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Journal of Controlled Release 338 (2021) 813–836

Contents lists available at ScienceDirect

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

Nano-engineered tools in the diagnosis, therapeutics, prevention, and mitigation of SARS-CoV-2

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ARTICLE INFO

Keywords:
Biosensors
Cytokine storm
Vaccine and therapeutics
Post-COVID complications
Targeted drug delivery

ABSTRACT

The recent outbreak of SARS-CoV-2 has forever altered mankind resulting in the COVID-19 pandemic. This respiratory virus further manifests into vital organ damage, resulting in severe post COVID-19 complications. Nanotechnology has been moonlighting in the scientific community to combat several severe diseases. This review highlights the triune of the nano-toolbox in the areas of diagnostics, therapeutics, prevention, and mitigation of SARS-CoV-2. Nanogold test kits have already been on the frontline of rapid detection. Breath tests, magnetic nanoparticle-based nucleic acid detectors, and the use of Raman Spectroscopy present myriads of possibilities in developing point of care biosensors, which will ensure sensitive, affordable, and accessiblemass surveillance. Most of the therapeutics are trying to focus on blocking the viral entry into the cell and fighting with cytokine storm, using nano-enabled drug delivery platforms. Nanobodies and mRNA nanotechnology with lipid nanoparticles (LNPs) as vaccines against S and N protein have regained importance. All the vaccines coming with promising phase 3 clinical trials have used nano-delivery systems for delivery of vaccine-cargo, which are currently administered widely in many countries. The use of chemically diverse metal, carbon and polymeric nanoparticles, nanocages and nanobubbles demonstrate opportunities to develop anti-viral nanomedicine. In order to prevent and mitigate the viral spread, high-performance charged nanofiber filters, spray coating of nanomaterials on surfaces, novel materials for PPE kits and facemasks have been developed that accomplish over 90% capture of airborne SARS-CoV-2. Nano polymer-based disinfectants are being tested to make smart-transport for human activities. Despite the promises of this toolbox, challenges in terms of reproducibility, specificity, efficacy and emergence of new SARS-CoV-2 variants are yet to overcome.

1. Introduction

The human race has continuously faced several outbreaks of contagious diseases and pandemics since its existence. Whether it is the Athenian plague of 430 BCE, the black death in China, the Spanish flu of 1918–1920 or recent outbreaks of Severe Acute Respiratory Syndrome (SARS) and Influenza virus (H1N1 pandemic) [1], every disease has uncovered the novel medical complications and the need of rapid development of inter-disciplinary medical care. Recent viral outbreaks, including influenza virus, coronavirus, Nipah virus and swine flu viruse, have significantly impacted the regional socio-economic potential of the world. Though most of the recent pandemics have been controlled by the medical community, the SARS-CoV-2 pandemic has introduced an enormous wave of challenges to health care sectors worldwide, particularly in rapid diagnostics, therapeutics and implementation. Till now, 202,015,252 cases of SARS-CoV-2 have been reported worldwide, with a death count of 4,285,724 people and the numbers are continuously increasing [2]. The SARS-CoV-2 has adversely affected the whole world's social and economic structure, pointing towards the urgent need for advanced multi-disciplinary research in health care, including diagnosis, therapeutics, and mitigation strategies towards such diseases in present and future. Multiple variants of SARS-CoV-2 have emerged across the world. The variants of concern that have gained attention are B.1.1.7, B.1.351, B.1.1.28.1, B.1.617, B.1.618. They have led to re-infections either after natural infection or post vaccination, as observed in the United States, Brazil and India [3]. Failure to detect the new variants is a massive concern of RT-PCR diagnostic tests, as observed in the case of B.1.351. Although several nations have vaccinated a large percentage of their population, the concerns of the COVID-19 outbreak are still persistent [4]. While multiple avenues like immunotherapy and repurposed drug research are being investigated to mitigate the viral infection, one also needs to discuss the underpinnings of

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https://doi.org/10.1016/j.jconrel.2021.08.046
Received 4 March 2021; Received in revised form 13 August 2021; Accepted 28 August 2021
Available online 31 August 2021

nanotechnology to revolutionize the efforts against SARS-CoV-2. The past 40 years have witnessed the explosive growth of nanotechnology as a tool-box for intelligent design in treating complex maladies. The global nanotechnology market is projected to cross US $ 125 billion by 2024. Currently, it holds over 85% share in the global market in nanomaterials, nanodevices, nanolithography and nanoparticles. By 2024, it is predicted to drive the global market for electronics, energy, biomedical, defence, and automation applications [5].

Nanotechnology in medicine finds importance in several overlapping molecular technologies. The nanoscale rapid diagnostics and biosensors have been used to detect and diagnose multiple diseases, including cancer, cirrhosis, viral and bacterial infections [6]. These sensors and detectors can sense the molecular changes before the onset of diseases, resulting in rapid prognosis and better surveillance of the respective condition. Efficient drug delivery systems and nano-therapeutics have also gained particular attention in increasing the efficiency of the drug and targeted drug delivery approach. The small size and high surface area of nanoparticles enable them for a sustained delivery without causing adverse toxicity. Understanding the genomics and proteomics of novel viral outbreaks, a mammoth task earlier has become a straightforward approach because of nanotechnology [7]. Direct and precise input of proteomics and genomics can be provided at the molecular and cellular level with several nano-tools [8]. Nanoparticles against pathogens, tissue engineering, gene therapy, implants and prosthetics have put the nanotechnology platform on the forefront of challenging medical problems.

Coronaviruses are a class of highly contagious airborne enveloped viruses with a positive single-stranded RNA genome with strains including SARS-CoV, MERS-CoV and recently emerged SARS-CoV-2. Coronaviruses are characterized by three glycoproteins (1) Spike protein (2) Membrane (3) envelope protein [9]. Nanotechnology has continuously been used to detect viral genome of corona, influenza, HIV, hepatitis, dengue and Nipah viruses [10]. Multiple nano-technological carriers have been used to develop novel vaccines against earlier outbreaks of coronaviruses. Many strains of coronaviruses, namely SARS-CoV, MERS-CoV and SARS-CoV-2 have been detected precisely using nanotechnology [11]. The angiotensin-converting enzyme 2 (ACE2) receptor-based therapeutics and the vaccine development have been aided with nano-polymeric and liposome-based carriers as potent therapeutics against coronaviruses.

The triune of nano-tools in detecting, therapeutics and mitigating this pandemic can definitely help the COVID-19 warriors and researchers to overcome the peril of SARS-CoV-2, though many unforeseen are yet to overcome. The sudden outbreak of the SARS-CoV-2 pandemic has also exposed the unpreparedness of human being to cope up such a pandemic in no time and meeting the sudden large-scale demand for medical equipment and practical sterilizing tools. The interdisciplinary approach of nanotechnology can relate to different approaches required to combat COVID-19 rapidly and effectively.

In this review, the triune of the nano-toolbox in the areas of diagnostics, therapeutics, prevention, and mitigation of SARS-CoV-2 will be introduced. In further sections, the role of nanotechnology in understanding the genome of SARS-CoV-2, biosensors for rapid detection, therapeutics and vaccine development, theranostics approaches, dealing the post COVID-19 complications, the challenges ahead and the future prospects will be elaborated.

2. How did nanotechnology help in understanding SARS-CoV-2?

Coronavirus disease 19 (COVID-19) pandemic caused by the latest spillover of SARS-CoV-2 from animal to humans was first reported in Wuhan, China, in late 2019. Wu et al. [12] initiated a study on a 41-year-old man working in a local seafood market, admitted in the Central Hospital of Wuhan on 26th December 2019 with respiratory illness. The patient tested negative for the presence of common etiological agents like the influenza virus, *Chlamydia pneumoniae*, *Mycoplasma pneumoniae* and other human adenoviruses through antigen-detection kits and quantitative PCR (qPCR). Hence, the authors performed metagenomic RNA sequencing of the bronchoalveolar lavage fluid (BALF) and using Illumins MiniSeq. The complete viral genome further led to identifying a novel RNA virus that which was later designated as SARS-CoV-2. More insights into genomic epidemiology, analysis of structural variants and mutation rate, and identification of transmission clusters have been made possible by the revolutionary Oxford Nanopore direct RNA-sequencing (DRS) platform based on single molecule detection RNA. The targeted amplification of the viral genome with multiplexed feature ensures a full consensus sequence in ~7 h [13–15]. The platform also presents exceptional opportunities to investigate epi-transcriptomic features of the viral RNA. DNA nanoball sequencing revealed the complex transcriptome of the virus, due to the discontinuous transcription events. It was understood that SARS-CoV-2 produces canonical genomic and subgenomic RNAs, unique transcripts through events of fusion, deletion, and frameshift mutations. Through nanopore DRS, 41 RNA modification sites were reported on viral transcripts with AAGAA as the most frequent motif [16]. In 2005, Atomic force microscopy (AFM) was utilized by Lin et al. [17] to decipher the surface nanostructures of SARS-CoV. This study demonstrated the single crown-like viral particle's quantitative measurements, 15 spherical spikes of 7.29 ± 0.73 nm diameter and the overall ultrastructure. The 3D-QSAR approach in nano-QSAR was utilized in elucidating the pharmacophore of SARS-CoV 3C like protease, which was found to be an attractive anti-SARS drug target [18].

SARS-CoV-2 targets the angiotensin-converting enzyme 2 (ACE2) receptor on the surface of airway epithelial cells, alveolar and vascular epithelial cells and lung macrophages through its spike glycoprotein (S). TMPRSS2, cellular serine protease is observed to process the S protein and eventually contribute to the viral entry. This induces a chain of events resulting in an inflammatory phenomenon of cell death called pyroptosis. The destruction of pulmonary cells triggers an innate immune response involving macrophages and monocytes, which release an array of cytokines. In severe cases, due to a dysfunctional immune system, a massive cytokine storm mediates a significant lung inflammation, hyaluronan formation and pulmonary edema. The ripple effect of this event triggers a multi-organ failure [19].

3. The triune of nanotechnology against SARS-CoV-2

Despite the progress made in mitigating SARS-CoV-2, significant challenges remain in translating the viral pathogenesis and biomedical know-how into clinically relevant disease management tools. While a cure or vaccine is underway, the triune of nanotechnology in detection, therapeutics, and protection and mitigation herald significant means to tackle the SARS-CoV-2 saga (Fig. 1).

3.1. Detection of SARS-CoV-2

For an early prognosis against COVID-19, it is necessary to diagnose and detect the infection of SARS-CoV-2 early. Nanobiosensors, cytokine sensors, breath sensors, saliva sensors, advanced spectroscopy tools and nanotechnology-based -rapid diagnostic testing can provide point-of-care and precise detection of the viral load even in its early phase [20].

3.2. Therapeutics and vaccine development

Therapeutics and vaccines are the backbone of any medical care. Anti-viral nanomaterials, hybrid nanomaterials with targeted anti-SARS-CoV-2 activities, photodynamic therapies (PDT), molecular imprinted polymer (MIP) technology can act as an acceptable and practical substitute to conventional therapeutics against SARS-CoV-2. Though trials are still underway to develop potent therapeutics, the role of nanoparticles as an anti-viral agent itself or as a carrier for anti-SARS-CoV-2 therapeutics cannot be neglected. Similarly, nano-carriers

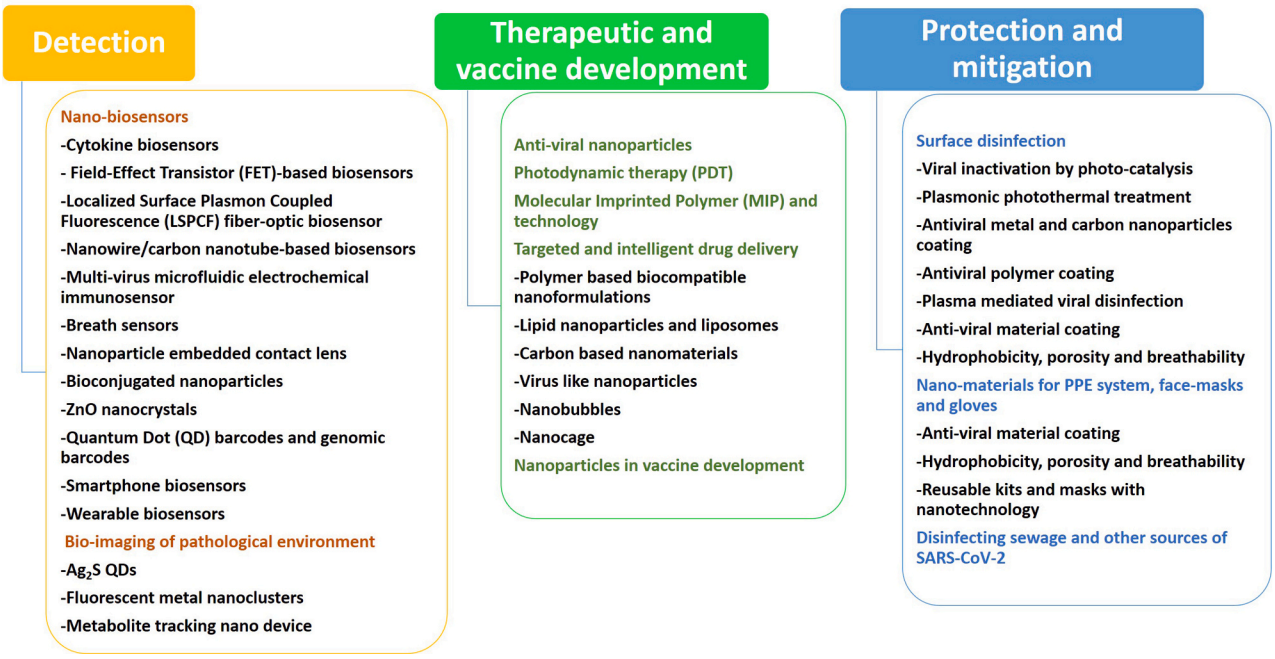

Fig. 1. The triune of nano-tool box against SARS-CoV-2.

are playing a vital role in the delivery of cargo components of vaccines against SARS-CoV-2. Recently, three vaccines developed by Pfizer-Biontech, Moderna and Oxford-Astra-Zeneca have been approved for human use. All the approved vaccines have nano-components as an integral part of the vaccine system [21–23].

