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Advances in nanotechnology application in biosafety materials: A crucial response to COVID-19 pandemic

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ABSTRACT

The outbreak of coronavirus disease 2019 (COVID-19) has adversely affected the public domain causing unprecedented cases and high mortality across the globe. This has brought back the concept of biosafety into the spotlight to solve biosafety problems in developing diagnostics and therapeutics to treat COVID-19. The advances in nanotechnology and material science in combination with medicinal chemistry have provided a new perspective to overcome this crisis. Herein, we discuss the efforts of researchers in the field of material science in developing personal protective equipment (PPE), detection devices, vaccines, drug delivery systems, and medical equipment. Such a synergistic approach of disciplines can strengthen the research to develop biosafety products in solving biosafety problems.

1. Introduction

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has created a societal imbalance, progressing into a life-threatening respiratory disorder posing a great challenge to the global healthcare system and economic status [1]. The unprecedented death toll globally since the outbreak is nearly 6,297,859 as of 4th June 2022 [2]. In response to this pandemic, the importance of bringing back the concept of biosafety became crucial considering the current scenario, and the impact on society and economy is still a global issue. Although the concept of biosafety is well known, it has been evolving with the emergence of new diseases. A recent review article by Yu *et al.* [3] provides a comparative explanation of the terms biosafety materials, biosecurity, and biosafety of materials. Biosafety materials can be simply understood as "materials for biosafety", which refers to the application of materials to address biosafety issues. Such materials can be applied to tackle pathogens like viruses and bacteria harmful to humans and the environment. Material science has always contributed largely to combating various viral infections by developing techniques useful in the structural elucidation of viruses, detection, designing vaccines, and other therapeutic strategies [4–6]. Also, biosafety guidelines by World Health Organization (WHO) have been implemented to safely assist the researchers in investigating SARS-CoV-2, and handling the virus specimen in laboratories [7]. Lack of effective preventive measures can lead to catastrophic outcomes in the case of SARS-CoV-2 outbreaks. Therefore, the need for fast and potent treatments opened the way for the integration of medicinal chemistry with material chemistry [8]. Synergistic application could act as quick relief as it offers potent medicinal administration on selective and specific targets within a short period. A recent article by Karges *et al.* [9] highlights the importance of the combination of chemistry and material science to overcome the health issues related to coronavirus disease 2019 (COVID-19).

A breakthrough discovery of the messenger RNA (mRNA) COVID-19 vaccine by Pfizer BioNTech's marketed as Comirnaty has received full approval from US Food and Drug Administration (FDA). Also, other authorized vaccines by FDA for emergency use are Moderna and Janssen COVID-19 vaccine [10]. Although immunization remains the best way of protection against COVID-19, the use of face-masks and COVID-19 detection tests to identify the infected is still in practice. Also, the need to increase the pace of immunization of the global population is currently in focus to deal with the new emerging variants. Before the vaccine administration, COVID-19 testing gained popularity in identifying the infected population and implementing the quarantine guideline that seemed mandatory to control the rapid spread of infection. The commercially available reverse transcriptase (RT) poly-

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merase chain reaction (PCR) assay for COVID-19 was widely employed in testing the unprecedented rise in infections. However, RT-PCR limits the point-of-care (POC) analysis as it requires trained staff and an expensive laboratory setup. Therefore, research has been oriented towards designing and developing assays with improved accessibility and rapid screening time. Several diagnostic tools with high sensitivity incorporating nanoparticles (NPs) in developing electrochemical biosensors [11], lateral flow assay [12–13], fluorescence-based sensors [14], and plasmon photothermal sensors have been developed. Recently, we discussed nanomaterials-based POC diagnostics for COVID-19 and spectral methods for the rapid detection of SARS-CoV-2 in our reviews [15–16]. Although the measures adopted to prevent the spread of COVID-19 by maintaining physical distancing, use of face masks, and quarantine guidelines are in practice, there is an urgent need for developing better ways to manage the ongoing pandemic threat.

Studies have revealed that the primary mode of SARS-CoV-2 viral transmission is through viral aerosols and droplets that are released into the air and enter the respiratory tract through viral aerosol inhalation [17]. In this regard, several guidelines on using PPE, maintaining social distancing, and using face masks are implemented to manage the spread of SARS-CoV-2 infection. Also, the use of N95 filtering respirators as PPE for healthcare workers is recommended by the Centers for Disease Control and Prevention (CDC) [18]. Thus, the increasing demand for an antiviral mask for respirators especially amongst healthcare professionals has led to the shortage of PPE, requiring the need to think about its reusability [19]. The used and discarded masks can also be the source of the spread of the virus, thus reusable masks with self-cleaning potential which can be easily decontaminated can provide the solution to this problem. Smartly knitted fabrics embedded with nanomaterials that themselves can act as sensors against SARS-CoV-2, serve as useful POC detection applications [20]. Development of novel safety equipment having an inbuilt capacity to detect and disinfect pathogens and viruses that act as an effective primary stage protective measure against such widespread bio-attacks [21,22].

Recurrent viral mutations and traditional antiviral treatment mechanisms have led to ineffective therapeutic methods resulting in the increased spread of fatal viral diseases. To overcome these limitations incorporation and application of biomaterials in such therapies can be adopted to achieve diverse and efficient treatment pathways (Fig. 1) [23,24,25]. Biomaterials such as poly (lactic-co-glycolic acid) (PLGA) nanosponge [26], Sialyl lactose-chitosan fibers [27], PLGA nano decoy [28] are used against SARS-CoV-2, influenza virus, Human Immuno Virus (HIV) respectively, and each application generates novel mechanistic antiviral pathway which could easily overcome various side-effects of the traditional treatment method. Efforts of modifying the masks with bactericidal, antiviral materials having reusability features are discussed in this review.

Since the early time, the emergence of infectious diseases has led to the development of several vaccines to tackle pandemic threats [29]. Engineered biomaterials can be useful for immunomodulation by enhancing the efficacy of vaccines, drug delivery systems and modulating the immune response to provide a life-saving solution for the rapid transmission of COVID-19 [30].

Understanding the mechanism of viral entry, replication, host immune response, innate or adapted immunity is crucial for developing new antiviral drugs and vaccines to control and eliminate the spread of infection. In this regard, a recent review article by Florindo *et al.* [31] provides a detailed overview of the cellular infection mechanism and immune-mediated approaches against COVID-19. Their review provides insightful information on the proposed mechanisms for SARS-CoV-2 entry in cells, viral replication, and host immune response. Without this information on the underlying mechanism of the viral entry and infection, the efforts by material science and technology would not be so effective in developing and redesigning the vaccine and therapeutics against COVID-19.

Researchers are screening previously approved antiviral drugs and repurposing drug candidates to speed up the clinical testing and treatment against COVID-19 [32]. Studies have been carried out on the combination of biomaterials and antiviral drugs that synergistically operate at different levels by inhibiting the viral entry and replication [26]. Rethinking biosafety is the call of the current pandemic to be considered not only in research laboratories but also by the public population [33]. Thus, in this regard, the multidisciplinary field of material science and biology can play a crucial role in implementing the ideas for the development of biosafety materials. In this review, we have explored the recent advances in biomaterial and nanotechnology as a biosafety approach in the treatment of COVID-19. We also highlight the studies carried out in understanding the mechanism of virus entry and the spread of the infection which is vital for developing new therapeutic immunology ideas.

2. Nanomaterials in diagnosis and detection

In response to this pandemic, the development of assays to efficiently diagnose COVID-19 infection was predominantly in focus before the vaccine administration, accompanied by social distancing and quarantine guidelines. The routine methods of detection involved assays and instrumentation techniques mainly by detection of viral RNA or antigen-based detection involving a variety of sample collecting methods but lacked POC analysis [34]. In this regard, quantitative paper-based electrochemical biosensor using gold nanoparticles (AuNPs) devoid of any required measures for RNA [11], and the graphene-based field-effect transistor (FET) device [35] is been developed with improved sensitivity and POC diagnosis. Also, the electrochemical biosensors use transition metal oxides with the surface nano-structures of the transducer which is conductive and the surface functionalization generally improves the susceptibility to outer stimuli by raising the electrical properties [36]. COVID-19 diagnostic methods are also designed to target RNA or complementary-DNA or any specific sequence of SARS-CoV-2 [37–38]. The application of nanomaterials in COVID-19 diagnosis can be classified into direct and indirect methods to get better clarity on nano-diagnostic tools.

2.1. The straight/direct application of nanomaterials for COVID-19 diagnostics

In the direct approach, the various properties of nanomaterials such as surface plasmon resonance, and extraordinary optical transmission (EOT) act as an integral part of the assay with a particular detection mechanism. A colorimetric assay was developed consisting of thiol-modified AuNPs functionalized by anti-sense oligonucleotides which are employed for SARS-CoV-2 detection by naked-eye, based on the color change. These anti-sense oligonucleotides coated NPs Au get agglomerated instantaneously in presence of target RNA sequences of SARS-CoV-2, which was indicated by a color change to blue from purple [39]. Another study reports a colorimetric biosensor comprising Au NPs of 20 nm size. This method is specific and sensitive to identifying the minute concentration of virus in the throat and nasal swab samples. This biosensor was fabricated with Au NPs which are covered by antibodies that bind spike (S) envelope (E), and membrane (M) proteins of SARS-CoV-2. In presence of viral load, extinction spectra of this functionalized Au NPs solution show a shift in the wavelength towards red [40]. Similarly, the two-dimensional (2D) Au nanoislands sensor chip (5.0–5.2 nm in thickness) functionalized by 1 nmol of thiol-cDNA of RNA-dependent RNA polymerase (RdRp)-COVID has been prepared to achieve the greatest coverage of the surface while suppressing the non-specific binding sites. This biosensor utilizes the photothermal effect for sensing and displays superior sensitivity for RdRp-COVID. The functionalized Au nanoislands produce the thermoplastic heat when excited with 532 nm wavelength, as a consequence

