



A Review on Nanotechnology-Based Interventions on Advancing COVID-19 Diagnosis, Prevention and Treatment

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Abstract

The COVID-19 emergency has created a widespread need for proper care, prognosis, and prevention of viral dissemination. Nanotechnology has been at the centre of attention for the rapid development of diagnostic instruments, antiviral therapy and vaccinations worldwide. This review highlights the current and continuing nanotechnology-based therapeutic and preventive techniques for combating COVID-19. Designing efficient nanocarriers, nanobiosensors, and nanodrugs to overcome the traditional limits of antiviral and biological therapies is reviewed. These methods ensure the effective and secure distribution of available treatment choices via restricting viral attachment/cell entrance, multiplication/replication, and direct inactivation. Moreover, a practical and safer vaccination approach is required to limit and minimise the transmission or recurrence of this pandemic. Nanocarriers can be employed to provide risk-free and robust vaccination techniques for COVID-19 vaccine candidates, such as nucleic acids and protein frameworks. Nanotechnology not only aids in managing the current COVID-19 outbreak but also offers opportunities for vaccinations, antiviral medications, prevention and quick detection of the post-pandemic era and potential future virus outbreaks. This review has extensively addressed the importance of nanotechnology in advancing nanoparticle-based diagnostics, immunoassays, biosensors, antibody assays and early detection kits for COVID-19.

Received: Aug 13, 2024

Accepted: Sep 05, 2024

Published Online: Sep 12, 2024

Journal: Journal of Nanomedicine

Publisher: MedDocs Publishers LLC

Online edition: <http://meddocsonline.org/>

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Keywords: COVID-19; Nanotechnology; Nanocarriers; Nanobiosensors; Nanodrugs; Pandemic.

Introduction

A novel coronavirus-triggering pneumonia was detected in the seafood market of Wuhan, China, in December 2019. Following a multi-dimensional examination, researchers concluded that the virus of the Betacoronavirus class was responsible for the Middle East Respiratory Syndrome coronavirus (MERS) and

Severe Acute Respiratory Syndrome (SARS) [1]. World Health Organization (WHO) named the SARS-CoV-2-caused illness "Coronavirus Disease 2019" (COVID-19) on February 11th, 2020. The COVID-19 occurrence was later designated a pandemic by WHO on March 11th, 2020. COVID-19 has affected most countries, re-



Cite this article: Arif Z, Khan H. A Review on Nanotechnology-Based Interventions on Advancing COVID-19 Diagnosis, Prevention and Treatment. *J Nanomed.* 2024; 7(2): 1068.

sulting in millions of infected patients and hundreds of thousands of fatalities worldwide [2]. Researchers believe that the pandemic will be challenging to tackle as SARS-CoV-2 is quickly absorbed by human cells [3]. The SARS-CoV-2 viral structure is unique due to the abundance of a spike protein (S1) and envelope protein, which makes the virus highly vulnerable to host cell receptors (ACE-2 enzyme, TMPRSS protein) [4,5]. The reported ease with which the S1 protein binds to cell receptors (ACE-2, TMPRSS2) resulted in enhanced viral multiplication. Along with respiratory problems, this virus also impacts other organs and numerous human processes [6-7]. This virus is among the most virulent in its class and primarily targets the lower respiratory tract. Transmission occurs predominantly by infected droplets produced by sneezing, coughing, touching contaminated surfaces or through human contact. COVID-19 symptoms were tiredness, fever, breathing difficulties and dry cough [8]. Lack of appetite, panting, stomach aches, sore throat, vomiting, dyspnea, diarrhoea, headache, and rhinorrhoea are some less prevalent symptoms. Multiple chronic conditions, such as diabetes, hypertension, and coronary heart disease, determine the extent of illness in individuals [9-10]. According to the reports, several COVID-19 individuals exhibit liver, eye, kidney, heart, and brain impairment, resulting in various organ complications [11-13]. The average incubation time was seen between 5 and 14 days before the onset of the disease [14]. The incubation period is 19 days in the reported asymptomatic individuals; thus, screening for the infection is much more complex [15]. Fluid management, antibiotics for secondary infections, and oxygen support are advised for the patient's condition. WHO identified the following therapeutic options based on animal, laboratory, and clinical data: Lopinavir/ritonavir, remdesivir, and lopinavir/ritonavir plus interferon-1a [16]. Healthcare standards and recommendations have shifted to emphasise the avoidance of human-to-human interaction, particularly normal working routines, travel, and transportation [17]. Furthermore, quarantine at home if experiencing signs, population tracking, and enhanced knowledge of COVID-19 were implemented. Moreover, major efforts have been undertaken to investigate therapy options for ZIKA, malaria, Ebola, and HIV (Human immunodeficiency virus)-related infectious disorders utilising current antiviral medications. Personal protective measures, such as practising good hygiene, wearing a mask, and observing physical/social distance have also developed to restrict the transmission. Besides an emphasis on SARS-CoV-2 dissemination, detecting the infection is extremely important for controlling illness progression and establishing effective therapies. The global battle to limit the virus continues, as more infectious varieties, such as the Delta (B.1.617.2) and other Omicron strains have developed (B.1.1.529). Omicron strain proliferates at an astonishing pace, of around 125 million infection rates occurring per day in January 2022, ten times quicker than the Delta strain. Despite increased COVID-19 vaccination rates, such as the administration of 3rd booster doses, and elevated levels of autoimmune resistance, some analysts predict the pandemic will finish in 2022. Although, SARS-CoV-2 will remain in worldwide distribution for the upcoming years. As a result, the virus will infect the entire world's population in the post-pandemic age.