3.3. Protection and mitigation

Protection and mitigation strategies against any pandemic are equally crucial as the detection and therapeutics development. Nano-tools with anti-viral nanoparticles, photocatalysis and plasma therapy, can effectively do the surface-sterilization of multiple frequently exposed surfaces. The problems of sterilization, breathability and cost-effectiveness of facemasks, gloves, PPE kits can also be tackled with nano-tools.

4. Detection of SARS-CoV-2

One of the most important aspects in effective treatment in a pandemic is the early and rapid detection which can significantly improve a patient's prognosis. The age-old gold standard diagnostics used in earlier times against HIV, Hepatitis C, dengue fever, malaria, tuberculosis include microscopy, lateral flow immunoassays, and ELISA. However, these tools are slow, costly, unable to differentiate between pathogens, and have a modest detection threshold [24]. Currently, real-time RT-PCR is employed for detection of SARS-CoV-2, which takes at least 3 h. The RNA preparation step can hamper accuracy. Also, developing countries have limited testing facilities and funds which pose limitations in detection. There has also been a demand for non-isotopic detection systems for biotechnological and medical research, food quality testing, etc. Hence, the emerging real-time technologies driven by nanomaterials could overcome these challenges [25].

4.1. Nano-biosensors

Biosensors for biomedical use primarily comprise of three components: (a) the detector for perceiving the stimulus; (b) the transducer for converting the stimulus into a measurable signal; and (c) an output system which can amplify and display the result in an appropriate form. Based on the signals sent by the transducers, biosensors can be categorized as field-effect transistor (FET), optical, electrochemical, mechanical, piezoelectric, surface acoustic wave, and thermal. Based on detecting components, they can be of three types: molecular biosensors (antibodies, nucleic acids, ion channels or enzymes), cellular biosensors, and tissue biosensors. Molecular biosensors have improved the specificity of nanotechnology diagnostics [25].

4.1.1. Potential cytokine biosensors

The hyper-inflammatory syndrome or the cytokine storm is an implication of an unsatisfactory prognosis in critical cases of COVID-19. This is generated by high viral titers, interferon (IFN) attenuation, the release of pro-inflammatory factors and accumulation of immune cells. Various studies have extensively reviewed cytokine storm progression, giving rise to multiorgan failure, sepsis or acute respiratory distress syndrome (ARDS) [26]. The leading players are the pro-inflammatory cytokines: IL-1, IL-6, IL-8, and tumour necrosis factor-alpha (TNF-α), C-reactive protein (CRP) (Fig. 2) that can be used as prognostic biomarkers.

However, to generalize this idea, periodic cytokine profiling, kinetic studies and the relationship between pro-and anti-inflammatory cytokines are needed. These variables need to be studied in large and diverse populations [27]. Using these studies, biomarker thresholds could be set which could distinguish between patients recovering quickly, requiring anti-inflammatory or other treatments. While the side-effects and effectiveness of immunomodulatory drugs are still being investigated, using inexpensive biosensors to detect the cytokine storm could help personalize immunomodulatory therapies and monitor their progression and efficiency [28].

A multisensor system [29] built for simultaneously sensing an array of biomarkers (IL-2, IL-6, IL-4, IL-10, IFN-γ, and TNF-α) would help in detection of disease stage (Fig. 3). Plasmonic multisensor built with a detection range between 10 and 10,000 pg mL^{-1} and a 1 μL sample size demonstrate the feasibility of using nanosensors in the fight against the COVID-19. It's signal transduction mechanism comprises of localized surface plasmon resonance (LSPR) of gold nanorods with dark-field microscopy, that measures real-time changes in cytokine binding to antibodies. This sensor is more informative than traditional end-point ELISA. In only 40 min, the whole chip is run, making this detection-

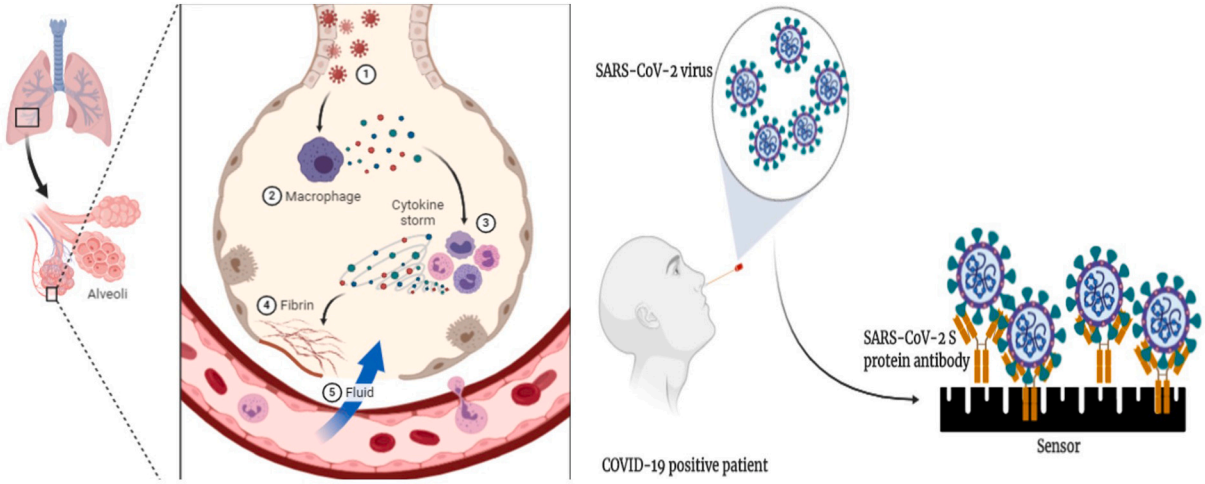

Fig. 2. Cytokine storm caused by SARS-CoV-2 infection and a representative antibody-based biosensor. The cytokine storm is generates in the following steps: (1) SARS-CoV-2 infects the respiratory airways and enters the lungs (2) Macrophages and other immune cells recognize the virus and produce cytokines (3) These cytokines attract more immune cells such as white blood cells which also produce cytokines, thus creating a massive cycle of inflammation that damages the lungs (4) pulmonary damage can also occur through fibrin formation (5) Weakened blood vessels further allow fluid to seep in and fill up the lung cavities, resulting in serious conditions and respiratory failure. (created using BioRender).

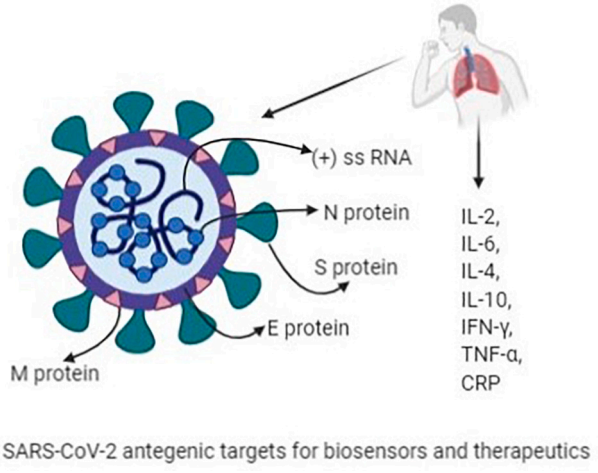

Fig. 3. SARS-CoV-2 antigenic targets, cytokines and interferons for biosensors and therapeutics. (created using BioRender).

platform a good choice in clinical decision-making in emergencies.

Another multisensory system [30] using electrochemical transduction system contains 32 electrodes, each multiplexed with an 8-port manifold to deliver 256 measurements in one hour. This system also requires an offline antibody capture step on the magnetic nanobeads. The device works on a dynamic detection range of between 0.1 and 104 pg mL^{-1}. A similar system was built using graphene oxide to fabricate nanoprobes that could simultaneously detect TNF-α, IL-6, IL-1β, spiked into the same mouse serum sample [31]. This was achieved using antibodies bound to three dissimilar signal reporters including nile blue, methyl blue, and ferrocene.

The multisensor-enabled paradigm could personalize and stratify the COVID-19 management and holistically guide dosing and timing of immunomodulatory therapies and vaccination intervals. This could maximize the benefits of therapeutic interventions and minimize deleterious effects. Detecting multiple cytokine storm components is a massive advantage over the conventional pathogen sensors, which can only detect one factor at a time, cost issues, and time factor [3]. A multisensor system (electric tongue) based on potentiometric sensors was employed by Eckersall and colleagues [32] to improve mastitis detection in robotic milking of farm animals. It detected the presence of organic and inorganic ions in the milk. Bovine mastitis, a global concern of the dairy industry, caused by pathogenic infection, results in inflammation of the mammary glands. It was imperative to detect the presence of pathogens and bacterial toxins in milk. This system is advantageous over the conventional system involving human inspection and manual measurement of electrical conductivity in the milk using individual electrodes. The multisensory approach has earlier served productively in detection and classification of human urine, fermentation growth media and broths, etc.

Seo et al. fabricated a field-effect transistor (FET)-based biosensor of 100 × 100 μm^2 detecting SARS-CoV-2 in nasopharyngeal swab specimens. It was based on immunological diagnostic method which does not require sample pre-treatment or labelling. Graphene sheets of the FET were functionalized with specific antibodies against S protein of SARS-CoV-2 using a probe linker. The nano-device could rapidly detect the virus in the culture medium, clinical samples and 1 fg/mL in phosphate-buffered saline, 100 fg/mL clinical transport medium. Even though SARS-CoV-2 encodes spike (S), envelop (E), matrix and nucleocapsid proteins (N), spike protein is the best candidate for use as a diagnostic antigen. This is because S protein is a major transmembrane protein, highly immunogenic, exhibits diversity in amino acid sequence among coronaviruses, thus enabling specific detection of SARS-CoV-2. FETs with deformed millimetre scale monolayer graphene channel was utilized to detect nucleic acids. This added ultra-sensitivity to the device due to which it could detect 600 zM and 20 aM nucleic acid in buffer and human serum samples [33]. A 10 min lateral flow rapid-immunodiagnostic kit was developed using lanthanide-doped polystyrene nanoparticles, in the detection of anti-SARS-CoV-2 IgG in the serum. The nucleocapsid protein of the pathogen was immobilized onto the nitrocellulose component of the kit to capture the specific immunoglobulins. This technique is reported to serve well in cases of clinical suspicion which test negative by RT-PCR and require chest computed tomography for confirmatory detection [34].

In 2009, state of the art, localized surface plasmon coupled fluorescence (LSPCF) fiber-optic biosensor was developed by Huang et al. to detect SARS-CoV nucleocapsid (N) protein [35]. It was observed that the N protein was detected as early as 1 day after infection, making it the suitable candidate for rapid detection. Gold nanoparticles used routinely possess optical properties such as localized surface plasmons (LSPs). The authors proposed a novel fiber-optic biosensor by combining LSPCF with

fluorescence sandwich immunoassay featuring mABs against SARS-CoV N protein. The biosensor demonstrated an enhanced detection limit of 0.1 pg mL^{-1} N protein diluted in serum as compared to just LSPCF fiber-optic biosensor which is as low as 1 pg mL^{-1} and conventional antigen capture ELISA using the same mABs was 12.5–25 ng/mL. Aptamer based biosensors for sensing antibodies, have evolved innovatively. They can differentiate between infected cells or active viral particles. Although aptamer-functionalized microfluidic devices have a long way to go due to challenges in coatings, microengineering, these devices present potential for all-in-one bioanalysis platforms [36].

4.2. Metal/Nanowire/carbon nanotube-based biosensors

Nanowire/carbon nanotube-based biosensors are known for high selectivity and ultra-sensitivity to detect specific proteins and DNA sequences. These captured molecules affect the conductance of the nanowires/nanotubes giving a readable output. Ishikama et al. [37] configured antibody mimic proteins (AMPs) on In_2O_3 nanowire-based FET biosensor to detect N protein of SARS virus. Fibronectin-based protein was used as an example of AMP. These unique affinity binding agents can be produced in bulk at low cost, were stable to wide range of pH, 2–5 nm and < 10 kDa and hence surpass antibodies. Unlike Si nanowires, metal oxide nanowires (In_2O_3, ZnO, and SnO_2) did not require insulating and can be easily derivatized. The authors claimed that the device could detect a subnanomolar concentration of N protein in a background of 44 μM bovine serum albumin. Patolsky and co-workers developed a nano-device for real-time electrical detection of influenza A virus using nanowire FET. The authors also discussed the possibility of simultaneous detection of various distinct viral diseases at a single virus level [38].

A highly sensitive multivirus microfluidic electrochemical immunosensor was developed by Han et al. [39] for simultaneous detection of H1N1, H5N1 and H7N9. ZnO nanorods with high isoelectric point (IEP) were employed on the upper inner surface of a PDMS senor. These interacted electrostatically with low IEP antibodies of the viruses. The device could detect upto 1 pg mL^{-1} of each virus due to enhanced sensitivity with ZnO nanorods. These ZnO nanostructures have demonstrated significant biocompatibility and biosafety in biological environments, making them reliable and trustworthy in biomedical engineering applications [40].

Breath sensors have been developed to diagnose respiratory illnesses. Gas chromatography-mass spectrometry studies of human breath showed several volatile compounds which change in diseased cases. Peng et al. utilized an array of gold nanoparticles that could differentiate the endogenous volatile organic compounds (VOCs) in the breaths of normal and lung cancer patients. They further identified 42 VOCs which represented lung cancer biomarkers [41].

Electrochemical detection of chikungunya virus was accomplished using molybdenum disulphide nanosheets imprinted with gold electrodes. Methylene blue was employed to detect guanine in single and double stranded viral DNA which corresponded to a voltammetric signal. This disposable sensor could detect the pathogen in the rage of 0.1–100 μM [42].

A non-invasive method to detect glucose concentration was developed using nanoparticle embedded contact lens. This reflectance spectroscopy-based biosensor utilized glucose oxidase and cerium oxide (III) to detect he glucose concentration. Detectable changes were observed in the reflection spectrum of contact lenses [43].

A rapid tool for detection of pathogenic bacteria was developed using bioconjugated nanoparticles. This ensured in situ pathogen quantification within 20 min. The authors tailored fluorescent-bioconjugated silica nanoparticles. Compared with conventional immunoassays where a few dye molecules are linked to antibodies, these tailored nanoparticles contained many dye molecules which produced a stronger signal of the antigen-antibody binding event. The device could accurately detect 1–400 *E. coli* O157 cells in samples of spiked ground beef [44]. Even though this technique requires laboratory equipment such as fluorimeter, it surpasses the deployment of trained human resource such as pathologists and BSL-3 biohazard set ups.