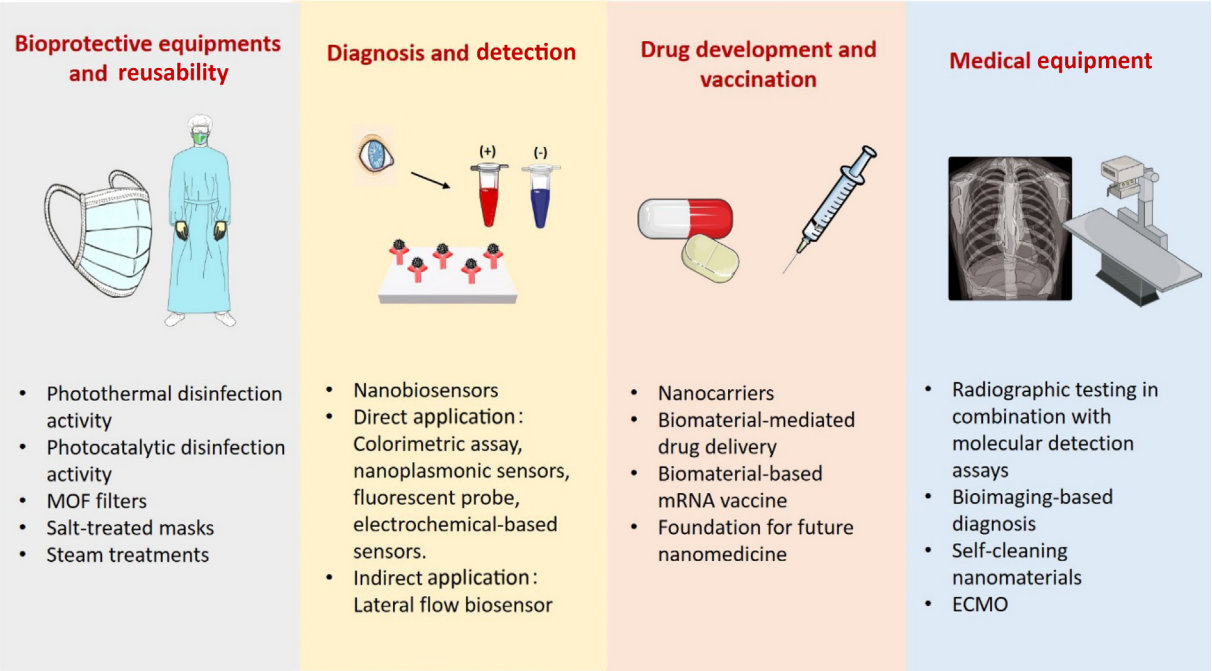

Fig. 1. Contribution of nanomaterials in the optimization and development of biosafety materials for diagnosis, prevention, and treatment of coronavirus disease 2019 (COVID-19) [24,25,30]. Abbreviations: MOF, metal-organic framework; ECMO, extracorporeal membrane oxygenation.

of this the *in situ* hybridization of target nucleic acid takes place [41]. The label-free nanoplasmonic sensors that employ localized surface plasmon resonance (LSPR) combined with optical transmission effect were developed by Huang *et al.* [42] which can rapidly identify SARS-CoV-2 pseudovirus in single-step. Such nanoplasmonic sensors were prepared by deposition of Au and Ti nanoparticles on a nanocup array by an electron beam evaporator. The Au NPs over the nanocup array were functionalized using the mixture 1-ethyl-3-(3-dimethylamino propyl)carbodiimide and *N*-hydroxysuccinimide (NHS) and ligated to SARS-CoV-2 monoclonal antibodies. Then, Au NPs were conjugated with the Angiotensin-Converting Enzyme II receptor (ACE2) protein or SARS-CoV-2 monoclonal antibodies, later it was mixed with the SARS-CoV-2 pseudovirus and allowed to bind with SARS-CoV-2 monoclonal antibodies which are coated over the nanoplasmonic sensor. SARS-CoV-2 pseudovirus response was recorded as a change in the optical density *via* a microplate reader.

For the detection of human IgG in serum samples, a fluorescence-linked immunosorbent assay was developed. This assay was used for the identification of SARS-CoV-2-specific IgG and IgM, and was found to be a very accurate, rapid, and highly sensitive method [4]. In this method, the mouse antihuman IgG coated on the Fe_3O_4 nanospheres is used to capture a specific target antigen and quantum dot nanobeads coated with rabbit antihuman IgG as a fluorescence probe. From the resulting sandwich structure of Fe_3O_4@mouse antihuman IgG and quantum dot nanobeads@ rabbit antihuman IgG after the magnetic separation, the intensity of fluorescence was recorded at 370 nm (excitation wavelength).

An interesting biosensing device based on FET was fabricated for the rapid detection of the COVID-19 virus. This FET biosensor was fabricated by functionalizing graphene sheets with a specific antibody against the SARS-CoV-2 S protein. This device can detect the SARS-CoV-2 S protein at a concentration of 100 fg/mL in a clinical transport medium and 1 fg/mL in phosphate-buffered saline. Further, this sensor identified SARS-CoV-2 in clinical samples with a limit of detection (LOD) of 2.42×10^2 copies/mL and a culture medium with LOD of 1.6×10^1 pfu/mL [35]. Similarly FET based -2D transition metal dichalcogenide (TMDC) WSe_2 semiconducting materials (2D TMDC-based FETs) was developed for rapid and label-free sensitive detection of SARS-CoV-2 shown in Fig. 2. The sensor is produced by functionalizing the WSe_2 monolayers with a monoclonal antibody against the SARS-CoV-2 S protein. SARS-CoV-2 antibody was immobilized onto the WSe_2 crystals *via* 11-mercaptoundecanoic acid (MUA), and further, activated with NHS and carbodiimide hydrochloride (EDC) solution. This device shows a LOD: 25 fg/μL in 0.01X phosphate-buffered saline [43].

An electrochemical paper-based sensor that uses Au NPs, which are functionalized by the developed single-stranded DNA probes, acts as the sensing element. Moreover, the conductive film is composed by coating the suspension of graphene nanoplatelets [44]. This sensor identifies electrochemical signals when the Au NPs coated single-stranded DNA interacts with the viral RNA. The nanomaterial-based biosensors as shown in Fig. 3, describe the methodological details of functionalized nanoparticles in the detection of COVID-19.

In another study, a multiplexed sensor array employing Au NPs was fabricated that offers breath analysis of alleged COVID-19 patients by altering electrical conductivity patterns [11]. It has been developed to detect the volatile organic compounds (VOCs) pattern for COVID-19, as viral agents have a microenvironment that releases VOC and various species produce a varied profile of VOC. In one more study, an amperometry-based electrochemical biosensor was reported which is highly responsive, precise, and accurate to identify the receptor-binding domain of S protein in SARS-CoV-2 in nearly 30 s at low concentration range (14 nM to 1,400 nM), the LOD roughly equals 0.7 nM [45]. This biosensor consists of Ti sheet topped with Co-spiked TiO_2 nanotubes, fabricated by electrochemical anodization.

The photothermal effect of Au nanomaterials is based on the LSPR ranging from visible to near-infrared region. The better light to heat conversion proficiency is shown by magnetic plasmonic NPs in the nano-PCR assay in contrast to conventional Au nanostructure materials used for plasmonic photothermal properties [46]. A biosensor was fabricated using a convenient device equipped with plasmonic thermocycling and fluorescence detection for fast detection of SARS-CoV-2 in 17 min. This method depends on the generation of heat upon irradiation of plasmonic substrate, metallic NPs [47]. This substrate is a mag-

netic core ($Zn_{0.4}Fe_{2.6}O_4$) enclosed with a thick Au shell. These substrates can considerably increase the electromagnetic field depending on LSPR. The detection time is lowered to nearly 17 min (the detection limit of 3.2 gene copies per mL in comparison to the bench-top polymerase chain reaction). Pan and co-workers have recently developed an RNA extraction free nano-amplified colorimetric assay for POC detection of SARS-CoV-2. It is a simple, low-cost, and rapid method for COVID-19 diagnosis in POC settings in resource-poor locations. This colorimetric test makes use of plasmonic AuNPs functionalized with antisense oligonucleotides (ASOs) that detect the nucleic acid from the SARS-CoV-2. The ASOs are specific for the nucleocapsid (N) gene that binds to their target sequence resulting in the aggregation of Au NPs giving a plasmonic response. The clinical samples evaluated show high specificity, accuracy, and sensitivity of the analysis with a LOD of 10 copies/μL [48].

2.2. Application of nanomaterials in COVID-19 diagnostics: An indirect approach

In the indirect method, nanomaterials act as carriers of biomolecules, i.e., NPs are combined with antibodies or binder proteins which will act as detecting reagents. Here, the properties of NPs are not directly involved in the detection assay. For example, NPs based lateral flow immunoassay was designed to detect anti-SARS-CoV-2 immunoglobulin-IgG in human serum [49]. Here, the polystyrene NPs doped with lanthanide, tagged with mouse anti-human IgG antibody and rabbit IgG antibody forms the conjugate pad. Upon loading the serum samples, they move toward the conjugate pad. After their movement, the NPs conjugated with antibodies are trapped at the control and the test line. A fluorescence signal, due to fixed lanthanide-doped polystyrene NPs, is seen on the nitrocellulose membrane after a brief incubation and further studied using a fluorescence reader. In another study, a multiplex reverse transcription loop-mediated isothermal amplification (mRT-LAMP) method combined with a biosensor assay was developed for the identification of COVID-19, which at the same time amplify and identify the target sequences, i.e., open reading frames (ORF)1ab and the N gene [50]. The mRT-LAMP reaction (Fig. 4) is carried in a single tube and the readout biosensor consists of a 4 mm dipstick with an adsorbent pad that detects the target including the control.

Similarly, reverse transcription multiple cross displacement amplification-based biosensors diagnose SARS-CoV-2 from samples of different origins [51]. Both these assays can be done in one step and use two primer sets targeting the N-gene and ORF1ab of SARS-CoV-2. The NPs based biosensor for both the assays consists of a conjugate pad, nitrocellulose membrane, sample pad, and an absorbent pad. Hence, these biosensors can identify three targets, the ORF1ab, N gene, and control. Another study reports RNA segregation by using magnetic NPs (in the RT-PCR technique once the sample is collected, the first step is the isolation of RNA). Carboxyl PVA-linked $ZNF@Si@NH_2$ NPs were employed for the extraction of RNA and segregation in presence of an external magnetic field [52].

3. Bioprotective materials and their reusability

Since the outbreak of COVID-19, it was quite apparent that the demand for medical consumables would massively increase, creating a rapid shortage in consumables. Thus, the implementation of technologies in improving manufacturing capacity, repurposing the existing and developing new materials was a crucial response to this pandemic. Along with the increased demand for PPE, the unprecedented need for testing to identify COVID-19 patients greatly demanded the use of nasopharyngeal (NP) swabs. Alternative ways, such as 3D printing technology was utilized to provide a potential solution for mass production of the consumable materials, enabling rapid repurposing, testing, and re-designing. Thus, 3D printing reduced the designing cycle time for new manufacturing methods [53].

The Occupational Safety and Health Administration (OSHA) in the USA defines PPE as ‘specialized clothing or equipment worn by an employee for protection against infectious materials” [54]. With the rapid rise in COVID-19 cases, the increasing demand for N95 filtering facepiece respirators (FFR) as an essential PPE has unprecedently increased. The shortage of bioprotective materials with their rapid demand requires the development of protective materials with contact-killing features that are more effective, sustainable, self-rechargeable, and reusable using safe standard protocols [55]. A review article by Huang *et al.* offers an overview of antiviral biomaterials with different mechanisms highlighting the challenges and emerging opportunities in therapeutics [56].

