Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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A systemic review on liquid crystals, nanoformulations and its application for detection and treatment of SARS – CoV- 2 (COVID – 19)

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ABSTRACT

The COVID-19 is a pandemic caused by the SARS-CoV-2 virus, has instigated major health problems and prompted WHO to proclaim a worldwide medical emergency. The knowledge of SARS-CoV-2 fundamental structure, aetiology, its entrance mechanism, membrane hijacking and immune response against the virus, are important parameters to develop effective vaccines and medicines. Liquid crystals integrated nano-techniques and various nanoformulations were applied to tackle the severity of the virus. It was reported that nanoformulations have helped to enhance the effectiveness of presently accessible antiviral medicines or to elicit a fast immunological response against COVID-19 virus. Applications of liquid crystals, nanostructures, nanoformulations and nanotechnology in diagnosis, prevention, treatment and tailored vaccine administration against COVID-19 which will help in establishing the framework for a successful pandemic combat are reviewed. This review also focuses on limitations associated with liquid crystal-nanotechnology based systems and suggests the possible ways to address these limitations. Also, topical advancements in the ground of liquid crystals and nanostructures established diagnostics (nanosensor/biosensor) are discussed in detail.

Contents

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1. Introduction

The end of 2019, saw the emergence of a dangerous viral infectious illness which originated from China and quickly spread over the world and eventually becoming a pandemic [1]. The outbreak was labeled as pandemic in March 2020 [1]. This uncommon and quickly spreading virus has been dubbed "coronavirus disease-2019″ (COVID-19) by the World Health Organization (WHO), with the viral agent being dubbed "severe acute respiratory syndrome – coronavirus-2″ (SARS-CoV-2). It has been a worldwide pandemic which is wreaking havoc on people's health and the economy [2]. SARS-CoV-2 causes severe respiratory issues by triggering an immediate immunological response, which is the predominant cause of death, with a mortality rate of 0.05–19.4% per country. SARS-CoV-2 is a single stranded, enclosed, positive-sense RNA virus from the genus betacoronavirus [3]. The genus includes the human coronaviruses (HCoVs):HCoV- HKU1, MERS and HCoV-OC43 which was responsible for the SARS pandemic in 2002–2004 and has 79 % nucleotide sequence similarity with SARS-CoV-2 and MERS- CoV. SARS-CoV-2 employs its required receptor, angiotensin-converting enzyme-2 (ACE2), to enter cells [4], which was initially discovered in 2003 as the SARS-CoV receptor [5]. ACE2 also serves as a receptor for the alphacoronavirus HCoV-NL63, which, together with HCoV-229E and the betacoronaviruses HCoV-OC43 and HCoV-HKU1, is a known source of mild upper respiratory tract infections [3].

Increased mucous production is caused by SARS-CoV-2, which obstructs the alveoli and reduces oxygenation in the blood. The endocytosis and amplification of the signal cascade in the lungs, which is initiated by cytokine storms, induces an inflammatory reaction in the lungs and an acute immunological response [3,6]. The virus has the potential to infect the digestive system as well as other key organs. It is capable of reaching any tissue that expresses the ACE2 receptor [4].The effect of the S protein, which seems to be a distinguishing trait of the infected cell for therapeutic efforts, is responsible for much more than 80% of SARS-CoV-2 and recipient cell membrane contacts [5]. HCoVs are among the top 10 viruses which cause human fatality. There have been around 176 million confirmed cases worldwide, with 3,811,561 SARS-CoV-2-related deaths [5]. Despite the fact that coronaviruses infect living creatures, some species, such as bats, which harbor the most diversity of coronaviruses, are impervious to coronavirus-related illness [7]. Fever, difficulty in breathing/shortness of breath, and cough are the most common COVID-19 symptoms. In more catastrophic situations, infection can lead to pneumonia, SARS, and even death. The associated symptoms appear within 2–14 days. The enormous impact of this pandemic will conceivably provide substantial difficulties to the global health department, as well as far-approaching ramifications for the international economy, if the viral transmission is not adequately handled in the near future. This review article provides an in-depth look into SARS-Cov-2, as well as a description of how it enters cells and produces havoc to immune response. Applications of liquid crystals and nanoformulations in various aspects of SARS-CoV-2 are also reviewed.

The infection has spread across countries and caused a high fatality rate in immunocompromised and diabetic patients, and elderly population. This highly infectious illness poses a significant danger to health-care systems. It wreaked havoc on the world's continents in ways that no one could have foreseen. As a result, a number of major funding agencies have issued a request for proposals to diagnose and treat the COVID-19 pandemic utilizing sophisticated technology-based approaches, including nanotechnology. Researchers in the field of nanotechnology may help combat COVID-19 by donating their time and expertise. The nanotechnology sector of diagnostics and healthcare offers some new research targets that might be constructed, enhanced, optimized, and developed for existing/new materials.Some of the potential research targets for COVID-19 include point-of-care diagnostics (POCD), novel pharmacogenomics, screening and monitoring, immunotherapies, research, technology and innovation, repurposing existing medicines for possible medicinal uses, antimicrobial/ antiviral nanocoating or spray-based coating for PPE development, viral RNA and magnetic nanoparticles (NPs) [6], and rapid detection kits.

Liquid crystals, a prospective branch of materials that are exceedingly sensitive, quick-responding, and minimal cost, are often employed to detect weak environmental stimuli and have received a lot of attention. Because of its self-assembly potential and functional variety, numerous research groups have focused on building liquid crystal-based biosensors during the last decade [8,9]. The discussed recent research on the formulation and development of biosensors based on liquid crystal is established on the fact that interactions amongst proteins, biomolecules, enzymes and liquid crystal molecules can have a direct influence on the orientation of liquid crystals. Using the sensing idea of biosensors employing liquid crystal, and also their signal recognition by testing interfacial contacts, the conversion, amplification, and quantification of information from targets into electrical and optical properties is discussed. Liquid crystal biosensing targets such as proteins, cells, microbes, nucleic acids, ions, glucose, enzymes, and other micromolecules necessary for human health are also introduced. Tunable stimuli-responsive liquid crystal biosensors have been reported to have bright prospects and great superiorities in biological applications because of their ability to self-assemble, chemical variety, and high sensitivity. Finally, difficulties and opportunities for the manufacturing and deployment of liquid crystal biosensors are reviewed in order to improve their performance and fulfill their potential in the biosensing business. The sensing mechanism of liquid crystal, according to Rastogi et al. [10], is based on a change in its molecular orientation when oil palm leaf NPs are added, with graphene oxide acting as an alignment layer. Optical texture analysis was used to capture this orientational shift. As a result, liquid crystal serves as a biomolec-

ular OPL sensor. To date, there have been just a few published research investigations on SARS – Cov 2 detection utilizing liquid crystal-based sensors. This review article addresses the development of liquid crystal-based sensor and immuno-sensor for SARS-Cov-2 diagnosis and its antibody that combats it [11]. The developed kit is a low-cost, quick, and reliable portable home kit based on a straightforward diagnostic approach for the SARS-CoV-2 virus's self-detection.

Expanding testing capabilities, developing effective medicines, and developing safe vaccinations that produce long-lasting immunity are all strategies that must be investigated. Biosensing, medication delivery, imaging, and antimicrobial therapy are just a few of the medical uses of NPs. SARS-CoV-2 is an infectious virus with a crown -like morphology and a size of 60–140 nm. Because of their structural similarities, chemically synthesized NPs can closely mimic viruses and have significant interactions with their proteins. As a result, NP-based solutions have future for combating this virus and hold a lot of fruitful outcomes. Previously NPs has been reported to be effective against a variety of viruses, particularly those belonging to the family of *Coronaviridae*. This comprehensive review addresses the concept of NPs in diagnosing, treating, and immunizing against the other two pandemic coronaviruses, the SARS virus of 2003 and the Middle East respiratory syndrome (MERS) virus of 2012.

Other coronaviruses, such as avian coronavirus, feline coronaviruses (FCoV), HCoVs, infectious bronchitis virus (IBV), coronavirus models, such as porcine epidemic diarrhoea virus (PEDV), transmissible gastroenteritis virus (TGEV), porcine reproductive and respiratory syndrome virus (PRRSV), and others mutated version of SARS- CoV-2, are also introduced. This review synthesizes key findings from previous antiviral research with fresh SARS-CoV-2 research to provide effective diagnostic tools and nanoformulation tactics in the future to battle COVID-19 and other pandemics.

2. Cellular mechanism for the SARS-CoV-2 pathway

Coronavirus infection causes the development of "replication organelles" [4]. SARS-CoV-2, similar to MERS-CoV, is classified as a first-generation virus: proprotein convertases, such as furin cleave its S protein in virus-generating cells into "S1 and S2" subcomponents [12,13]. The "S1"subcomponent contacts ACE2, whereas the "S2"subcomponent binds to the membrane and attaches the S protein. When a new cell is infected, the "S2" subcomponent also carries a fusion peptide (FP) and additional gears essential for membrane fusion [14]. SARS or MERS coronavirus are assumed to arise from the endoplasmic reticulum (ER) and contain viral replication complexes, confiscating them from cellular innate immune components.The replication site infuses retroviruses structural proteins and sequencing RNA, which are subsequently transmitted to the (ERGIC) ER–Golgi intermediate zone, wherein virus congregation and budding occur [15,16].The proteins S (spike), E (envelope), M (membrane), and N (nucleocapsid) are the only ones built-in into the virion structure. The S protein, which is a trimer with the semblance of a crown (corona), facilitates important entry processes such as receptor binding domain (RBD) and membrane fusion [4]. One of the trigger for SARS-CoV-2 is the generation of a S2′ site by the fragmentation of a second site internal to the "S2" subcomponent. This S2′ position becomes visible when the virus interacts with ACE2.The cleavage of S2′ spot either by TMPRSS2 (transmembrane protease serine 2) [17,18] at the surface of cell or in the endosomal compartment by cathepsin L [19] after ACE2-mediated endocytosis [20], releases FP [4]. Every step of this process is crucial because the viral genome requires cytoplasmic access, which is only possible when the opening between the viral and cell membranes grows and the two membranes are entirely linked. RBD affinity for ACE2 has also enhanced as a result of frequent recent mutations (Supplementary table 1 (TS1)). Unfortunately, this adaptation gives the virus considerable leeway to tolerate immune-evasion alterations, which will likely reduce the virus's affinity for ACE2.