Raman Spectroscopy presents distinct spectral features for target molecules and is therefore recognized as a promising tool in detection. Kang et al. [45] established the direct utility of glucose Raman spectra in vivo monitoring. In the fight against COVID-19, this technology could be used as a signal transduction mechanism, for a lateral flow test built with antibody-coated nanoparticles. Its detection limit in whole blood was 5 pg mL^{-1}. These sensors are now modelled to link to smartphones to increase their feasibility and robustness [46].

A biosensor comprising of antibody-coated ZnO nanocrystals was developed by Cao et al. [47]. It was built using a rapid and inexpensive colloidal dispersion fabrication method. Impedance spectroscopy was utilized to detect the C-reactive protein (CRP) antigen at a lower limit of 1 ng/mL. CRP is a key biomarker in COVID-19 patients, and hence this biosensor could be applied in the pre-diagnostic treatment.

Multiplexed detection systems have been made possible using quantum dot (QD) barcodes and genomic barcodes. QDs have been routinely used in proteomic and nucleic acid detection due to their unique property of photostable bright fluorescence. Hauck and *co*-workers describe QD barcodes as polystyrene microspheres containing varying ratios of QDs, with each individual colour relating to an antigen or nucleic acid target. The detected biological entity could be a gene, protein or an entire pathogen [48]. Based on the principle of quantum dots and microfluidics, a multiplexed, high-throughput blood-borne infectious disease detection system was generated by Klostranec et al. The system could detect serum biomarkers of hepatitis B, C and HIV with a sample volume of <100 μL within 1 h with higher sensitivity than the FDA-approved methods. This proof-of-concept device could be further investigated to develop a portable handheld point-of-care diagnostic system which could revolutionize disease spread in developing countries [49].

4.3. Smartphone biosensors

Since smartphones have an enormous global market, using them in controlling the pandemic has become an appealing option. The proposed mobile immunosensors [50] for IL-6 consist of a colorimetric detection paper using gold nanoprobes which generate coloured spots that get detected with the smartphone app. It used augmented reality to control the photographic parameters by compensating for variable light. The system can detect modulations in IL-6 in 18 min at a minimum concentration of 12.5 pg mL^{-1}.

4.4. Wearable biosensors

An ideal means for continuously detecting cytokine levels and relating it to the progression of COVID-19 treatment would be using wearable biosensors. While this idea is still not in practice, a few concepts have been recently proposed by Russell et al. [51]. The first concept is a needle-shaped microelectrode for real time detection of IL-6 levels. This design works on the interaction between IL-6 and antibodies linked to the electrodes that changes the impedance of the sensor surpassing the use of labels [37]. The second concept is an electrochemical biosensor consisting of a wire electrode altered with aptamers that undergo a configurational change upon binding their target. This alteration brings about a change in a redox active dye (methylene blue) which generates a square-wave voltammetry. This sensor could detect real-time levels of vancomycin in rats [52]. The third game changing concept is based on intradermal delivery of several biocompatible near-infrared (NIR) quantum dots using dissolvable microneedles. By fine-tuning the fluorescence of the QDs, the pattern emitted can be made exclusively detectable upon illumination with NIR light. This pattern can be detected with a machine learning algorithm in a smartphone [53]. Such technologies can revolutionize mitigating measures in a

pandemic.

Table 1 represents various detection methods for pathogens proposed recently. The real-time reverse-transcription polymerase chain reaction (RT-PCR) test is the most widely used method of diagnosis of COVID-19. It detects the presence of viral RNA in the sample. Although the test demonstrates high sensitivity, the requirement of experienced laboratory staff, expensive equipment, and 48 h to generate results are some of the pitfalls of this test. It has also been observed that the test generates false negatives in the early stage of infection, due to which several groups are trying to improve the methodology and developing quick detection methods. The existing point of care detection system developed by Abbott Diagnostics has allowed direct detection of viral RNA in clinical samples, without the need for RNA extraction. But this method can test one sample at a time and has also demonstrated ~48% false negatives due to inappropriate samples and transport conditions. Several serological tests have also been developed that can detect IgA, IgG or IgM antibodies to spike or nucleocapsid protein. However, the challenge of potential cross-reactivity between SARS-CoV-2 antibodies and those of other coronaviruses minimizes the accuracy of these tests. It also requires high-quality antibodies. The other tests include whole-genome sequencing of the virus, although comprehensive, but time-consuming and very expensive. The nanopore target sequencing (NTS) is a combination of the advantages of RT-PCR and whole-genome sequencing wherein the target sequence is amplified and sequenced. The latest CRISPER-Cas method of detection utilizes the Cas13a, which is reprogrammed with CRISPER RNAs. The Cas13a can be activated after recognition of the target sequence of viral RNA. This leads to cleavage of a reporter RNA bound to a fluorescent quencher (Fig. 4). SHERLOCK and DETECTR are the CRISPR based ultrasensitive COVID-19 diagnostic systems which detect viral infections in <30 min inexpensively. These kits are commercially available and do not require any expensive equipment [54]. Among other RNA-based technologies are paper-based biosensors which get triggered upon the presence of target RNA, leading to the unwinding of the hairpin RNA thus exposing ribosomal binding site and enabling downstream translation [55].

In the midst of the current pandemic, the global demand for an economical, easy-to-use, rapid, sensitive and reliable detection system is increasing. While biosensors (magnetic/optical/electrochemical/mechanical) reduce the long turnaround times of detection, they also possess several challenges. The use of fluorescent dyes, radioisotopes, unstable enzymes, magnetic labels adds additional complexities of size, biocompatibility, detection of ultralow quantities of target components, optimal surface: volume ratio, thermal heating. For a successful point of care biosensor platform, one needs to optimize all these parameters. These detection systems have the potential to be extended to the detection of other pathogens and viruses. Various industries such as Zepto Life Technology, LLC (USA). Dongguan Bosh Biotechnologies, Ltd. (China), Flux BioscFlux Biosciences, Inc. (USA) and T2 Biosystems, Inc. (USA) have been working on magnetic nanosensor based point of care diagnostic devices. T2SARS-CoV-2 Panel, an NMR based nanobiosensor developed by T2 Biosystems is given the emergency use authorization by the FDA in response to the COVID-19 pandemic [54–55].

4.5. Biomolecular/protein corona biomarkers for assessing blood clotting

Thrombosis is a major outcome of COVID-19 related complications. Using theragnostic nanotechnologies, early diagnosis of thrombosis, delivery of thrombosis inhibitors have been developed. Biomarkers for thrombosis include P-selectin, D-dimer, *E*-selectin [56]. Although nanoparticles loaded with anti-thrombotic drugs have demonstrated its theragnostic effect, the approach has certain shortcomings. Once the nanoparticle comes in contact with the complex physiological fluids mostly containing proteins, it coats the nanoparticle with a layer called the biomolecular or protein corona. Corona interferes with the targeting molecules on the surface of the nanoparticle, causes platelet aggregation, resulting in adverse effects [57–59]. However, this creates a unique opportunity for diagnostic applications. The composition of the coronas on the surface of nanoparticles reflects the health of the plasma donor, presenting opportunities for personalised and disease specific biomolecular/protein coronas. It can help in diagnosis of diseases by tracing specific biomarkers. In COVID-19 patients, these corona nanoparticles can form the basis of sensory nanomedicine to assess the risk of blood clotting. The novel proteome of corona contains complement proteins, immunoglobulins, coagulants [60]. Mirshafiee et al. [61] demonstrated that a precoating of nanoparticles with immunoglobins can improve the settlement of similar components from the blood plasma. Hence, precoating nanoparticles with blood clot-related proteins such as factor VIII, factor XIII, tissue plasminogen activator, fibrin, protein Z, fibrinogen could intensify the settlement of similar proteins into the layer of corona. This will create a unique and robust system to sense the even the subtlest signs of clotting early. The sensing can be performed using colorimetric platforms, smartphone sensors, plasmonic nano sensors, etc. [62].

Table 1
List of detection platforms for pathogenic infections.

Detection platform	Examples of pathogens detected	Assay time	Limit of Detection	Sample matrix	Comments	References
RT-PCR	SARS-CoV, MERS-CoV, HIV, Ebola, HBV, HCV, bacteria, fungi, protozoa	48 h	~10 copies/μL sample	Serum, nasal or throat swabs	Amplification of the target region after RNA extraction, trained personnel, laboratory equipment	[24,25]
Point of Care (ID NOW), Rapid detection systems	SARS-CoV-2, Influenza A and B, RSC,	~13 mins	~125/mL	Nasal or throat Swab	12 to 48% false negatives 1 sample/run	[49,55]
ELISA, lateral flow immunochromatography assays, antibody-based assays, fluorometry	IgA, IgG, or IgM antibodies to spike (S) or nucleocapsid (N) protein or other pathogenic determinants of viruses and bacteria	1.5 h	~0.15 pg-1.3 ng/mL of antigen	PBS, Serum	Cross reactivity issues	[24,34,51]
MALDI-TOF/MS	H5N2	1 h	$10^{4.5}$–$10^{5.5}$ $TCID_{50}$	Virus lysate	Expensive, uses magnetic separation	[20,41,55]
Magnetic nanosensors	Influenza virus, *E.coli*, *Mycobacterium tuberculosis*, HIV, *S. aureus*, SARS-CoV-2	<30 min	<5 ng/mL for SARS-CoV-2 anti-S antibodies	PBS, serum, water, nasal swab, milk	Highly sensitive, portable, economical,	[30,55,183]
CRISPER-Cas method (prophylactic anti-viral CRISPR in human cells: PAC-MAN), iSCAN one pot assay	SARS-CoV-2, Influenza A	1 h	10 RNA copies/reaction	PBS, serum	Uses CRISPER RNAs and Cas13a, detection using a fluorescent quencher, robust, sensitive	[55,107]
Nanopore Target sequencing	SARS-CoV-2	6–10 h	10 plasmid copies per reaction	PBS, serum	Combination of whole genome sequencing and RT-PCR	[13–16,55]

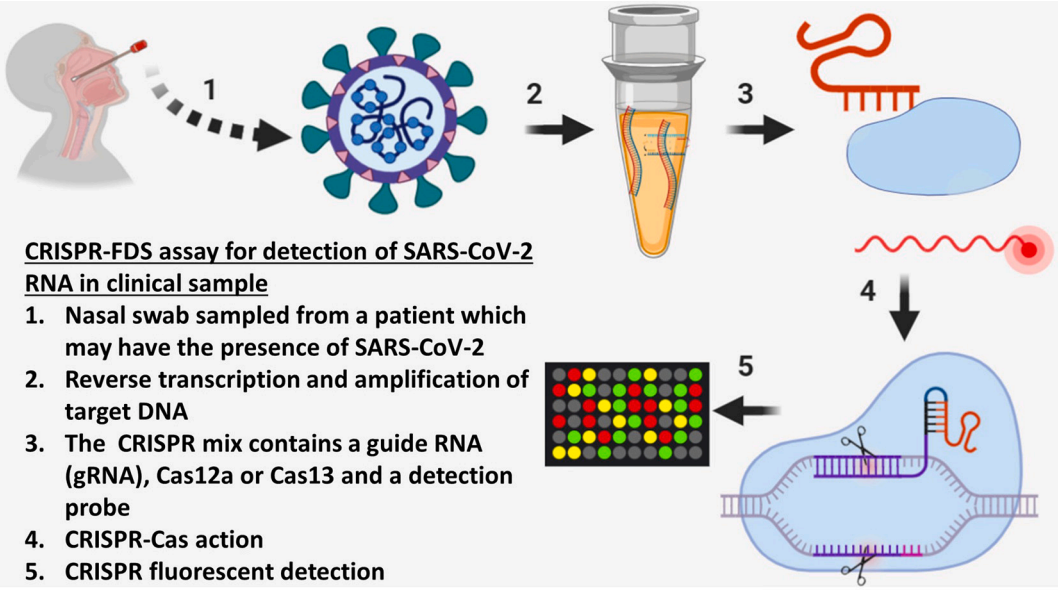

Fig. 4. CRISPR-Cas based fluorescent diagnosis system (FDS) for quick COVID-19 detection. (created using BioRender).

4.6. Bio-imaging of pathological environment

Imaging has become an indispensable tool in early diagnosis, clinical trials and general medical practice. This avenue is routinely deployed in early-stage detection of certain cancers. The routinely utilized techniques include X-ray imaging, magnetic resonance imaging, micro-computed tomography, ultrasonic imaging, positron emission tomography, electron tomography, optical coherence tomography. Even though these excellent bioimaging procedures offer a wide scope, the cost, technological barriers, biocompatibility with markers contribute to the limitations of these techniques [63]. Brain imaging for the prognosis and diagnosis of SARS-CoV-2 induced neurological concerns can be also addressed using Fluid-Attenuated Inversion Recovery images, Diffusion-Weighted Imaging, Diffusion Tensor Imaging [64].

Nanoimaging introduces a deeper understanding of complex biological systems, surpassing the need for destructive sampling as seen in conventional chemical imaging techniques. It also ensures spatial-temporal sampling of the local environment for downstream analyses. Since viral infection is a complicated process, involving various interactions with cellular structures, nanoimaging can give a good insight into SARS-CoV-2 pathogenesis [65].

Fluorescence imaging, commonly referred to as optical imaging, is a rapidly growing avenue as an alternative to the above-mentioned techniques. Typical labels, fluorescent dyes, quantum dots (QDs), plasmonic nanomaterials, near-infrared (NIR) molecules have been utilized successfully. However, the high photo-bleaching rate, background noise, limited luminescence life and toxicity, have repeatedly posed challenges in its use [66]. Lanthanides are popular for their step wise energy levels through which they generate emission energy in the UV–visible to NIR regions. Lanthanide doped nanostructures especially gallogermanates, have been widely investigated since they are able to produce intense red and NIR persistent emission, which is suitable for bioimaging. Ag_2S QDs with emission in the NIR region, demonstrated fluorescence, high biocompatibility. These can be utilized for in vivo anatomical imaging due to their deep tissue penetration, elevated spatial and temporal resolution owing to the unique emission window [67]. Manivannan et al. reviewed the use of various graphene QDs and carbon QDs for biosensing of microbial pathogens [68]. Chiral zirconium QDs with blue fluorescence emission were developed to sense the infectious Influenza A bronchitis virus [69]. In another study, QD fluorescent labels were developed to enhance the sensitivity of SPR–assisted fluoroimmunoassay, to sense norovirus virus–like particles [70]. Ma et al. demonstrated the use of QD-labelled transcription activator-like effectors (TALEs) for live cell imaging of single HIV-1 pro-viral DNA sequences [71].