In this context, developing cost-effective point-of-care (PoC) devices giving robust, rapid, and reliable insights is critical. The equipment should be easy to handle on-site and, in the field, with no requirement for skilled personnel. As a result, researchers believe that bio-nanotechnology is the finest scientific tool for effectively managing COVID-19. However, professionals from

diverse domains must be involved in designing, developing, and implementing a structured approach. This review investigates the significance of nanotechnology-based innovative nanosystems in fabricating Personal Protective Equipment (PPE), medicines, vaccine development, and diagnostic tools. Integrating nanotechnology to handle SARS-CoV-2 and its other variants is critical to stop transmission, diagnose the virus quickly and reliably, and slow its spread. Nanotechnology will likely play a key role in COVID-19 management in the post-pandemic era and the worldwide pursuit of long-term viral pandemics [18]. The nanotechnology community's researchers propose the following research targets in the battle against COVID-19 (Figure 1).

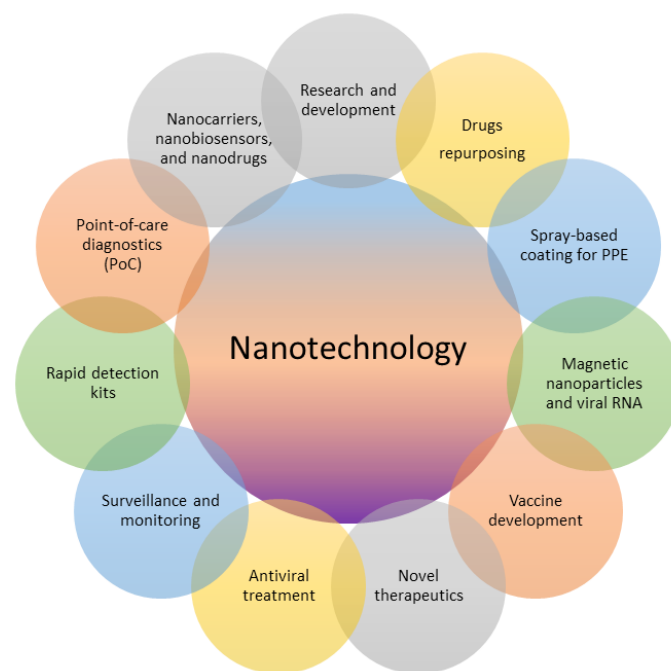


Figure 1: Promising nanotechnology research targets for combating COVID-19.

Detection and diagnosis of SARS-CoV-2: SARS-CoV-2 diagnosis in the initial stages mainly focuses on the virus genomic structure [19]. The SARS-CoV-2 virus is 60-140 nm in size, making them difficult to detect and isolate [20,21]. Since the beginning of the pandemic, rapid tests have been required with better accuracy, reliability, and specificity [22-24]. Detection and diagnosis are important for rapidly implementing interventions to reduce COVID-19 spread [25]. The pandemic proved difficult owing to a shortage of quick detection equipment for the virus's selective identification [26]. At the pandemic's beginning, RT-PCR and serological assays were performed to diagnose COVID-19 infection [27]. These COVID-19 detection techniques are based on particular nucleic acids and proteins [19]. To identify viral genomes, RT-PCR was used. Serological tests (protein-based tests), including Immunochromatographic Test (ICT), chemiluminescence assay, enzyme-linked immunosorbent assay, and immunofluorescence assay largely dependent on the immunological response to the virus [28-30].

According to health practitioners, handling the COVID-19 pandemic is a topic of SARS-CoV-2 virus identification on a large scale. Rapid testing of large populations in cities and metropolitan regions necessitates establishing a low-cost, innovative, and efficient analytical approach to identify SARS-CoV-2 [31-33]. According to the WHO assessment, there is an urgent need for improved diagnostics and the advancement of nuclear body and protein detection assays for SARS-CoV-2 [27]. Introducing nano-technological methods for COVID-19 management allows

selective detection of the virus. It also assists in determining the correlation between viral load with its pathogenicity and disease development [34-36]. A compartmentalization-based strategy is a cornerstone for developing a nano-based biosensor for SARS-CoV-2 viral protein detection, even in epidemic outbreaks and high-alert zones. There are several approaches through which nanoscience and nanotechnology solutions can aid in better-comprehending testing demands [37-38]. This section focuses on several ways nanotechnology can assist in a better understanding of the COVID-19 screening requirements. The various prospects from nanotechnology and nanomaterials applications against SARS-CoV-2 are depicted in Figure 2.