SARS-CoV-2, on the other hand, appears to be more reliant on TMPRSS2 than cathepsins, according to research conducted so far [4]. Alternatively, CoV-2′s with SARS affinity for TMPRSS2 might potentially be explained by the SARS-CoV S protein's strict folding, which permits accurate cathepsin L (a low substrate specificity protease) exposure to the S2′ site. Because of variation in the folding of the SARS-CoV-2 S protein, cathepsin digestion is not limited to the S2′ site. This results in neighboring strands being over digested, rendering the fusion process useless. SARS-CoV-2 would be compelled to choose TMPRSS2 over cathepsins under these conditions (role of cathepsins as mentioned in [4]). If this is the case, SARS-furin CoV-2′s and TMPRSS2 dependencies appear to indicate a choice of less terrible possibilities. The widespread usage of TMPRSS2 inhibitors is more likely to result in viral modifications that allow it to escape the inhibitory impact of interferon-induced transmembrane proteins (IFITM) proteins and exploit cathepsins more accurately. This entails the value of using combinational treatments that target both routes (camostat mesylate plus hydroxychloroquine). Camostat mesylate, as a serine protease inhibitor, inhibits the TMPRSS2-mediated entrance route. The entrance route for cathepsin-mediated enzymes is impeded by the acidification of endosomes, which hydroxychloroquine and chloroquine both inhibit. RBD affinity for ACE2 has also enhanced as a result of frequent recent mutations (Supplementary table 1 (TS1)). Unfortunately, this adaptation gives the virus considerable leeway to tolerate immune-evasion alterations, which will likely reduce the virus's affinity for ACE2.

3. Detection of SARS-CoV-2 using liquid crystal as biosensors

Liquid crystals are a new type of sensing material that has qualities that are akin to liquids and solid crystals in terms of flowability and order. Because of its advantage of functional versatility and self-assembly, liquid crystals have a remarkable capacity to amplify signals and sense environmental forces, and have indeed been commonly used in biosensing devices. Interactions between biochemical species and liquid crystal molecules can produce direct changes in liquid crystal molecular orientation, which can be exploited to sense substances in liquid crystal-based sensing systems. The mechanics of liquid crystal-based biosensor processes are primarily based on liquid crystal molecule rearrangement, with a variety of detecting methods for capturing the optical and electrical properties of liquid crystal molecules being researched. Because of its advantages of low cost, high sensitivity, and quick response, liquid crystal-based biosensors have lately attracted a rising number of researchers, as shown in Supplementary table 2 (TS2).

Liquid crystal-based biosensing devices have overcome some initial hurdles. However, there is still a long way to go before liquid crystal biosensors can be used for commercial application, with four major difficulties to address:

(1) Despite what some research claim at the nanoscale level, electrostatic phenomena or binding behaviors plays a central role in contacts and detection [21,22], internal mechanisms and detection are still unclear.
(2) Liquid crystal microdroplets have been used to implement all documented lasers that may offer optical feedback in liquid crystal biosensor. Other cavities (including the random

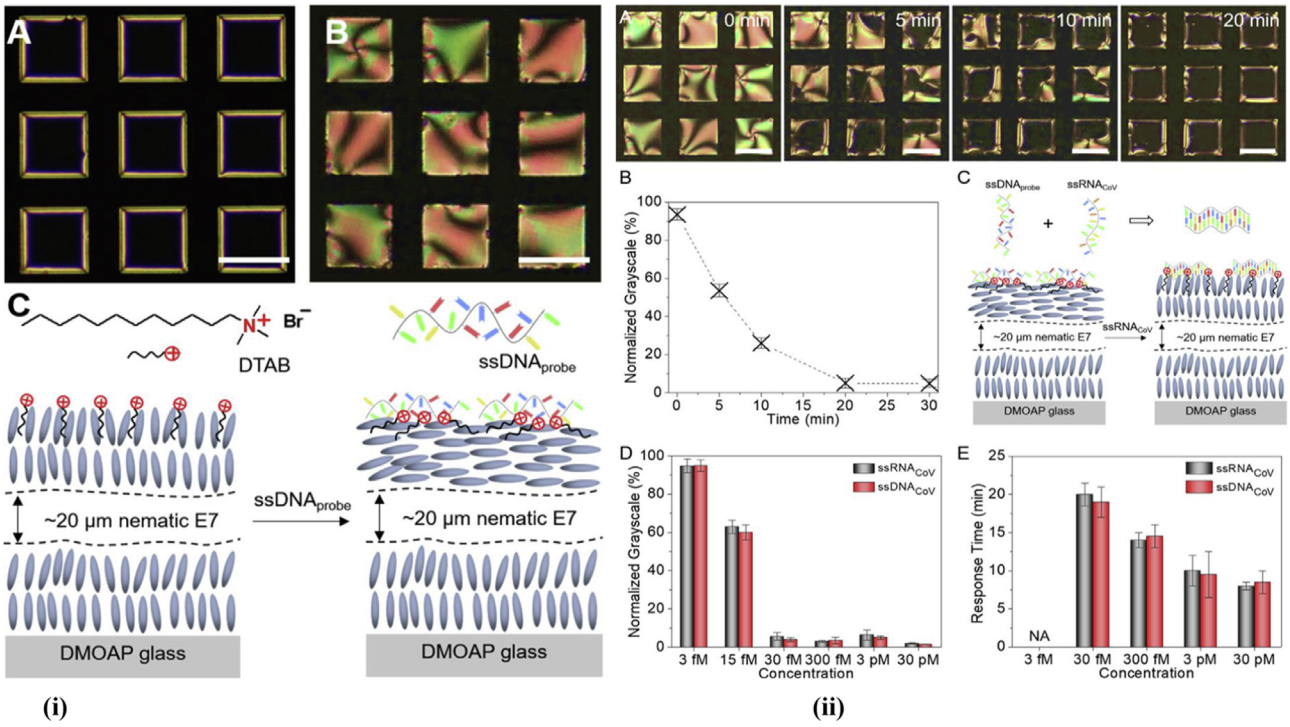

Fig. 1. (i): Probe DNA adsorption at the aqueous-liquid crystal interface with cationic surfactants (A and B).Optical micrographs (crossed polarizers) of the E7 film were obtained following the adsorption of (A) DTAB and the subsequent adsorption of (B) the ssDNA probe. 100 mm scale bars (C) The liquid crystal film decorated with DTAB and its generated optical response to the ssDNA probe's adsorption is depicted schematically [9]. **(ii):** SARS-CoV-2 RNA adsorption at the aqueous-liquid crystal Interface (A) Crossed polarizer optical micrographs showing the dynamic reaction of the DTAB/ssDNA probe-decorated E7 film to ssRNACoV adsorption. 100 mm scale bars (B) Change in normalized grayscale of E7 films' with time following ssRNACoV adsorption. (C) Schematic representation of the liquid crystal film's decorated with DTAB/ssDNA probe and its optical response to ssRNACoV adsorption. (D & E) Change in normalized grayscale and response time of E7 films decorated with DTAB/ssDNA probe with ssRNACoV and ssDNACoV concentrations. The error bars represent the average of three different measurements [9].

laser or original F–P cavity) should be able to examine the biological system behaviors and may be able to circumvent the form limits on microdroplets for lasing production.

(3) To meet the commercialization requirement, stable sensor systems and responsive signals are necessary. In the production of liquid crystal biosensors, there are still certain unstable aspects. Deviations in liquid crystal microdroplet sizes and liquid crystal cell thicknesses, for example, provide a barrier to biosensor accuracy. Furthermore, signal examination using computer-aided tools/software or artificial intelligence (AI) must not be overlooked; otherwise, analyzing such a vast quantity of telemetry data, such as grey values and bright areas obtained by computer image processing to substitute naked-eye illustrations, will take a significant amount of time.

(4) Due to the stored elastic energy, some particular biomolecules (for example, lipids [23]) can alter the orientation of liquid crystal molecules as anisotropic elastic materials. Further, more research is the need of the time to see if the behaviors of liquid crystal molecules may regulate the activities of living organisms in the opposite direction. This might lead to new ideas and proposals for liquid crystal materials that allow for bidirectional control of liquid crystal and biomolecules.

The detection of SARS-CoV-2 using thermotropic liquid crystals as a possible diagnostic tool was reported by Xu et al. [9]. As shown in Figs. 1 and 2. Herein, four steps were involved which are as follows:

1. A surface functionalized with DTAB (dodecyltrimethylammonium bromide), a cationic agent, was produced on sheets of the widely used nematic liquid crystal E7 that were micrometer (μm) thick. On a glass substrate adorned with DMOAP, or dimethyloctadecyl [3-(trimethoxysilyl) propyl] ammonium chloride, E7 molecules were arranged in homeotropic orientation.
2. At the aqueous - E7 interface which was decorated with DTAB, a nucleotide corresponding to the targeted SARS-CoV-2 ssRNA motif was immobilized. Electrostatic interactions drew oppositely charged ssDNA (negative charge) and the DTAB (positive charge) at the aqueous-E7 interface.
3. With the adsorbed ssDNA probe, ssRNACoV was delivered to the cationic DTAB loaded E7 interface. The temperature was then raised to the T_m of ssRNACoV's i.e., 48.7 °C. During the process, E7 surface temperature was maintained using a Peltier hot stage (Linkam PE120).
4. Pictures obtained with a CCD camera on a polarized microscope were used to quantify the optical manifestation of the E7 films adsorbed with RNA.

