks            | Netherlands | [54]     |
| Mask     | Silver                    | Nonwoven     | Anson nanobiotechnology        | China     | [55]     |
| Mask     | Silver                    | Nonwoven     | Nanoshel                       | USA       | [56]     |
| Filtration system | Graphene | microporous conductive foam | LIGC Applications              | USA       | [59]     |
| Mask     | Graphene                  | polypropylene melt-blown | BIAM                           | China     | [58]     |
| Mask     | Copper                    | Cotton       | coppercompression             | USA       | [63]     |
| Mask     | Copper                    | Polyprolene  | Thefunshop                    | USA       | [64]     |
| Mask     | Copper                    | Nylon        | Coppermask                    | USA       | [65]     |
| Mask     | Copper                    | Cotton       | Hydrafacial                   | USA       | [66]     |
| Mask     | Copper                    | non-woven propylene | Theramasks                 | USA       | [68]     |
| Mask     | Copper                    | Nylon        | XTI                            | USA       | [69]     |
| Mask     | TiO$_2$                    | non-woven propylene | Sonovia                       | Israel    | [70]     |

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concluded that it remains on metal, wood, paper, glass and plastic surfaces for up to 5–9 days. Another study proclaims specifically that SARS-CoV 2 and SARS-CoV 1 remains on cardboard, plastic, copper, and on stainless steel surfaces for up to 3 days. To this end, few chemical disinfectants have been adopted that proved effective against disinfecting and sterilizing surfaces such as peroxides, halides (specifically chlorines), alcohols, and quaternary amines.[71] It has been analyzed that the pathogens can be disinfected and inactivated by applying chemical formulations within 1 min of exposure that consists of 70–80% ethanol or isopropanol, 1.45% glycerin, 0.5% hydrogen peroxide or 0.1% sodium hypochlorite. Also, irradiation with UVC light at 1–1.2 J/cm shows effective disinfection activity against SARS-CoV with more than five folds logarithmic reduction in 5 min. [72] In this regard, many common potential chemical-based methods, as well as physical disinfection methods, have been studied that includes the use of hydrogen peroxide, ClO₂, NaOCl, alcohols, detergents, C₂H₅O, O₃, heat, UV rays, gamma irradiation, microwave, etc.

In spite of the reassuring results from chemical and physical disinfectants, there are many drawbacks associated such excessive use of hydrogen peroxide, ethanol and other harsh chemicals which damage the fiber of the mask and reduce its effectiveness towards inhibiting the virus. On the other hand, the UV irradiation at 1–1.2 J/cm is insufficient to disinfect the inner layer of the mask, therefore requiring increase in the power density which however may damage the mask completely. In this vein, nanotechnology offers effective and efficient disinfection strategies to combat sanitizing surfaces. For instance, if a layer of nanoparticle with antimicrobial and antiviral property incorporated on the surface, it will limit the growth of viruses as well as frequent disinfection won't be required. A preliminary evaluation by Belagna et al. demonstrated that coating facemasks with silver nanoclusters or silica nanocomposites can imbue the facemasks with viricidal properties against SARS-CoV-2.[73] Similarly, NanoTechSurface, Italy, came up with a self-sterilizing formulation using TiO₂ and silver ions for surface disinfection.[74] In early 2021, Hosseini et al., developed a hydrophilic CuO film coating that reduced COVID-19 infectivity by 99.8% in 30 minutes on a glass surface when compared to a non-coated bare glass surface.[114] Furthermore, the CuO coating retained hydrophilicity for a minimum of 5 months and could be cleaned with 70% ethanol or 3% bleach solution.

3. Nanotechnology based diagnostics for coronaviruses

Depending on the strategies opted by clinical laboratories for diagnosing COVID-19, nanotechnology-based testing can be currently divided on the basis of assay principle, as illustrated in Figure 3. Conclusive diagnosis of COVID-19 involves screening for various biomolecular targets such as nucleic acid extracts (RNA) from oral/nasal swabs, immunoglobulins from serum, and proinflammatory markers associated with the disease. And of the conventional methods, RT-PCR based diagnosis is considered the gold standard due to its high accuracy, but the concomitant factors such as long assay duration, requirement of skilled personals, and infrastructural facilities often results in continuous delays and impediments in diagnosing individuals infected by SARS-CoV-2 virus; thereby, exacerbating efforts to control the spread of the virus. However, recent developments in nanotechnology may ameliorate the situation, considering its contribution to biosensing applications and how it has revolutionized molecular diagnostics in recent decades. It offers new opportunities for producing inexpensive and scalable detection methods. Also, contemporary nanotechnology-based diagnostics are highly sensitive compared to conventional techniques in that they can detect extremely low concentrations of pathogens in a short period of time, sometimes even before symptoms start appearing. Such diagnostic methods have never been more in demand than in the middle of the current pandemic. In fact, many companies have recognized this demand and have been marketing point-of-care-testing (POCT) devices which rely on NP-based sensing platforms to detect SARS-CoV-2 as listed on Table 2. These convenient POCT devices abrogates the need for skilled personals, reduces the number of hospital visits, and facilitates early detection. Current rapid POCT for detecting SARS-CoV-2 are typically nanoparticle-mediated sandwich immunoassays. Immunoassays exploit antigen-antibody interactions by either using viral antigen clones to determine the presence of host antibodies which develops in patients to counteract the virus, or by making use of monoclonal antibodies (mAbs) to detect viral antigens. Further research carried out in this direction includes the following assays for the detecting SARS-CoV-2.

3.1. Colorimetric assay

Colorimetric assays enable detection of analytes through simple color-coded information which can easily be discerned with naked eyes. The use of gold nanoparticles (AuNPs) in colorimetric biosensing is well known owing to the ideal optical properties, high extinction coefficient, and photostability of AuNPs. These optical properties are exploited to produce the necessary color-coded information in the presence of analyte. And perhaps this strategy is best exploited in colorimetric immunoassays, of which lateral flow assay (LIFA) immunoassays are the most commercial as they can be easily translated into inexpensive POCT diagnostic kits.[75] These AuNP based LFIAs work mainly on two principal techniques; “color amplification technique”, wherein the intense red color of AuNPs act as coloring agents and the “color change method” wherein the color of AuNPs upon aggregation changes from red to purple (this aggregation is primarily caused due to the interaction between conjugated AuNPs with target analyte).