Studies have also shown that *N, N*-dodecyl methyl polyethyleneimines (PEIs) and their derivatives coated on glass slides can successfully kill the influenza virus and airborne pathogenic bacteria such as *Escherichia coli* and *Staphylococcus aureus* [57]. The virucidal action on contact is due to the presence of erect polymeric side chains called tentacles that rupture the bacterial cell membranes. Authors have suggested that the influenza virus is protected by a lipid membrane, thus the hydrophobic polycations of *N, N*-dodecyl methyl PEIs damage it thereby inactivating it. They also elucidated the effect of various structures of PEI derivatives on the virucidal activity of the coated surface. In another approach, *N*-halamines are excellent antimicrobial agents owing to their stability, non-toxicity, rechargeability, and efficacy against a wide range of microbes [58]. The antimicrobial mechanism involves the transfer of oxidative halogen to the cell in contact, which

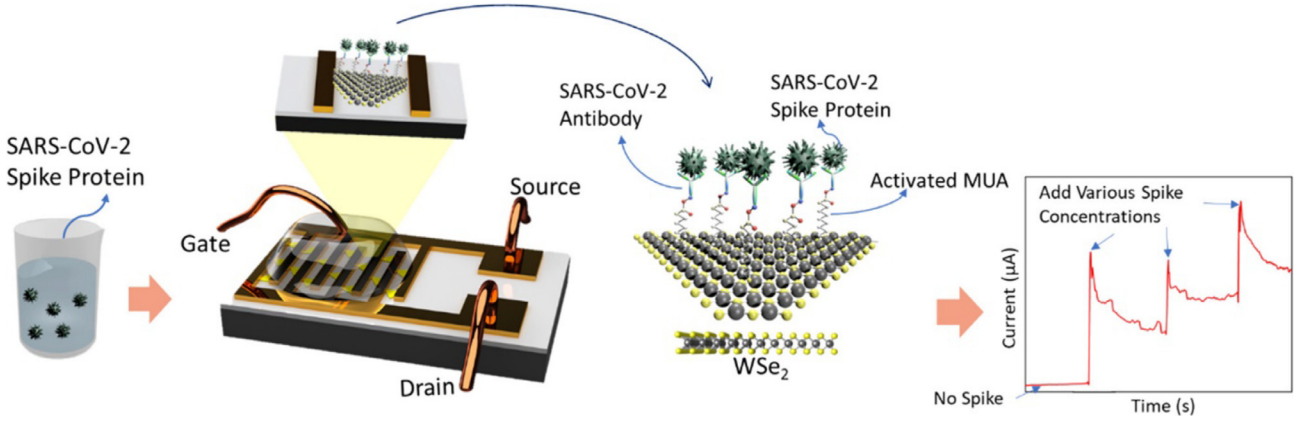

Fig. 2. Schematic illustration of the fabricated monolayer WSe_2-based FET COVID sensor [43], Copyright 2021 American Chemical Society. Abbreviations: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; MUA, 11-mercaptoundecanoic acid.

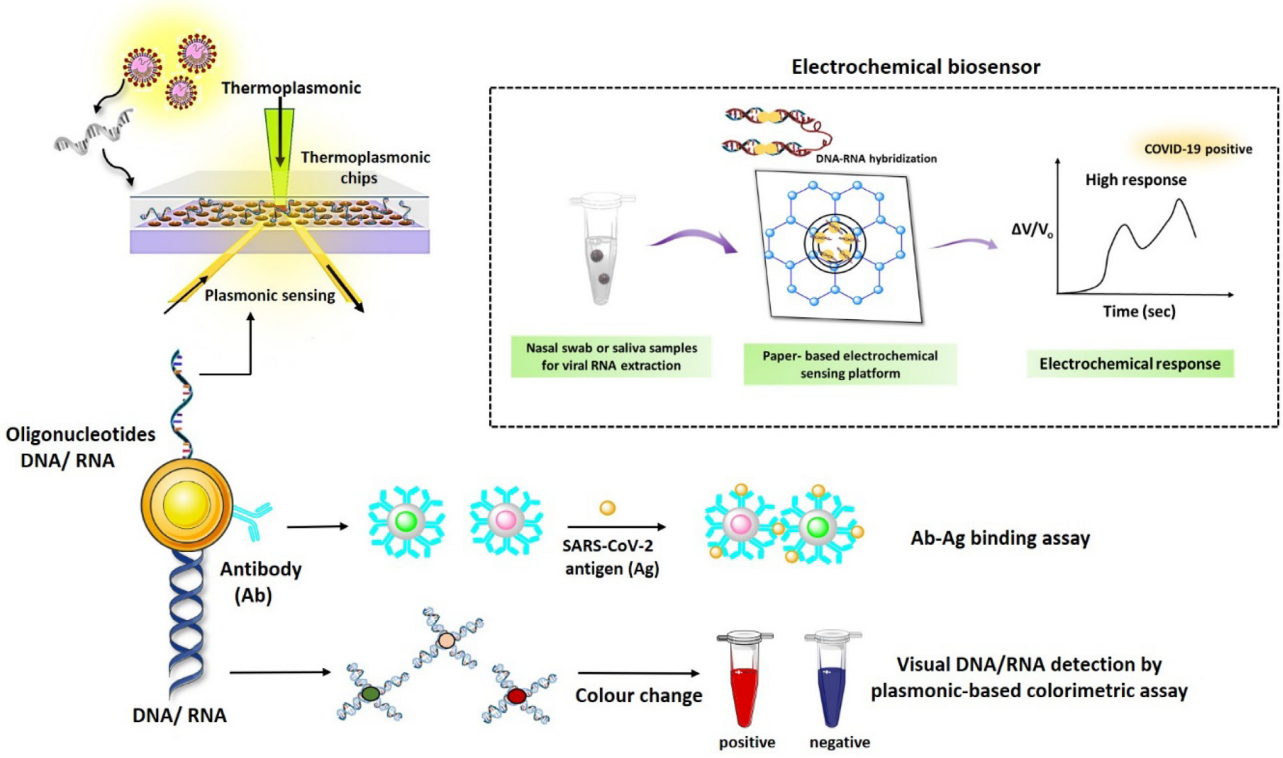

Fig. 3. Schematic illustration of various detection methods for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using nanomaterial- based biosensors [44,39–41].

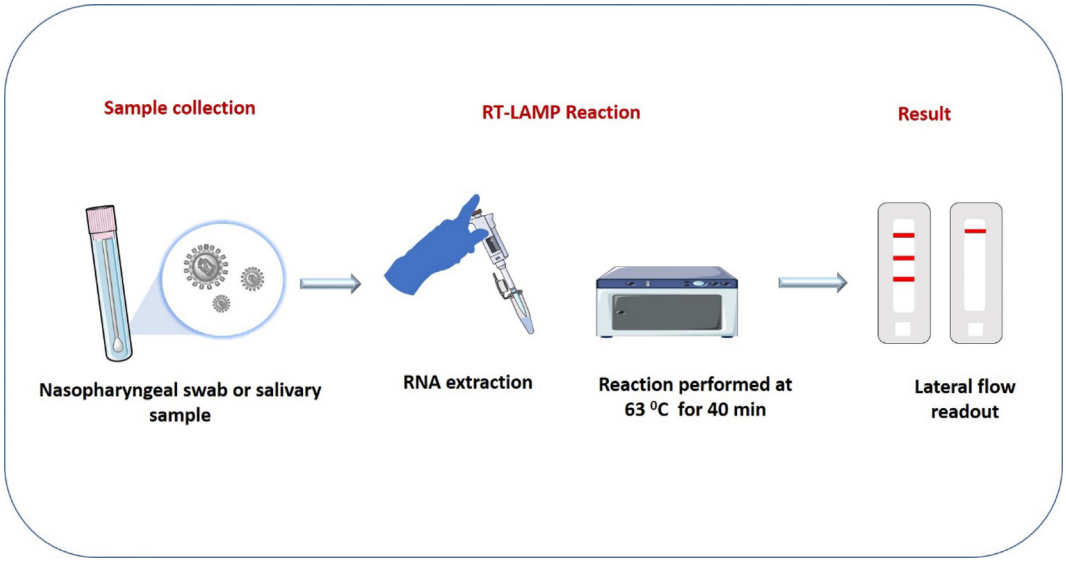

Fig. 4. A general schematic representation of multiplex reverse transcription loop-mediated isothermal amplification (mRT-LAMP) method combined with a biosensor assay [50].

then penetrates and oxidizes the amino acid thereby inactivating it [59]. One example of *N*-halamine application is 1-chloro-2,2,5,5-tetra methyl-4-imidazolidinone-coated on surgical masks and air filters by employing an inexpensive coating process that exhibited antimicrobial activity, which can be useful in developing masks having virucidal activity [60].

Gao and his team [61] developed an IONzyme (Fe_3O_4 nanozyme) which inactivates the influenza A virus by readily inducing envelope lipid peroxidation and defunctionalizing the neighbouring proteins responsible for the infection. The IONzymes destroy the viral lipid envelope by direct contact *via* enhancing its lipid peroxidase level, producing free radicals that destroy neighbouring proteins and thus, preventing the infection in the host cell. This IONzyme can be a broad-spectrum antiviral biomaterial against lipid enveloped viruses due to its lipoxidase-like activity and is biocompatible, cheaper, highly stable, and multifunctional. They loaded this IONzyme in facemasks and were

able to inactivate different types of Influenza A virus rapidly and thus can be used as protective equipment because of its antiviral properties. A rechargeable anti-bactericidal membrane was developed by Ding and his team [62] consisting of rechargeable *N*-halamine moieties grafted into a fiber which was a combination of an electrospun poly (vinyl alcohol-co-ethylene) nanofibrous membrane (ENM) and covalent functionalization of the surface by dimethylol-5,5-dimethylhydantoin (DMDMH). The ENM exhibited high rechargeable active chlorine content (>2,000 ppm) and high inactivation efficacy against *E. coli* bacteria. Moreover, it also showed high filtration efficacy and appreciable mechanical properties. This membrane can be used as a layer in protective equipment thus making it capable of inactivating the bacteria, thus serving as a bioprotective material.

Similarly, metal–organic framework (MOF)-based air filters with tunable functionalities have potential capabilities to remove particulate matter but generally lack biocidal efficacy [63]. In this regard, Li *et al.* [64] developed a zinc-imidazolate MOF (ZIF-8) based air filter integrated with excellent antimicrobial and photocatalytic disinfection activity. Its photocatalytic disinfection activity was attributed mainly due to the reactive oxygen species (ROS) especially H_2O_2 and $\bullet O_2^-$ produced by the reduction of surface adsorbed oxygen by the photoelectrons trapped in the ZIF-8 surface. The photoelectrons *via* ligand to metal charge transfer are trapped by Zn^+ centers present on the surface of ZIF-8. Its photocatalytic disinfection activity was found to be superior to the other semiconductive photocatalysts like anatase TiO_2 and ZnO. The MOF filter was produced by hot pressing ZIF-8 precursors and polyethylene glycol at 100 °C on non-woven fabrics (NWFs) by a procedure developed by Chen *et al.* [65]. This MOF-based filter was a trilaminar mask with a MOF filter sandwiched between two NWFs. They were successful in demonstrating the ability of ZIF-8 MOF-based filters in contact-killing of airborne pathogens (>99.99%) with 97% particulate matter efficiency. Another fascinating material has been designed by Sun and co-workers [66] for bioprotective nanofibrous membranes (RNMs) with day-light driven rechargeable with high antibacterial (>99.9999%) and antiviral (>99.999%) efficacy. These photoactive NMs effectively produced ROS in day-light, storing the biocidal activity, and under dark or dim-light conditions could efficiently release the ROS (Fig. 5) exhibiting high biocidal efficacy. The NMs comprised of the poly (vinyl alcohol-co-ethylene) nanofibrous network grafted with various benzophenone and poly-phenol-based photosensitizers. These grafted photobiocides on irradiation with light produced ROS in presence of oxygen.