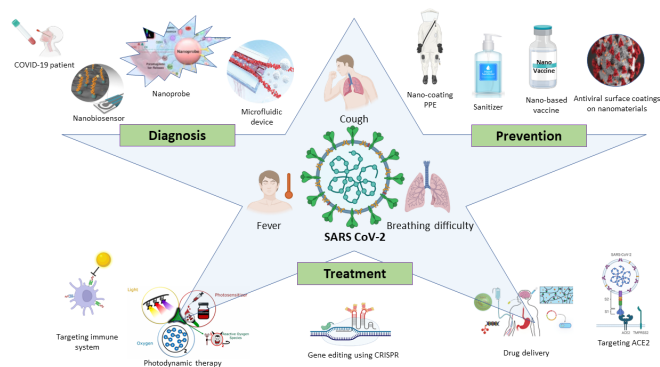


Figure 2: Schematic illustration of applications of nanomaterials in diagnosis, prevention and treatment for SARS coronavirus. BioRender generated the illustration (<https://biorender.com>, accessed on February 18th 2024).

Nanotechnology-based diagnostics for SARS-CoV-2: Nanotechnology has multiple uses and is a cost-effective and efficient approach for improving SARS-CoV-2 detection assays [20]. Throughout the pandemic, we have seen significant growth in the emergence of several COVID-19 diagnostic tests. In this context, nanobiosensors are an integral part of this process. Nanomaterials' introduction optimizes the sensor's sensitivity by adopting electrical, optical, and catalytic characteristics offering more analytical sensitivity for diagnostics [29-39]. Nanobiosensors offer a viable environmental and clinical monitoring alternative to traditional laboratory equipment [40]. Nanomaterials, including carbon nanotubes, quantum dots, metallic, silica and polymeric nanoparticle, are already employed for viral detection [21-41]. The nanoparticle's surface is coated by specified biomolecules produced from the virus, such as an antibody, peptide/pentabody, antigen (hemagglutinin antigen H1N1), and RNA/DNA [42]. Nanomaterials with high surface-to-volume ratios enhance the interactions between the analyte and the sensor raise the limit of detection and lowers the time of detection [43].

Gold nanoparticles (AuNPs) have been extensively employed for biosensing applications to diagnose several viruses. This is because of their biocompatibility, photostability, optical, electrical, and catalytic capabilities, as well as their ease of production and functionalization [44-47]. AuNPs-based COVID-19 diagnostic improves test sensitivity and reproducibility increases detection range, and decreases detection time [21]. In addition to AuNPs, nanowires are also very efficient for recognising SARS virus. In_2O_3 nanowire sensors and fibronectin-based Antibody Mimic Proteins (AMP) with superior binding affinity and selectivity for identifying nucleocapsid proteins. The virus's presence alters the electrical potential of the In_2O_3 nanowire, which is quantified by electronic means. The nanosensor could identify viral particles at sub-nanomolar concentrations [48].

As a result, nanosensor advancement research is dependent on ultra-sensitive detection methods that can integrate high-speed, and low-cost equipment. In this framework, the purpose of these systems based on nanotechnology is to examine the incorporation of heterogeneous features (biological, magnetic, optical, or electrochemical) to adopt a more accurate and rapid diagnosis response [49]. Nanotechnology has been intensively researched in creating novel detecting systems, as evidenced throughout this article.

Colorimetric biosensors: Colorimetric biosensors detect analytes by simple color changes observable to the naked eye. MERS-CoV virus detection using a colorimetric test based on AuNPs reported by H. Kim et al. (2019) [44]. In this assay, modified thiolated probes are linked with the upstream protein gene E and capped AuNPs [23]. These probes recognise a specific protein from the viral genome of the SARS-CoV-2. The AuNPs agglomerate is causing a color shift in the absence of the virus. The biosensor interacts with viral genetic material, blocking AuNP aggregation and preventing the transition of its optical properties in viral presence. These color changes can be easily seen or can be localized by plasmon resonance transduction [50]. These colorimetric tests are incredibly fast, efficient and low-cost [51-52].