By increasing the concentration from nanomolar to femtomolar quantities, the findings demonstrated the E7 surface's detection limit for the target ssRNA. Polarizing layers were integrated throughout the sensor's architecture to help detect the confirmation shift in the liquid crystals using visible light. To provide constant sensor lighting, the sensor gadget was paired with a holding clip and an appropriate smartphone app. The COVID-19 project's next urgent step is to move the test into a clinical assess-

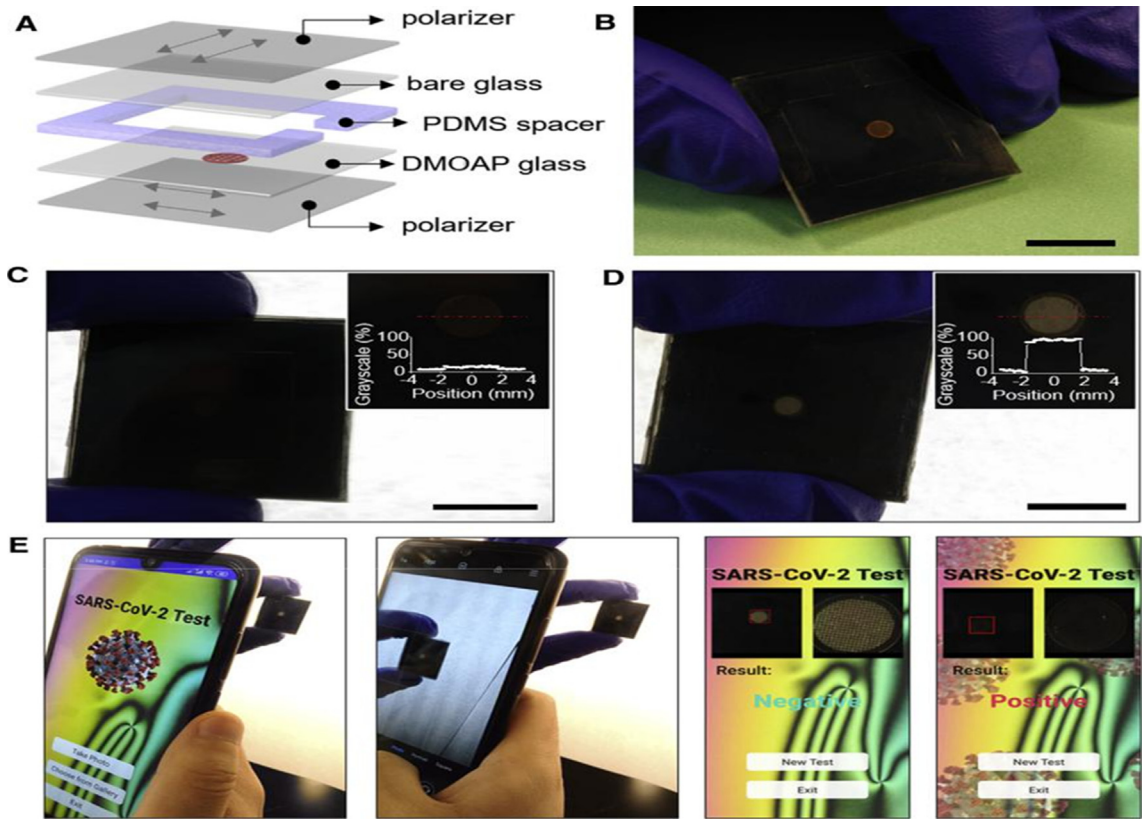

Fig. 2. Devise design and schematic illustration of a liquid crystal-based ssRNACoV diagnostic kit. (C and D). After adding 30 fMssRNACoV and 30 fMssRNASARS to the liquid crystal-based detection kit, optical elucidation of the kit under a light was performed. The inset shows the normalized grayscales of TEM grids following the adsorption of ssRNACoV on 1 cm scale bars. (E) Readout of negative (on adsorption of 100 nMssRNASARS) and positive (on adsorption of greater than 30 fMssRNACoV) test findings using a smartphone app [9].

ment phase, which will include testing in a biosafety level 3 (BSL-3) laboratory with authentic patient samples.

4. Liquid crystal – Based immunosensor

Jeon et al. [11], developed a new immunosensor based on liquid crystals to detect antibodies to SARS-CoV-2 N protein. The antigen was immobilized on nanostructure's surface and the antigen–antibody interaction was monitored. This phenomenon was explored for developing biosensors and the produced biosensor demonstrated a quick optical response to the change in orientation order of the liquid crystal molecules. In the absence of antibody, the liquid crystal molecules were arranged in the direction of nanostructure anisotropic topography as depicted in Fig. 1a in [11]. Henceforth under polarizing optical microscope (POM), a uniform texture was observed (Fig. 1b [11]). On introduction of antibodies, antigen–antibody complexes were created which distorted the parallel organization of liquid crystal molecules. This resulted in randomized liquid crystal molecule orientation (Fig. 1c [11]), which was detected as random texture under POM (Fig. 1d [11]). The establishment of this methodology for SARS-CoV-2 antibodies recognition provided a selective and a sensitive biosensing platform. The findings imply the proposed immunosensor is an easy, inexpensive, and label - free biosensing platform. Furthermore, it may be used in clinical practice to identify the existence of prior COVID-19 infected individuals because it only requires a 2 μL sample volume and allows for a quantitative evaluation of the selectivity for antibody recognition.

4.1. Preparation of antigen immobilized nanostructure surfaces

Oblique deposition method using electron beam evaporator was employed to create a gold substrate. Anisotropic nature of nanostructure topology on fabricated substrate was confirmed from the observed topological image with an amplitude of 1 to 4 nm and a wavelength (λ) 20 to 50 nm [24]. The alignment behavior of liquid crystals on the modified substrate was studied after the formation of self – assembled monolayers (SAMs). SAMs was formed on the gold substrate using a 1 mM ethanolic solution combined with 11-mercaptoundecanoic acid (MUA) and 1-decanethiol at 7:3 ratio. When the lone-pair of electrons in the sulphur of MUA's sulphhydryl functional group and 1-decanethiol contact with gold, a weak coordination bond was formed [25-50]. An optical sample cell was fabricated by using the glass substrate coated with trichloro (octyl) silane (OTS) and injecting liquid crystals. Under POM, the liquid crystals' optical response had a consistent texture, indicating the uniform distribution of liquid crystal molecules on the substrate surface. As a consequence of this finding, liquid crystal molecules appear to be oriented in the direction of the anisotropic nanostructure topography generated by oblique deposition of gold, resulting in homogeneous liquid crystal cell texture.

To immobilize the SARS – CoV – 2 N protein antigens on the mixed-SAM-functionalized nanostructure, the N-hydroxysuccinimide NHS/EDC (N-(3-Dimethylaminopropyl)-N′-ethyliquidcrystalarbodiimide hydrochloride) protocol was utilized. The antigen was then incubated in an aqueous solution for 30 min to produce a strong amide bond between the antigen and the car-

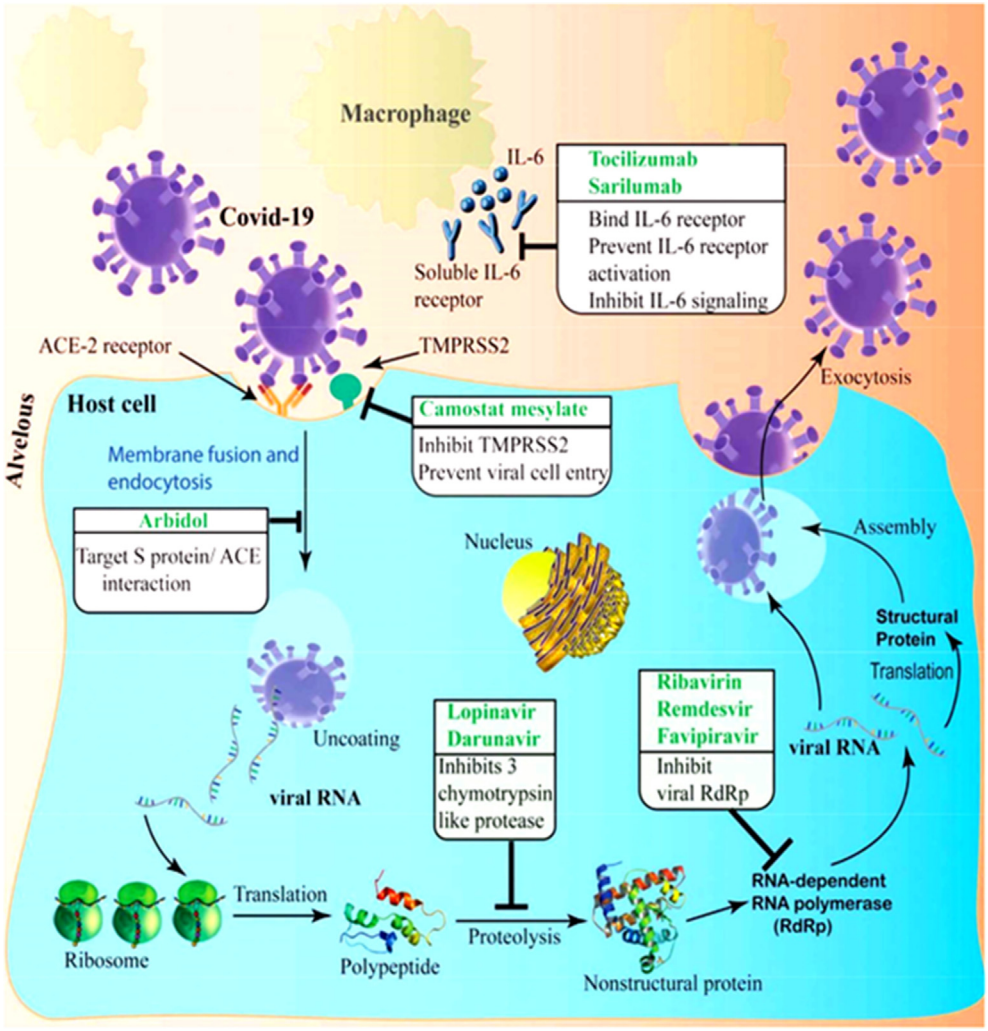

Fig. 3. COVID-19 pathway points and potential repurposing pharmacological target [3,63].

boxylic (–COOH) functional group activated by the NHS ester [28]. Liquid crystal alignment is hampered by high concentration of immobilized antigens, however; low concentration of immobilized antigen lowers the target antibody's limit of detection (LOD). As a result, Jeon et al. [11] performed a study to validate improvements in the liquid crystal optical micrographs by examining birefringence pictures of optical sample cells immobilized with antigens at different doses in order to optimize the areal density distribution of antigens. Under POM, consistent liquid crystal textures were seen while examining optical micrographs of sample cells to substrate modified with 10 and 100 nM antigen in phosphate - buffered saline solution(PBS) (Fig. 3a,b in [11]). The observed textures had defect or disclination lines which were different from the regular textures. Liquid crystal alignment defects were created because of the protein or other macromolecules on the solid surface [29,30]. Nonetheless, they are consistent textures rather than haphazard ones, since the region had uniform brightness except for the defect line, and the brightness variance between 0° and 45° was considerable. Random liquid crystal textures were seen under POM at doses greater than 100 nM, on the other hand (Fig. 3c, d in [11]).