The nanofibrous membranes modified by 4-benzoyl benzoic acid (BA), benzophenone tetracarboxylic dianhydride (BD), and chlorogenic acid (CA) were named BA-RNM, BD-RNM, and CA-RNM respectively. BDCA-RNM was obtained by grafting CA on BD-RNM. Ultraviolet (UV) -visible spectra of BA-RNM, CA-RNM, BD-RNM, and BDCA-RNM at different daylight irradiation times were studied. Further, they have evaluated the rechargeable biocidal property of these RNMs using light-absorbing transient (LAT) moieties and diphenylmethanol (DPM) as illustrated in Fig. 6. They further investigated the pathogen contact killing ability of the NMs by integrating them with masks and protective suits. It served as a promising scalable biocidal layer with long-term durability and robust breathability, effective against pathogens in the aerosol or liquid form. In a similar approach, Kumar *et al.* [67] designed a reusable photoactive face mask with antiviral and self-sterilization property. They carried out spray-coating of a natural hydrophobic biopolymer Shellac/CuNPs nanocomposite hybrid on a polypropylene nonwoven surgical mask.

This nanocomposite coating served as a hydrophobic surface with outstanding photocatalytic activity by the production of free radicals under solar illumination. The increase in surface temperature of this mask to > 70 °C resulted in the production of free radicals that destroyed the nanosized virus-like particles thus, imparting the self-cleaning ability to the mask (Fig. 7). An excellent example of the reusability of masks was developed by Quan *et al.* [68] by coating a film of NaCl salt on the air filter for virus deactivation. On exposure to viral aerosols, the salt film on the fiber surface dissolves and recrystallization of salt takes place due to supersaturation caused by evaporation. Due to evaporation, there is an increase in salt concentration which in turn increases the osmotic pressure during drying and thus physically damages the virus by membrane perturbation. These salt recrystallization-based filters showed long-term stability and high fil-

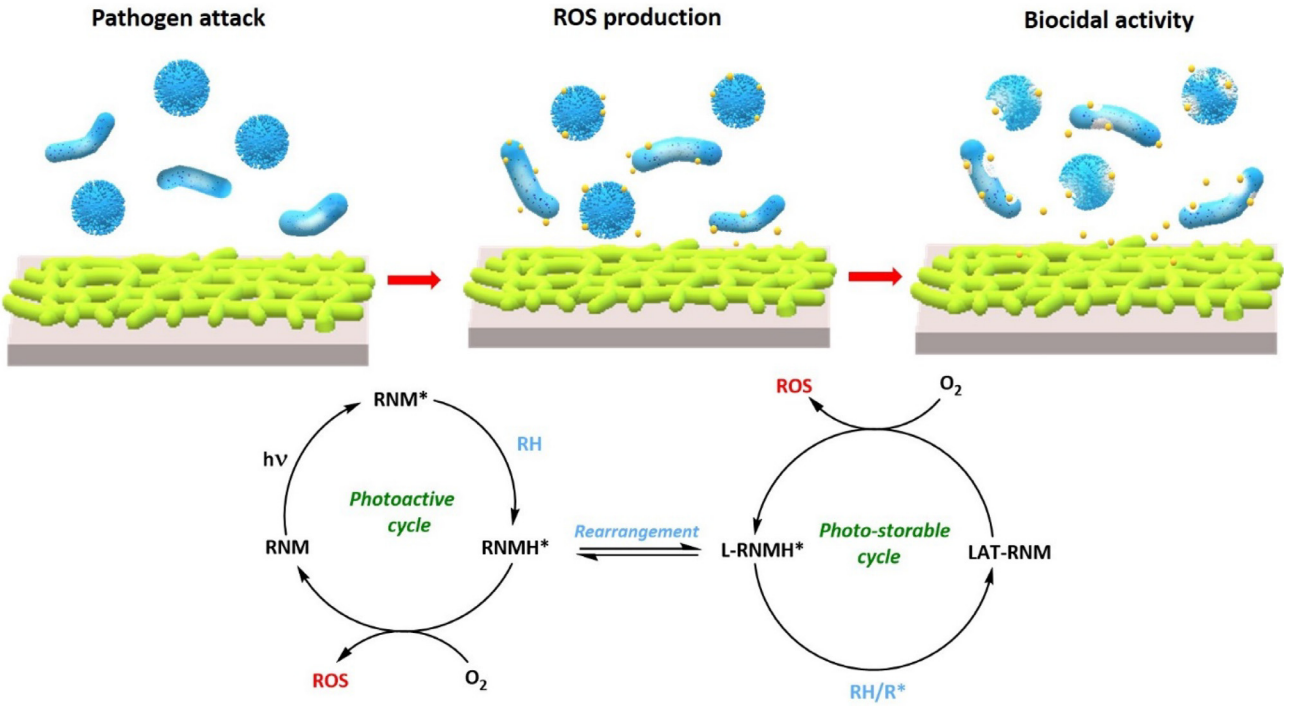

Fig. 5. Schematic representation of the biocidal activity of RNMs by ROS production and their photoactive and photo-storable biocidal cycles [66]. Abbreviations: RNM, bioprotective nanofibrous membrane; ROS, reactive oxygen species; LAT, light-absorbing transient.

tration efficiency than bare filters as evidenced by the fact that the former protected the mice completely against the influenza aerosols.

Recently, Qio and co-workers [69] have developed a vanadium-based artificial enzyme $Zn_2V_2O_7$ (VO*x*-AE) from the calcination of a vanadium-doped zeolitic imidazolate framework. This VO*x*-AE was found to efficiently mimic peroxidase and haloperoxidase-like activity wherein they generated ROS, **.**OH, and **.**O_2^- which is responsible for its antibacterial application. From the experimental studies and DFT calculations, they proposed a unique mechanistic pathway for the generation of ROS (Fig. 8). The Zn-O-V bridge present in VO*x*-AE is responsible for the generation of these ROS *via* the electron transfer from Zn to V. The V-d_{yz} orbital is stable charge filled near the Fermi level which interferes with the sigma bond formation between the V-$d_z^2$and O-p_z orbitals in H_2O_2 which facilitates the oxygen intermediates adsorption and dissociation. VO*x*-AE showed a higher turnover number and V_{max} in catalyzing H_2O_2. The VO*x*-AE showed catalytic destruction of a drug-resistant bacteria, methicillin-resistant *Staphylococcus aureus,* and showed comparable wound healing activities to vancomycin and were found to show low cytotoxicity. In another study, MOF/Ag-derived [70] nanocomposite was evaluated for a synergistic sterilization effect attributed to its excellent metal ions releasing ability as well as its strong photothermal conversion ability. ZIF-8 was used as the precursor for the synthesis of C-Zn/Ag MOF. Firstly, C-ZIF was synthesized under high-temperature pyrolysis (800 ˚C) under argon gas. The organic skeleton was reduced to a graphitic carbon skeleton and other small molecules formed were removed by argon gas. In the above process, Zn^{2+} also gets reduced to Zn.

Finally, an *in situ* displacement reaction between Zn and Ag^+ in $AgNO_3$ occurs forming ZIF-8 derived C-Zn/Ag nanocomposites. The synthesis and characterization of C-Zn/Ag nanocomposites are illustrated in Fig. 9. Due to PTT upon NIR radiation, the nanocomposite was able to produce a massive amount of heat which can destroy the bacterial membranes and can also release Zn^{2+} and Ag^+ abundantly which can produce a chemical change in bacterial cells and finally cause cell death. The nanocomposite showed low cytotoxicity. The *in vivo* studies proved that the nanocomposite provides fast and safe wound sterilization effect comparable to vancomycin. A review article by Zhou *et al.* [71] describes several nanomaterials used as antiviral protective materials with potential antimicrobial efficiency that can be integrated into face masks and other protective equipment. This review also gives an insight on improving the antiviral capability of this equipment by product engineering, tuning the structural features of the material to increase filtration efficiency, and incorporating nanomaterials in the protective equipment that has entrapping potential with antiviral properties.

The increasing demand and disposal of the mask are leading to an economic and environmental crisis; thus, reusability and decontamination of the pre-used masks have been urgently assessed while preserving their integrity of the mask. Studies have revealed that out of the basic disinfection methods, chemical and UV methods denatured and disrupted the filtration efficiency, thus degrading the polypropylene by