Electrochemical biosensors: These biosensors are among the highly promising COVID-19 viral detection tools. The sensor comprises a series of carbon electrodes enhanced by AuNPs to improve signal responsiveness and sensor sensitivity. The AuNPs were used to immobilise the recombinant spike (S1) protein of COVID-19. The antibody attaches to the immobilised spike protein, resulting in a decline of peak current in the absence of viral infection. However, in virus presence, fewer antibody attaches to the immobilised viral antigen and may be used to evaluate current changes. Due to its array of electrodes, this sensor can recognize various coronaviruses [39]. Another study created an electrochemical genosensor for identifying the SARS and COVID-19 viruses. For sensor building, a monolayer of thiolated oligonucleotides is placed on a screen of gold nanostructured carbon electrodes. A small fragment of the viral nucleocapsid protein is recognised by the oligonucleotide sequence. The existence of a virus was identified by enzymatic amplification. This sensor can detect viral target sequences with great sensitivity [53].

Chiral biosensors: Chiral biosensors with fast reaction times are incredibly beneficial for detecting SARS and the COVID-19 virus. The latest study reported the development of chiral zirconium (Zr) quantum dots to identify the COVID-19 virus. The formulation employed Zr quantum dots, COVID-19-specific antibodies, and magnetic nanoparticles. In the vicinity of the virus, the Zr quantum dots and magnetic NPs tightly attach to it and exhibit magneto plasmonic fluorescence. External magnets were used to segregate the magneto plasmonic-fluorescent nanohybrids, and the fluorescence intensity was assessed to identify viral presence or not. The detection limit of the chiral sensor is 79.15 EID/50 L [54]. Another work employed a chiral immunosensor comprised of layers of quantum dots and chiro-plasmonic AuNPs. This immunosensor is capable of identifying COVID-19 infections in human clinical samples. The viral sample was combined with the AuNPs-coated antibody and quantum dots, and the circular dichroism technique was used to measure the shift in the chiral optical response. They discovered that the chiro-immunosensor had a lower coronavirus detection limit (47.91 EID/50 L) [55].

Paper-based Analytical Devices (PADs): These diagnostic assays are portable and cost-effective technologies [56]. Colorimetric DNA sensor designed by Teengam et al. (2017) was based on a paper to identify MERS-CoV [51]. Another probe acpcPNA (a cationic pyrrolidinyl peptide nucleic acid), was utilized to identify MERS-CoV DNA. As compared to RNA and DNA probes, PNA probes are superior as they are physiologically and chemically inert and successfully hybridise with the corresponding target. A lysine moiety induced a positive charge at the probe's C-terminus. The positive charge on acpcPNA interact with either negatively charged target DNA/ citrate-capped Ag NPs. The PNA probe attaches to Ag NPs, causing its aggregation in viral DNA absence. The presence or absence of viral DNA is then indicated by a color shift. Combined with a paper-based analysis device (PAD), this assay can be used as a PoC diagnostics. Considering ideal situations, this device has a detection limit of 1.53 nM [44].

2.1.5 Surface plasmon resonance (SPR): This quite sensitive optical method can detect deviations in refractive index at the metallic surface, allowing real-time monitoring of biochemical interactions in SPR-based biosensor devices. In light of the favourable function of biosensors based on SPR developed for SARS-CoV-2 virus detection [57, 58], a much more advanced device for SARS-CoV-2 detection was described recently [59]. It is a Plasmonic Photothermal (PPT) biosensor with dual functions that leverage the PPT action with localised SPR. It comprises 2-dimensional gold nanoislands having complementary genetic material receptors which can hybridise SARS-CoV-2 particular sequences. The thermoplasmonic heat created by lighting the gold nanoislands at their plasmonic resonance frequency raises the hybridization temperature in situ, assisting in the discrimination of similar gene sequences and increasing the selectivity of the biosensor.

Graphene-based Field-Effect Transistor (FET): Seo and colleagues (2020) announced biosensing devices that allowed for the quick, on-site screening of viral SARS-CoV-2 in patient samples. Graphene nanosheets present on the sensor coupled to a specific sequence of antibodies against spike (S) glycoprotein of SARS-CoV-2. A cultured virus, an antigenic protein, and a swab sample from the nasopharynx of COVID-19 patients were used to evaluate the biosensor's functionality [31]. The authors claimed that the technology has the benefit of not requiring sample pre-treatment because the sensor was capable of recognizing the S antigen glycoprotein of SARS-CoV-2 transported in universal transport media. Furthermore, it displayed remarkable specificity, separating the antigen protein of SARS-CoV-2 from the MERS-CoV. Contamination of nanomaterial-based biosensors is caused by sensitive bioreceptors, which may be tackled via an aerosol-mediated method or CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) for increased sensitivity and shorter reaction time [42].