4.2. Anti-SARS-CoV-2 N antibody detection

The antigen–antibody immune complexes were generated when the SARS-CoV-2 antibody solution was incubated on the antigen-immobilized surface and expected to disrupt the uniform arrangement of liquid crystals. The ethanolamine solution was added before incubating the antibody solution to avoid imprecise binding produced by residual –COOH (carboxylic) functional moieties that did not attach to the antigens on the surface. A random liquid crystal texture was created by observing the optical texture response of the optical sample cell treated with antibody (1 g/mL) in PBS solution for 3 h (Fig. 4a in [11]). This finding supports the hypothesis that the antigen–antibody complexes produced on the nanostructure disrupt the alignment of liquid crystal molecules, ensuring a shift from even to uneven distribution of the liquid crystal molecules. This indicates that SARS-CoV-2 antibodies may be detected using a liquid crystal-based immunosensor. It was the first time a liquid crystal-based sensor was used to detect anti-SARS-CoV-2 antibodies.

The grey scale values of the SARS-CoV-2 liquid crystal optical pictures taken at 0° and 45° were identical, indicating that the liquid crystal textures were random. However, at 0° and 45°, the grey scale values of the liquid crystal optical pictures for the two control proteins, albumin from human serum HSA and BSA, were considerably different, showing that the liquid crystal textures were not uniform. This research demonstrated that liquid crystal-based immunosensor can quantify the difference in optical texture response between control proteins and SARS-CoV −2 antibody, making it potentially useful as a portable sensor gadget that can be examined with a smartphone app.

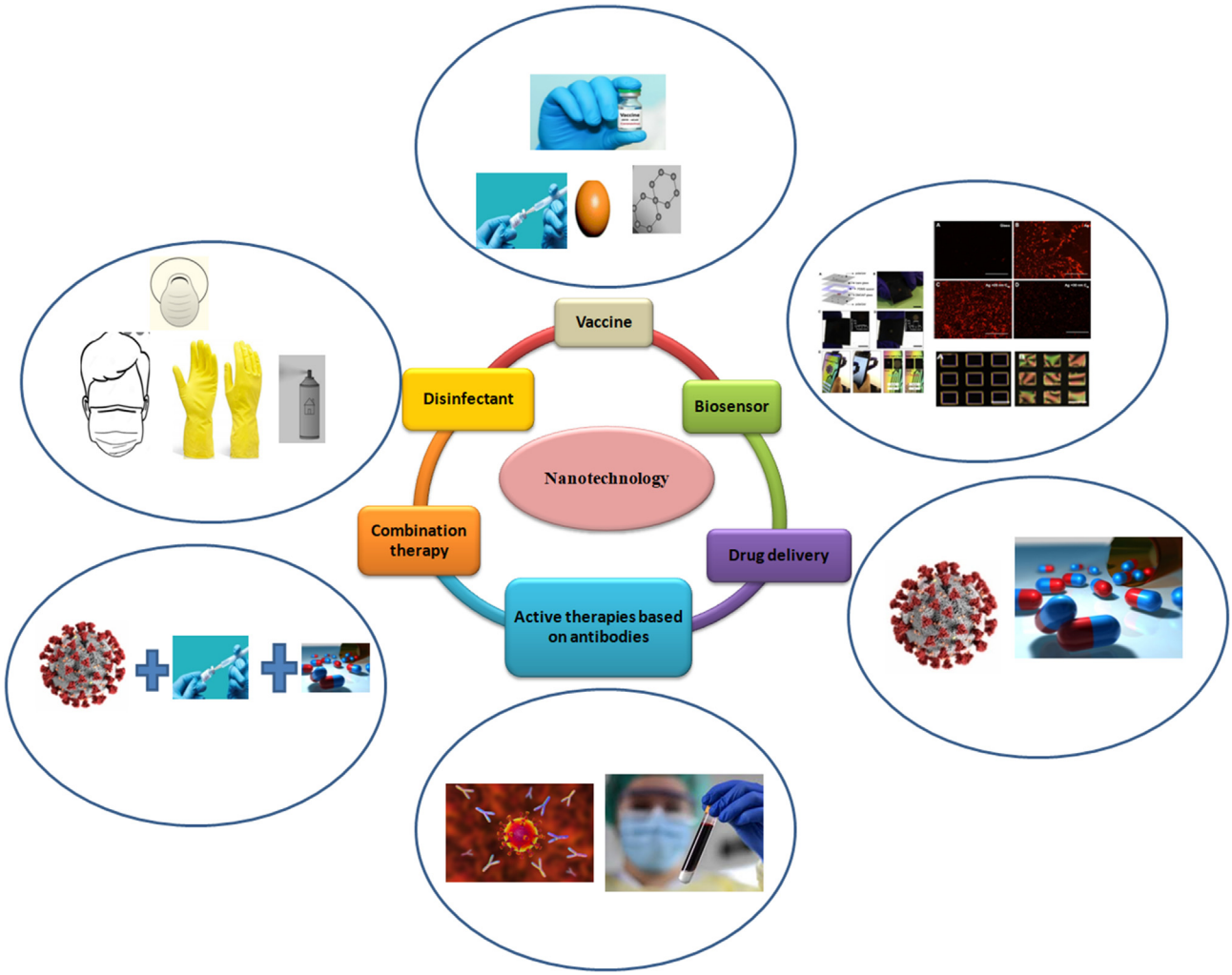

Fig. 4. Potential uses of nanotechnology in the fight against SARS-COV-2 [3,86].

The optical thicknesses of 0.98 ± 0.11 and 2.40 ± 0.24 nm was demonstrated for surfaces treated with SAM and antigen (100 nM) mixed solution. This rise suggested the attachment of antigens to the gold surface that had been mixed-SAM functionalized. The thickness of the surface increased dramatically after engagement with the solution of SARS-CoV-2 antibody, reaching 4.11 ± 0.25 nm. When compared with the antigen-immobilized surface, the thickness was around 1.7 nm, which is greater than the 1.4 nm increase observed for immobilized antigen. Thus, there was an increasing discrepancy because of increase in antibody's molecular weight, (Mw = 140.32 kDa) than the antigen's Mw, 47.08 kDa. The thickness of the surface following absorption in the solutions of control proteins, however, was noticed to be 2.60 ± 0.16 nm and 2.70 ± 0.14 nm, respectively. Consequently, no significant change was obtained when compared to the thickness of the immobilized antigen surface. This study demonstrated that the SARS-CoV-2 antibody recognizes the antigen selectively, ensuing rise in optical thickness, implying that antigen–antibody complex formation promoted the orientational change of liquid crystals.

At each stage of the gold surface's development the precise intermolecular reaction process was monitored using the surface plasmon resonance (SPR) biosensor by detecting real time refractive index shift of the incoming light. The gold chip used in the SPR study was functionalized with –COOH groups by pre-absorption in a mixed SAM solution. To stabilize the SPR signal, the solvent was pre-run in each reaction step in order to clearly identify the change in the resonance unit value (RU). First, the SPR signal was stabilized by injecting a large volume of deionized water (DI) water into the fluidic module. After flowing NHS/EDC solution in DI water through two channels for 200 s (300–530 s), the antigen was immobilized on the surface by flowing an antigen solution (100 nM) in PBS through two channels for 160 s (710–870 s).As a result, the measured refractive index increased by 750 RU between 1850 and 2600 RU indicating the immobilization of the antigen on the COOH-functionalized gold substrate. The remaining COOH functional groups were blocked by running the ethanolamine solution in DI water for 150 s (1050–1200 s). Target antibody and control protein HSA were injected into the target and control channels, respectively, after washing with PBS solution (1400–2560 s). The target channel's refractive index was around 1300 RU, whereas the control channel's refractive index increased by about 200 RU. The result indicates the selective binding of the SARS-CoV-2 antibody to the antigen-immobilized gold surface. The SPR signal analysis revealed the real-time modification of COOH-functionalized gold surface at each step, and the refractive index shift between the target and control channels confirmed the selective recognition of antibody for SARS-CoV-2.The finding backs with the theory of the textural shift in liquid crystal images observed under POM caused by the SARS-CoV-2 antibody's selective binding event.

5. Nanodiagnostic application in SARS-CoV-2

In the case of SARS-CoV-2 detection, nanotechnology can be used in the following ways: chiral biosensors (NPs conjugated with chiral molecules); point-of-care testing (POCT) (make a diagnosis of infected people exclusive of specimens submission to authorities by using simple color changes caused by nanostructures); nucleic acid testing (nucleic acid amplification using NPs under isothermal circumstances); electrochemical sensors (enhanced efficiency and sensitivity with the use of metallic NPs) [31].

5.1. Nanostructured biosensors

Medicine is one of the domains where nanotechnology is gaining attraction [32,33]. In terms of bioavailability and specificity, nanostructure-based delivery methods surpassed traditional delivery techniques. The majority of the added value comes from NPs' physicochemical properties, such as their high surface area to mass ratio, tunable size, and easily functionalizable structure. They can improve therapeutic effect by stabilizing drug in the systemic circulation for targeted, controlled, and long-term delivery [34]. Their potential benefits include in vivo imaging, multiple targeting, and combination medication administration. All of these concepts can be used to combat the COVID-19 pandemic.

Traditional time-consuming processes, such as quantitative RT-PCR, can be reduced with NP-based biosensors, resulting in significant improvements in quick diagnosis [35]. Within 10 min, the SARS-CoV-2 biosensor, which uses thiol-modified antisense oligonucleotide-capped glycol nanoparticles, may identify COVID-19 cases by color change which is observable to the naked eye [59]. In conjunction with a lateral flow diagnostic device, the glycol nanoparticle platform provides a low-cost, rapid diagnostic time of less than 30 min. By linking infection progression with socio demographic characteristics, nano biosensors coupled with bioinformatics might give personalized techniques that can further enhance focused screening, monitoring of asymptomatic patients (carriers), and detecting discharged patients for re-infection [36]. A variety of nanostructured biosensor applications are shown in Fig. 4 [36].