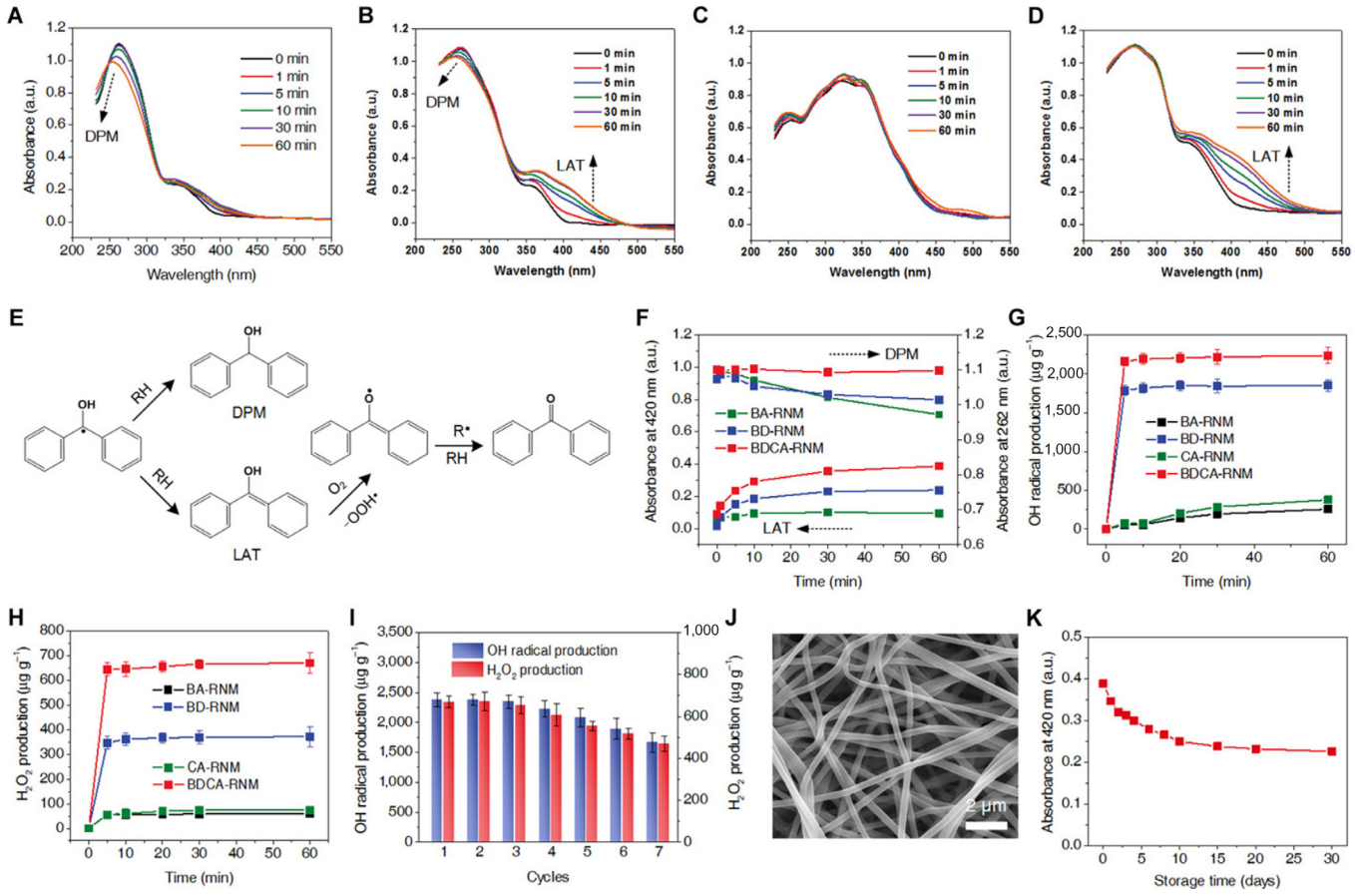

Fig. 6. Photo-induced rechargeable biocidal capability of bioprotective nanofibrous membranes (RNMs). A-D) UV–visible spectra of BA-RNM, BD-RNM, CA-RNM and BDCA-RNM respectively. E) Mechanism of the diphenylmethanol (DPM) and light-absorbing transient (LAT) species formation. F) Absorbance at 262 nm and 420 nm of DPM and LAT species as a function of irradiation time. G) and H) Amount of OH• and H_2O_2 released by RNMs under dark conditions after 1 h of daylight irradiation. I) Rechargeable capability of BDCA-RNM after seven cycles of charging and quenching J) FE-SEM images of BDCA-RNM after seven cyclic recharging. K) Change in LAT structure of BDCA-RNM against time [66].

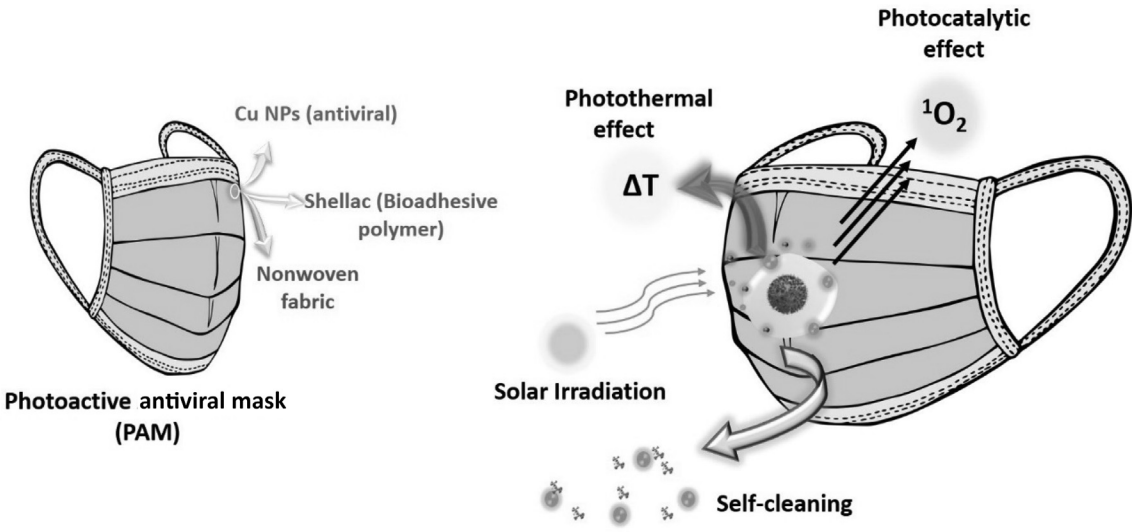

Fig. 7. Schematic demonstration of the photocatalytic, photothermal inactivation of the virus present in respiratory droplets and hydrophobic self-cleaning processes after solar irradiation [67]. Abbreviations: NPs, nanoparticles.

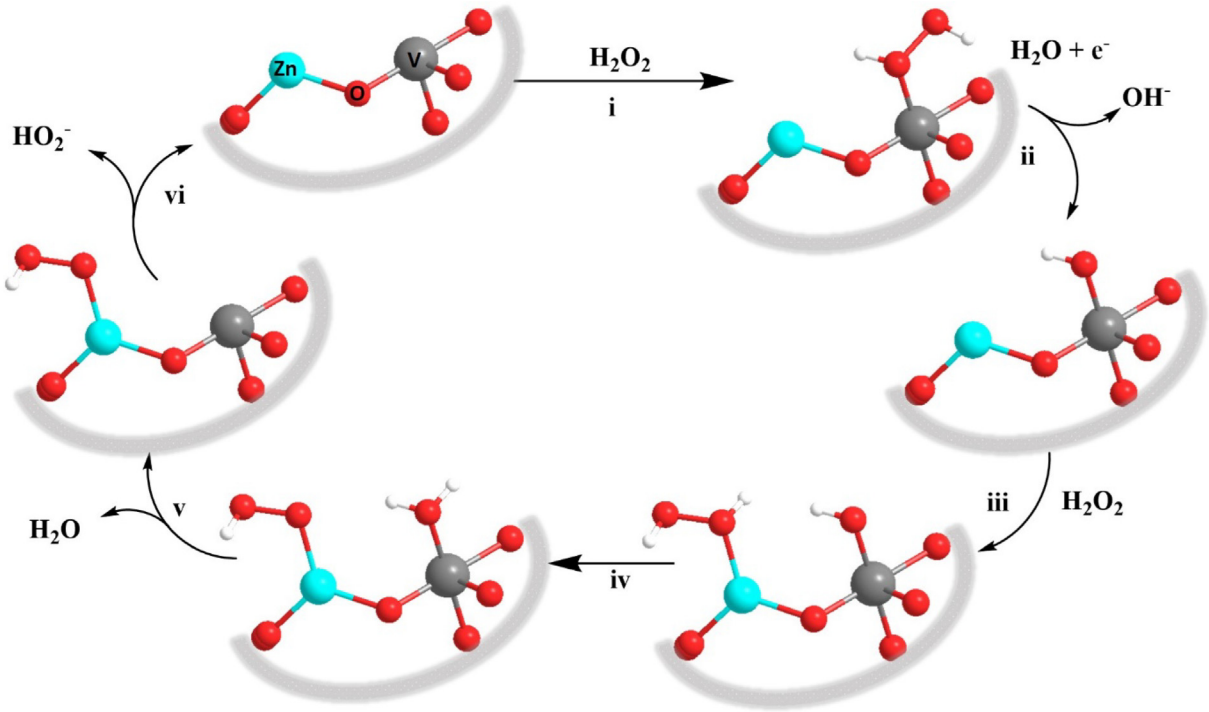

Fig. 8. The proposed mechanistic pathway for ROS generation by VO_X- AE at the active site (Zn-O-V bridge) in the presence of H_2O_2 [69].

breaking the chemical bonds [72]. A recent study by Liao *et al.* [73] on the reusability of N95 masks evaluated the disinfection methods for safer reusability of particulate respirators without compromising the mask protection. They suggested that UV irradiation can be the second choice, although the masks withstand 10 cycles of treatment but undergo degradation affecting the mechanical strength of the respirator. However, they recommend that heating under various humidities < 100 °C could preserve the filtration ability in a pristine N95 respirator. The steam treatment method was also found to be effective, however, care needs to be taken as prolonged steam treatment to disinfect mask may result in degradation of its filtration ability.

4. Vaccine development

Vaccine development primarily relies on the immune correlates against the viral infection for both humoral and cellular immunity. The elucidation of SARS-CoV-2 antigenic determinants is a potential target for vaccine design [74]. Studies have shown that S and N proteins are dominantly targeted by the immune response of SARS-CoV infected patients. Upon infection, the S protein is the main target for capturing antibodies that are responsible for virus entry in the host cell and the highly immunogenic N protein is abundantly expressed [75]. Recent studies suggest a glycan-controlled opening of the

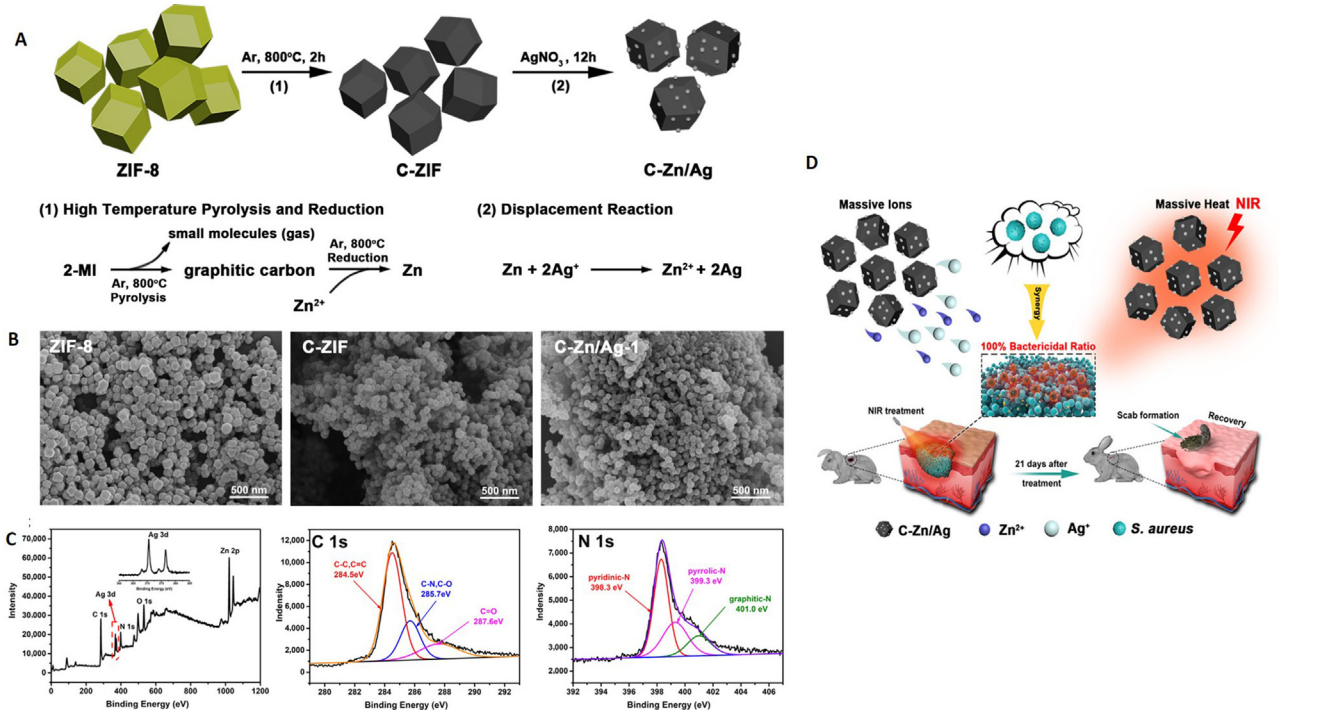

Fig. 9. Schematic representation of the metal-organic framework (MOF) / Ag^{+} nanocomposites with synergistic sterilization effect and photothermal conversion ability. A) Fabrication process of C-Zn/Ag nanocomposites and B) Scanning electron microscopy (SEM) images of zeolitic imidazolate framework-8 (ZIF-8), C-ZIF, and C-Zn/Ag-1. C) X-ray photoelectron spectra (XPS) of C-Zn/Ag-1. D) Schematic representation of overall photo to thermal conversion of C-Zn/Ag nanocomposites for synergistic sterilization [70], Copyright 2020 American Chemical Society.