Viral nanoparticles (VNPs) or virus-like nanoparticles (VLPs) are smart formulations with attractive applications owing to biocompatibility and biodegradability properties. VNPs can be infectious or non-infectious plant or animal viruses, bacteriophages. VLPs are non-infective systems lacking any genomic material. These nanomaterials have rapidly evolved in the last 30 years, encompassing various chemistries and tailoring techniques to allow functionality in imaging, targeting and therapeutics [72]. VLPs can be loaded along with thousands of copies of contrast agents to increases the local concentration and therefore the signal-to-noise ratio. This can be used predominantly when these NPs are tailored to target specific tissues and cells [73]. Gadolinium (Gd), a contrast agent can be quite toxic; but VLPs are generally cleared rapidly from circulation and tissues thus ensuring no systemic toxicity. A tobacco mosaic virus loaded Gd-dodecane tetraacetic acid, tailored to target VCAM-1, could detect and delineate atherosclerotic plaques in $ApoE^{-/-}$ mice in MRI. Going beyond paramagnetic metal complexes such as Mn and Gd, new generation agents are being developed to improve resolution and provide functional information [73].

QDs have also been utilized in labelling internal/ external components of the virus particle to track the process of infection. QDs were encapsulated into the capsid of vesicular stomatitis virus glycoprotein (VSV-G) pseudotyped lentivirus (PTLV) in host cells with no modifications on the viral surface. The modified viral genomic RNAs (gRNAs) conjugated with QDs, contained a packaging signal (Psi) sequence which ensured its encapsulation and packaging into the viral particle. QDs demonstrated that post entry, the signals were observed in the Rab5+ endosome. The signal further moved to the infected host cells' microtubule organizing centre (MTOC) along the microtubules [74].

Fluorescent metal nanoclusters are a novel class of fluorophores with applications in sensors and bioimaging. These fluorophores possess excellent properties of biocompatibility, photostability, and size-dependent fluorescence. In order to synthesize high-quality metal nanoclusters, the key features to be considered include: (a) strong interaction between ligand and metal nanocluster (b) strict reducing conditions like sonication or light irradiation should be employed to improve the quantum yield. (c) long shelf life. The routinely used biologically important scaffolds for the synthesis of nanoclusters include

DNA, peptides and proteins, dendrimers, and polymers [75]. Various studies have demonstrated the application of Ag nanoclusters as novel fluorescence probes for the selective detection of metal ions, including Hg^{2+}, Cu^{2+} in the human body and drinking water [76]. Small molecule sensors based on Ag or Au nanoclusters demonstrated the detection of ATP, or dopamine using guanine rich DNA template or BSA stabilised nanoclusters. A turn-on cocaine detection system using DNA template and Ag nanoclusters was developed by Zhou et al. [77]. A sensor based on a hybrid system comprising of graphene oxide and duplex DNA functionalized Ag nanoclusters was developed for multiplexed analysis of an array of genes of hepatitis B virus, HIV, and *Treponema pallidum* [78]. A study on Ag nanoclusters demonstrated its use in bioimaging through spectral shifts. Ag nanoclusters synthesized a poly acrylic acid-Ag-nanoclusters, readily shuttle nanoclusters to high-affinity ssDNA regions, resulting in loss of nanocluster fluorescence and generation of DNA-Ag-nanocluster emission. These spectral shifts demonstrated antibody location by staining the non-fluorescent DNA-conjugated antibodies. This approach has been utilized in labelling live cells and staining microtubules, monitoring the transfection process with minimum disturbance in the living cells [79].

Metabolite tracking is a necessary requirement for biomedicine. Patabadige et al. [80] demonstrated a nano-enabled and label-free imaging approach to monitor the metabolite flux in the microenvironment. The device comprised of three components: a microfluidic region which is the engineered habitat to mimic the key features of the natural environment, patterned nanoporous membrane which enables the diffusion of metabolites between the neighbouring components and a sampling network which functions as a bowl to collect metabolites as they diffuse through the upper nanoporous membrane and to channel the samples into appropriate analysis tools. The authors utilized this approach to detect metabolites in plant root exudates which the collected samples were analysed by GC–MS. They reported that the lower limits of detection for the sampled analytes were in the range of 1.5 nM to 180 nM. This break-through system can provide a holistic understanding of the metabolites and chemical signals that drive the pathogenesis of SARS-CoV-2 and other pathogens.

5. Nanoparticles against SARS-CoV-2: Therapeutic and vaccine development

It is wisely said ‘viruses are the most beautiful nano-creatures’. Nanoparticles have widely been used as therapeutic agents and in drug-delivery systems against a myriad of diseases, including viral infections. The emergence of SARS-CoV-2 has again lit the face of nanotechnology with the hope to aid a helping hand in this ailing situation of COVID-19. To prevent the SARS-CoV-2 infection, nano-drugs can find the following targets. Some evidences can also be taken from encouraging results of nanomedicine against earlier cases of disease outbreaks.

5.1. Anti-viral nanoparticles

Anti-viral nanoparticles have focused on the three main mechanisms to design therapeutics against SARS-CoV-2.

5.1.1. Inhibition of viral entry inside cells

The SARS-CoV-2 entry inside the human cells is facilitated by binding to the angiotensin-converting enzyme 2 (ACE2) receptor on target cells [18]. Han and Kral [81] in their computational study demonstrated the nano-sized peptide inhibitors extracted from ACE2 could block ACE-2 and SARS-CoV-2 binding. In another study, lipopeptide EK1C4 demonstrated the inhibitory actions against S protein-mediated membrane fusion and inhibited entry of SARS-CoV-2 with an IC_{50} of 4.3 nM [82]. Though there is still a long way to find a therapeutic that could effectively inhibit the SARS-CoV-2 entry, lessons could be taken from the anti-viral agents used against earlier coronavirus infections as they share the same viral entry mechanism inside the cells. Chitosan nanoparticles targeting SARS-CoV nucleocapsid protein [83] and peptides derived from the membrane-proximal (HR2) and membrane-distal (HR1) heptad repeat region of the spike protein [84] have earlier been demonstrated potent inhibition of SARS-CoV entry inside the cells. Virus like nanoparticles displaying ‘S’ proteins and novel gold nanorods-based HR1 peptide inhibitors have earlier been shown to inhibit entry of another coronavirus (MERS-CoV) [85,86]. HTCC polymer (N-(2-hydroxypropyl)-3-trimethylammonium chitosan chloride) with different degree of substitution showed significant inhibitory effect on HCoV-NL63, HCoV113 OC43, and HCoV-HKU1 by inhibiting the viral entry [87]. Either the anti-viral nanoparticles themselves or the hybrid anti-viral nanoparticles have shown effective inhibition of coronaviruses by binding with the different receptors of the membrane proteins.

For entry of viruses inside the cells, they utilize several nanopores and nano-ranged Cell-Penetrating Peptides (CPPs). To optimize the size range of nano-therapeutics, one must consider the route of entry, subcellular trafficking and distribution of the particles to minimize their dilution [88].

5.1.2. Inhibition of viral replication

Currently, there is no approved nano-drug available to inhibit replication of SARS-CoV-2; however, autophagy-modulation mediated inhibition of SARS-CoV-2 replication by precise and targeted nanomedicine has been suggested by Shojaei et al. [89]. Multiwall and single-wall carbon nanotubes (MWCNT, SWCNT), carbon dots (CD) and carbon nanodiamonds are promising nanomaterials to inhibit the virus replication directly. Carbon nanotubes are known to acidify the cytoplasm and alter the cellular temperature owing to its photo-thermal effects [89]. Nanodiamonds and carbon dots can modulate the viral replication pathways and immune responses of primary macrophages [90]. Seven different carbon-dots showed a concentration-dependent inhibition of human coronavirus HCoV-229E by inhibiting the entry receptor and replication of the viral particles [91]. Quantum dots-conjugated RNA oligonucleotide functionalized in a biochip was found to inhibit SARS-CoV ‘N protein’, essential for its replication [92]. Metal nanoparticles show multifarious modes of actions including replication inhibition, DNA and RNA damage and generation of ROS contributing to its broad-spectrum anti-viral activity [93]. Three-chymotrypsin-like protease inhibitors (3-CL) discovered during the last decade can also help to inhibit SARS-CoV-2 replication [94]. Not only nanoparticles themselves act as anti-viral agents but can also serve as a vehicle for drug delivery of replication inhibitors.

5.1.3. Inhibition of cytokine storm

The cytokines storm has emerged as a major cause of mortality among COVID-19 patients causing acute respiratory distress syndrome (ARDS) [88]. Several sub-populations of the immune system, particularly, IL-6 has been associated with the hyperimmune activity. Nanoparticles can help the immune-modulatory drugs to reach their targets specifically, silencing only a subset of the immune response to lower pro-inflammatory cytokine production. Multi-drug nanoparticle comprising squalene, adenosine and α-tocopherol has been designed to treat lethal hyper-inflammation in animal model in a targeted approach [95]. Zadeh et al. [96] postulated nano-engineering of gut microbiota to increase chronic phase proteins and interferon signaling in lung cells to protect against cytokine storm. Further, cytokine storm was successfully treated by [5-(*p*-Fluorophenyl)-2-ureido] thiophene-3-carboxamide (TPCA-1) loaded platelets derived extracellular vesicles [97].

LIF (leukemia inhibitory factor) is produced by mesenchymal stem cells (MSC) which works antagonistically against cytokine storm; however, their potency or production must be enhanced multi-fold to cope with the response generated during COVID-19. ‘LIFNano’ is a nano -technologically synthesized substitute of LIF which is almost 1000 times more potent than its counterpart, which can protect the lungs against the hyper-inflammation [98]. Further, immuno-modulatory actions of octadecylamine-functionalized nanodiamond (ND-ODA) and

dexamethasone (Dex)-adsorbed ND-ODA (ND-ODA–Dex) have already been tested against rheumatoid arthritis for their anti-inflammatory actions in macrophages in vitro [99]. Cytokine storm is also associated with death in certain respiratory ailments and rheumatoid arthritis. The role of nanotechnology in rescuing these conditions can be taken as examples for dealing with cytokine storms.

However, the precise inhibition of cytokines must be considered before designing nanomedicines to avoid other bacterial and viral infections in already suppressed immune system. Immunotoxicity should also be considered while working with nanomedicines as it can also lead to cytokine storm [100].

5.2. Photodynamic therapy (PDT)

PDT and photobiomodulation (PBM) can emerge as novel approaches as therapeutics against COVID-19. Using non-invasive PBM, lasers can directly act on the chest area, inhibiting cytokine storm as well as lasers acting on bone marrow can immune-modulate and increase the synthesis of stem cells [101]. Intravenous lasers of different wavelengths can directly act as anti-viral agents (aPDT) and have been used successfully against HPV, HIV, Dengue and hepatitis virus [102]. Earlier, Geralde et al. [103] demonstrated the inactivation of *Streptococcus pneumoniae*, causative agent of bacterial respiratory tract infection by PDT using extracorporeal illumination with a 780 nm laser. As primary infection in case of COVID-19 also occurs in the lower respiratory tract, different photo-sensitizers such as methylene blue, graphene, fullerenes can be administered via nasal route against SARS-CoV-2 [88]. Though PDT and PBM therapies can reduce the therapeutic cost drastically, there are some limitations such as extreme hydrophilicity and different, unexpected immune response can be elicited by sensitized virus. Further, gaining a mechanistic insight of PDT and choice of carriers need to be optimized before projecting it as potent therapeutics against COVID-19.

5.3. Molecular Imprinted Polymer (MIP) and technology

Molecular imprinting technology is the latest development in nanotechnology where cross-linked polymer matrices are synthesized using a template 'a target compound'. Once the polymerization has taken place, the template is removed, leaving a permanent chemical memory of the cross-linked polymer template [104]. MIP has been used as a theranostic system in targeted drug delivery and self-monitoring for cancer cell therapeutics, which can also be exploited against SARS-CoV-2. This technology can be used to synthesize "monoclonal-type" plastic antibodies to combat COVID-19 [105]. Using MIP, specific monoclonal antibodies can be synthesized to selectively bind the SARS-CoV-2 spike protein, and thus inhibiting the entry of viral particles inside cells. This technology can also be used for mass-screening and rapid detection of COVID-19 cases.

5.4. Targeted and intelligent drug delivery

Mild to severe toxicity of drugs used for the treatment of COVID-19 has been reported [106], which are often off-target. Nanotechnology can help in sustained and targeted delivery of drugs and vaccines to their targets, reducing the toxicity and enhancing the efficacy and half-life of the drugs. Some of the nano-carriers which can be exploited against SARS-CoV-2 are as follow:

5.4.1. Polymer based biocompatible nanoformulations

Both natural and synthetic polymers have been used for sustained and controlled drug delivery. If nanoformulations are attached with the target ligand on their surface, the targeted drug delivery can be achieved avoiding the negative consequences [107]. Several polymers including poly(lactic-*co*-glycolic acid) (PLGA), polyvinyl alcohol(PVA), poly lactic acid (PLA), polyethylene glycol (PEG), hyaluronate, alginic acid and collagen have been approved by FDA for drug delivery [108]. Recently, a company named 'Bioavanta-Bosti', Switzerland has announced nanoformulation named Novochizol™ which is a chitosan nanoparticle aerosol formulation which can be used for targeted delivery of anti-SARS-CoV-2 therapeutics to the lungs of the patients [109]. Similarly, the nanosponges made with polymeric carrier PLGA and outer surface covered with the plasma membranes derived from human lung epithelial type II cells or human macrophages have shown neutralization of SARS-CoV-2 and reduction in their infectivity [110]. Inorganic nanoparticles have also emerged as a potent carrier of therapeutic cargo. Silica/polyP nanoparticles were used to encapsulate inorganic polyphosphate (polyP) which inhibited the binding of S protein to ACE2 (angiotensin-converting enzyme 2) [111]. PLGA nanoparticles have been used to deliver interleukin for immunomodulation of viral diseases [112]. Polymeric nanoparticles can be an excellent source of targeted drug delivery in vaccine and therapeutics development against SARS-CoV-2. Modulation of several parameters including viscosity, shape, size and loading capacity, further provides polymeric nanoparticles with an added advantage to be used as carriers in therapeutic development against SARS-CoV-2.