5.2. Detection using nanomaterials and smartphone

Nanopapers and nanochannels are nanomaterial-based sensors that allow smartphones or the naked eye to identify lateral-flow devices at the observation level. They provide cost-effective viral detection solutions. The next generation of SARS-CoV-2 detection will be battery-operated and smartphone camera-based amplifications using inorganic quantum dots [37]. Smartphone-based sensing systems are semi-automated, personalizable, user-friendly, and require minimal training to implement. The sensor system is linked to the smartphones; NPs are used in the background; the sensing system performs the analysis; and lastly, the smartphone interprets the data. It is more personalized than PCR and requires less time [38]. Supplementary table 3 (TS3) lists some of the nanomaterials that have been studied for COVID-19 diagnosis.

5.3. Nps for detection of SARS-COV- 2

Because of its accessibility, selectivity, sensitivity, and specificity, RT-PCR is employed in most viral RNA detection protocols [39]. There are certain disadvantages to RT-PCR procedures, such as low extraction efficiency, the usage of time-consuming processes, and false positives owing to contamination. Because of its large surface area and ultrasmall size, NPs have been used to improve virus detection effectiveness not only in RT-PCR but also in other virus detection methods such as an enzyme-linked immunosorbent assay (ELISA) and reverse transcription loop-mediated isothermal amplification (RT-LAMP) [40,41]. In terms of viral detection, metal NPs, carbon nanotubes, silica NPs, quantum dots, and polymeric NPs have all been investigated as summarized in Supplementary Table 4 (TS4).

6. Treatment of SARS-CoV-2 (COVID-19) using nano based systems

6.1. Role of antiviral materials

6.1.1. Antiviral nanostructure materials

Nanostructures could also help COVID-19 infected patients to avoid significant organ problems, co-infections, and post-recovery syndromes. External vesicles, exosomes, and artificial nerve conduits are antiviral nano biomaterials that can pass over the blood brain barrier (BBB), enhance synaptic plasticity, modulate immunity against inflammation and pain after a stroke, promote neuronal regeneration, and heal COVID-19 [42] neuropathic pain. The use of lipid nano emulsions to nano target cytokine receptors has shown promise in reducing dementia and brain inflammatory neurodegeneration, which is a risk factor for Alzheimer's disease. To summarize, all of these nano therapeutic options have the potential to give timely answers for fighting the pandemic and laying the groundwork for future research.

Some nanomaterials have been shown to exhibit antiviral properties through ion formation, the production of reactive oxygen species (ROS), photodynamic and photochemical effects, and associations with lipopolysaccharides to prevent viral binding and penetration [43]. It has been shown that certain NPs emit ions in dispersion, and that some of these ions have antiviral capabilities against coronavirus. Metal ions have been demonstrated to interact with essential viral enzymes, although there are likely other undiscovered processes at play [44-88]. Zn^{2+} ions, as an example, have been shown to decrease SARS-CoV replication by inhibiting elongation of RNA polymerase in the presence of RNA [45]. Likewise, Warnes et al. [47] discovered that copper surfaces can harm human coronavirus 229E's membrane and contact spikes, causing morphological changes and exposing the viral DNA, which was also destroyed. The inactivation of the coronavirus was caused by ions created by the copper surface, whereas the production of ROS on the copper surface boosted cytotoxic properties. Although this study used massive material, investigations have demonstrated that the number of ions released by metals is proportional to their surface area, therefore nanoparticle exposure might increase ROS production. As a result, copper NPs may have more cytotoxic properties than bulk copper [46,48], and certain copper NPs are already doped in the masks to exploit the beneficial aspect of copper. Different antiviral compounds, their mode of action and persistence, and uses are listed in Table 3 and 4 [42].

It's also worth noting that metallic NPs' photothermal and photo-catalytic characteristics have the potential to disinfect surfaces. Coronaviruses have been found to be inhibited by heat, with the temperature variable depending on exposure time; a half-hour exposure at 60 °C can reduce coronavirus by at least 4 log10, buta 1-minute exposure at 80 °C can achieve the same reduction rate [49]. Photothermal treatment is now being utilized to inhibit cancer cells, however; it is also effective to inhibit viral cells [50]. This method might work with other viruses too, while it hasn't been tried against coronaviruses. Murine leukemia virus, for example, is effectively inhibited using gold nanorods (GNRs) triggered by an 805 nm laser [51]. In addition, when ROS is formed as a result of the excitation created by UV light exposure, the photocatalytic action occurs [50]. Nakano et al. [52], reported on the photochemical activity of titanium dioxide NPs (TiO_2) to inactivate influenza

virus. As previously stated, the formation of ROS can result in antiviral action against coronaviruses; consequently, NPs having photo-catalytic characteristics could be another route to coronavirus inactivation. The use of 'revolutionary' materials like graphene nanostructured materials in the battle against coronavirus is currently under investigation. These materials, on the other hand, can be particularly efficient against viruses because they produce ROS, inactivates encapsulated RNA viruses, demonstrate biochemical interactions with viruses, have a negative charge and have a competitive inhibitory mechanism [53,54]. Furthermore, the graphene's action mechanisms and the beneficial properties of its by - product have prompted scientists to suggest new investigations to battle SARS-CoV-2 in a variety of relevant domains and functions [55].

6.1.2. Antiviral drugs

Antiviral medicines are another notion that can render coronaviruses inactive [56,57]. Knowledge of how antiviral medications inactivate viruses and how they interact with SARS-CoV-2 proteins should lead to a better understanding of potential coating materials that can be employed on abiotic surfaces to recreate the same effect. Antiviral medications work in a variety of ways, including synthesizer, phosphorylation, proteolytic, and cyclosporin inhibitors, as well as adsorption and fusion blockers, enzymatic activity and channel blockers. All of these target distinct phases of the viral cycle. The interaction of antiviral medications with coronavirus S proteins may be the most useful to focus on since it can reveal information about how other chemicals interact with spike proteins. Viral cells engage with host cells via glycoprotein and ligands, allowing them to infiltrate the cells [58]. Certain medications, such as inhibitors of viral surface proteins, can target and block viral cell-host cell interaction or fusion [59,60]. Supplementary table 5 (TS5) shows some useful repurposed drugs that interact with spike and glycoproteins, and typical mechanism of action is restricted access (which focuses on the virus's adhesion to the host and penetration into it) [60].

Drug repurposing aims to tackle the pandemic by repurposing medications that have already been found for other known medicinal objectives. This is a viable method since it reduces the time it takes to discover a new medicine. The antibiotics lividomycin, quisinostat, spirofylline, burixafor, pemetrexed, edotecarin, diniprofylline, fluprofylline, chloroquine (CQ), hydroxychloroquine (HCQ), remdesivir, tocilizumab, lopinavir/ritonavir, ivermectin, and azithromicin,in addition zinc supplements combined with CQ, silibininwith doxepin, and many glucocorticoids (betamethasone, dexamethasone, hydrocortisone, fludrocortisone, ciclesonide, and triamcinolone) also showed potential effectiveness in combating pandemic [61,62]. At various phases of the viral cell cycle, Fig. 3 depicts their mode of action and interaction [63]. Repurposed pharmaceuticals have well-established safety profiles, allowing for a smoother clinical transfer and less dangerous and quicker uses.

To pick "potential candidates" from the available pharmaceutical and pharmacological compounds, various in silico methods can be used with big drug databases. Simulations of the combined treatment of HCQ and azithromycin targeting inner and outer viral proteins using molecular dynamics forms revealed promising efficacy with diverse possible mechanisms of action [64-113].The HCQ-azithromycin combination therapy exhibited a superior clinical performance in terms of mortality rates among geriatric persons, emergency medicine division transfers, prolonged hospital stays, and latency of viral shedding [65]. Ivermectin is an equitable, acceptable, and practicable method for the cure and preventative measures of COVID-19, according to an experimental sequencing, *meta*-analysis, and comprehensive review.

7. Nanovaccines

The SARS-CoV-2 vaccine's clinical testing phases were completed only in three to six months, making it the quickest of all epidemics and pandemics [67]. The notion of "nanovaccinology" was born as a result of the use of nanomaterials in vaccination production and delivery. The benefits of employing nanoparticle-based vaccinations, which are made up of biologic, organic, inorganic, hollow polymeric NPs, include improved stability, facile antigen absorption, and robust response, high doses, customizable size and surface features, and high dosages [68]. Because of their smaller immunological titer, less overall toxicity, greater selectivity, and porous structure, nano biochemical materials can be used as vaccine additives to increase immunization efficiency [69,70].Vaccines consisting of protein NPs and virus-like proteins (VLPs) are in the process of production. SARS- CoV vaccines based on the RBD are also thought to be effective [71]. VLNPs are attractive NPs that distinguish themselves from antigen-producing cells, are easily detected, and induce an immune response [72]. They can be transported more efficiently through the lymphatic and capillary systems, lowering systemic inflammatory responses, enhancing vaccination immunity and effectiveness, patient security, and strengthening the immune system. When vaccines based on nucleic acid were combined with solid lipid NPs, dendrimers, and cationic liposomes, they showed improved delivery effectiveness and durability [73]. Exosomal S protein of SARS- CoV vaccines resulted in an induced and accelerated anti-body neutralizing action [74].

High mucosal protection in the lungs is provided by NPs-based inhalational vaccines, which are the principal candidate in respiratory illnesses like SARS-CoV-2 [75]. For managing respiratory illnesses like SARS-CoV-2 [76], reliability, accessibility, and both central and localized immunological response are all advantages of olfactory vaccination delivery. The capacity of PLGA NPs complexed with ACE2 specific receptors from mesenchymal cells and macrophages to counteract virus infection rate is discovered [77]. Extracellular vesicles carrying ACE2 ambushes and ACE2 mRNA encapsulated in lipid NPs adequately captivated SARS-Cov-2 [78,79]. Silica NPs coupled with polyethyleneimine demonstrated facile entrapment, preservation, and distribution of DNA/RNA invaders into cells, as well as a putative stimulating function, high loading capacity, interfacial adhesion, and improved endocytosis [79].