SARS-CoV-2 S protein mechanism [76], sialic-acid containing glycolipid mediated pathway [77] that can assist in viral entry and spread of infection.

The vaccine targets are ideally expected to induce high titers of neutralizing antibodies (nAb) while maintaining a long-lasting immune memory [78]. Studies are also focused on understanding COVID-19 vaccine efficacy and their mechanistic links with nAb responses that would aid in strategic vaccine developments [79]. A recent review by Dai et al. [80] discusses the viral targets exploited for COVID-19 vaccine development, also highlighting the once in clinical trials. The COVID-19 vaccine candidates can be described in six different categories as depicted in Fig. 10 [81]. The protein-based vaccine includes the protein subunit vaccines, inactivated virus vaccines, and virus-like particles. Amongst the four major structural proteins, the S protein responsible for the recognition and viral entry serves as the main target for COVID-19 vaccines. The adenovirus expressing full-length S- protein vaccine developed for COVID-19 is under phase III clinical trials [82,83,84]. The gene-based vaccines include the DNA vaccines and mRNA vaccines that deliver the viral antigen encoding genes into the host cells producing viral vector vaccines *in vivo* [85]. Third category is the combination of protein-based and gene-based vaccines which includes live-attenuated viruses that are weakly or non-pathogenic, which mimic a live virus infection and induces broad antibody response by generating S proteins as well non-structural and accessory proteins.

The live-attenuated virus and inactivated virus vaccines serve as whole virus target which triggers the immune response by mimicking live virus infection. There are three vaccines based on inactivated virus strategy developed in China that are in phase III clinical trials [86–88]. Moreover, a review by Krammer *et al.* [81] provides more insightful information on the vaccine development for SARS-CoV-2. The nanoscale delivery system can play a predominant role in the success of the immune-mediated approach to vaccine development [89–90]. Several nanoscale delivery systems have been developed to achieve systematic delivery while overcoming the other limitations of degradation and low cellular uptake [91]. Nanotechnology-based approaches have addressed the problems arising due to the inherent stability of the mRNA, DNA, peptide, and oligonucleotide-based adjuvants in developing effective vaccines [89]. The groundbreaking technology by Moderna and Pfizer for utilizing lipid nanoparticle-based mRNA vaccines, approved by FDA is effective in controlling the rapid spread of COVID-19 [92]. Various biomaterial-based vaccine adjuvants studied are heat shock proteins, bisphosphonates, self-assembling peptides, nanoparticles (liposomes, alum particles) which can be useful for further boosting the immune response of the vaccine against COVID-19 [93–94].

Recently, a developed mRNA-based SARS-CoV-2 vaccine candidate (called ARCoV) by Zhang *et al.* [95] is under phase I clinical trial. In this approach, the mRNA is encapsulated within the lipid nanoparticle encoding the receptor-binding domain of SARS-CoV-2 as an antigen target. The liquid formulation of this vaccine is stable for at least one week at room temperature. The vaccine immunization was confirmed by a single dose or two doses of ARCoV in mice and non-human primates inducing anamnestic antibody and T cell response giving complete protection against the multiple SARS-CoV-2 strains. A low dose of ARCoV immunization induces higher neutralizing antibodies in comparison with the other reports utilizing convalescent serum [96] and DNA vaccine candidates tested in rhesus macaques [97] that showed lower neutralizing antibody titers. The ARCoV vaccine also exhibited full protection against SARS-CoV-2 lung infection. In another approach, Corbett *et al.* [98] have designed mRNA-encoding SARS-CoV-2 S protein (mRNA-1273) with high efficacy against SARS-CoV-2 infection without any immunopathology, which is evaluated for phase III clinical trial. Studies are carried out addressing the safety issues of the inactivated or live-attenuated vaccine candidates for SARS-CoV-2 infection [99]. Also, chimpanzee adenovirus-based vaccines have been explored inducing protective immunity against MERS-CoV infection [100].

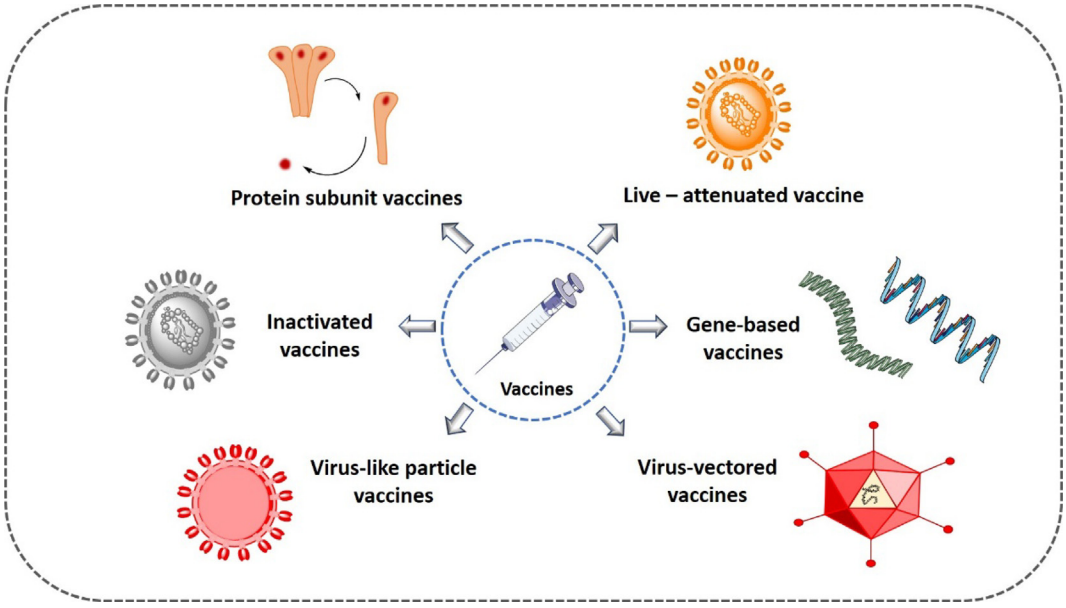

Fig. 10. Schematic illustration of various strategies used in vaccine development for coronavirus disease 2019 (COVID-19) [80–81].

The recent development of biomaterial COVID-19 vaccine based on mesoporous silica rod (MSR) loaded with recruiting factor, adjuvant and antigen provides robust cellular and humoral response against SARS-CoV-2. This novel approach by Langellotto *et al.* [5] in designing MSR vaccine facilitates a sustained release of immunostimulatory factors (granulocyte–macrophage colony-stimulating factor, toll-like receptor – 4 agonists monophosphoryl lipid A, and, SARS-CoV-2 viral protein antigens) loaded in MSR as depicted in (Fig. 11) in generating adaptive immunity with a durable immune response even against the weakly immunogenic receptor binding domain of the S protein. They experimentally demonstrated the immune response generated by the MSR vaccine formulated with SARS-CoV-2 antigen and the cumulative *in vitro* release (Fig. 12). Compared to other vaccine technology, the MSR vaccine is completely synthesized at room temperature which offers advantages over storage and transportation without any refrigeration required even at the vaccine administration site. Also, the final lyophilized form retains the bioactivity which allows further formulation wherein the antigen mixture can be reconstituted before injection. This offers a huge advantage for developing potential vaccines for the emerging SARS-CoV-2 variants which is the current research problem.

Recent studies also suggest that an intra-host evolution of SARS-CoV-2 in long-term infected immunosuppressed patients could be the source for the emergence of immune escape variants [101]. The outcome of SARS-CoV-2 variants with high potential of transmittance and severity of the infection being more, research has been driven towards studying the effectiveness of COVID-19 vaccines on these variants [102]. Thus, research progresses towards evaluating the vaccine efficacy and effectiveness on the variants and their escape from a vaccine-induced immune response [103]. Nonetheless, with the outcome of SARS-CoV-2 variants exhibiting a clear escape from vaccine-induced immune response, studies on designing future vaccines are crucial.

5. Drug development and treatment

Nanocarriers are widely employed as drug delivery vehicles to deliver small bioactive molecules and drugs in a single system. Such encapsulation of drug molecules within a nanoparticle offers several advantages including targeted delivery, control release, reduces systematic toxicity, and improved intracellular uptake. One such study on investigating nanolipogel as an emerging nanocarrier is made up of lipid-shell nanoparticles with a hydrogel core fabricated for encapsulation of drugs and delivery of antiretroviral drugs [104]. Biomaterial-mediated drug delivery has been widely investigated for treating viral infections with their relevant antiviral mechanism [105]. Several small organic molecules are used in the designing of metalloenzyme inhibitors as potential drug candidates against SARS-CoV-2. Such metal complexes have been described in a review article by Karges *et al.* [106] giving the mechanistic details of various metal complexes in targeting various proteins or enzymes involved in SARS-CoV-2 viral infection. For instance, ACE2 is a Zn metalloenzyme as well as a transmembrane protein; which is one of the cellular entry receptors for the viral S protein of SAR-CoV-2. Ott and his group were successful in showing that Au complexes functionalized with alkynyl ligands and *N*-heterocyclic carbene and Auranofin inhibits ACE2 [107,108]. Similarly, Papain-Like Protease (PL^{pro}) along with 3-Chymotrypsin-Like Protease ($3CL^{pro}$) are vital enzymes of SARS-CoV-2 and are the proteins responsible for viral replication, viral maturation, transcription, and its infectivity. Three complexes among the Au complexes and Auronofin discussed above developed by Ott and his co-workers were also shown to inhibit PL^{pro}. Auranofin was considered to be the most potent antiviral agent against SARS-CoV-2 as it can also inhibit the redox enzymes like thioredoxin reductase as reported by Marzo and Messori [109]. Also, a series of Ebselen derivatives have been screened for $3CL^{pro}$ enzymatic assay [110]. They also found that certain derivatives exhibited improved inhibition of $3CL^{pro}$ than Ebselen. Also, Re(I) tricarbonyl complexes have been found to inhibit the 3CLpro [111]. Also, an enzyme essential for the viral replication of the genome is the helicase (Nsp13). In this regard, studies have shown that Bi(III) complexes serve as potential replication inhibitors of SARS-CoV-2 [112].