5.4.2. Lipid nanoparticles and liposomes

Lipid nanoparticles, liposomes and biomimetic lipid polymer hybrids are one of the most extensively used nano-carriers in vaccine and therapeutic development against SARS-CoV-2. Most of the vaccines undergoing clinical trials by major pharma giants have either liposomes or lipid nanoparticles (LNPs) as the carrier of vaccine component to provide stability and effective cargo delivery (Table 2). The Pfizer and BioNTech vaccine, which recently showed 95% efficacy in phase 3 clinical trials, has used LNPs to deliver BNT162 mRNA-based vaccine [21,22]. The 'Moderna' vaccine which has also shown 95% efficacy in phase 3 clinical trials has also used lipid nanoparticles based platform to deliver mRNA-1273 [22] (Fig. 5). LNPs also enhance the cellular and mucosal uptake and reduce the vaccine system's clearance by mucosal cilia [9]. LNPs have been used as a siRNA carrier to suppress cytokine storm by silencing the chemokine receptor CCR2 [113]. Pindiprolu et al. [114] hypothesized the lipid nano-carriers mediated delivery of antiviral salinomycin in COVID-19 patients' lungs. Earlier, Ohno et al. [115] reported the SARS-CoV clearance and generation of cytotoxic T lymphocytes by synthetic peptides coupled to the surface of liposomes. Liposomes with their ability to escape the immune system, non-toxic nature and biocompatibility have assured the safe use for cargo delivery of therapeutics and vaccine components. However, their compatibility with the deliverable components should always be checked before proceeding towards further development.

5.4.3. Carbon based nanomaterials

Nanodiamonds, carbon dots, graphene, graphene oxide, single wall and multiwall carbon nanotubes are the major carbon based materials which can be used for detection, drug delivery and mitigation of COVID-19. Nanodiamonds can carry exceptionally high hydrophilic and hydrophobic cargo owing to their high surface area to volume ratio [7]. Besides this, they also possess the intrinsic ability to activate the immune system [116]. Graphene and graphene based nanomaterials conjugated with polymers have shown excellent properties for viral growth and cytokine storm inhibition along with the delivery of therapeutics [117]. Functionalized carbon nanotubes are already known for targeted and controlled drug delivery [118]. Earlier, Loczechin et al. [91] had demonstrated anti-viral activity of functionalized carbon dots against human coronavirus. The diverse carbon-based nanomaterials can be a great choice as a carrier for vaccine development or as a hybrid therapeutic solution based upon their properties to deliver multiple range of cargos and biocompatibility. Their ability to modulate immune responses along with targeted drug delivery can be exploited against SARS-CoV-2.

Table 2
Role of nanotechnology in vaccine development against coronaviruses.

Vaccine	Nano component/role of nanotechnology	Mechanism	Limitation/Status	Strain of coronavirus	Reference
Gold nanoparticle-adjuvanted S protein	Gold nanoparticles	Induced antigen-specific IgG response	Failed to reduce eosinophilic infiltration	SARS-CoV	[201]
novel lipid nanoparticle (LNP)-encapsulated mRNA-based vaccine	Lipid nanoparticles	recombined mRNA of the S protein in vitro	95% efficiency in phase 3 clinical trials by Moderna In use my multiple countries Some side effects reported after vaccination	SARS-CoV-2	[21,202]
LNP-encapsulated mRNA encoding RBD	Lipid nanoparticles	RBD mRNA reacted strongly with a SARS-CoV-2 RBD-specific antibody	Under clinical trials by RNAcure Biopharma	SARS-CoV-2	[203]
Liposome encapsulated mRNA	Liposome	recombined mRNA of the S protein in vitro	Preclinical trials	SARS-CoV-2	[204]
LNP-nCoV-saRNA	LNP	robust neutralization of a pseudo-virus, proportional to quantity of specific IgG	Phase 1clinical trial by Imperial College, London	SARS-CoV-2	[205]
Three LNP-mRNA	LNP	Targets spike protein and RBD	Approved by FDA for use against COVID-19 and the vaccine has been in use in many countries by Pfizer/BionTech Low neutralizing antibody generation against delta variant of COVID-19	SARS-CoV-2	[22]
Inactivated vaccine	Alum adjuvants	–	Approved for emergency use by WHO, developed by SinoVac	SARS-CoV-2	[182]
Subunit vaccine	Matrix M adjuvant	–	Under phase III clinical trials by Novavax	SARS-CoV-2	[182]
pulmonary surfactant-biomimetic nanoparticles	biomimetic liposomes	potentiate heterosubtypic influenza immunity	–	SARS-CoV-2/ influenza virus	[182]
aluminum salt (alum) adjuvanted inactivated vaccine	Alum nanoparticles	induced SARS-CoV-2–specific neutralizing antibodies in mice, rats, and nonhuman primates	Under phase II clinical trials	SARS-CoV-2	[206]
Single domain antibodies	Nanobodies	induced SARS-CoV-2–specific neutralizing antibodies	In vivo studies yet to be done	SARS-CoV-2	[207]
Self-replicating RNA-based therapeutic vaccine (LUNAR-COV19 STARR™)	RNA nanoparticles delivery systems	Enhanced adaptive cellular (CD8+ cells) and balanced (Th1/ Th2) immune response	In ½ clinical trials	SARS-CoV-2	[208]
Gold nanoparticles	GNPs	activating CD8+ (T-killer) cell-mediated immune response	In vivo studies yet to be done	SARS-CoV-2	[121]
virus-like nanoparticles (VLNP)	Protein nanoparticle scaffold	Promotes B cell immune response	Yet to undergo clinical trials	SARS-CoV-2	[209]
SARS subunit vaccine	Peptide nanoparticles	Neutralizing antibody and strong humoral response	Pre-clinical trials	SARS-CoV	[210]
Purified coronavirus spike protein nanoparticles	Spike nanoparticles	Induce coronavirus neutralizing antibodies in mice	Successful clinical trials by Novavax completed	SARS-CoV, MERS-CoV	[211]
virus-like particle (VLP)	one component self-assembling protein nanoparticle (1c-SApNP)	Generates neutralizing antibodies	Clinical trials by Ufovax Provisional patent filed	SARS-CoV-2	[212]
Recombinant vaccine	Attenuated adenovirus	Strong humoral response	Clinical trials by Janssen Pharmaceuticals, Inc. (Belgium) Severe side effects with blood clotting and low platelets count	SARS-CoV-2	[107]
LNPs loading mRNA	LNP	Generates neutralizing antibodies	Phase 3 clinical trials by Translate Bio/Sanofi Pasteur (United States)	SARS-CoV-2	[107]
ChAdOx1 nCoV-19 vaccine	chimpanzee adenovirus	Generates neutralizing antibodies and strong humoral response	Developed by University of Oxford/ AstraZeneca Vaccine in use by multiple countries Rarely serious side effects including blood clotting, thrombosis and capillary leak syndrome has been observed in some vaccinated persons	SARS-CoV-2	[23,213]
Modified Vaccinia Ankara Virus Like Particles (GV-MVA-VLP™)	Virus like nanoparticles	elicit protective T cell as well as antibody responses	In clinical trials by Geovax	SARS-CoV-2	[214]
AdCOVID™	Adenovirus	decreased cellular inflammation and lower concentrations of IL-6	In clinical trials by Altimmune Did not stimulate an adequate immune response in healthy volunteers as nasal spray	SARS-CoV-2	[215]
recombinant S-protein subunit	Silica nanoparticles	Elicits appropriate immune response	In clinical trial phase III by Nanogen biopharmaceuticals	SARS-CoV-2	[216]
Plant-based vaccine	VLP	Generates neutralizing antibodies	In Phase III clinical trials by Medicago Pharmaceuticals	SARS-CoV-2	[217]
zycov-d	Plasmid DNA	Generates neutralizing antibodies	In Phase III clinical trials by Zydus candila Safe for pediatric use	SARS-CoV-2	[218]

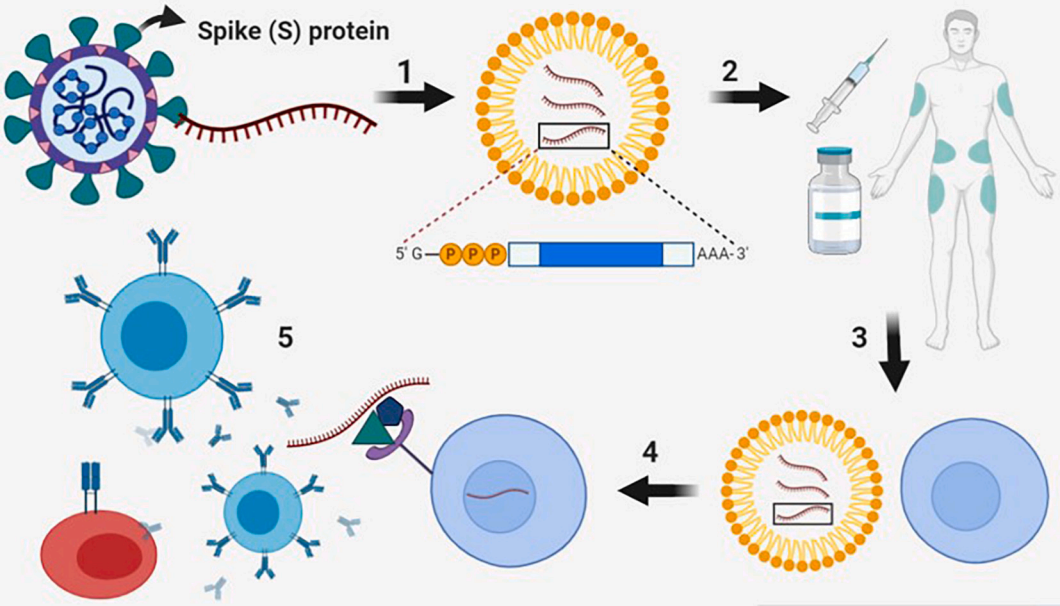

Fig. 5. A schematic of development and action of SARS-CoV-2 mRNA vaccine. (1) Based on the genetic sequence of the SARS-CoV-2 Spike protein, mRNA is synthesized (2) The synthetic mRNA is encapsulated in lipid nanoparticle for delivery (3) The vaccine is administered (4) Between human cells and the lipid nanoparticle, the Spike protein instructions are shuttled in the form of mRNA (5) inside the human cells, the cellular translation machinery used the synthetic mRNA to produce corresponding viral proteins (Spike). These are then displayed on the cell surface. This presentation stimulates the human immune system (B and T cells) to mount a protective immune response against SARS-CoV-2. (created using BioRender).

5.4.4. Virus-like nanoparticles

As described earlier, virus-like nanoparticles have also demonstrated their multiple uses in detection and vaccine development against SARS-CoV-2 (Table 2). Naskalska et al. [119] developed HCoV-NL63 VLPs using a baculoviral system which could effectively deliver cargo and electively transduce cells expressing the ACE2 protein. Recently, SARS-CoV-2 VLPs were developed using a mammalian expression system, which possessed molecular and morphological properties of native virion particle [120]. VLPs have also been used for delivery of CRISPR/Cas 9 proteins, which can emerge as a major therapeutic solution to COVID-19 [7]. Another landmark against COVID-19 was recently achieved when the first mass vaccination program was started in the UK with the vaccine developed by Oxford–AstraZeneca. This vaccine is a chimpanzee adenovirus-based vaccine (ChAdOx1 nCoV-19) expressing 'S' protein of SARS-CoV-2 [23].

5.4.5. Nanobubbles

Nanobubbles are the gas filled cavity in the aqueous medium which can be exploited for targeted drug delivery using ultrasound waves [121,122]. A company named 'Nanobble' [123] has postulated the use of ozone filled nanobubbles against SARS-CoV-2. Ozone being a strong oxidizing agent, has the anti-viral activity and has been used in water disinfection [124]. However, ozone being a strong oxidizing agent, sufficient precautionary measures and data analysis should be performed to avoid more harm than good of this therapy.

5.4.6. Nanocage

Nanocages are the hollow nanostructures which can be engineered on their surfaces, the interior and the exterior to enhance biocompatibility and targeted cargo delivery [125]. They have high loading capacity due to their spacious and porous interior and the possibility to engineer their exterior for targeted delivery [126]. SET-domain containing 6 (SETD6) is known to inhibit viral infection mediated inflammation, but its use is restricted owing to the short half-life and poor intracellular delivery. In 2020, Kim et al. [127] developed ferritin based nanocages for delivery of methyltransferase SETD6 for COVID-19 therapy. However, the toxicity assessment of nanocages must be considered before their use.

6. Nanoparticles in vaccine/drug development

6.1. Nanoparticles in vaccine development

Many vaccine candidates are available today in market against SARS-CoV-2 including the vaccines developed by Pfizer/BioNtech (USA, Germany), Moderna (USA), Astrazeneca/University of Oxford (UK), Sinovac (China), Bharat Biotech (India) and Sputnik V (Russia).

Most of the successful vaccines developed have used either nanocarrier based platform for targeted delivery of synthetic mRNA or have used VLP platforms [21–25]. Vaccination can be the best way to produce 'herd immunity' and stop the spread of this pandemic. The vaccines can be of the following types based on their active components [10].