Smartphone-assisted sensing: Sensing systems based on smartphones have semi-automated user interfaces with greater user-friendliness owing to lower expertise and guiding requirements. Sensing systems may be constructed with cell phones and utilised by ordinary individuals with the correct use of hardware and software. A peripheral module can be connected to the phone in various ways. A sensor system can be linked to a smartphone using proprietary interfaces such as an audio headphone connector, USB (Universal Serial Bus), power, NFC (Near Field Communication), and Bluetooth [60]. Nanomaterials are employed within peripheral devices to provide faster and bet-

ter outcomes. A sensor system analyses the samples, displaying the results on the smartphone. It is faster than other diagnostic tests like PCR. Geotagging is available in a smartphone-based cloud database. Geolocation aids surveillance in real-time. Sensing based on the smartphone can detect disease coverage and build a library of data [61].

Nucleic acid testing: One of the most critical milestones in creating sensors was the transcription of the viral genetic sequence [19]. The RNA-dependent RNA polymerase (RdRP) gene, which controls the gene portion of ORF1ab of the open reading frame, nucleocapsid phosphoprotein (N) and envelope protein (E) are known to have conserved sequences amongst the SARS-related viral genomes. The primer and probe initiative aims for identification with high analytical sensitivity and has focused on these domains [50-62]. Another subject of the application of extensively used nanotechnology is the isolation of viral RNA linked to the application of molecular diagnostics. According to studies, magnetic nanoparticles may be utilised to extract viral RNA of SARS-CoV-2 from clinical samples for identification by RT-PCR [63-64]. This eliminates the need for extensive RNA extraction, improving the sensitivity of the approach. Another essential aspect to emphasise is the utilization of hybrid systems, integrating the usage of biomolecules originating from nanostructured viruses, a strategy commonly employed in the construction of sensors [21].

RT-LAMP (Reverse transcription loop-mediated isothermal amplification technique): It is an amplification method based on isothermal coupled with biosensors based on nanoparticles for COVID-19 diagnosis [65]. This technique helps to eliminate any special laboratory tools, shows high sensitivity and specificity, and displays rapid results [66]. It consists of amplifications that is helicase-dependent, loop-mediated isothermal, and recombinase polymerase. The outcome of the amplification reaction can be easily visualized on a nanoparticle-based biosensor device. This biosensor was utilised to analyse clinical samples drawn from patients and exhibited no cross-reaction with samples with non-SARS-CoV-2 patterns [19-67]. Similarly, Wang et al. (2016) used nanoparticles to integrate RT-LAMP with chemiluminescence for viral detection [68].

LFIA (Lateral flow immunoassay): The Diagnostic tool LFIA identifies pathogens in biological materials, water, and food. It is frequently utilised as a PoC diagnostic due to its convenience, low-cost and affordability [69]. To identify C-reactive protein, melamine in milk, ochratoxin A in wine, and many more are among its remarkable performance. Chen et al. (2020) created a nanoparticle-based device that gives results in less than 10 minutes. This device utilizes the LFIA principle to identify the serum of anti-SARS-CoV-2 IgG in COVID-19 patients [24]. Coronavirus, recombinant nucleocapsid phosphoprotein, was bonded to the membrane and bind with target IgG. The fluorescent reporter is a mouse anti-human IgG antibody coated on NPs.

Treatment strategies for COVID-19: Antiviral drugs and immune modulators are the only therapy available to treat COVID-19. It has the potential to inactivate or change viral surface proteins as well as limit viral replication [70, 71]. Several drugs, including lopinavir, hydrochloroquinone, ritonavir and remdesivir are used to treat COVID-19 patients [72]. However, these treatments are frequently associated with adverse effects, and a majority of these drugs have specific actions that don't effectively stop the infection and kill the virus [10-73]. COVID-19 develops resistance, making the available drugs ineffective [4-42]. Furthermore, certain medications are only effective at high dos-

es, resulting in toxicity to host tissues and causing adverse effects. [74-75]. Hydroxychloroquine and chloroquine have been linked to cardiotoxicity, nephrotoxicity, and hepatotoxicity [76], whereas ribavirin has been linked to hemolytic anaemia [77]. Most antiviral medication adverse effects are mainly due to their deposition in non-target organs. In this way, tailored drug delivery techniques and lowering drug toxicity are gaining significant attention for improving antiviral therapy effectiveness [78]. The lack of a single antiviral medication for SARS-CoV-2 infection, care remains a significant problem. [79]. Simultaneously, scientists employ high-throughput drug discovery tools to create novel small compounds, redesign existing medications, and create formulations for infected candidates [80, 81]. In this regard, nanotechnology provides incredibly valuable options for developing advanced therapeutic strategies to enhance the antiviral activity of candidate drugs.