Nanomaterials enabling the delivery of antiviral therapeutics into a cell, with reduced side effects can provide potential therapeutic solutions in drug discovery and development for COVID-19 treatment. The various strategies for achieving targeted drug delivery to the lung and cardiovascular system using biomaterial platforms is been covered in the recent review by Zarubova *et al.* [30]. The similarities between the human immunodeficiency viruses (HIV) and SARS-CoV or SARS-CoV-2 have been exploited in repurposing drugs that have been clinically approved for the development of potential therapeutics for COVID-19 [32,113]. Gillies and co-workers [114] developed multifunctional dendritic sialopolymersomes encapsulated with antiviral

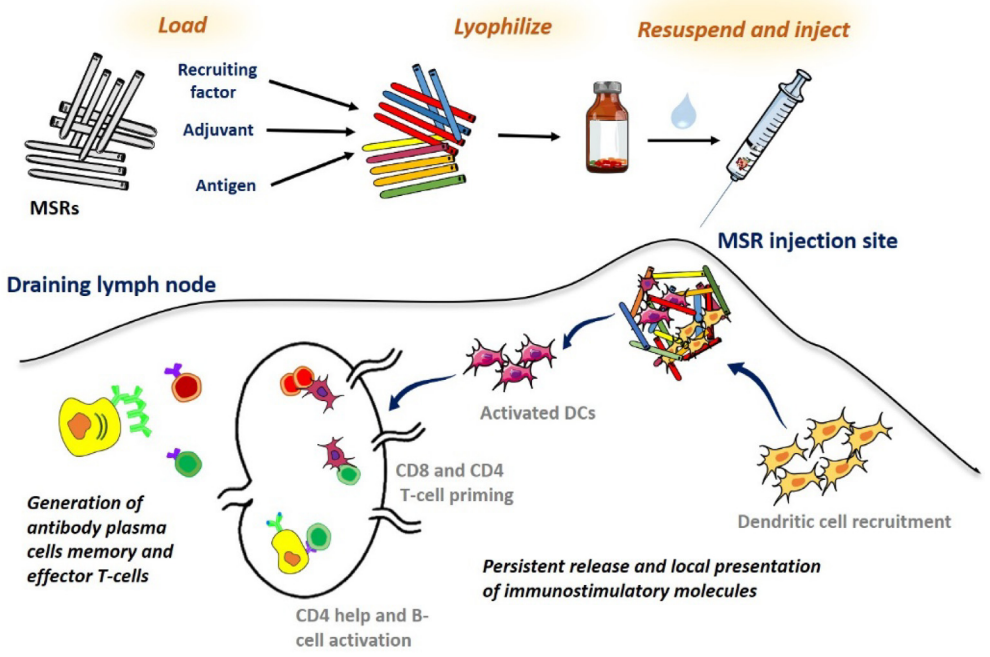

Fig. 11. Schematic illustration of the use of mesoporous silica rods (MSRs) for vaccination [5].

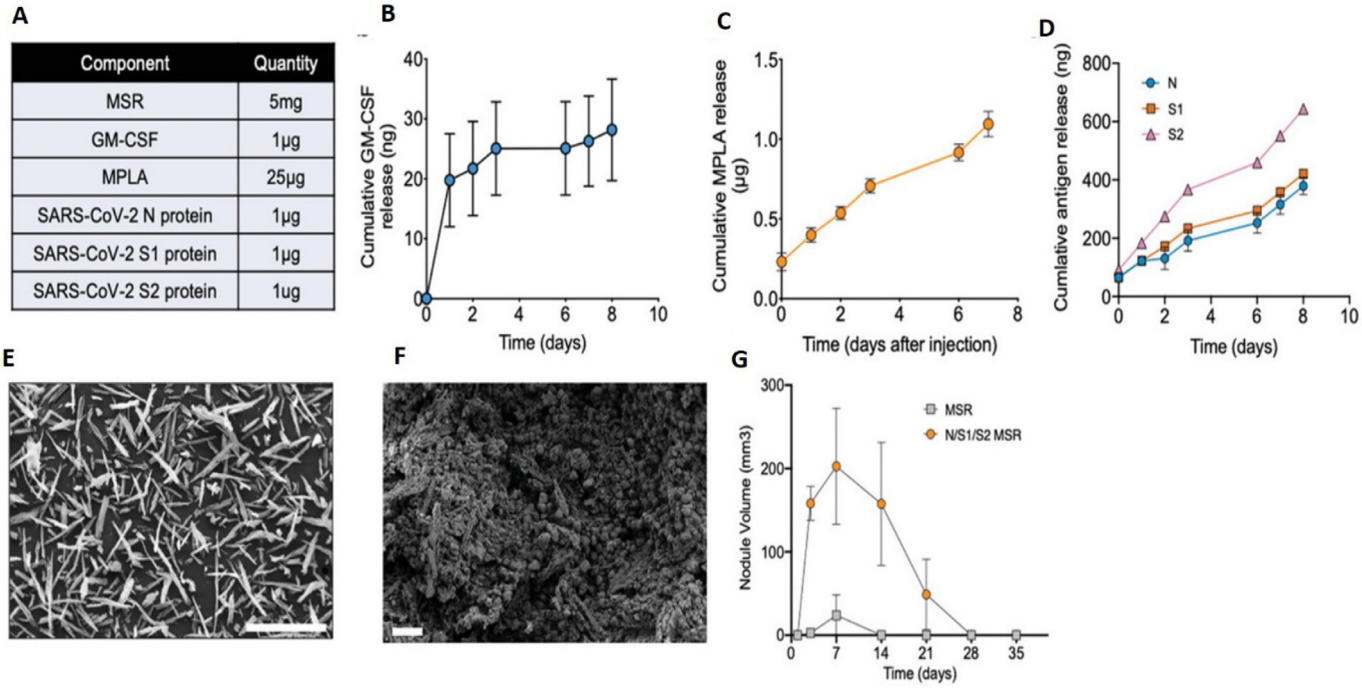

Fig. 12. Data representation of MSR vaccine formulated with SARS-CoV-2 antigens and sustainable release of vaccine adjuvants. A) Components of SARS-CoV-2 MSR vaccine with corresponding quantities. Cumulative *in vitro* release of B) GM -CSF, C) MPLA, D) antigens (N, S1 and S2) from MSRs vaccine. SEM images: E) unloaded MSRs before injection and F) SARS-CoV-2 MSR vaccine explanted 7 days after subcutaneous injection. G) MSR scaffold volume after injection over time [5], Copyright 2021 Wiley. Abbreviations: MSR, mesoporous silica rod; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

drug zanamivir (Influenza virus inhibitor) in its aqueous core actioning the viral infection process mechanism at two levels. The functionalization of polymersomes with surface azide was carried out followed by treating it with four equivalents of dendron relative to azide as illustrated in Fig. 13. First, the sialic acid N-acetylneuraminic acid (Neu5Ac) was conjugated to PEG -Poly (ε- caprolactone) polymersome surface to prevent viral entry by inhibiting the viral binding of hemagglutinin to sialic acids on host cells. Secondly, the viral replication was inhibited by preventing the release of progeny virus by zanamivir drug encapsulated within the polymer core. The developed system served as

a potential target binding and drug release biomedical materials. However, the *in vivo* and *in vitro* of this system still needed to be evaluated to demonstrate its antiviral efficacy.

The recently approved drug in Japan, Remdesivir drug, acts as an RNA-polymerase inhibitor against COVID-19 which is used as an emergency drug for COVID-19 patients [115]. Similarly, a guanine analog favipiravir that interferes with the viral RNA-polymerase function is also assessed for COVID-19 treatment [116]. The results from the recovery trial have revealed that low-cost steroid dexamethasone may save lives of COVID-19 ventilated patients, but the results are waiting for its approval [117]. The current treatment available to combat COVID-19 also focuses on the systematic treatment towards antiviral and anti-inflammatory therapies to prevent severe lung inflammation. The cardiovascular complications associated with COVID-19 with several coagulation disorders, in particular for the treatment of venous thromboembolism, low molecular weight heparin as a prophylactic anticoagulant is currently recommended [118]. To overcome endothelial damage and thrombotic risk some of the newly efficient anti-complement, drugs such as eculizumab [119] and narsoplimab [120] have been tested. Antiviral biomaterials including polymers, hydrogels, and metal nanoparticles are widely investigated for developing effective therapeutic transformations. The combination of clinically approved biomaterial-based therapeutics can serve for the development of a systematic drug delivery system with better efficiency in COVID-19 treatment.

6. Medical equipment

The emerging SARS-CoV viruses are known to cause lung inflammation resulting in fatal ALI. According to Chen and co-workers [121], acute respiratory failures during SARS-CoV infection can be controlled by tuning the anti-S antibody response. They proposed the underlying mechanism for virus-mediated acute lung injury (ALI). In 2012, Clay *et al.* [122] evaluated the SAR-CoV-specific immune response and lung inflammation in the SARS-CoV infected monkey. In this regard, radiographic testing in combination with molecular detection assays could be a better diagnosis in the treatment of COVID-19 infected patients. An automated deep-learning pipeline has been developed for disease diagnosis and discrimination of COVID-19 infection, and viral and non-viral pneumonia from chest X-Ray images [123,124].

One of the treatments given to SARS-CoV-2 patients is using extracorporeal membrane oxygenation (EMCO) machine that combines an oxygenator and blood pump to reduce thrombotic complications. This machine also utilizes a gas exchange membrane using polymethyl pentene material [6] or hollow silicon rubber fibers [125]. A Maquet Cardio help device is a portable EMCO machine developed by incorporating an oxygenator and blood pump in one small unit [126]. Such advances in the biomedical field can be useful for the early medication of infection for better clinical decision-making. Material chemistry and nanotechnology can be applied to develop self-cleaning filters in ventilators, also 3D-printing technology can be useful in fabricating new designs. A smartphone-based reagent-free nanostructured colorimetric device was developed for the detection of oxidative disinfectants. This can be useful in evaluating the disinfection treatment methods for the COVID-19. It consists of a transparent flexible polyethylene terephthalate substrate as a sensing element integrated with Au and Ag nanostructures. It works on the ability of the disinfectants to oxidize the Ag nanostructures, producing a colorimetric change detectable by a smartphone. The detection occurs in 5 min and only contact of the disinfectant with the sensing assembly is necessary and does not require any external reagents. The devices had LOD (~1 ppb) and showed good reproducibility [127].