1. Inactivated vaccine
2. Attenuated vaccine
3. Peptide and protein vaccine
4. Outer membrane based vaccine
5. Nucleic acid based vaccine
6. Non-replicating viral vaccine
7. Replicating viral vaccine
8. Virus like particle vaccine

Nanoparticles can be a key component for the synthesis of vaccines, or they can be developed as a carrier of the active ingredient in vaccine. Lipid nanoparticles (LNP), polymeric particles, liposomes, emulsions, VLPs and Carbon based nanodiamonds are biocompatible and non-toxic nano-carriers can enhance solubility and stability of vaccine (described in Section 5.4). Particles below 1000 nm have shown increased uptake by macrophages and dendritic cells [128], making the nanocarriers a perfect choice for effective antigen recognition and presentation to elicit an antigen-specific humoral response and cell-mediated immunity. Surface modification of nanocarriers with toll-like receptors, mannose receptors and immune-cell target receptors facilitate the targeted delivery of vaccine cargo, thus increasing the vaccine efficiency [129]. The

vaccines developed by 'Pfizer', 'Biontech' and 'Moderna' have used the mRNA nanoparticles with LPN nanocarriers (discussed in Section 5.4.2). The solid LNP nanocarriers protects the mRNA from the immune system, delivers it safely inside the cell membrane, where the bare mRNA can encode the protein antigen, thus providing immunity against SARS-CoV-2 (Fig. 5) [129]. The mRNA/DNA nanotechnology has emerged as a novel and effective approach against COVID-19. They generally consists of viral mRNA/DNA strands encapsulated in lipid based nanocarriers. The two mRNA vaccines BNT162b2 – BioNTech/Pfizer and mRNA-1273 – Moderna are widely used for the vaccination across the globe, with CVnCoV reaching to phase 3 clinical trials [130]. Huang et al. [131] investigated the mRNA vaccines formulated in liposomes administrated in multiple routes against SARS-CoV-2 and observed that RBD-encoding mRNA (RBD-mRNA) formulated in liposomes (LPX/RBD-mRNA) developed anti-RBD antibodies in mice system. The drawback of mRNA vaccines is their dependency on cold chain storage, which does not only add to the cost, but also deprives the poor nations from availing this technology [132]. The nanotechnology along with with CRISPER/Cas technology can help further in improving therapeutic delivery of vaccines in the physiological conditions [133].

The second strategy utilized by 'Oxford-AstraZeneca' and 'Sputnik V' to develop a vaccine against SARS-CoV-2 uses the non-replicating adenovirus based platforms that encode the spike protein of the SARS-CoV-2 and elicit immune response [7]. Table 2 summarizes the use of nanotechnology in the key developments of SARS-CoV-2 vaccine, side effects, and its earlier contribution against coronaviruses. Adjuvants also play an essential role in the successful development and administration of vaccines. The tailored designed nanoparticles provide multifunctional approaches for an adjuvant, increasing its bioavailability and controlled release of antigen and targets specific immune activities [7].

Vaccine developed rapidly have certainly raised the hopes and believes that COVID-19 can be a story of the past, but the rapid emergence of new variants of SARS-CoV-2 can dig a hole in this believe. The existing vaccines have shown good effectiveness against the newly emerged highly infectious B.1.617.2 (Delta) variant [134], though decline in production of neutralizing antibodies after three months of vaccination can be a concern [135]. Further, COVID-19 vaccine with a pediatric perspective is urgently required in which nanotechnology can play a pivotal role in developing targeted approaches.

6.2. Nanoparticles in drug development

Nanomedicines holds the future for the drug delivery system, and this era of COVID-19 is the right time to prove it right. Last four years has seen FDA approval of three nano-drugs Vyxeos, Onpattro and Hensify for the treatment of acute myeloid leukemia, transthyretin amyloidosis and cancer respectively, with more than 450 clinical trials investigating the therapeutic potential of nanomedicines for different illness [136]. Many repurposed drugs have been used in the battle against SARS-CoV-2, and they have constantly faced the problems of solubility and sustained release. The antiviral drugs such as remdesivir, favipiravir, arbidol, darunavir, chloroquine, hydroxychloroquine and baricitinib which can be repurposed against COVID-19, face the problem of low solubility and have been tried for increasing the solubility by different modes of nano-encapsulation [137]. The PEGylated dendrimers of remdesivir, the approved drug against COVID-19, showed 100 times more solubility than the bulk remdesivir [138] (SPL). The slow release will allow the subcutaneous delivery of the drug instead of the traditional intravenous injections, easing the outpatient treatment and reducing the burden on healthcare systems. Similarly, selenium nanoparticles functionalized arbidol nanoparticle have shown enhanced apoptotic death in H1N1 influenza virus by increasing the reactive oxygen species (ROS) production [139]. The nano-encapsulation does not only provide the enhanced solubility, but also offers the sustainable release of the active principle and enhanced half-life of the drug, able to cross many biological barriers. The efficacy of the immune-modulator and metabolism based drugs against SARS-CoV-2 can be improved using nano-formulations. A rapid formation of regulatory bodies which can control the nano-encapsulation parameters and bridge the cross-sectoral and cross-technological gap for healthcare is highly desirable in this pandemic condition. Given the limited options available for COVID-19 treatment, nano-encapsulation can decrease the number of dosing with increased bioavailability.

Not only as drug carriers, but the nanoparticles themselves can act as potent anti SARS-CoV-2 agents. Alhakamy et al. [140] nano-conjugated the two FDA approved drugs, viz. sitagliptin and glatiramer acetate., and observed a significant decrease in IC_{50} value against SARS-CoV-2 than their bulk counterpart. In silico studies revealed that the nano-conjugated drug had the high binding affinity towards the COVID 3CL protease, thus inhibiting the viral replication. Two dimensional Ti_3C_2Tx and $Mo_2Ti_2C_3Tx$ MXene were able to decrease the SARS-CoV-2 viral load in vero cells in four different genotypes, with high biocompatibility and anti-inflammatory actions. They were able to modulate the metabolic pathways, membrane trafficking, GPCR signaling along with the inhibition of SARS-CoV-2 replication [141]. In a novel study by Li et al. [142], ACE2 nanodecoys derived from human lung spheroid cells (LSCs) have been developed which could bind and neutralize the SARS-CoV-2. The inhalation therapy of nanodecoys in cynomolgus macaques promoted the viral clearance from their lungs. Inhalation therapy also provides an added advantage of increased drug availability to the lungs, reducing the systemic release of the drug [137].

Nanoparticles mediated delivery can overcome the gastro-intestinal tract barrier during oral delivery of drugs for better accessibility and absorption by small intestine. It can also overcome the epithelium forms, blood-retina and blood-aqueous barriers for better ocular delivery of the drugs [143]. Moreover, there are other internal barriers such as blood-brain barrier (BBB), blood-testes barrier (BTB) which can be overcome with the help of nanotechnology for developing better drug delivery routes against COVID-19. (Fig. 6).

6.3. Post-COVID-19 therapeutics and nanotechnology

The terror of COVID-19 does not end with the successful treatment of the disease itself, rather it brings a whole set of post-COVID complications. Post-acute COVID-19 syndrome characterized by persistent and long term symptoms of SARS-CoV-2 infection can result in organ specific sequelae [144]. The post COVID major organ specific sequelae and the role of nano-therapeutics has been summarized in Table 3. The drug-delivery vehicles discussed in Section 5.4 can be utilized for better release and availability of the bulk drugs used for post-COVID-19 sequelae. Moreover, the long term side effects after SARS-CoV-2 and the arising variants need to be assessed for development of better nano-therapeutics.

7. Protection and mitigation against SARS-CoV-2

Protection against SARS-CoV-2 and the mitigation of this disease are as important as the other two pillars 'detection and therapeutics development' to successfully win this difficult battle. Nanotechnology with the cost-effective, rapid and robust technologies can aid a helping hand in protection and mitigation against this pandemic.

7.1. Surface disinfection

SARS-CoV-2 can survive on both rough and smooth surfaces, providing an excellent mean for indirect transmission of the virus. Following tools of nanotechnology can provide an edge over the traditional disinfectant methods (Fig. 6).

7.1.1. Viral inactivation by photo-catalysis

Titanium dioxide (TiO_2) nanoparticles are the excellent examples of surface disinfection by photo-catalysis and have been used against

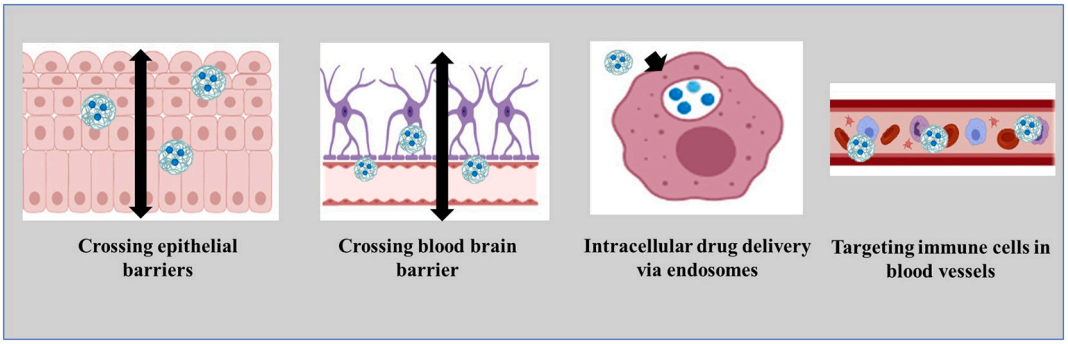

Fig. 6. The biological barriers that antiviral NPs can overcome to deliver the therapeutic effect.

disinfection of many viral agents. TiO_2 NPs coated on windows, walls and used in water purification shows significant anti-viral activity when illuminated with UV light [145], which can be rediscovered against SARS-CoV-2. TiO_2 and SiO_2 nanocoating are used as self-disinfecting materials in hospitals as photo-activated particles can kill microbes by surface-leaching [146]. However, their toxicity and standardization of the techniques should be done on a case by case basis.

Further, Miyako et al. [147] developed NIR laser-driven carbon anti-viral nanohorns., which was able to show photo-catalysis against pathogens. Nanoparticles showing photo-catalytic properties can be used as paint or spray materials to disinfect the SARS-CoV-2 prone exposed areas.

7.1.2. Plasmonic photothermal treatment

Nanorods of certain metals such as gold (Au) and silver (Ag) can heat up and clean the surface when activated at a certain wavelength [86], a phenomenon known as a plasmonic photothermal treatment. This newly developed technology can be used to coat the most critical surfaces to protect against SARS-CoV-2.

7.1.3. Anti-viral metal and carbon nanoparticles coating

Metals have been used for their anti-microbial activity since ages [148]. Several metal nanoparticles including Ag, Au, ZnO, Cu, CuO can be used for spray coating of the surfaces to kill SARS-CoV-2. During the spread of COVID-19 in Milan, Italy, a formulation of TiO_2 and Ag nanoparticles were used for disinfecting the surfaces by the 'Nanotech Surface Company' [149]. Earlier research of Han et al. [150] demonstrated the quick inactivation of SARS coronavirus on the surface by Ag/Al_2O_3 and Cu/Al_2O_3 metal catalysts. Recently, a company named 'Nanoshel' [151] has come up with a proposal to sprinkle silver based nanoparticles by overhead sprinklers on persons as they pass through specific designed tunnels. Similarly, 'BGN technologies' [152] and the 'Ebrahimzadeh laboratory' [153], Iran are also working on the metal nanoparticles-based surface coatings and hand sanitizers respectively. Carbon-based nanomaterials (described in Section 4.2 and 6.4.3) are known for their theranostic potential to detect, deliver and kill the viruses.

Both metal and carbon-based nanoparticles have shown excellent anti-viral activities when applied as surface coatings and disinfecting materials. Several companies have also come up with the formulations based on these nanoparticles; however, their choice of selection should be thoroughly checked for toxicity and cost-effectiveness.

7.2. Anti-viral polymer coating

Nanopolymers, either having intrinsic anti-viral properties or are used to deliver anti-viral agents, can be coated on different surfaces, including wall, glass, fibers, cloths, and plastics to disinfect them. Chitosan and polyacrylamide derivatized nanoparticles with their anti-viral activities can be used in the coating of surfaces to protect against SARS-CoV-2 [86]. Dwivedi et al. [154] in their article suggested Ag/CS nanocomposite coating of surfaces encapsulating *Curcuma longa* to protect against SARS-CoV-2. Jones et al. [155] modified cyclodextrins as a broad spectrum anti-viral against herpes simplex virus (HSV), respiratory syncytial virus (RSV), dengue virus, and Zika viruses which can be used as a surface coating against SARS-CoV-2. Different artificial small molecules showing anti-viral properties against SARS-CoV-2 can also be designed as anti-viral coating with encapsulation with suitable polymers [156]; however, nanopolymers safety should completely be assured before their commercial use.

7.3. Plasma mediated viral disinfection

Plasma, considered as the fourth state of matter is an ionized gas where the atoms and/or molecules are uncovered of their outer-shell electrons. Radiofrequency plasma treatment using Ar/O_2 gas mixture against microbes and their toxins in a sealed bag has been reported by Belgacem et al. [157]. Plasma activated water has emerged as an alternative disinfectant of SARS-CoV-2 by inactivating S protein [158]. Though this technology is nascent, regulated development in this field can provide a new paradigm in the sanitization of exposed surfaces.

7.4. Nano-materials for PPE system, face-masks and gloves

Since the outbreak of COVID-19, facemasks and gloves have become a household name to mitigate the spread of SARS-CoV-2. Similarly, PPE kits have become ubiquitous in hospital surroundings. COVID warriors have to face many problems, including severe skin rashes as a side effect of prolonged use of PPE, facemasks and gloves. Nanotechnology can provide the more comfortable, breathable, efficient, hydrophobic and cost-efficient solution to these problems (Fig. 7). Copper and brass containing ~70% copper has been reported to inactivate the CoV-229E through the generation of ROS. In the current pandemic, silver or zinc oxide-based biocides are already approved. Hence, using formulations and nanostructures containing silver, zinc and copper is a worthwhile option to mitigate the viral spread [159]. Chen et al. [160] reported the antiviral activity of graphene oxide sheets with silver nanoparticles and graphene sheets alone against feline coronaviruses, enveloped and non-enveloped viruses. These sheets have also been investigated in making of PPE. The use of polyurethane/CuO nanocomposites in antimicrobial filter for air purification has also been investigated [159].

7.4.1. Ocular protection using therapeutic contact lenses

Ocular protection is a critical necessity to avoid risk of ocular transmission of SARS-CoV-2 in doctors and other health care workers. Natural products have demonstrated several bioactive properties such as anticancer, antiviral, antidiabetic etc. [161,162]. Griffithsin, 121 amino acid lectin isolated from a red alga *Griffithsia* spp. has been found to efficiently inhibit the entry of Porcine reproductive and respiratory syndrome virus (PRRSV), HIV, SARS-CoV, MERS-CoV and HCZ. This

Table 3
Role of nano-therapeutics in combating post COVID-19 complications.