Various pharmaceutical corporations and research organizations are actively working on NP-based vaccines [80-129]. Supplementary table 6 (TS6) shows some of the nanovaccines on the WHO's list that are now being tested in clinical or pre-clinical stages [3]. The vast majority of NPs in nanovaccines are disposable, hypoallergenic, non-toxic, and low in toxicity, making them safe and effective alternatives to traditional immunizations.

8. Nanotechnology to combat COVID – 19

Because nanotechnology facilitates targeted medication or vaccine administration to biologically unapproachable locations, enhances loading and transporting drugs, and offers inherent virucidal action, it has enormous potential in combating the COVID-19 pandemic [83,84]. It may also include alternate disinfection techniques that are easy, quick, and cost-effective, as well as focused pulmonary medication delivery and approaches to build better immunomodulating materials. Antibiotic, anti-inflammatory, theranostic, protective equipment, biosensing, immune engineering, and vaccine techniques against the pandemic can all benefit from it [85]. Fig. 4 describes the numerous uses of nanotechnology in the struggle against the COVID-19 pandemic. Viruses and nanoparticles both function at the nanoscale, [86]. NPs are the ideal candi-

dates for immune and vaccine engineering research since they resemble viruses in terms of size and constituents. This makes it possible for the NPs to attach to, encapsulate, and passivate the virus, which makes diagnosis, treatment, and control much easier [87,88]. Nanomaterials, in general, can either create an external shock that kills the virus or directly come in contact with the virus through their surface features.

Several ways for smart nanotheranostic application are being researched, including integrating pharmacological targeting with nanothernostics to administer therapies with simultaneous authentic feedback tracking; little chance of overdosing or underdosing; and noninvasive modeling techniques. Multifunctional nanotheranostics include radioactively labeled nanostructures, synthetic NPs, organic NPs such as polymeric, carbon-based nanospheres, and vesicular nanosomes have all been used in nuclear imaging [89].Quantum dots in laser scanning technology enable in vivo viewing of specific intracellular signaling as well as concurrent therapy depending on the observational learning [90]. Nanorobots can plan out a path for nanotheranostics to combat a wide range of illnesses, including the latest pandemic. Multimodal computer modeling of pathogenic mechanisms and creation of more efficacious therapeutics, and artificial intelligence can aid this advancement. As possible pandemic therapeutic strategies, patient-specific models and nanorobots based on nuclei acid with sophisticated nano platforms and multilayered nanostructures are being investigated [91]. As shown in Fig. 5, therapeutic nanostructures can prevent viral entrance, decrease viral multiplication, transport medications as nanomedications into host organs, and aid vaccine granulation and administration.

They are primarily interested in the SARS-CoV-2 entrance and life-cycle, with a focus on the S protein, which is the most crucial component for viral entry and host cell interactions [54,139]. Nanomodification of repurposed pharmaceuticals such as dexamethasone and CQ revealed a potential anti-edema, anti-fibrotic, and anti-inflammatory mechanism that predicted nanoparticle uptake in cells [93,94]. Drug delivery using nanostructures can be passive (drugs loaded and conveyed by nanocarriers) or active (drugs delivered by themselves) (drug molecules themselves are nanosized). Because SARS-CoV-2 infects the nasal cavity, nasal cavity-based nanodelivery is critical and promising for targeted COVID-19 control using a simple, affordable, noninvasive, and fast absorbable method [95]. These methods are thought to boost treatment efficacy without jeopardizing patient safety. Several nanodeliveries with increased antiviral activity against SARS-CoV-2 have been explored and published, with the promise that they can help synergize the worldwide pandemic response [96]. Table 1 shows some of the findings from this study.

9. Nano-preventive applications

As certain inquiry reports in Table 2 show, nanomaterials can eventually enhance COVID-19 preventive techniques by increasing the efficiency and efficacy of surface disinfection, sanitization, and protective equipment.

As shown in Fig. 7 [110], the use of NPs in the construction of PPE results in new and enhanced qualities in terms of resistance, effectiveness, comfort, and safety. In the following sections, the use of nanotechnology in COVID-19 preventive measures is discussed.

9.1. Surface disinfection using nanotechnology

During the pandemic, several chemical disinfectants are frequently used in personal, home, and medical facilities to ensure complete sanitation. Alcohols, phenol-based disinfectants, quaternary ammonium compounds, chlorine-releasing agents, iodophores, and high-level disinfectants such as formaldehyde are examples of these [111]. However, sanitizing surfaces on a regular

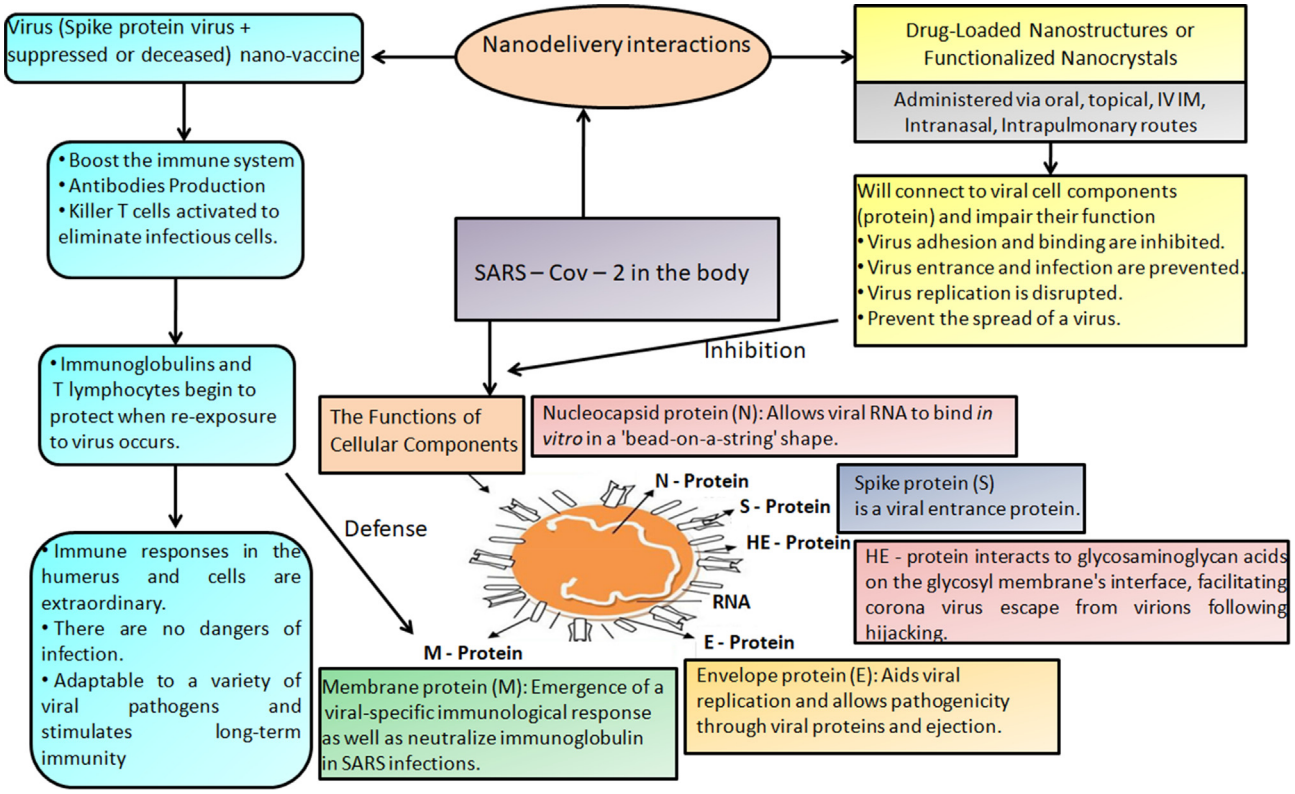

Fig. 5. SARS-CoV-2 cellular components, functions, and interactions with nano delivery management systems are summarized [3].

Table 1
Nano- based formulations for COVID-19 treatment.

S No.	Nano- Formulation	Features	Benefits	References
1.	Biomimetic NPs and dexamethasone	Using leukocyte-derived nanovesicles to encapsulate dexamethasone (leukosomes)	-A substantial chance of surviving -Immune response resolution has improved. -Dexamethasone's therapeutic activity has been improved.	[97]
2.	Liposomal remdesivir	Remdesivir nanoliposomal carrier aerosolized	-The drug is injected directly into the lungs. -Side effects have been drastically reduced, andimproved effectiveness -Self-administration is simple at home. -A successful COVID-19 therapy option	[98]
3.	ACE2-Rich NPs based on Membranes	NPs generated from ACE2-rich cell membranes	-Viral binding to host cells was prevented by competitive inhibition. -Anti-SARS-CoV-2 that works and is simple to make	[99]
4.	AuNPs with peptide functionalization	A novel peptide has been added to the AuNP to make it more functional.	-With RBD, forms the most stable complex. - SARS-CoV-2 RBD inhibition has a lot of promise. - COVID-19 antiviral medicines that work	[100]
5.	Nanosponges	Macrophages are connected to cellular nanosponges made from human cell membranes.	-Inhibit viral entrance and attachment by mimicking ACE-2. -SARS-CoV-2 has been neutralized and is no longer able to infect people. - Inhibition of viral infectivity in a dose-dependent manner	[77]
6.	Liposomal lactoferrin	Lactoferrin (Lf) is a multifunctional glycoprotein that has been incorporated into liposomes.	-Noninvasive oral and intra-nasal applications -Antiviral action has been improved. -A Phase 2 clinical study is now underway.	[101]
7.	Metallic NPs with a CQ/ HCQ coating	HCQ/CQ adsorption on Ag, Au, Ag, Au, and Pt NPs.	-Reduced negative consequences - Toxicity is low. -Antiviral activity has improved.	[102]
8.	Inhalable liposomal HCQ	Preparation of HCQ encapsulated in liposomes for inhalational delivery	-Pharmacokinetics have been improved. -Aerosolized delivery is efficient -Antiviral levels that are targeted, with a lower effective dosage and fewer dosing frequency -A long-term release -Systemic exposure is reduced.	[103]

Abbreviations: ACE2, angiotensin converting enzyme-2; CQ, chloroquine; HCQ, hydrochloroquine; NP, nanoparticle; RBD, receptor-binding domain.