The LIFA format is essentially a dipstick method. The dipstick is framed in a plastic cartridge containing the analyte capturing reagents (either a mAb directed at the antigen or an antigen that is recognized by patients’ antibodies) immobilized...
only at particular locations along a nitrocellulose membrane, and labelled detector mAbs that identify the same target (the viral antigen). In the presence of a target analyte, the detector mAbs capture them and interact with the immobilized reagents which then engenders in the evolution of a colored line confirming the presence of the target analyte. One to two drops of blood from a finger prick are usually sufficient for LFIA. For the detection of novel coronavirus SARS-CoV-2, POCT LFIA kits have been developed to detect antibodies (IgM and IgG) against the virus. Since the virus belongs to the same family as that of MERS and SARS, the process of antibody generation is assumed to be similar, so IgM and IgG antibody detection is believed to be an indication of virus infection. It is accepted and reported that the IgM antibody provides the first line of defense and is detected in the patient’s blood 3–6 days after being infected with the virus SARS-CoV-2, whereas IgG is detected about eight days after the onset of infection. Therefore, rapid detection of IgM / IgG antibodies will allow early diagnosis and treatment of COVID-19 disease.

Li et al., developed the first POCT LFIA for detection of SARS-CoV-2, product that simultaneously detects both IgM and IgG in a human blood sample in less than 15 minutes (Figure 4A–B). It is a paper-based membrane strip consists of four parts, arranged in a horizontal manner encased in a cassette – containing a sample pad on which the patient’s serological sample is placed. Proteins from the sample then traverses across the strip towards the conjugate pad through capillary action. At the conjugate pad, the targeted proteins bind to the AuNP-antibody conjugates. To facilitate selectivity and overall accuracy of this method, the nitrocellulose membrane strip contains capture antibodies at two defined zones. The first zone immobilized with anti-human-IgM, IgG antibodies, i.e. test zone and the other immobilized with anti-rabbit-IgG antibodies, i.e. control zone. As the complex reaches specific zones, it interacts with the capture antibodies and gets immobilized. Due to the immobilization, one could see either a red line as in the case of non-aggregated AuNPs or a blue line in case of clustering/aggregation of AuNPs (due to the coupling of plasmon band). Chinese CDC agencies validated the clinical efficacy of this test product, and they carried out in 8 hospitals by collecting blood samples from 397 SARS-CoV-2 infected individuals (PCR confirmed) and 128 uninfected individuals. The results demonstrated high sensitivity of 88.66% and specificity of 90.63% that prompted the product to use in testing laboratories, hospitals, and clinics. Since then, many companies around the world have followed suit and developed
POCT LFIA for diagnosing infections by detecting IgM and IgG antibodies generated in infected patients based on the same principle, with often enhanced sensitivity and specificity and/or shorter duration.\(^\text{[77]}\) Table 2 provides the list of such commercialized kits.

Other than IgM/IgG detection, researchers developed diagnostic tools that determine nucleocapsid and spike protein of SARS-CoV-2. The Genomics Research Center, Academia Sinica, in Taipei, Taiwan, developed the first monoclonal antibody against the nucleocapsid (N) protein of SARS-CoV-2.\(^\text{[78]}\) Later, Mertens et al., developed an antigen testing technology named COVID-19 Ag Respi-Strip. This was the first study which evaluated on the utility and diagnostic accuracy of a disposable-rapid-antigen-based test kit in early diagnosis of COVID-19, which employed an immunochromatographic (ICT) assay which detects the presence of SARS-CoV-2 antigens in less than 15 minutes. It is a membrane-based technology utilizing colloidal gold NPs and mAbs which target the conserved nucleoprotein antigens of both SARS-CoV and SARS-CoV-2. Further analysis indicated that it is reproducible with the observer disagreement of being just 1.7%, and has a diagnostic accuracy of about 82.6%.\(^\text{[79]}\)

Besides, protein molecules such as Abs or Antigens, nucleic acids (NAs) can also serve as molecular targets for detection assays. The main drawback with selecting viral nucleic acids as targets is that they are often ensconced in protein capsid which renders it difficult to probe NAs at a molecular level. So, it is often necessary to extract the NAs from the protein capsid often by denaturing and dissolving the protein capsid. Moitra et al., advanced a colorimetric assay, utilizing the intrinsic optical properties of plasmonic AuNPs capped with thiol-functionalized antisense oligonucleotides (ASOs). ASOs bind specifically to N-nucleo (nucleocapsid phosphoprotein) region of SARS-CoV-2. Using this technique and isolated RNA samples, one can diagnose for the presence of COVID-19 within just 10 minutes. The AuNPs capped thiol-functionalized ASOs agglomerates only when SARS-CoV-2 target RNA sequence is present and this agglomeration of the particles results in a change in

**Table 2. Commercial NP-based-POCT kits for diagnosing SARS-CoV-2.**

| Test Name                                    | Test Type         | Provider/Manufacturer                        | Specimen type                        | IgG or Protein detected                  | Turnaround time/ additional information | Country of Origin | References |
|----------------------------------------------|-------------------|---------------------------------------------|--------------------------------------|-----------------------------------------|----------------------------------------|------------------|------------|
| COVID-19 IgM/IgG Rapid Test                  | lateral flow immunoassay | BioMedomics antibodies-online GmbH         | whole blood, serum, & plasma serum | IgG and IgG both | 10-15 minutes | USA             | [85]       |
| Novel Coronavirus (2019-nCoV) Antibody test Kit (Colloidal Gold Assay) | lateral flow immunoassay | Biologics Limited                         | conformity serum/ plasma/ venous whole blood | IgM and IgG antibodies | 10 minutes, High sensitivity = 91.54%, specificity = 97.02% | Philippines | [87]       |
| 2019-nCoV IgG/IgM Antibody Detection Kit (Colloidal Gold) | lateral flow immunoassay | RayBiotech                                | serum, plasma or whole blood         | IgM and IgG antibodies | 5-10 minutes | United States   | [88]       |
| Coronavirus (COVID-19) IgM/IgG Rapid Test Kit (dual cassettes) | lateral flow, Sandwich-based | CTK Biotech                             | serum, plasma or whole blood         | anti-SARS-CoV-2 IgG and IgM | 15 minutes sensitivity = 97.1%, sensitivity = 97.8% | Australia | [89]       |
| OnSite COVID-19 IgG/IgM Rapid test           | luminescent immunoassay | Diazyme Laboratories                      | blood sample                         | IgG/IgM                  | 10 minutes, Sensitivity = 97.27%, specificity = 99.62% | United States | [90]       |
| Diazyme DZ                                   |                   |                                             |                                      |                          | 15 minutes, Sensitivity = 99.9%, for IgG and 85% for IgM, specificity = 98% for IgG and 96% for IgM | Brazil | [91]       |
| Active Xpress + COVID-19 Antigen Complete Kit |                   |                                             |                                      |                          |                                        | United States | [92]       |
| Rapid Test for Coronavirus SARS-CoV-2 (nCoV) Coronavirus IgG Antibodies in Cassette |                   |                                             |                                      |                          |                                        | China             | [93]       |
| 2019-NOVEL CORONA-VIRUS (2019-nCoV) IgG/IgM GICA RAPID TEST KIT |                   |                                             |                                      |                          |                                        | Brazil             | [94]       |
| Vazyme 2019-nCoV IgG/IgM Detection Kit (Colloidal Gold-Based) |                   |                                             |                                      |                          |                                        | United States | [95]       |
| SARS-CoV-2 (Covid-19): Diagnosis by IgG/IgM Rapid Test |                   |                                             |                                      |                          |                                        | China             | [96]       |
| Rapid Test for COVID-19 IgM/IgG Antibody Detection Kit |                   |                                             |                                      |                          |                                        | United States | [97]       |
the color of the solution. Further, as a confirmation step and to rule out random agglomeration, RNase is added to this solution. This addition of RNase degrades the RNA on the RNA-DNA hybrid and engender in the precipitation of the