Outlook on COVID-19 treatment and vaccination efforts based on nanotechnology: Nanomaterials in the nanometre range are a key component in antiviral therapy by improving drug transport and usage efficiency of water-insoluble medicines. Nanomaterials authorised by the US Food and Drug Administration (FDA) are utilised in therapeutics to increase loading efficiency and lower drug concentration, which is necessary for bioactivity owing to controlled or prolonged release [82]. Selenium, silicon, silver, silver sulphide, polylactic acid, gold, zinc oxide and other nanoparticles are frequently used for COVID-19 treatment [83]. Research conducted by Leuschner et al. (2011) points to using nanotechnology to manage cytokine storms [84]. Cytokine storm is among the clinical consequences of COVID-19 as it leads to organ dysfunction and rapid clinical degradation [85, 86]. Application of nanosystems such as metallic, polymeric and lipid NPs, drug encapsulation micelles and liposomes enables the enhancement of pharmacological therapeutic characteristics [87-88]. The efficacy and safety of COVID-19 therapy might improve through the application of nanotechnology that allows targeting particular areas, drug encapsulation, and lowering drug toxicity [89, 90]. This section reviews some methods in which nanotechnology is employed to treat COVID-19 patients.

Theranostic nanoparticles: Itani et al. (2020) explored the theranostic nanoparticles application for COVID-19 therapy, emphasising intranasal delivery [91]. Theranostic NPs offer the selection of diagnostics-based targeted therapy, allowing the transport of multiple therapeutic components such as antibodies, peptides and siRNA. Different forms of theranostic nanoparticles, such as virus-like or automatically-mounted proteins, inorganic and organic, have been considered suitable for intranasal delivery. These nanoparticles might be used to produce vaccinations together with therapeutics against COVID-19. Dexamethasone, the first SARS-CoV-2 treatment medication, was developed using nanotechnology. SARS-CoV-2 infections may be managed by employing an anti-fibrotic mechanism and anti-edema, successful administration and therapy employing different nano-based techniques.

Polymer Nanoparticles (PNPs): PNPs are an excellent transmission mode because their features and functionalities may be tailored to their unique purpose. The addition of a therapeutic agent to chitosan-derived PNPs can enhance PNP penetration and persistence in the mucosal environment [92]. In most cases, the virus attaches to host cell receptors. S protein is important in cell binding and entrance during SARS-CoV-2 infection. S protein has two subunits: S1, aid in adhesion and S2, facilitate

membrane fusion and cell entrance. The human ACE2 receptor interacts with S1 protein in alveoli. ACE2 expression is seen in kidney proximal tubule cells, cardiac cells, esophageal cells, epithelial cells, cholangiocytes, enterocytes, and urothelial bladder cells [93]. Chloroquinone is extensively used to inhibit viral endocytosis, which behaves similarly to nanoparticles. PNPs, such as polylactic acid are commonly employed to encapsulate chloroquinone, accelerating its transport and cellular absorption effectiveness [94].

Gold nanoparticles (AuNPs): The potential of AuNPs to rapidly generate an immunological response by APCs (Antigen-Presenting Cells) makes them appealing for advancement in the vaccine. AuNPs possess feature of being readily converted for distribution through the nasal cavity [95]. It also has the capacity to boost the immune response by migrating to the lymph nodes and interacting with CD8+ (cytotoxic) T cells [96]. HSPGs (heparan sulphate proteoglycans) are cell surface receptors that some viruses (notably coronaviruses) employ to attach to cells. To mimic this receptor, Baram-Pinto et al. (2010) used mercaptoethanesulfonate (Au-MES NPs) capped to AuNPs. The nanoparticles inhibited many viruses, including Respiratory Syncytial Virus (RSV), lentivirus, Herpes Simplex Virus (HSV), dengue and Human Papillomavirus (HPV), demonstrating a broad-spectrum capability [97-98]. AuNPs seem more favourable than silver nanoparticles since they are less toxic.

Silver nanoparticles (AgNPs)

Due to biocompatibility, AgNPs are more accessible among synthetic nanoparticles. These compounds are biodegradable and can disintegrate in water to generate non-toxic compounds. AgNPs prevent viral particles from invading host cells. The Coronavirus Transmissible Gastroenteritis Virus (TGEV) is suppressed by silver nanowires and silver nanoparticles at lethal concentrations [99]. Cell death caused by viral transmission is reduced by AgNPs. Ag₂S NPs may suppress coronavirus replication by prohibiting viral particles releasing from host cells [100]. These nanoclusters greatly raise pro-inflammatory cytokine levels, thus, assisting in viral infection reduction. Yang et al. (2016) demonstrated that curcumin-modified AgNPs were efficient anti-viral agents that suppressed the virus before it infects the cells [101].

Zinc oxide (ZnO) nanoparticles: They are more effective at preventing infection caused by H1N1 virus. It has also been demonstrated that Zinc (Zn) can suppress the replication of viral genetic material of SARS-CoV-2 [102]. Zn promotes the formation of antiviral cytokines and boosts the immunological response to minimise inflammation. The essential SARS-CoV-2 protein, RdRP, contributes to genome accuracy. By blocking this protein, the replication of viral genome can be altered.