Table 2
COVID-19 prevention with nano based protective equipment.

Nano-based PPEs	Formulation characteristics	Advantages of nano-based PPE	Reference
Ag nanocluster/ silica composite facial masks	Silver nanocluster/silica composite coating deposited on impregnated in facial masks	■ ●Promising virucidal property, ●Enhanced SARS-CoV-2 titre reduction, ●In crowded areas, it is quite safe to use ●Filtering masks have a longer operating life. ●Waste production is reduced	[104]
Metal oxide nano-compounded hand sanitizer	Non alcohol-based neosporin, muprocin, and tetracycline NPs combined with sanitizers from soap solutions	●Provide excellent antiviral protection ●Hand sanitizers that are gentle on the skin	[105]
Zinc oxide nanospray	Zinc (II) oxide NP (ZnO-NPs) are employed as a disinfectant nanospray	●Anti-SARS-CoV-2 activity at cytotoxic doses is high. ●Cellular toxicity in the host is minimized ● Enhanced antiviral activity against SARS-CoV-2	[106]
Silver NP (Ag NPs)- based surgical masks	Ag NP-impregnated surgical masks	●99.999 % microbial decrease against a wide variety of bacteria. ● Repetitive use of surgical masks ● Effective decontamination	[107]
Graphene nano-based PPEs	Coating onto fabrics such as face masks and gloves	●Excellent antimicrobial efficacy ● Providing both physical and chemical mechanisms of damage	[108]
Nanofiber membrane reusable masks	Masks manufactured with melt blown fabrics and nanofiber membrane from spider-web bionic nanofiber membrane (nanocobweb-biomimetic membrane)	●Masks have been disinfected and recycled ● Can effectively alleviate the mask storage ● Improved disinfection tolerance and repeatability ● High aerosol rejection efficiency	[109]

basis is challenging and there are always chances of again contamination [112,113]. The use of nanostructured approaches to surface disinfectants is being investigated for smart surface coatings with intrinsic virucidal materials and self-disinfecting abilities [114,115]. Inherently antiviral NPs, polymerization with intrinsically pathogen-resistant NPs, metallic surface coatings, and nanotexturing are some of the used approaches [116].

Virus can be inactivated by a variety of metal and metal oxide NPs, including Au NPs, Ag NPs, ZnO NPs, CuO NPs, SiO NPs, nanosized copper iodide NPs (CuI NPs), and quaternary ammonium cations (QUATs) [112]. Metallic NP-based disinfectants offer intriguing attributes in terms of manufacturing method and affordability, toxicity and safety, survival rate, antiviral activity, sustainable and environment friendly, non - irritating, and non - foaming capabilities, all of these are important for preventing virus transmission [117]. It may be synthesized from natural resources such as plant parts, insects, and animals utilizing the green synthesis method. Because of their higher effective surface area, they have an adsorbent property and a regulated release of disinfection molecules [118,119]. It can be used to coat surfaces to allow them to oxidize and release antibacterial ions for disinfection. Controlled and prolonged ion diffusion from metals like Cu alters antiviral features of surfaces [120]. It is also dermatologically safe and good at protecting public spaces from COVID-19 risks [121]. Nanopolymers can coat surfaces in a variety of ways. A polymer solution will be dropped to cover the surfaces and then allowed to evaporate using a basic drop-casting procedure. A dip coating technique can be used in the second approach, which involves dipping a substrate in a polymer solution and then removing, evaporating, and drying it. The polymeric solution is cast onto the surface, followed by solvent evaporation in a cast-coating technique [122]. Surfactant-coated NPs have particular antistatic, stabilizing, and antiviral coating capabilities for surface disinfection [90]. Apart from coatings, NPs such as Ag NPs have shown antiviral properties against viruses such as SARS-CoV-2 when applied in nanopowder form, and may be used in face masks and air filters [123,124]. Copper NPs have been shown to have antiviral properties against HCoVs by degrading and inactivating the viral DNA, suggesting that they might be used to combat the current pandemic, SARS-CoV-2 [125]. Cu NP-loaded surfaces can also readily deactivate SARS-CoV-2 and can be created with less cost and stability than Ag NPs, according to recent studies [126,127]. The antiviral efficacy of Cu NPs conjugated with quaternary ammonium compounds was also improved [128]. COVID-19 distribution on surfaces can be limited by replacing plastic and stainless-steel components with Cu alloy [129]. Photothermal inactivation of SARS-CoV-2 from surfaces may also be accomplished by lighting Ag and Au NPs and nanorods at an appropriate wavelength to cause viral inactivation by heating [130]. Other surface disinfection strategies include encapsulating things with photoactive nanomaterials and employing electromagnetic radiation to destroy SARS-CoV-2 cells [131].

Abo-zeid et al. [132], found that iron oxide NPs, both Fe_2O_3 and Fe_3O_4, may bind with viral spike protein, preventing it from attaching to host cells. They also created reactive oxygen species (ROS), which rendered SARS-CoV-2 inactive on surfaces. Other option for sterilizing public utilities and large gathering spaces is titanium dioxide (TiO_2) nanocoating. It has a multifunctional applicability for decontaminating and decreasing COVID-19 transmission due to its UV induced photocatalytic characteristics. Through TiO_2-doped paints, air filtration aerosolized filters, TiO_2-impregnated ventilation systems, and Cu and Ag-loaded TiO_2 nanowires, it provides a practical and cost-effective disinfection technique, even for distant areas. SARS-CoV-2 disinfection was also demonstrated within six hours on surfaces covered with aluminium alloy NPs [133,134].

By deactivating the virus from surfaces, the physicochemical features of graphene nanomaterials can be employed to restrict the spread of the COVID-19 pandemic. By performing photothermal activities and attaching to the viral S protein, graphene and its derivatives inactivate the virus, inhibiting cellular connections with host cell receptors [135]. Water treatment with light-activated, layered graphitic carbon nitride nanostructures prevents viruses like SARS-CoV-2 from infecting the environment. Nanostructured anionic polymers demonstrated pH-adjusted, fast, and continuous disinfecting capacity, suggesting that it might be a promising option for self-disinfecting viral inactivation [136]. Nanobased air ionizers and surface purifiers, which may be used to decontaminate buildings and public offices, have recently been researched and produced [137].

9.2. Personal protection equipment improved by nanotechnology (PPE)

Textiles like as headgear, goggles, masks, gloves, facial protection, and dresses or gowns are examples of PPE. They are essential components for COVID-19 transmission prevention. The primary premise for its use of COVID-19 prevention is that nanostructures utilized in PPE modification adsorb viral particles for viral inactivation and filtering effectiveness [138]. The primary issues with traditional PPE are its low anti toxicity, difficulties in breathing, heat dissipation, and reusability [81]. Uncertainties are also growing about which, how, and how much they allow COVID-19 transmission, particularly in workplaces and highly crowded gathering locations, necessitating the creation of more reliable, cost-effective, efficient, and reusable PPE [139]. Appropriate awareness of the purpose and use of PPE by health care workers and the general public, as well as maintaining a sufficient supply system, are important aspects in the pandemic's immediate prevention. As a result, their deployment on a global scale has not been sufficient to stop the transmission [140,141].

During the pandemic season, environmental safety and waste management are also challenging issues. It imposes a significant burden on the environment and resulting in a health hazard, including carcinogenic health effects, prompting the search for other alternative technologies for the manufacturing of biomedical equipment and the treatment of COVID-19-related wastes [142,143]. Furthermore, single-use PPE types contribute to environmental contamination and are potential biohazards. The discarded PPEs and its breakdown products are endangering aquatic species and human life, also it may persist for many years [144,145]. The possible long-term repercussions of these environmental impacts on aquatic ecosystems and human health were shown by Hasan et al. [146], as follows: physiological impacts (reproduction hampered, oxidative stress, lower survival, metabolic damages), long-term effects (microbiome changes, water quality degradation, ecosystem modification) and physical effects (immunosuppression, carcinogenicity, geno-toxicity, neurotoxicity) [146]. This suggests that new technologies are required to establish eco-design techniques for PPE manufacture [147].

In order to reduce the negative impact on environment, nanostructures can play a role by replacing single-use PPE with revolutionary reusable, self-cleaning, effective, and efficient antiviral solutions. This may be accomplished by combining antiviral NPs, nanofibers, and NP-coatings with photothermal and photocatalytic sterilization to provide super-hydrophobicity, synergistic effects, and self-cleaning properties [148]. Nanomaterials having inherent antiviral activity, such as Ag NPs, graphene oxide (GO), CuO NPs, two-dimensional carbides, and nitrides that may trap and inactivate viruses, are being studied for these applications [149]. In addition, a fluorescent NP penetrant examination may be utilized to detect interior faults in used masks, providing data for the creation of reusable masks, structural optimization, and standardization

[150].The primary benefits of PPE modifications employing nanomaterials and nanotechnology are reduced material consumption and supply concerns, efficient filtering owing to high surface areas, cost-effective transmission control, and viral neutralization due to functionalization with chemically active groups [151].

Different protective respiratory masks have reported size- and time-dependent particle removal performance, which can be enhanced by nanostructured systems [152]. Ag nanocluster/silica composite nanocoating impregnated in facial masks had a promising virucidal function, lowered the SARS-CoV-2 titer, and was safe to use in crowded locations [153]. Furthermore, SiO_2 and Al_2O_3 NPs coated with polypropylene or polyethylene had super water repellent qualities; TiO_2 and MgO NP coatings had self-sterilizing activity; indium-tin oxide NPs generated electromagnetic/infrared protective clothing; and ceramic NPs boosted abrasion resistance [154,155]. Surface oxidation, the release of free radicals or toxic ions, ROS production, photoreaction, inhibition of viral contact, entrance, and binding are all described as processes in these NP coating effects [156].Nanotechnology can further improve filtration efficiency by enhancing viral particle capture and retention, allowing for quick viral inactivation following capture, reducing the effects of inhaled humidity on particle redistribution, and creating a very thin, high-efficiency reusable filtering media.