Figure 4. (A–B) Schematic representation of rapid SARS-CoV-2 IgM-IgG complex antibody test detection device. With permission this image has been reproduced. Copyright 2020, Wiley online library. (C) Schematic illustration for the optical detection of SARS-CoV-2 RNA mediated by the congruously Designed ASO-Capped AuNPs. With permission this image has been reproduced. Copyright 2020, American Chemical Society. (D) Design and fabrication of the Lateral flow test strip and Assay. With permission this image has been reproduced. Copyright 2020, American Chemical Society. (E) The conceptual design of the dual-functional LSPR biosensor as developed by Qui G and co-workers; the plasmonic sensing graph indicates that the system can detect the presence of various nucleic acids even in the picomolar range. With permission this image has been reproduced. Copyright 2020, American Chemical Society. (F) Schematic representation of COVID-19 FET sensor. Graphene is employed as the sensing material on which antibodies for the SARS-CoV-2 spike is conjugated. With permission this image has been reproduced. Copyright 2020, American Chemical Society.
aggregated particles which can be visually verified (Figure 4C). The addition of RNase also increases the overall reproducibility and reliability as it enables the test to target two different N-gene regions of SARS-CoV-2 RNA. It thus ensures the reliability of the assay even in the case of mutation in one part of the viral gene. Recently, researchers at NTNU’s Department of Clinical and Molecular Medicine and the Department of Chemical Engineering in collaboration with St. Olavs Hospital have developed a testing method that uses tiny iron oxide nanoparticles (FeONPs) coated with silica that acquires a strong affinity for SARS-CoV-2 RNA. The method first involves suspending silica coated FeONPs in a solution that can break open the virus to release the genetic material. The patient samples are added to this solution and consequently, the viral RNA adheres to the silica coated FeONPs which can then be magnetically isolated from the sample and analyzed for the presence of SARS-CoV-2. Upon comparing this method to conventional commercial tests, the researchers noted that this method is superior in terms of sensitivity.

3.2. Fluorescent based assay

Fluorescence-based LFIAEs have lately been gaining traction over conventional colorimetric assays due to the limited range of detection provided by colorimetric assays. However, fluorescent dyes typically are prone to photobleaching and cannot be used as an ideal reporter due to its poor stability or quantum yield. To overcome these limitations, without compromising on speed or faciliteness, NPs are being rapidly incorporated into the detection methods. For instance, Chen et al. developed a lateral flow assay, using recombinant nucleocapsid phosphoprotein and Lanthanide-doped polystyrene nanoparticles (LNPs) for the detection of anti-SARS-CoV-2-protein IgG in human serological samples. It describes a straightforward and rapid LNP-based immunoaassay to monitor the prognosis of COVID-19 and to evaluate the various treatment options (Figure 4D). The coefficient of variation (CV) values were found to be 7.71%–9.69% (intra-assay) and 11.51%–14.63% (inter-assay). Since the CVs were 7.71%–9.69% (intra-assay) and 11.51%–14.63% (inter-assay) and 11.51%–14.63% (inter-assay), the CVs were <15%, this assay concluded as reproducible. The experimental results validate the requirements of clinical diagnostic reagents.

3.3. SPR based assay

Surface Plasmon Resonance (SPR) acts as a multipurpose optical platform commonly used to study the refractive index change at plasmonic material surfaces in real-time. A photon-driven collective oscillation of the conduction band electrons on the surfaces of extremely small plasmonic material structures (as in case of metallic NPs) is termed as LSPR (localized surface plasmon resonance). In the vicinity of small structures (nano-scale range), the plasmonic field demonstrates high sensitivity with a change in refractive index and molecular binding of the LSPR sensing systems. Thus, LSPR can serve as a model platform for label-free detection of even traditionally-negligible quantity of analytes in real time.

Qui et al., 2020 developed a fast and reliable multi-functional LSPR-based biosensor by integrating the photothermal capabilities and plasmonic sensing attribute in detecting SARS-CoV-2 viral nucleic acid (SC-NA) on a single plasmonic nano-absorber chip composed of gold nano-islands (AuNi) as illustrated on figure 4E. The rise in temperature via photothermal effect increases the accuracy with which SC-NA hybridizes with the complementary sequence (conjugated on the AuNi), after which, the shift in resonance peak (due to the LSPR attribute of AuNi) upon binding accurately indicates the presence of SC-NA. Overall, through this configuration, one can attain a real-time and label-free detection of any nucleic acid sequences in general but particularly for this purpose, ORF1ab COVID, RdRp-COVID, and E genes from SARS-CoV 2. Interestingly, in situ plasmonic photothermal (PPT) enhancement on the AuNi chips significantly enhanced the specificity of nucleic acid detection and hybridization kinetics. The in situ PPT enhancement also discriminates the RdRp genes between SARS-CoV and SARS-CoV-2. Further, this LSPR biosensor can detect the presence of analytes of any concentrations above 0.22 pM and also provide an easily implementable diagnosis platform, which taken together can advance the progress of diagnostic accuracy and reduce the dependence on PCR-based tests alone.

3.4. Electrochemical Biosensors

Biosensors convert biochemical signals into electrical signals by generally employing a potentiometric, amperometric, cyclic voltametric, or impedimetric transducers. The biochemical signals can be from proteins, nucleic acid, certain carbohydrates, etc. The biochemical signal is generated when target molecules interact with capture molecules immobilized on an electrode coated with an electronically conducting, semiconducting, or ionically conducting material. They can be readily miniaturized using microfabrication techniques and incorporated into field-effect devices (e.g., ISFETs).