Cell-derived vesicles: Cell membrane nanovesicles with high amounts of ACE2 and numerous cytokine receptors act as nanodecoys competing with virus infected host cells. According to reports, nanodecoy strongly inhibits SARS-CoV-2 multiplication and infection, effectively binds and suppresses inflammatory cytokines such as GM-CSF and IL-6 [103-104]. As a result, a therapy option based on cell membrane nanovesicles might be a viable solution to SARS-CoV-2 and cytokines. Exosomes are nanovesicles with sizes ranging from 30nm-150nm that are released for all forms of cell-to-cell communication. They are evolving nanomaterials in emerging therapeutics, diagnostic research and cell regeneration [105]. Exosomes carrying the SARS-CoV-2 S protein have previously been demonstrated to

elicit an enhanced neutralising antibody titer by priming with a SARS-CoV-2 S protein vaccination and then advancing with an adenovirus vector vaccine [106].

Chitosan nanoparticles: Chitosan is commonly used in the manufacture of nanoparticles due to its low toxicity and biodegradability [107]. The findings indicate that chitosan NPs can transport medications to the lungs, offering a feasible treatment option for COVID-19 [108, 109]. Cationic chitosan impairs spike protein attachment to the ACE2 receptor via interacting with the S protein of SARS-CoV-2. Chitosan NPs can also be utilised to treat intestinal responses produced by the occurrence of COVID-19 due to their mucoadhesive features [110]. Cyprus researchers designed chitosan NPs for aerosol application, which permits drug adherence and aims to lung epithelial tissues as well as sustained release, lowering the toxic potential of the medications. The researchers claimed that chitosan NPs, known as Novochizol, enable the encapsulation of various medicines and their delivery to the lungs in order to combat major COVID-19 infections. Novochizol aerosols can offer a dose of medications to a patient for ½ hr to 3 hrs [111].

Nitric oxide (NO) nanoparticles: The administration of nitric oxide (NO) NPs may be an option for treating COVID-19. Research involving SARS-CoV-1 found that NO suppresses viral multiplication through the cytotoxic response of intermediate molecules such as peroxynitrite [112]. While SARS-CoV-2 affects NO producing endothelium cells, transporting NO from nanoparticles might provide an option for NO replenishment along with a reaction towards endothelial cells viral attack. Nitric oxide can hinder the initiation of inflammation based on hypoxia-reoxygenation/ischemia-reperfusion, maintain adequate blood flow, control lipid peroxidation and cell damage, enable the removal of cell fragments, regulate the cytokine cascade and minimise damaging vascular permeability [113].

Iron oxide (FeO) nanoparticles: Abo-Zeid et al. (2020) conducted docking simulation research based on a plan to reutilize FDA-certified FeO NPs to suppress COVID-19 infection. Although FeO NPs have already been accepted for treating anaemias, several studies suggest they may exhibit antiviral action. As stated by the authors, FeO NPs can bind with the region related to the S1-RBD protein receptor, employed by infected SARS-CoV-2 host cells, and might use them to cure COVID-19 [114].

Nanosponges: Zhang and colleagues (2020) used plasma membranes from lung type II epithelial cells/ human macrophages and created cell nanosponges. These nanosponges contain binding cell surface receptors that target SARS-CoV-2 which they use to penetrate the cell. SARS-CoV-2 is neutralised after being trapped by the nanosponges, stopping it from penetrating more cells [104].

Carbon Quantum Dots (CQDs): Loczechin et al. (2019) employed CQDs in combination with boric acid to suppress the HCoV-229E human coronavirus. The CQDs' functional groups (boronic acid) interacted with the glycoprotein S and the virus's receptors, interfering with the virus's attachment to the cell [115]. Furthermore, CQDs produced from curcumin had higher water solubility and improved antiviral activity compared to naturally occurring curcumin. These carbon dots proved efficient towards blocking viral attachment to the cell's surface [116]. Du Ting et al. (2020) demonstrated that curcumin-based cationic carbon dots function as multisite viral inhibitors [117]. Carbon dots significantly inhibited virus-negative-strand RNA synthesis and viral budding. To prevent viral replication, the car-

bon dots increased the levels of interferon-stimulating genes (ISGs) and pro-inflammatory cytokines.

Lipid nanoparticles (LNPs): LNPs are sustainable due to their lipid properties and are used preferentially in areas including biology and medicine. Amongst different LNPs, spherical liposomes are hydrophilic on the interior and hydrophobic (lipid bilayer) on the exterior are best for intranasal delivery [118]. An unstable antiviral compound ML336 that is strongly hydrophilic towards Venezuelan Equine Encephalitis Virus (VEEV) was administered into mice infected to VEEV via lipid-coated mesoporous silica nanoparticles [119]. Moreover, siRNA delivery utilising LNPs can specifically target organs while preventing a circulatory system breakdown [120].