Moura *et al.* reported designed a portable equipment that specifically classified the chest X-ray images for normal, pathological, and COVID-19 clinical conditions. It employs three complementary deep learning approaches to differentiate and analyze diverse individuals infected with COVID-19, other pathological conditions similar to COVID-19, and normal patients [128]. A noncontact POC imaging tool

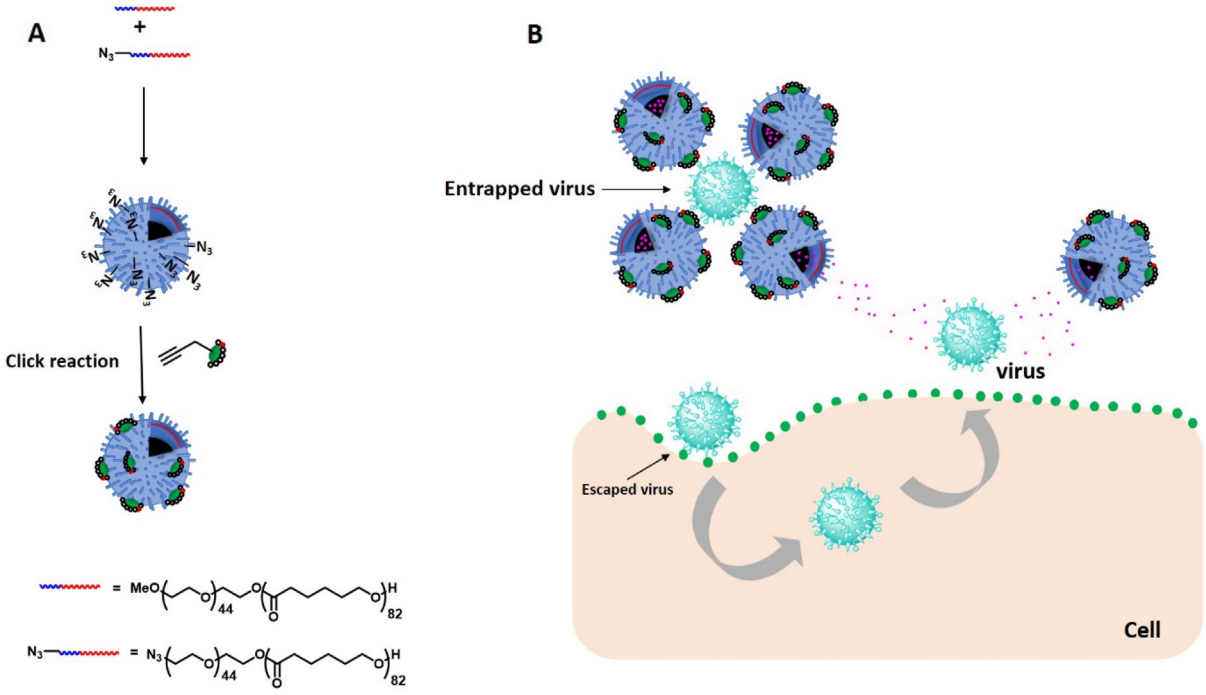

Fig. 13. Multifunctional dendritic sialopolymersomes with drug release properties. A) Synthesis of dendritic sialopolymersomes. B) Mechanism for functionalized dendritic polymerosomes [114].

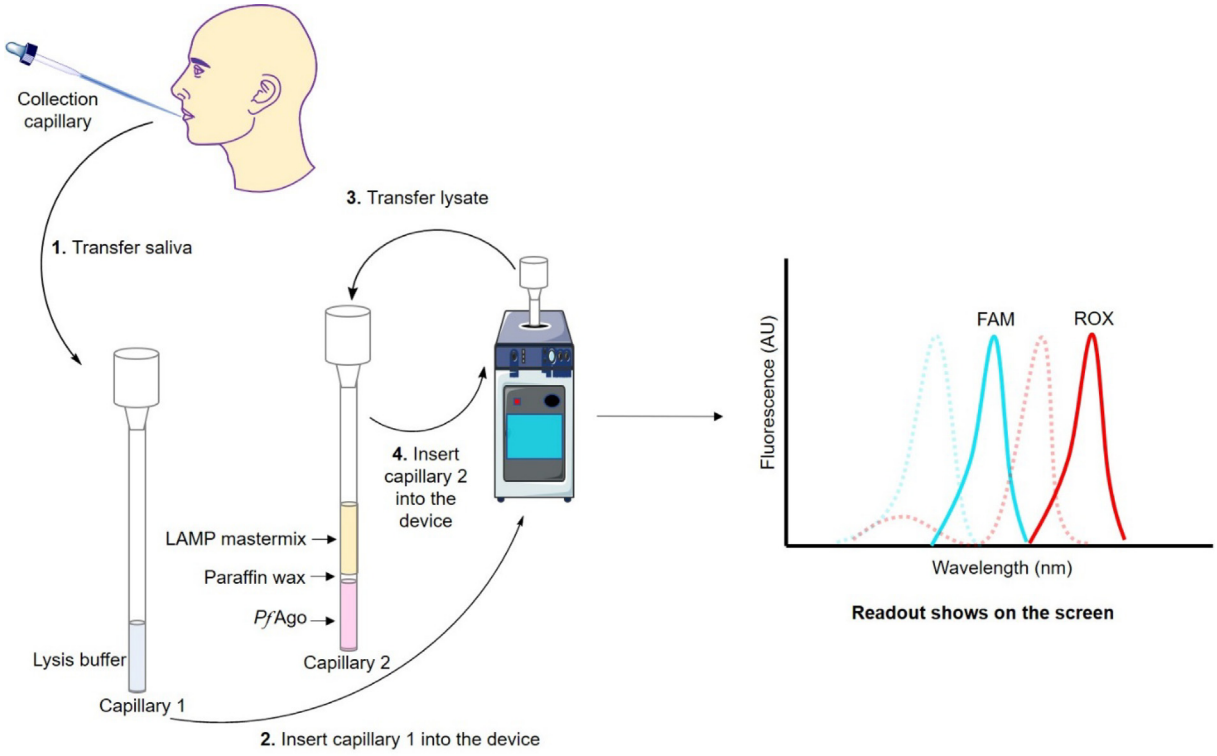

Fig. 14. Schematic illustration of Scalable and Portable Testing (SPOT) workflow assay [130].

was developed to detect COVID-19 with upto 92% sensitivity. Using the portable thermal camera the images of the backs of with and without COVID-19 individuals were captured and this was connected directly to smartphones. From the thermal images, the multiple texture and shape features were extracted by advanced image processing algorithms [129]. Another portable device for COVID-19 diagnosis, termed as Scalable and Portable Testing (SPOT) system powered by a battery is a very sensitive, rapid, and accurate. This device employs a 3D printed casing and internal precise temperature control with fluorescence detection (Fig. 14). The SPOT assay employs a one-pot mRT-LAMP followed by argonaute protein from the hyperthermophilic archaeon Pyrococcus furiosus (PfAgo) based on the detection of target sequence. It also enables the detection of the N gene and E gene from the saliva samples in a multiplexed reaction with the LOD of 0.44 copies/μL and 1.09 copies/μL, respectively, within 30 min [130].

Thus, the advancement in biomedical technology for developing better instrumentation for imaging and portable devices with required nanotechnology settings can be useful in improving the diagnostic approaches for COVID-19.

7. Conclusion

This review focuses on the recent advances in nanobiotechnology, immunology, and the biomedical field in the development of biosafety materials and provides a rational solution to fight against the SARS-CoV-2 infection. The emerging multidisciplinary research involving material science and biology in developing novel detection sensors for COVID-19 testing to improve accessibility, rapid screening, and efficiency is well suited for POC analysis. The current increasing demand for PPE desires the need for reusability which will have a significant impact on lowering the current socio-economic and environmental burden. 3D-printing technology plays a crucial role in improving mass production and re-designing consumable materials, thus bridging the gap between demand and supply. With the learning from the SARS-CoV-2 structural components and its mode of action, the huge efforts in investigating the immune response in the generation of antibodies and the development of vaccines. Understanding the immune-mediated effect at the different stages of infection, comorbidity condition, the age and the effect on pulmonary immunopathology of the infected patient can guide in the designing of COVID-19 specific vaccines and therapeutics. Along with the immunity responses related to SARS-CoV infection, it is important to have knowledge on the viral clearance and control the lung inflammation to prevent ALI. With the tremendous advances in biomaterial-based technology, the existing therapeutic strategies can be further improved in the treatment of COVID-19. Thus, the efforts from the scientific community to create awareness of the development and application of biosafety materials are important.

8. Future perspective

The emergence of viral infections has always posed a challenge in managing the spread of fatal infectious diseases across the globe. As witnessed from the current COVID-19 pandemic the large demand for PPE, lack of sufficient hospitalization facilities, and delay in drug and vaccine development had a serious impact on the population. The impact of prolonged lockdown and the fear of the outbreak due to the emergence of new variants continues to affect socio-economic activities. Hence, focusing more on the concept of biosafety materials by the scientific community is crucial in developing materials that can be useful to combat future pandemics in better ways. In this regard, learning from the COVID-19 pandemic the need to develop efficient sterilization methods or standard protocol for reusability of PPEs that can be easily accessible not only in hospitals but also to the general public is important. Tuning the surface chemistry of nanomaterials in the fabrication of PPE could enhance the efficiency with additional features, serving as sensors, POC analysis, and efficient reusable materials. Also focus on 3D-printing technology in designing and manufacturing PPE and swabs for diagnostic testing is limited. The advances in biomedical technology can be applied to medical imaging instruments and portable devices to improve diagnostic approaches.

From the previous reports [121,98], it is evident that the mRNA vaccine can offer a platform for designing new vaccine candidates with

potential immunogenicity and robust protection against SARS-CoV-2. The vaccine efficiency by employing a new adjuvant design by employing a combination of biomaterials and nanoparticles. The current scenario of the emergence of new SARS-CoV-2 variants resistant to the neutralizing antibodies generated after vaccination has posed a global threat. Thus, an urgent need in driving the COVID-19 research toward the understanding of the dynamics of viral evolution is becoming crucial for controlling the infection. Moreover, re-designing and developing future vaccines that can broaden the specificity of the immune response against the emerging new variants of concern is the current challenge. A combination of biomaterials with clinically approved drugs may serve to further enhance the therapeutic efficacy with systematic localized delivery. The pace of screening and testing of these therapeutics can be speeded with the help of computational studies. Moreover, the urgent need for systematically categorizing the treatment for patients based on the disease stage, high-risk patients, age, history of heart failure, and comorbidity conditions is currently crucial. Nevertheless, dexamethasone is awaiting its approval, a well-designed study on finding such a cheap steroid may save the lives of COVID-19 patients in serious cases. There is wide scope for redesigning the biomaterials with low cytotoxicity, improved drug release profile, and biocompatible. Also, the selective targeting of different biomaterials at infected tissue sites still needs to be better understood. Thus, it provides flexibility to explore the functionality and better understand the underlying mechanism of biomaterials in the treatment of viral infections. Effective treatment for COVID-19 will help to reduce the stay of hospitalization of infected patients, and the burden on the healthcare workers.

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Conflict of interest statement

The authors declare that there are no conflicts of interest.

Author contributions

Rasmi V. Morajkar: Visualization, Writing – Original Draft. **Akhil S. Kumar:** Writing – Original Draft, Visualization. **Rohan K. Kunkalekar:** Conceptualization, Writing – Review & Editing. **Amit A. Vernekar:** Conceptualization, Visualization, Writing – Review & Editing.

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