Layqah et al., was the first to design a novel electrochemical immunosensor for detecting MERS-CoV recombinant spike protein S1. AuNPs were electrodeposited on a disposable array of carbon electrodes for the preparation of the sensing electrode, which can be later used for simultaneously detecting CoV viruses. The test takes only up to 20 min, achieves a LOD of about 0.4 pg mL⁻¹ for the human coronavirus (HCoV), and about 1.0 pg mL⁻¹ for MERS-CoV. Furthermore, the electrochemical immunosensor provides the capability of miniaturization, high sensitivity, low cost, and on-site high throughput screening of multiple samples.

Field-effect transistor (FET) based biosensors are potentially one of the best candidates for POCT, clinical diagnosis, and potentially doing away with the requirement of highly skilled personnel. These devices present various advantages such as requiring only a small amount of analytes to make instantaneous measurements. The use of graphene in sensing
platforms owing to its extraordinary properties such as large specific area, high carrier mobility, and electronic conductivity, has been well reported. Therefore, Graphene-based FET can be used in fabricating biosensors which are highly sensitive to rapid changes in analyte composition, which is of high demand for immunological diagnosis.\textsuperscript{[103]} Concordantly, Seo et al. designed a graphene-based biosensing device functionalized with SARS-CoV-2 spike antibody via 1-pyrenebutyric acid N-hydroxysuccinimide ester (PBASE) for SARS-CoV-2 detection platform (Figure 4F). This sensor can detect the presence of SARS-CoV-2 antigens at concentrations as small as 1 fg/mL. Additionally, it could also discriminate between SARS-CoV-2 antigens and MERS-CoV antigens with no cross-reactivity. This indicates the potential for this device to detect SARS-CoV-2 virus from clinical samples in a highly sensitive and selective manner.\textsuperscript{[84]}

Keeping up with the trend, Beduk et al. recently developed a COVID-19 POC device composed of gold nanostructures, graphene, and immunoglobulins. The graphene is imprinted on the device surface (polyimide substrate) via laser scribing technology, the gold nanosheet is deposited on the electrodes, and the SARS-CoV-2 antibodies are attached to the electrode on which the samples were added. The change in electrochemical signals indicating the presence of virus is read by a portable device that can be connected to a smartphone for rapid diagnosis.\textsuperscript{[104]}

4. Nanomedicine and Nanovaccines

4.1. Existing therapeutic agents for targeting coronavirus

In the present scenario, the whole world is facing the scarcity of specific and approved therapies for the management of COVID-19.\textsuperscript{[105,106]} Various research groups from all over the world are working either individually or collaboratively on a variety of therapeutic interventions including conventional approved antiviral drugs, small-molecule drugs, new vaccines, mAbs, convalescent plasma treatment, interferon-based, and cell-based therapies.\textsuperscript{[106,107]} According to ClinicalTrials.gov of NIH, over 5500 studies (5574 on May 24, 2021, to be precise) have been registered from all over the world to find a reliable antiviral treatment for COVID-19.\textsuperscript{[107]} However, drug therapy and vaccine development are time taking process which needs multiple validation steps to establish a safe and effective treatment for COVID-19. Considering this current global emergency, the conventional speed of the routine drug development pathway will not suffice. Therefore, various health experts have suggested repurposing the existing drugs for the treatment of COVID-19, such as antiviral drug used in the treatment of hepatitis B (HBV), hepatitis C (HCV), influenza, filoviruses with the support of other cardiovascular and respiratory management drugs.\textsuperscript{[108]} However, these drugs mostly serve as palliatives and do not eliminate the virus. Even the broad-spectrum antivirals such as Favipiravir\textsuperscript{[109]} and Remdesivir\textsuperscript{[110]} (the protide which is considered to be a first in class medication by the FDA) are limited in their efficacy in decimating the novel coronavirus.

Vaccines were once believed to be a decisive solution, but the resurgence of mutated forms of SARS-CoV-2 (such as the variant B.1.617) and its ability to re Infect survivors suggest that it will develop into an endemic like the seasonal flu with seasonal flare-ups.\textsuperscript{[1,111]} However, vaccination can still be a promising tool in the disease management like in the case of flu and with advanced delivery techniques such as PittCoVacc, which is a microneedle array (MNA)-delivered recombinant protein subunit vaccine targeting SARS-CoV-2 (Figure 5) developed by Researchers at University of Pittsburgh, USA, it may

![Figure 5. Schematic representation of microneedle assisted COVID-19 vaccine delivery platform.](image-url)
become easier to administer vaccines more regularly and conveniently.\textsuperscript{[112]}

4.1.1. Immunosuppressants and immunomodulators

Several studies have indicated that severe forms of COVID-19 cases are often associated with an increase in hyper-inflammatory immune response (including cytokine storms or cytokine release syndrome) which contributes to heightened mortality in such cases\textsuperscript{[113,114]} (Figure 6). Several immunosuppressants drugs like Colchicine, Anakinra, Sarilumab, Tocilizumab, etc. were investigated for their efficacy. However, the results from clinical trials are rather inconclusive as of now; most of them perform very poorly \textit{in vivo} even if they had promising outcome \textit{in vitro}.\textsuperscript{[115–118]} Apart for these, there are few other immunosuppressant drugs which are currently under investigation like adalimumab (anti-TNF), ixekizumab (anti-17 A) and eculizumab (anti-C5).\textsuperscript{[119]} In one clinical data, anti-CD147 drug i.e. meplazumab found to inhibit both T cell chemotaxis and virus cell entry.\textsuperscript{[120]} Despite not having conclusively proven that immunomodulators can effectively decrease mortality, there is a strong consensus among experts and sound scientific rationale to treat COVID-19 patients with immunomodulators alongside antiviral drugs.\textsuperscript{[114,119]}

4.1.2. Mesenchymal stem cells and convalescent plasma therapy

Due to stimulatory effect on growth factors and cytokines secretions, mesenchymal stem cells (MSCs) have immunomodulatory and tissue repair activities against adult respiratory distress syndrome (ARDS).\textsuperscript{[121]} Theoretically, convalescent plasma or immunoglobulin-based therapies have potential benefits over other targeted therapies, as it readily provides disease specific antibodies that target the pathogen. However, out of 217 registered clinical investigations on ClinicalTrials.gov under passive immune therapy for COVID-19, only one study has reported a slight improvement in clinical and inflammatory outcome in infected patients, albeit results are inconclusive in regard to any amelioration in mortality rates.

4.2. Nanomedicine for the management of respiratory virus

From the last two decades, variety of nanomaterials have been explored in the treatment of various infectious diseases including bacterial, fungal and viral infections.\textsuperscript{[122]} Due to their large surface-area-to-volume ratio and the possibility of functionalizing with a distinct variety of functional groups, nanomaterials are the best options for dealing with viruses including blocking their interaction with cell receptors and their entry inside the cells.\textsuperscript{[21,122]} This section is mainly focused on the application of nanomaterials in developing nanomedicine against corona viruses and other respiratory viruses (Table 3).