S. no	Post COVID-19 organ specific sequelae/ complications	Complications	Role of nano-therapeutics	Characteristic features	Ref
1.	Pulmonary sequelae	Acute respiratory distress syndrome (ARDS) caused by cytokine storm of COVID-19 resulting the pulmonary fibrosis	a. Nano-formulating dexamethasone b. Poly (ethylenimine) (PEI—C) polyplex encapsulating siPAI-1 c. Poly (ε-caprolactone) (PCL) encapsulated Pirfenidone d. Liposomal encapsulation of trans-crocetin e. Polyetherimide nanoparticles of β2-Adrenergic receptor DNA	a. Potentiating its anti-oedema activity and anti-fibrotic effects by inhalation therapy and intravenous injection b. Inhibits PAI-1 and TGF-β and decreased collagen deposition in lungs c. Inhibition of TGF- β1 mRNA and EMT transition in A549 cells d. Enhanced oxygenation in COVID-19 related ARDS patients on ventilator e. Increases alveolar fluid clearance, thus reduceing lung edema	[144,219–223]
2.	Mucormycosis (Black fungus disease)	Post COVID complication of the severe fungal infection of *Mucormycetes* fungus due to suppressed immune system caused by	a. Nano-fiber based amphotericin B b. nanoemulsion NB-201	a. Controlled oral delivery of anti-fungal agent b. Utilizes the surfactant benzalkonium chloride effective against Mucorales	[224,225]
3.	Neurological sequale	psychiatric symptoms persisting or presenting months after initial infection of COVID-19 including anxiety, depression, sleep disorder, brain inflammation, stroke, nerve damage	a. Nanoemulsions of rolipram (anti-depressant) b. Carbon dots c. avidin-functionalized nanomicelles (avidin-NMs) d. Dalargin along with poly (butyl cyanoacrylate) nanoparticles	a. Internalized by neutrophils and reduced the distribution in the brain b. Efficiently crosses BBB for drug-delivery c. Shifts the identification of brain-target proteins from focusing on differential expression instead of focussing on differential endocytic rates. d. Efficient crossing of BBB	[226–230]
4.	Hematologic sequale	High thrombotic risk post COVID-19 associated with increased inflammatory response of C-reactive protein (CRP), procalcitonin, interleukin (IL-6) and ferritin	a. Nano-scale assembly of novel short peptides containing L-Arg and L-Asp or L-Glu b. Multiarm-nanovesicles with lipid nanovesicle coated with polyethylene glycol (PEG) terminally conjugated with a cyclic RGD (cRGD) peptide c. recombinant tissue plasminogen activator bound to polyacrylic acid-coated nanoparticles d. Heaprin-conjugated carbon naocapsules	a. Enhanced anti-thrombotic activity by 100 fold b. Delivery of tissue plasminogen activator and targeted thrombolytic therapy c. Delivery to the targeted site by magnetic guidance of the nanoparticles d. Superior antithrombotic activity in vitro and in vivo but they also had the ability to extend the thrombus formation time far longer than an injection of heparin or CNCs alone	[144,231–234]
5.	Cardiovascular sequale	Increased cardio-metabolic demand, arrhythmias, postural orthostatic tachycardia syndrome and inappropriate sinus tachycardia post COVID-19 infection	a. vascular endothelial growth factor (VEGF)-PLGA nanoparticles b. Graphene oxide nanoparticles loaded with IL-4 plasmid DNA	a. Increases in vascular density in the peri-infarct region, reduced infarct sizes, and improvements in LV contractile function 4 weeks post-treatment. b. Increased polarization of M1 and M2 macrophages with increased cardiac repair	[235,236]
6.	Renal sequale	Tubular pathogenesis and acute kidney injury (AKI) by infiltration of CD68+ macrophages into the tubulointerstitium after SARS-CoV-2 infection	a. Polycationic cyclodextrin nanoparticles containing siRNA b. TRX20-prednisolone-loaded liposomes c. Renal clearable nanocarriers	a. Can be used for targeted deliver in acute kidney disease b. Reduced IgA and C3 deposition in glomerular disease c. Can escape the macrophage uptake and renal clearance	[237–240]
7.	Endocrine sequale	Destruction of pancreatic β cells resulting in onset of diabetes after COVID-19	a. Oral nano-drug delivery system with phytochemicals b. Nanonetwork of insulin with PLGA (poly(lactic-co-glycolic acid)) nanoparticles c. Insulin-loaded polymeric PLGA nanoparticles functionalized with Fc fragments on the surface d. Magnetic nanoparticles coated with peptide-major histocompatibility complexes (pMHC–NPs)	a. Enhanced bioavailability of anti-diabetic phytocompounds b. Releases insulin at basal levels and releases a burst of insulin upon exposure to ultrasound c. Increase in absorption efficiency of insulin by improved transport across the intestinal epithelium d. Incraese in population of naive low-avidity autoreactive CD8+ T cells into memory-like autoregulatory cells to prevent diabetes 1 in mice	[241–244]
8.	Dermatological sequale	Development of skin rashes and hair loss post COVID-19	a. Topical Nano-hyaluronic Acid b. Topical Minoxidil-Loaded nanoparticles	a. Enhancement in elasticity and firmness of the skin b. can increase the bioavailability of minoxidil for treatment of hair loss	[245,246]
9.	Multisystem inflammatory		a. Nanoencapsulation of glucocortecoids in PEGylated	a. Though nano-delivery systems for MIS-C are not in use, it can increase	[144,247]

(*continued on next page*)

Table 3 (*continued*)

S. no	Post COVID-19 organ specific sequelae/ complications	Complications	Role of nano-therapeutics	Characteristic features	Ref
	syndrome in children (MIS-C)	Immune complex injury due to autoantibody formation, activation of complement system and cytokine storm	liposomes, polymeric micelles, polymer-drug conjugates, inorganic scaffolds, and hybrid nanoparticles.	the bioavailability and targeted release of immune-modulators.	
10.	Gastrointestinal and hepatobiliary sequelae	COVID-19 alter the gut microbiome of the infected patients	Nanotechnology based sensing, mapping and alteration of microbiome	Can help in delevlopment of point-of-care (PoC) devices and therapeutics	[248]

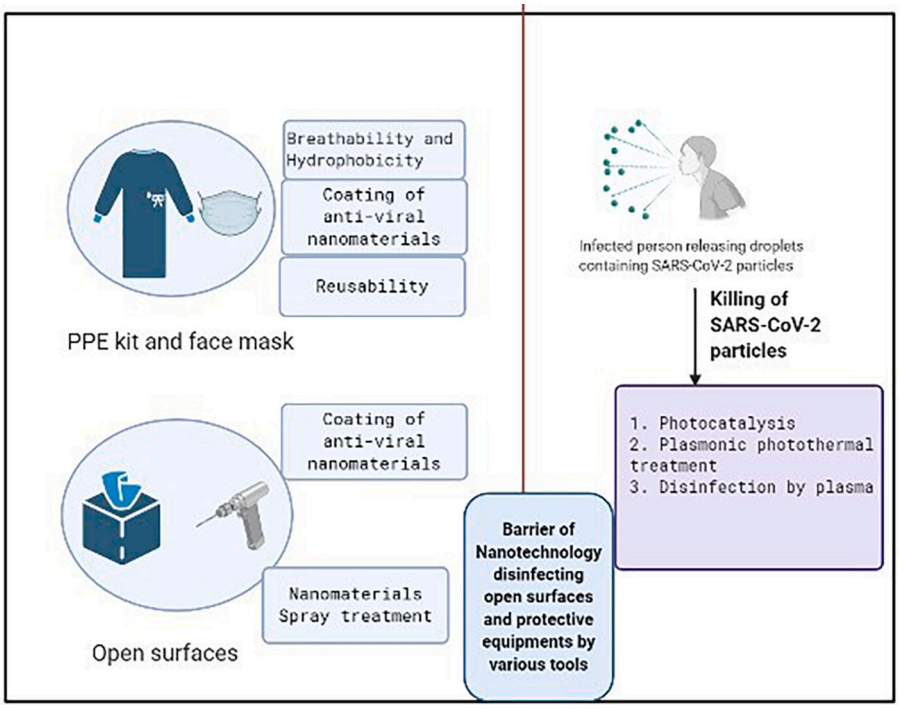

Fig. 7. Role of nanotechnology to mitigate SARS-CoV-2.

natural product interacts with the multiple glycoproteins on the viral envelope and thus blocks the entry. The compound is very non-toxic, stable, and resistant to proteases and detergents [163]. Generally, eye drops have a low bioavailability of 1–3 min in tears due to blinking and drainage by nasolacrimal duct [164]. Ocular protection in the current pandemic can be delivered by griffithsin containing sustained-releasing therapeutic contact lenses. Griffithsin being a small protein, can be nano-encapsulated, thus enabling sustained delivery. Such a technique has been described earlier and has demonstrated transparency, controlled release of drugs, tolerability, and permeability[165].

7.4.2. *Anti-viral material coating*

As discussed earlier, metals, carbon based nanoparticles and polymer based encapsulated anti-viral materials can be used in coating of gloves, face-masks and PPE kits. The fibers coated with photo-activated TiO_2, two-dimensional carbides and activated carbon particles have shown enhanced adsorption and degradation of viral particles [88,166]. Aydemir et al. [167] proposed coating of masks and nasal filters with ACE2 enzyme loaded nanoparticles for protection and mitigation against COVID-19. Ahmeda et al. [168] designed an anti-viral facemask composed of PLA and cellulose acetate polymer containing copper oxide and graphene oxide nanoparticle by electrospinning technique to control COVID-19 in Egypt. Another aspect of mitigation is developing robust fabric structures which will not retain moisture and hence avoid contaminating microorganisms. A novel PPE textile coated with chitosan and silver nanoparticles demonstrated high antimicrobial activity [169]. Polyamide 6.6 fibers (PA66) embedded with Zn ions when woven into PPE fabrics were reported to reduce the titer of Influenza A H1N1 virus, SARS-CoV-2 and offer protection against the viral spread. The advantage of this embedded fabric was that even after ~50 washes the zinc content and virus inactivation property remained stable[170].

7.4.3. *Hydrophobicity, porosity and breathability*

Hydrophobicity is an important parameter to develop PPE kits as it inhibits the anchorage of tiny droplets responsible for viral spread. Similarly, porosity and breathability are important aspects for the comfort of the mask and kit bearer. For creating hydrophobicity, 'nanowhisker' technology is used where surface tension of tiny fibers is increased to prevent anchorage of droplets [171]. Carbon-based and cellulose fibers nanomaterials can be used as a porous and breathable substitute to conventional PPE fibers [172].

7.4.4. *Reusable kits and masks with nanotechnology*

Reusability of kits and masks does not only save the cost but is also an environment-friendly approach to mitigate COVID-19. Recently, 'LIGC application limited' launched the anti-viral and reusable microporous graphene masks [173]. A hydrophobic and reusable nanoporous template was developed by El-Atab et al. [174] to reuse N95 masks with a replaceable filter membrane.

7.5. Disinfecting sewage and other sources of SARS-CoV-2

Sewage and wastewater can potentially act as a reservoir and an indirect transmitter of SARS-CoV-2. Mallapaty [175] postulated that mRNA content of SARS-CoV-2 in sewage and wastewater could predict the degree of severity of COVID-19 in that particular area. Nanotechnology can play a theranostic role in detecting SARS-CoV-2 through SERS, magnetic nanosensors, and the mitigation of the disease [176]. Bhalla et al. [177] suggested use of wastewater biosensors for early warning of disease outbreak. Photocatalytic activities of TiO_2 nanoparticles can be used to kill the virus in sewage water. Researchers from Rice University, USA have developed "trap and zap" wastewater-treatment technology to deactivate SARS-CoV-2 in wastewater [178]. Here, they employed graphitic carbon nitride to adsorb the viral particle which can be disinfected further by photocatalysis. Similarly, the research team from Harvard University, USA, is working on engineered water nanostructure with a size of 25 nm and containing reactive oxygen species to inhibit pathogens [179]. Nanotechnology can also help in combating the plastic pollution generated, which has become a massive problem after the onset of COVID-19 [180,181]. The discarded PPE kits, gloves, facemasks and their components can be appropriately decomposed with nano-tools, including sensors and photocatalysis.

8. Industries fighting SARS-CoV-2

Nanotechnology industries are on a continuous run to develop appropriate weapons against SARS-CoV-2 [55,182–186]. Fig. 8 summarizes the industries working towards nano-based products currently developed and deployed in the containment, diagnosis and treatment of COVID-19 pandemic, which promise:

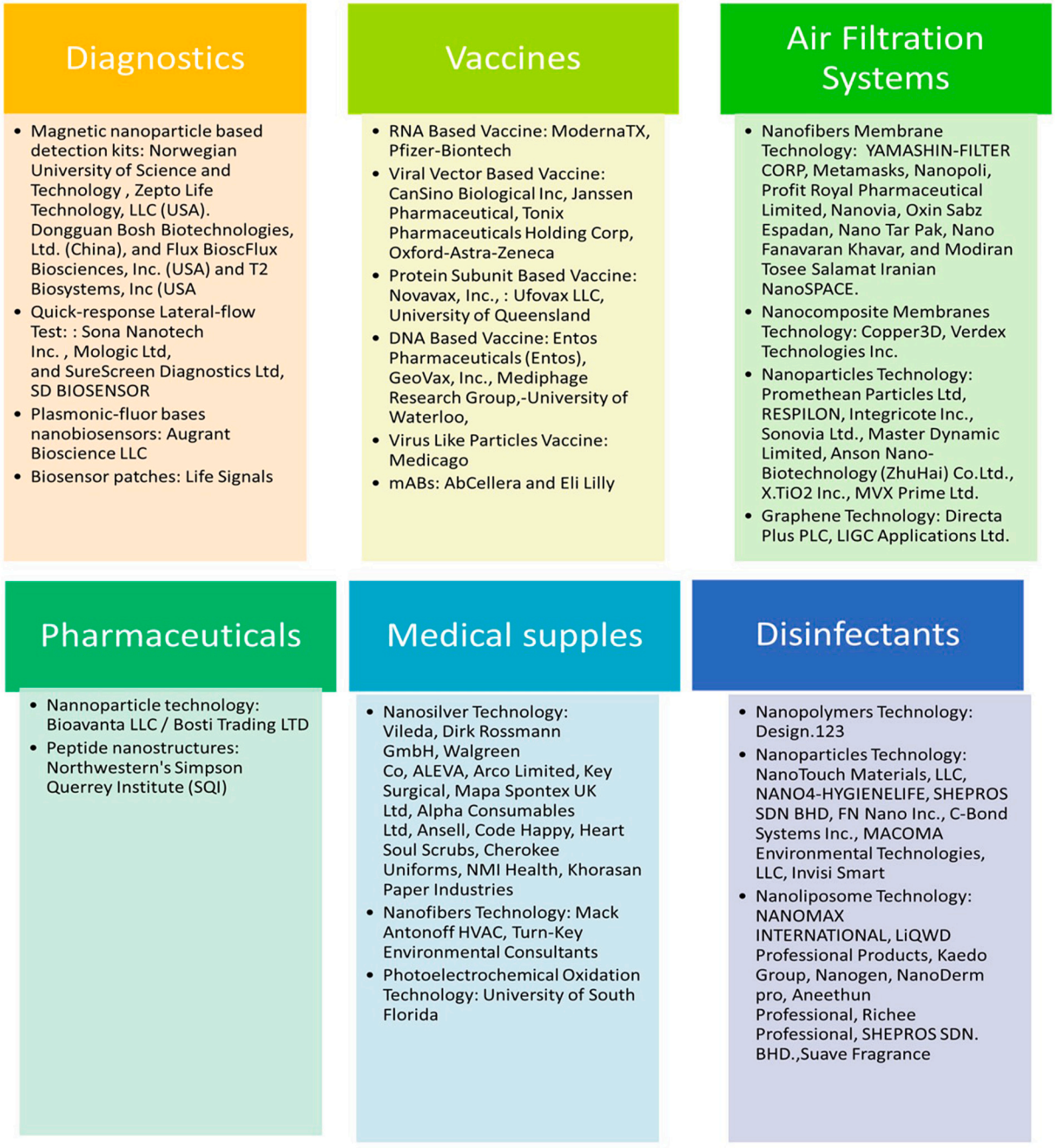

Fig. 8. A consortium of nanotechnology industries working towards diagnosis, therapeutics and mitigation of COVID-19 [51,118,160–163].