Nanofiber technology for face masks can minimize breathing resistance, increase comfort by reducing pressure, and improve filtration efficacy against extremely tiny virus particles (less than 50 nm) [157]. Researchers developed a reusable, recyclable, adjustable, antibacterial, and antiviral respirator facial mask that could be mass produced. The new design is based on a filtering system made up of a nanofibrous matrix of polylactic acid and cellulose acetate that contains CuO NPs and GO nanosheets which were electrospun [158]. Surgical masks using nanofiber filters decreased air-flow resistance, increased filtering efficiency, improved pollutant deactivation, and lowered the danger of breathing infections [159]. Other personal protective equipment (PPE) such as gowns, face shields, gloves, boots, and goggles can also benefit from the use of efficient and multifunctional nanostructure [160].

10. Conclusion, limitations and future perspectives

The COVID-19 pandemic has wreaked havoc on society and the economy and still poses a threat to people everywhere. The effect on physical, intellectual, social, and economic resources is immeasurable with more than 4.5 million fatalities and more than 221 million confirmed COVID-19 cases. Understanding the illness's clinical symptoms is one of the key prerequisites for efficient mitigation during the breakout of any novel disease. However, diagnosis and prognosis become challenging in the absence of any distinctive defining traits. It worsens misconceptions and causes a delay in limiting the spread of illness. There is a lot of information on the subject thanks to several clinical research studies, systematic reviews, and *meta*-analyses. However, a deeper comprehension is required for the identification of the disease progression biomarkers, and risk factors causing negative COVID-19 outcomes. Among the conventional methods of diagnosis, Real-time RT-PCR and serological methods, for instance, continue to be the most widely used detection techniques in large hospitals, while biosensors, point-of-care testing, nanotechnology-based approaches, smartphone surveillance of infectious diseases, amplicon-based metagenomic sequencing, and smartphones are still anticipated to be developed as large-scale screening techniques that can even in some cases, like biosensors, be used in the home settings. The gold standard for molecular clinical diagnostics RT-PCR tests, were easily accessible. However, in order to carry out characterization, these tests need lengthy times and sophisticated tools. Numerous additional technologies have shown promise as future diagnostic aids. For instance, column agglutination test (CAT) and serological methods both have significant drawbacks. The need for quick, simple-to-use, cost effective and reliable methods to locate and identify the virus emerged. For this purpose, Liquid crystal material was used by Xu et al. [9], as a potential diagnostic tool for SARS – CoV – 2 detection.

Smart and targeted nanodelivery systems with effective preventive, efficient diagnostics, and greater efficacy therapies were created by combining biomaterial science, nanotechnology, and medicine. A number of nano-scale drug delivery technologies, such as nano-capsules, biomagnetic NPs, nanotubes, quantum dots and polymeric NPs, deliver the appropriate medicines slowly and precisely. These technologies may be able to help in controlled release of drug, site-specific delivery and stability aspect, all of these will be critical in combating the COVID-19 pandemic [164]. For SARS-CoV-2, a nanobased vaccination (mRNA-LNP) is being developed and has been proven to be effective. The use of nanobiomaterials for developing COVID-19 vaccines and treatments promises more effective and diverse uses.

Metallic NPs have already demonstrated its effective antiviral properties. As a result, placing these NPs on the surface of various materials such as masks, medical equipment, gloves, and other protective materials might help inhibit viral propagation. Furthermore, NPs have been shown to interact well with biomolecules such as DNA and proteins, implying that using NPs in diagnostics delivers rapid, sensitive, and accurate findings. Advanced vaccinations, personal protective equipment, nano based sensors, surface coatings, disinfectants and therapeutic compounds that will increase treatment success rates are presently in development, clinical trials, and even on the market [161,162]. These nano-advanced goods will primarily aid low-resource medical infrastructures and developing countries by providing simple, low-cost operations. Functionalized biocompatible NPs and broad-spectrum antiviral nano drugs have been produced, stopping the virion from re-replicating inside the host in an irreversible and permanent manner [163]. Positive outcomes have also been reported for antiviral drugs and nanovaccines with lung targeting, remote loading, decreased systemic immunotoxicity, superior circulation and retention time, prodrug forms of controlled and localized release, combination therapeutics, reduced dosage, lowered dose, augmented cellular uptake and toxicity.

Despite the fact that COVID-19 has only been around for a short period, it has spawned a slew of new research and patents. More than 10% of these patents are related to "nano" themes, such as the use of nanostructured materials as vectors, adjuvants, markers, nanocarriers, filters and intrinsic antimicrobials for diagnostic, therapeutic, immunization, and preventative techniques [165]. The practical use of nanomedicine with industrial consequences is still being in research and development to improve safety, reusability, high sterilizing capability with a low dose and eco- and user-friendly features [67].

Overall nanostructured based diagnostic tools, drug development and delivery systems are now offering the globe drastically improved diagnostic, therapeutic, and preventative alternatives to stop the pandemic effectively and quickly. If all scale-up, regulatory and safety challenges are resolved, nanotechnology has the potential to protect the globe from the present and future pandemic crises.

10.1. Limitations

Despite significant benefits, clinical translation of nanoproducts has yet to be established. Unpredictable side effects, long-term destiny, safety and toxicity issues, expense and complexity of NPs preparation, and the necessity for pure study designs with

adequate sample numbers and established methodologies are all obstacles that must be resolved. On the other hand, there are likely limitations to nanoformulations' promising advantages, such as the difficulty of sterilizing parenteral formulations properly, low entrapment efficiencies, biomolecule denaturation risks, off-target accumulations, bio distribution profile and uncontrollable burst release effects.

1. Despite the fact that the lungs are the greatest targets for COVID-19 treatment, direct and targeted intranasal and pulmonary nanodelivery is linked to significant respiratory site and lung function damage. To ensure nanomaterial safety, more proof is needed of cellular damage, intolerable inflammation, fibrosis, geno-immunotoxicity, small granulomatous lesions, and oxidative stress caused by abnormal NP accumulation in the alveoli, which may result in alveolar cell damage, blood vessel penetration and translocation to other parts of the body. Designing nanocarriers in such a manner that the nanoformulation is not recognized by scavenger cells is very difficult and requires a lot of work before clinical translation.
2. Other cited problems include scaling up, a complicated production process, and a lack of information on how and how much NPs affect organisms, as well as people's aversion to new technology.
3. Ethical, scientific, biosafety, and regulatory agency acceptability difficulties obstruct nanomedicine's ability to develop safe and high-quality nanodrugs, especially antivirals for this pandemic.
4. Despite the fact that medication repurposing saves time, clinical outcomes and relevant authorities could not completely justify the benefits of repurposed pharmaceuticals. Unsatisfactory outcomes from CQ and CQ, remdesivir hepatotoxicity, problematic safety/efficacy issues, unestablished harm or advantages of ACEIs from CPT's nonspecific mechanism, and safety concerns about corticosteroid usage were also noted. Nanostructures used to repurpose pharmaceuticals can aid in the development of effective treatment solutions with low safety and effectiveness problems.
5. Pfizer and BioNTech's new vaccines have been linked to severe allergy-like responses, which are thought to be caused by messenger RNA non packaging chemicals (mRNA). Polyethylene glycol (PEG) in vaccinations can cause anaphylaxis, a potentially fatal response characterized by complex respiratory and cardiovascular problems.
6. Presently, there is no licensed or effective therapy for SARS-CoV, SARS-CoV-2, or MERS-CoV, is available against human coronavirus. However, research into FDA-approved or repurposed medicines as antiviral options are still continuing. Although repurposed medications that target viruses utilizing a number of hypothesized pathways have demonstrated to be effective, they are not yet recommended for usage outside of clinical studies.

10.2. Future Perspectives

Selective liquid crystal detection on different SARS-CoV-2 genome sequences as well as similar control sequences is required. In addition, a biosafety level 3 (BSL-3) laboratories will execute a huge detection of full-length SARS-CoV-2-RNA-containing patient samples to validate its reliability. In the future, researchers should look into more advanced deep-learning methods for image analysis which have been successfully used in semiconductors, liquid crystal chemical sensors, and a variety of image-based medical diagnostic tests such as ultrasounds, X- rays and magnetic resonance imaging (MRI).

With the potential and difficulties presented by nanoscience, nanomedicine, and biotechnology in consideration, the pharmaceutical industry must devote inexhaustible resources to the development of nanotherapies to combat COVID-19. In the near future, the research might focus on efficiently targeting antiviral nanocarriers and tailored therapy using precision nanomedicine. In conclusion, nanostructured delivery systems can help with COVID-19 management because they can potentiate immune response modulations that would otherwise be difficult, have reduce non target accumulation and associated toxicities, precise targeting, provide alternative vaccine delivery routes, protect drugs and vaccines from degradation and inactivation in the body environment and have promising biocompatibility and biodegradability that can be controlled [166]. There is need to come up with better antimicrobial/antiviral therapeutic agents which have better efficacy and fewer side effects [167].

The relationship between transmissibility and illness severity raises several important considerations. Although a virus's severity can diminish as it evolves in a species, but the risk of transmission and hospitalization is enhanced because of recent changes in SARS-CoV-2 mutations. It's possible that the link between transmissibility and hospitalizations is due to a common underlying mechanism: higher affinity for ACE2 can improve both. Replication in the upper respiratory tract can be increased because of enhanced ACE2 binding, leading to more efficient transmission, as well as replication in the lower respiratory tract and systemically, leading to more severe disease.

One open question is whether, as a result of RBD mutations like N501Y, the S protein has reached its maximum affinity for hACE2, or it will continue to evolve and improve both pathogenicity and risk of transmission. Or, instead, may opposing selection factors lead to more disease spread but a milder sickness? If variations between the upper and lower respiratory passageways allow the virus to adapt specifically to, nasal epithelial cells, the link between transmission and sickness severity could be broken. The pandemic appears to be shifting gears at the time of writing, going from an early period of viral adaptation to its new human host to a prolonged period when immune escape will impact S protein development. The appearance of future vaccine antigens is a significant topic here. Vaccination against all major circulating variants is required as the S protein evolves so the current immunization strategies (Supplementary table TS1) may become outdated. For a practically extrapolatable result, extensive scientific study and joint interdisciplinary efforts are required.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

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