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**Figure 6.** The hypothetical progression of COVID-19 from the initial phase to late phase in severe cases. Reproduced with permission from ref.\textsuperscript{[116]}
In 2015, Heyou Han and his co-workers demonstrated the broad-spectrum antiviral activity of GO and rGO nanocomposite against both DNA virus i.e., pseudo rabies virus (PRV) an alpha herpesvirus and RNA virus (PEDV) an alpha coronavirus. In this work, they proposed that nanocomposite having the presence of negative charge and sharp-edged single layer are essential for the destruction of virus as shown in Figure 7A. In 2016, Chen et al. reported on the antiviral activity of graphene

| Table 3. Application of NPs-based antiviral agents against coronaviruses and other respiratory viruses. | Nanoparticle type | Type of respiratory/corona virus | Experimental model or cell line used | Antiviral mechanism | Limitations | Ref. |
|---|---|---|---|---|---|---|
| Single layered GO and rGO nanostructures | PRV an alpha herpesvirus and PEDV an alpha coronavirus | Vero cells (PEDV) and PK-15 cells (PRV) | Destruction of virus by sharp-edged single layered nanosheets | Detailed mechanism needs to be established | [123] |
| GO–Ag nanostructures | respiratory syncytial virus (RSV) | RSV infected fcwf-4 cells | i) direct inactivation of RSV, ii) interfering between virus and host cell interaction and iii) interfering in the virus replication process | Proposed mechanism needs to be established | [124] |
| Curcumin and β-CD functionalized graphene oxide nanoparticles | feline coronavirus | fcwf-4 cells, mice | Endosomal acidification in fcwf-4 cells (a necessary process for virus uncoating and cellular entry) | It has only been tested in vitro against Feline coronavirus, and in vivo demonstrations for antiviral activity have not been performed. | [125] |
| PEG-PLGA nanoparticles of diphyllin | porcine epidemic diarrhea virus (PEDV) i.e. alpha coronavirus | alpha coronavirus infected Vero cells | Inhibits alpha coronavirus proliferation through blocking RNA synthesis and budding | No in vivo experiments have been performed. | [126] |
| Ag,S nanoclusters | porcine epidemic diarrhea virus (PEDV) i.e. alpha coronavirus | alpha coronavirus infected Vero cells | Inhibits alpha coronavirus proliferation through blocking RNA synthesis and budding | No in vivo experiments have been performed. | [127] |
| PIH-AuNRs HR1 inhibitors | MERS-CoV | 293T/MERS/EGFP, ICR Mice | Inhibition of MERS-CoV S2 subunit-mediated membrane fusion with HR1 inhibitors. | Has only been demonstrated with MERS-CoV and only inhibits viral entry not proliferation. | [128] |
| Boronic acid functionalized CQDs | HCoV-229E | Huh-7 cell monolayers, infected with HCoV-229E MDCK-SiAT1 cells | Inhibition of protein S receptor interaction and inhibition of viral RNA genome replication | This work was demonstrated only in vitro | [129] |
| ZnO-NPs | H1N1 influenza virus | Under preclinical investigation against COVID-19 | — | Antiviral mechanism is unknown | [130] |
| Novochizol (a chitosan based nanocarrier) | influenza viruses (H1N1, H3N2, and H9N2) | MDCK cells | By blocking the virus entry in host cell through conformation deformation of hemagglutinin (HA) | No in vivo experiments performed to validate mechanism in live bodies | [131] |
| Porous gold nanoparticles | influenza viruses (H1N1, H3N2, and H9N2) | MDCK cells | — | Antiviral mechanism is unknown | [132] |
| Redox nanomaterials of manganese salt and citrus extract | influenza viruses (H1N1, H3N2, and H9N2) | MDCK cells | — | Antiviral mechanism is unknown | [133] |
| EM-coated spiky nanostructure | Influenza A virus | IAV infected MDCK-II cells | Inhibition of virus replication by blocking the interaction between virion and host cell | This work is performed only at a cellular level | [134] |
| GO nanosheet structure | SARS-CoV 2 | Vero cells | Decomposition of SARS-CoV 2 spike protein and virus neutralization | — | [135] |
| GO nanosheet structure | SARS-CoV 2 | Vero cells | In vitro inhibition of infection by the interaction of GO nanosheets with the spike protein | Antiviral and mechanism of interaction is yet to be established. The work is performed only in vitro. | [136] |
| 2-D nanomaterials (bismuthine, graphene, phosphor- ene, P-doped graphene and functionalized P-doped graphene) | SARS-CoV 2 – spike protein and Mo2Te4 protein | — | Decomposition of spike protein by all types of 2-D nanomaterials followed by less affinity towards ACE-2, (ii) deactivation Mpro protein to avoid infection spread. | The proposed mechanism needs to be established. | [137] |
| Polyglycerol sulfate and aliphatic chains of different length functionalised graphene. | Feline coronavirus (FCoV) and SARS-CoV 2 | A549, HBE and kidney Vero E-cells | Viral entrapment through electrostatic and hydrophobic interactions. Along with disintegration of viral membrane by direct penetration of aliphatic chain. | — | [138] |
oxide–silver (GO–Ag) nanoparticles against the feline coronavirus (FCoV) as well as the infectious bursal disease virus (IBDV).\textsuperscript{124} However, they have not concluded the detailed antiviral mechanism of their nanocomposite. Later, Yang et al. proposed a synergistic action of curcumin and β-CD functionalized GO NPs against respiratory syncytial virus (RSV) infections.\textsuperscript{125} They proposed three possible antiviral mechanisms for their nanocomposite: i) direct inactivation of RSV, ii) interfering between virus and host cell interaction and iii) interfering the virus replication. However, they have not performed any experiment to support their proposed antiviral mechanism. Hu et al. demonstrated a promising approach for the treatment of feline infectious peritonitis (FIP) caused by feline coronavirus using a PEG-PLGA nanoformulation of diphyllin. FIP is one of the most severe and mortal viral disease in cats. In this work, the authors have demonstrated the better activity of PEG-PLGA NPs of diphyllin compared to its conventional formulation.\textsuperscript{126} Later Du et al. demonstrated the antiviral activity of Ag\textsubscript{2}S nanoclusters against the porcine epidemic diarrhea virus (PEDV) i.e. alpha coronavirus. They proposed that Ag nanomaterials inhibits alpha coronavirus proliferation through blocking RNA synthesis and budding (Figure 7B).\textsuperscript{127} Huang et al. designed gold nanorods-based HR1 inhibitor (PIH-AuNR) against MERS-CoV\textsuperscript{128} Heptad repeat 1 (HR1) inhibitors are much appreciated in the treatment of MERS-CoV-infections because they prevent HR1/HR2 mediated fusion between MERS-CoV membranes and that of host cells. Peptide pregnancy-induced hypertension (PIH) is a well-known potent inhibitor of HR1. In this work, they reported a complex of PIH-AuNRs HR1 inhibitors, which selectively target S2 protein of corona virus and disrupt its membrane fusion activity with host cell. Figure 7C represents the role of HR1 inhibitors in inhibiting MERS-CoV S2 subunit-mediated membranal fusion. Later in 2019, Sabine Szunerits and co-workers developed anti-HCoV CQDs nanomaterials functionalized with boronic acid.\textsuperscript{129} Here the reason for selecting CQDs as nanocarriers was its size i.e. 10 nm due to which it can easily slip inside the cells through endocytosis and can subsequently interact and interfere with the viral protein. Further, they concluded that boronic acid ligands have activity against the S protein of coronavirus which further helps in inhibiting the viral invasion of the host cells, thus preventing viral genome replication step (Figure 7D).