1. Low-cost, scalable mass detection methods for detection of viral particles,
2. New anti-viral vaccines, drug delivery platforms and novel nano-therapeutic solutions
3. Improved airborne virus filters, and PPEs, anti-viral nano-coatings on fabrics, woods, plastics

The fourth industrial revolution Industry 4.0 [187] has significant potential to satisfy the customized necessities of the COVID-19 pandemic. It is a smart system comprised of a flexible production line provided by digital technologies such as artificial intelligence (AI), internet of things (IoT), Big data, Virtual reality, Holography, Cloud computing, 3D scanning and printing. The working structure of Industry 4.0 technologies can benefit the mitigation of COVID-19 in areas such as efficient planning and contact tracing strategies for risk assessment, innovative methods of manufacturing biosensors, therapeutics, etc., smart supply chain of detection kits, therapeutics, and other medical aspects., using robotic systems for treatment of infected patients to reduce contact risk, delivery of emergency information using social platforms using telemedicine services and remote areas' health management and storage of sensitive healthcare and population data for future emergencies.

9. Future aspects and challenges in developing the nano-toolbox

Nanotechnology has continuously been used in health care, along with several other technologies. In today's latest developments, nanotechnology is playing a pivotal role in shaping the future of such pandemics. Not only in diagnosis, therapeutics and mitigation technologies, but nano-tools can be helpful in vaccine storage, development of warm vaccines, and successful transportation and distribution of approved vaccines in remote places and in low-income countries. Currently, when the biggest challenge lies in the successful and safe administration of COVID-19 vaccines, slow release of single-dose vaccine, microneedle patches, self-administration of vaccines does guarantee not only cost-effectiveness but also the prolonged uses of vaccines [182].

Further, repurposing a drug successfully against SARS-CoV-2 is the need of the day to save time and human resources. Encapsulating drugs in nanoformulations and the targeted drug delivery can significantly improve the clinical outcome and help in lowering the mortality rate of COVID-19. Rapidly sequenced genome and proteome of pathogens with the help of nanotechnology can provide an insight into their mutation rate and their severity. Nano-tools clubbed with bioinformatics can help in the prediction of future pandemics and their better management.

The big data analysis and artificial intelligence (AI) can be clubbed together with nanotechnology for the rapid discovery of the drug leads, nanosensors and drug delivery systems (Fig. 9). The quantum computers (QCs) capable to analyse big data in no time can help in detecting optimal drug-delivery nano-vehicles, nano-sensors by QCs added simulations, exploiting machine learning and analysing the big experimental data [188]. AI along with machine learning (ML) and QCs can validate the novel hypothesis by its tools including artificial neural networks (ANNs) and target fishing [189]. The AI can be used to predict the possible outbreaks of the SARS-CoV-2 and emergence of new mutations and variations., based on which nano-tools can be employed for the rapid detection and mitigation of SARS-CoV-2. The combination of CQs, ML and AI along with nano-tools will enable the healthcare system to translate the research output into optimized targeted nanotherapeutics according to the different variants of SARS-CoV-2 and unique patient type [190].

The SARS-CoV-2 pandemic has alerted the humankind to push their limits and alarmed for better preparedness to deal with such pandemics. Nanotechnology, with its powerful armour can provide a range of tools which can be used in early detection and mitigation of any other future viral outbreak so that it could be stopped in time.

Though triune of nano-tools in detection, therapeutics, and protection and mitigation are a 'pandora box' of opportunities and latest technologies, they still have to overcome many challenges to be developed as a reliable and robust tool to fight this pandemic. The major concerns and challenges associated with nano-tools are as follow:

9.1. Nano-toxicity

Non-targeted nano-toxicity and safety of nanomaterials applications are the most critical concerns regarding their uses against COVID-19. Nanoparticles show geometry, surface and concentration-dependent

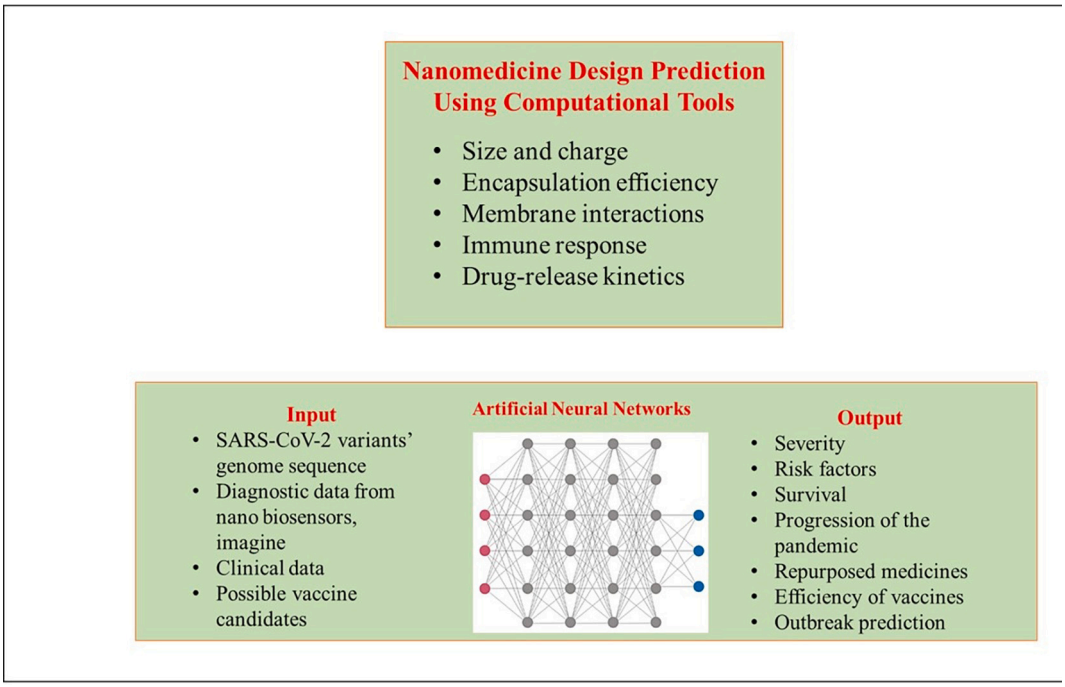

Fig. 9. Designing nanomedicine using computational tools and the role of artificial neural networks in theragnosis of the COVID-19 pandemic.

toxicity and antimicrobial activities [93,191]. Their bio-distribution pattern reveals that they tend to accumulate in the liver, kidneys, and brain via the circulatory system and affect the immune system [192]. Similarly, high doses of nano-polymers have shown neuronal cell death. COVID-warriors spraying nano-based disinfectants should be made aware of the associated health hazards, and precautionary measures should be taken. In the current scenario, where unknowns are maximum against SARS-CoV-2, use of a wrong particle or high concentration of a nanoparticle can lead to adverse effects creating panic and doubt over the whole nano-system.

9.2. Stability of nanoparticles

The properties of nanoparticles are dependent on their shape and size [30]. The aggregation, dissolution in solvents and unwanted reactions of nano-formulations can severely hamper their stability and properties. While designing nano-tools against SARS-CoV-2, the stability of the particles should always be considered apart from their activity. Use of potential stabilizers, cryoprotectants and optimization of surfaces are some of the parameters which can provide stability to the particles.

9.3. Scalability of the nano-devices, nano-therapeutics and vaccines

Though there is a plethora of literature suggesting the role of nanotechnology against SARS-CoV-2, products available in the market based on nano-tools are scarce. The academia-industry tie-ups, funding and supporting to nano-start-ups, quick decision making, supporting government policies and efficient quality control are some of the key points to scale-up the production of nano-devices, nano-therapeutics and nano-vaccines to win the war against COVID-19. For making the products affordable, use of cost-effective technologies, low-cost polymers, dual-purpose reagents and reduction in process and purification cost should be encouraged [90].

9.4. Leaching of particles and environment consequences

This point is particularly critical regarding the nano-coating of surfaces. Nanomaterials used in the coating of the surfaces can leach and cause adverse environmental consequences generation nanoparticle pollution. Similarly, microplastics generated by face-masks and PPE kits can post significant environmental pollution [181]. Pasricha et al. [193] studied the release of nano-silver coated on three different fabrics and found significant silver ion in wastewater. Release of nanoparticles from nano-based products and subsequently caused nano-ecotoxicology in both aquatic and terrestrial systems were documented by Bundschuh et al. [194]. Nanotechnology should work as a solution to the global health crisis of COVID-19 than to emerge as an environmental contamination itself.

9.5. Different concentration and reaction to different surfaces

SARS-CoV-2 has a different half shelf life on different surfaces. The viruses can remain alive on smooth surfaces even after 7 days, whereas on porous surfaces, it can be reactivated after 3 h on tissue paper [195]. Nano-disinfectants and coatings should be designed, and concentration should be adjusted according to the surface of application for their sustained release and higher anti-viral activity.

9.6. Rapid scientific development with reproducibility

As of now, there is no therapeutic solution available for COVID-19. Rapid scientific developments and transition to technology are required for nanotechnology to lead in this health crisis from the front. For early detection of this disease, the challenge lies in the accurate recognition of symptoms avoiding cross-reactivity with other types of coronaviruses [177]. Biosensors and therapeutic solutions offered by nanotechnology should be economical and have high sensitivity and reproducibility to reach every corner of the world.

9.7. Unforeseen consequences

While the impact of nano-tools on human health is high, there are still many questions which are yet to be answered. All the data documented in literature reports the bioavailability of the nanoparticles, however, their behaviour, once they enter into the patient's body infected with SARS-CoV-2, their behaviour in targeted and non-targeted organs are entirely unknown. The conventional risk assessment may not be sufficient for engineered nano-tools in this time of the pandemic.

Further, gaining public trust, solving ethical issues and adaptation to new technologies will not be easy. Siegrist et al. [196] in their study found that the public is more concerned about nanotechnology than experts and industry. The public perception and their trust is an essential pillar on which a successful technology can be founded. Scientific communities, industries and policymakers need to come together to cope-up this exceptional health crisis with unprecedented innovations gifted by nanotechnology.

9.8. Emergence of new infectious variants of SARS-CoV-2

After the onset of COVID-19 pandemic, cases of emergence of new variants have been reported in many countries including South Africa, Brazil, India and UK [197–199], which can hamper the traditional detection methods and approaches towards vaccines and therapeutics. Specifically, the delta variant of SARS-CoV-2 which has caused second wave of COVID-19 in India, with high infectious rate and reduced sensitivity to antibody neutralization is a matter of concern [200]. Nano-tools can help in development of rapid and accurate sensors for diagnosis of the variants. Sustainable release of drug and active principle by the use of nanocarriers can prolong the generation of neutralizing antibodies against different variants, reducing the number of dosing and pressure of the heath-care systems.

10. Conclusions

The good 'nano-tools' have provided a ray of hope to combat the harmful nanoparticles 'SARS-CoV-2′. The high-throughput and reliable nano-sensors, anti-viral nanoparticles, and smart drug delivery vehicles can substitute the conventional diagnostic and therapeutic methods currently employed against SARS-CoV-2. However, the understanding of nano-bio-interactions and biological responses with nano-tools and SARS-CoV-2 is required. With the emergence of novel variants of SARS-CoV-2, challenges still lie ahead in successful and economical administration of approved vaccines to the last man in the queue. Further, coating of different surfaces with anti-viral nanoparticles and exploiting nano-fabrics for construction of safer and comfortable protective equipment and gears can prevent the indirect spread of the disease without compromising the comfort of 'COVID warriors'. Nanotechnology allows the scientists of multiple disciplines to work together and come up with a better and fast solution among this global health crisis. Supportive policies, merger of artificial intelligence and big data analysis with the nanotechnology, and the collaboration between academia and industries are required to convert the scientific hypothesis into useful products within a limited period. A critical approach to nano-toxicity, the stability of the particles, and the acceptance of technology among different socio-economic stakeholders are required before accepting any technology or therapeutic product to avoid unforeseen circumstances. Today, when the world is battling with an unprecedented health crisis, this extraordinary technology can build the strong pillars on which the advanced research can be constructed to put a full-stop to the SARS-COV-2-saga.

Acknowledgements

SK thanks UGC, New Delhi for awarding her with JRF and SRF. MK thanks CSIR, New Delhi for awarding her with the pool scientist scheme.

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