Ghaffari et al. demonstrated the antiviral activity of PEGylated ZnO NPs which showed an inhibition rate of 94.6% against H1 N1 influenza virus. However, exact antiviral mechanism of ZnO-NPs is still unknown.\textsuperscript{130} Very recently, Vladislav Fomenko invented a novel nanoformulation i.e. Novochizol which is a chitosan based intra-pulmonary drug delivery formulation.
having strong interaction to lung epithelial tissues.[131] This formulation can be used to carry or encapsulate APIs, small molecule or biologics for localized delivery and sustained release. This formulation is in the preclinical evaluation and can be used to treat COVID-19 patients in future. Very recently, Kim et al. has demonstrated the use of porous gold AuNPs against the treatment of influenza viruses (H1 N1, H3 N2, and H9 N2).[132] In this work, they found that porous AuNPs have ability to inhibit the viral membrane fusion process by blocking the virus entry in host cell through conformation deformation of hemagglutinin (HA). HA is a conserved surface protein available in many influenza virus strains that facilitates the binding of viruses with host cell receptors.

It is well reported that use of hydrogen peroxide to produce excess of reactive oxygen species (ROS) can inactivate pathogens by breaking down its basic structure.[133–136] However, direct application of hydrogen peroxide to human body may cause severe toxicity or several other complications. In a recent work, Nie et al. reported a new concept for inhibiting the virus replication. Using spiky nanostructures, they exploited the concept of geometry-matching topography for the inhibition of influenza A virus (IAV).[136] In the study, they found that spiky nanostructures of 5–10 nm can be easily inserted into the gaps of glycoprotein of the influenza A virus. By using TEOS precursor and CTAB as a stabilizer they first synthesized the spiky nanostructures of around 150 nm which they then coated with erythrocyte membrane (EM) to target the IAV. Using these EM-coated spiky nanostructures they have successfully demonstrated the inhibition of IAV virion binding to the cells. In a post-infection study, they observed the reduction of >99.9% virus replication at the cellular non-toxic dosage (Figure 8). They propose that this novel concept of inhibiting virus replication and subsequent infection can be used to inhibit other virus strains, including SARS-CoV-2.

Recently, it has been revealed that 2D Graphene nanosheet and its derivatives possess potential antiviral property against SARS-CoV-2. Fukuda et al. reported the inactivation of SARS-CoV-2 by graphene oxide (GO) nanosheet which is primarily composed of robust carbon backbone and oxygen containing functional groups (epoxy, hydroxyl and carboxyl groups). They proposed two step targeting mechanism which involves adsorption via electrostatic interaction between the negatively charged GO nanosheet and positively charged spike protein of SARS-CoV-2 followed by protein decomposition and virus neutralization.[137] In another study of GO nanosheet conducted by Unal et al., the interaction between GO nanosheet against spike glycoprotein of SARS-CoV-2 (open and closed), host ACE2, complex protein of spike-ACE2 and mutated spike were studied using molecular docking technique and the nature of interaction was reported. Further the inactivation of SARS-CoV-2 were also demonstrated in vitro experiments using GO nanosheet.[138] Using molecular dynamic simulation, Khedri et al. reported the potential antiviral activity of various 2D nanomaterial (graphene, bismuthene, phosphorene, p-doped graphene, and functionalized p-doped graphene) against SARS-CoV-2. They investigated the interaction involved and observed that these nanomaterials could distort the spike glycoprotein and restrain main protease (Mpro).[139] Despite extensive research work in antibodies targeting SARS-CoV-2, yet the mutations caused in spike region could escape neutralization which necessitates the development of inhibitor with broad spectrum activity and this has been highlighted by Donskyy et al. In this regard, they developed a graphene derivative, which involved functionalization of graphene nanosheet using polyglycerol sulfate (PGS) and variable length aliphatic chains. It was reported that functionalized graphene derivatives possessed both virustatic and virucidal activity against Feline coronavirus and SARS-CoV-2 by means of synergetic hydrophobic and electrostatic interactions along with the direct penetration of aliphatic chain against the viral membrane leading to its disintegration.[140]

4.3. Nano-Vaccines against SARS-CoV-2

Immunization is a proven tool of biomedical intervention for life threatening pathogenic diseases, however occurrence of rapid and subtle genomic changes in pathogens has led to an elusive condition on the development and implementation of vaccines. It is worth mentioning here that the contemporary challenges which permeate the field of vaccinology for most part is attributed to the lack of desirable immuno-protective targets and in the development of formulations having the potential to induce effective immune responses while doing away with the debilitating or inconvenient side effects.[141] Apart from that, at times several factors hamper and impact the efficacy of vaccines, which includes immune status, sex/age specific differences in immune responses and distinct genetic/ epigenetic backgrounds.[142] A myriad of efforts has been undertaken to develop vaccines with strong immune responses to override the shortfalls. Despite the advancement in the evolution of vaccines, immunization coverage remains partial. With the rapid development of material sciences, the advent of nanotechnology in the field of vaccinology seems promising and holds tremendous prospects due to the unique properties of NPs that make them ideal vectors for vaccine delivery by providing protection to the vaccines from premature degradation while, enhancing depot effect, increasing cellular uptake via endocytosis, triggering both humoral and cellular immunity, and improving overall stability of the vaccine[143,144] (Figure 9). In addition, NPs themselves act as immunomodulatory agents or adjuvants that enhance the immunogenicity of the antigens,[143] it is also shown that some nanovaccines induces higher production of polyclonal antibodies.[144] The following section provides an overview about the different nano-based vaccines for SARS-CoV-2 which are currently available on market as well as those being explored at different stages of preclinical/clinical evaluation (Figure 10). An extensive list of nanovaccines under development is also given in Table 4.
4.3.1. DNA Based vaccines

A Canada based healthcare biotechnology firm Entos pharmaceuticals have announced development of a DNA vaccine through their Fusogenix nanomedicine platform. The Fusogenix platform comprises of a proteo-lipid vehicle (PLV) that is made up of a biocompatible neutral lipid combined with Fusion-Associated Small Transmembrane (FAST) proteins, which ensures excellent fusion and highly efficient delivery of genetic payloads directly into the cytosol of target cells. Entos aims to develop a pan-coronavirus vaccine that can encode for multiple epitopes of key immunogenic proteins of SARS-CoV-2, so that a robust and strong protective immune response could be generated against multiple structural components of the coronavirus. The company completed in vivo preclinical studies which led to the identification of two candidate Fusogenix DNA vaccines (Covigenix) against SARS-CoV-2 (Figure 10A) which showed high immunogenicity, high neutralizing antibody levels, balanced T-helper cell immunity and efficacy. Further validation of the safety, efficacy and immunogenicity of the candidate vaccines has been carried out successfully in phase I/II human clinical trials and is moving on towards phase III trials.

A team of experts from the Mediphage research group at University of Waterloo in Canada are involved in the development of a DNA-based nasal vaccine that can be administered through nasal route in the form of a spray (Figure 10C). The vaccine comprises of an engineered bacteriophage that carries the specific antigenic sequences of SARS-CoV-2 along-with it.
and designed in such a way that it specifically infects the cells of the respiratory tract. Upon infection, the vaccine will direct the production of virus like particles of the encoded antigens resembling in structure of the novel coronavirus which will result in the generation of a prompt immune response against COVID-19 and protect the tissues present in lower respiratory tract. The DNA-based nasal vaccine is expected to act both as a vaccine and a therapeutic. Incorporating NPs, another group at Penn State University is also working towards the development of a DNA-based NP aerosol vaccine against COVID-19 that can be inhaled directly into the lungs.\(^{148}\) The NP vector is being designed to specifically target the respiratory immune cells, where it will deliver the DNA sequences coding for viral antigens and stimulate an immune response against the expressed viral proteins. This approach is based on a universal flu vaccine developed by the group earlier, which they are now repurposing to tackle the COVID-19 pandemic.

### 4.3.2. RNA Based Vaccines

Moderna’s mRNA-1273 candidate vaccine for SARS-CoV-2 in collaboration with the National Institute of Allergy and Infectious Diseases, a part of National Institute of Health, USA is a commercially available COVID-19 vaccine and was the first vaccine to be tested in humans (Figure 10D).\(^{149}\) The vaccine consists of a mRNA copy of the prefusion stabilized form of the spike (S) protein of the novel coronavirus encapsulated within a novel lipid nanoparticle (LNP) system composed of the proprietary ionizable lipid, SM-102, and 3 commercially available lipids, cholesterol, DSPC, and PEG2000 DMG. Employing similar technology, Moderna has previously developed mRNA vaccine candidates formulated in cationic lipid NPs against SARS-CoV and MERS-CoV viruses. The vaccines encoded antigenic viral full-length S, S1, or S2 proteins from the viruses that generated high titers of neutralizing Abs in mice.

In addition to Moderna’s RNA vaccine, Arcturus therapeutics in collaboration with Duke-NUS Medical School, Singapore have come forward to develop a RNA vaccine against COVID-19 by combining two platform technologies: LUNAR\(^{\text{TM}}\) and STARR\(^{\text{TM}}\) into a single platform (Figure 10E).\(^{150}\) The LUNAR\(^{\text{TM}}\) platform is
blind phase 1 trial in China have shown capable immunoge-
neutralizing antibodies in the patients. The vaccine induced dose-
in the USA and Germany as well as the randomized double-
blind phase 1 trial in China have shown capable immunoge-
nicity and positive safety profile. The vaccine induced dose-

dependent generation of RBD-binding IgG and SARS-CoV-2
neutralizing antibodies in the patients. Currently, this and
Moderna's vaccine has been approved by FDA for use.

4.3.3. Self-assembled protein subunit vaccines

Novavax had previously developed the SARS-CoV-2 vaccine
NVX-CoV2373, using its proprietary recombinant protein nano-
particle technology (Figure 11). The NVX-CoV2373 vaccine is
currently under phase III of clinical trials and is used in
combination with Novavax's proprietary adjuvant Matrix-M to
improve the efficiency of immune responses & stimulate high
titers of neutralizing antibodies. Matrix-M adjuvant is a well-
tested and documented saponin based platform blended with
synthetic cholesterol and phospholipid, which forms stable NPs
to carry the antigens. Previous studies using this adjuvant have
shown the ability of Matrix-M to improve the immunogenicity
of the target antigens by modulating the migration of antigen-
presenting cells towards the site of injection and subsequently
enhancing antigen presentation in the local lymph nodes.

Pfizer and BioNTech firm have formulated a lipid nano-
particle based nucleoside-modified mRNA (modRNA) vaccine
BNT162b1. The mRNA encodes for the receptor binding domain
(RBD) trimer found on the spike glycoprotein of SARS-CoV-2. The
results from the Phase I/II human clinical trials carried out
in the USA and Germany as well as the randomized double-
blind phase 1 trial in China have shown capable immunoge-
nicity and positive safety profile. The vaccine induced dose-

dependent generation of RBD-binding IgG and SARS-CoV-2
neutralizing antibodies in the patients. Currently, this and
Moderna's vaccine has been approved by FDA for use.

| Type of vaccine | Vaccine candidate | Antigen | Nanoparticle component | Manufacturer | Stage of development | References |
|-----------------|-------------------|---------|------------------------|--------------|----------------------|------------|
| DNA             | Covigenix         | Multiple epitopes | Proteo-lipid vehicle | Entos pharmaceuticals | Phase I/II human clinical trial | [145] |
| DNA based nasal vaccine | DNA based nanoparticle aerosol vaccine | | VLP | University of Waterloo | Preclinical stage | [147] |
| mRNA-1273       | Self-replicating RNA | S protein | Lipid nanoparticle | Moderna Inc. and NIAD | Approved for use | [149] |
| Self-assembled protein subunit | BNT162b1, a nucleoside-modified mRNA (modRNA) | S protein | Lipid nanoparticle | Pfizer and BioNTech | Approved for use | [151, 152] |
| mRNA            | NVX-CoV2373 with Matrix-M adjuvant | S protein | Recombinant protein nanoparticle | Novavax | Phase III human clinical trial | [153] |
| Self-assembled protein subunit | 1 C-SagNP vaccine technology platform | | Self-assembled protein nanoparticle scaffold with S proteins | Ufovax | Preclinical stage | [155] |
| Virus-like particle | Plant-based VLP production platform technology | S protein | Hollow shell of self-assembled hepatitis B virus proteins decorated with SARS-CoV-2 Spike proteins | Vector Institute, Russia | Phase I human clinical trial | [156] |
| | | | | | | |

References

[145, 146]
adjuvant Matrix M, elicited a strong humoral immunogenic response in mice and transgenic cattle.

Another candidate protein subunit vaccine is being developed and tested by Ufovax, an offshoot vaccine manufacturing start-up from Scripps research using their patented C-SApNP vaccine technology platform (Figure 11). The vaccine consists of a genetically encoded, single component, self-assembled receptor binding domain protein nanoparticle scaffold with proteins protruding from nanoparticle scaffold surface. The vaccine is said to inactivate the corona virus by inducing the immune system to rapidly generate antibodies. It is expecting to undergo clinical trials in the recent future.

A viral peptide vaccine named EpiVacCorona developed by Vector Institute, a Russian biological research center has been approved for early use in Russia, based on the results of a Phase I/II clinical trial. The vaccine is expected to complete its Phase III clinical trial soon. Another protein vaccine currently being tested in Phase I/II clinical trial is SpyBiotech’s vaccine which comprises a mixture of proteins. The vaccine consists of proteins from hepatitis B virus which assemble themselves into a hollow shell. This shell is then decorated with SARS-CoV-2 spike proteins to be used as vaccine.

4.3.4. Virus like particle (VLP) vaccine

Among all approaches that are being directed towards vaccine development, virus like particles seems to exhibit an exciting new approach by mimicking the native structure of viruses and shows a way to the immune system for easy recognition and subsequent stimulation. Medicago, a Canadian based biopharmaceutical company has crossed the first stage in developing a candidate vaccine by successfully producing virus like particles (VLPs) of novel coronavirus SARS-CoV-2 using their plant-based VLP production platform technology. The company uses plants as mini-biofactories to produce therapeutic proteins and VLPs for vaccine production. The vaccines are in phase III clinical trials since March 2021. In addition to this, the company is also using this technology to produce antibodies against SARS-CoV-2 that can be directly used as a therapeutic to provide...
protection to patients against this virus. Similarly, Zheng et al., recently synthesized an inhalable nanovaccine which consist of particles that highly resemble SARS-CoV-2 in structure by incorporating the receptor binding proteins of the virus, liposomes and a synthetic double stranded RNA, poly(I:C). The liposomes in the particles function as biomimetic pulmonary surfactant (bio-PS) which enables rapid intake of the VLPs into epithelial cells lining the respiratory tract. The easily delivered VLPs seems to elicit a strong respiratory mucosal immunity and the respiratory secretions of treated mice exhibited high titers of secretory immunoglobulin A (sIgA).\textsuperscript{1596}

5. Conclusion and Outlook

Evidently, conventional antiviral therapies are not equipped to handle the current pandemic. Therefore, it is in our best interest to diversify our research approach and seek long-term solutions that can help in the prevention, diagnosis, and treatment of not just COVID-19 but of future viral diseases of similar nature as well. So far, the incorporation of nanotechnology seems to have aided us mostly in developing measures to reduce the infectivity of SARS-CoV-2 and to an extent in diagnostics. But even with nanotechnology or other equally promising domains such as synthetic biology, artificial intelligence, in silico drug designing, etc. and with platforms such as bioorthogonal chemistry, prodrug, protide, etc., the cure for COVID-19 still eludes us. The crucial reason for this is that most of these revolutionary domains and platforms are still nascent with regards to its applications in anti-viral therapeutics, possibly because they were mostly researched and utilized on diseases with traditionally high mortality such as cancer. This is especially true for nanotechnology which has focused mostly on addressing localized and stationary afflictions in the body such as in tumor therapeutics, nanomaterial-based organ grafts, etc. Also, it has only been over two years since the pandemic was declared, which has not been sufficient time to develop novel solutions to address it. Moreover, there also exist various limitations associated with implementing nanotechnology in managing diseases like COVID-19, especially when it comes to treatment. That is, even though the incorporation of nanomaterials leads to low cost and sensitive diagnostic platforms, it still falls short in terms of being able to eradicate viral particles within the body. This is partly due to the lack of research and
availability of strategies in employing nanomaterials within the body; for instance, in vivo behavior of nanoparticles in regards to in vivo antiviral activity, systemic clearance, immunogenic crosstalk, and other potential side effects are still not well researched or understood. Furthermore, given the severity of the situation and the sudden carnage it has wreaked upon the world, many nations and enterprises are not willing to immediately risk their resources on unconventional technologies, they would rather choose the tried and familiar method at first; precisely why our first response was not conventional viral vaccines which had been fast tracked through clinical trials.

However, there is still a lot of room for experimentation, discovery, and innovation in managing COVID-19 and similar viral diseases using the toolkit provided by nanotechnology. In section 2, we already witnessed a myriad of new nanomaterial incorporated fabrics and disinfectants that keep various microbes at bay including SARS-CoV-2, but this may still be the tip of the iceberg; various nanomaterials, nanoparticles, structural variants, and strategies are yet to be investigated. We also witness a trend of moving towards more electronic based diagnosis in section 3, this can be attributed to the enhancement in stability, speed, durability, and robustness of nanostructure-based electrochemical diagnostic systems over the conventionally “complicated” lab diagnostic techniques. And in section 4 we saw how all major players and corporations in vaccine development are attempting to formulate nanoparticle-based vaccines given their advantages over conventional and relatively ineffectual vaccines with shorter shelf-life. Again, there is also room for entirely novel strategies, for instance, in section 3 and 4 we saw few researchers utilizing GOs to discriminate and preferentially bind to the viruses; this property can be further exploited in multiple ways, an example will be to experiment with GO-prodrug or GO-protide conjugates against SARS-CoV-2. And surely as our understanding of the viruses and viral immune responses continue to rise, we would discover more distinct molecular targets, novel therapeutic strategies, and more effective preventive measures. Lastly, whatever the cost, it is imperative that we try and exhaust all possible avenues in our pursuit of securing a future wherein all pathogenic diseases are to those who live then as what smallpox is to us of the present; and if we are fortunate, COVID-19 may be the last of the pandemic outbreaks.

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Conflict of Interest

The authors declare no conflict of interest.

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