Dendrimer nanoparticles (DNPs): DNPs interact strongly against viruses. The subsequent system enhances the antiviral activity and has a robust anti-infection impact on the host. Furthermore, successful reports of DNPs being utilised as a therapy for viral contagious illnesses including influenza and HIV have been recorded [121].

Virus-Like nanoparticles (VLNPs): VLNPs are capsids that include adjuvants and structural proteins produced by viruses. VLNPs can provide a potentially immunogenic epitope, enhancing immunogenicity. Since VLNPs are relatively small and can function as adjuvants, altering the adjuvants can generate a considerably more robust immunological response. It has been shown that intranasal administration of VLNPs using the influenza virus serves as a vaccine by releasing a significant number of antibodies and T cells capable of stimulating various immunological responses to boost immunity and minimize future infection [122].

Graphene oxide: The anti-viral activity of Hypericin (HY) conjugated graphene oxide (GO) complex (GO/HY) was examined by Du et al. (2019). This complex suppressed viral duplication, virus inactivation or adhesion to the host cell [123]. Graphene oxide, like hypericin has inherent antiviral characteristics [124]. Akhavan et al. (2012) reported that when treated with visible light, graphene tungsten oxide composite sheet inactivates viruses. The virus was found to be inactivated owing to photo-damage of the viral capsid protein, which was guided by the viral RNA release [125]. Yang et al. (2017) improved solubility of curcumin and also its biocompatibility by encapsulating it in Graphene Oxide Nanoparticles (GSCC). Curcumin-loaded graphene oxide is functionalized with sulfonate groups, that facilitate to imitate the cell surface and block viral adhesion via a competitive inhibitory effect. Furthermore, the GSCC displayed antiviral activity both before and after viral infection of the target cells [126]. Graphene is efficient in limiting viral adhesion in Human Immunodeficiency Virus (HIV), but AgNPs in combination with Graphene Oxide (GO) are advantageous against some enveloped viruses and feline coronavirus (FCoV). Graphene's antiviral potential will be essential in the battle of COVID-19 [83].

Nano-based vaccines: NPs have gained importance as a possible choice towards creating a brand-new generation of vaccines. Moreover, nano-based vaccines improve antigen stability, traverse cell membranes, targeted delivery of an immunogen, absorption by Antigen-Presenting Cells (APCs), shield antigens from premature degradation, and prolonged antigen exposure [127]. Many nanocarriers have been studied, including immune-stimulating complexes, liposomes, lipids, emulsions, virosomes, proteins, virus-like particles, polysaccharides and polymers. [128-129]. Vaccine effectiveness can be strengthened further

by making selective changes to the NP-antigen conjugates to generate the ideal amount of immune response [130-131]. Among these qualities are the ability to adjust the shape, the surface charge of the NPs and size, and surface functionalization with a range of ligands, making them appropriate carriers for vaccines [132]. Research has demonstrated that for vaccine production, the S protein is a potential target; nonetheless, tailoring the antigen design is crucial to achieving an immunological response [133-134]. Other antigens, like nucleoproteins and unstructured proteins, appear as promising targets for generating “cocktail” vaccines against SARS-CoV-2 [135]. This strategy is further explored by Epivax, while developing a cocktail vaccine to provide a moderate defense [136]. Arcturus Therapeutics in the United States is working on another suggested vaccine. The objective is a combination of self-replicating RNA with LUNAR®, a non-viral NP delivery method to make protein inside the human body. Another technology scientists discovered is STARR™, which is efficacious at extremely low concentrations and is 30 times more effective than conventional mRNA in pre-clinical animals [52].

Ufovax created an automated mount protein-nanoparticle vaccine platform (1c-SApNP) for vaccination. SARS-CoV-2 proteins easily penetrate from a protein NP framework in the vaccine prototype, seeking to activate the immune response and antibody formation to neutralise SARS-CoV-2. The business emphasises that the massive production procedures for these vaccinations have been verified by an external industrial partner [52]. COVID-19 vaccine candidates were created shortly after the entire genomic sequence of the virus was published. WHO identified 136 vaccine candidates for COVID-19 that were developed as of June 9th 2020, with ten now in the clinical development stages [137]. Furthermore, 16 nano-based vaccines have been manufactured for COVID-19 management. With more excellent knowledge of the interaction of NPs with the immune system, nanotechnology might be able to administer safer, quicker and more effective vaccinations than traditional approaches.

COVID-19 prevention through nanotechnology: Good hygiene practices are advised to avoid the transmission of coronavirus, particularly in settings where people come into close touch with patients. Proper handwashing with soap and water or using alcohol-based sanitizers can help to stop viral transmission. Recent research has demonstrated that coronavirus may survive and spread on plastic surfaces, glass, cloth, wood, and metal for several days. It can be eliminated by ethanol or hydrogen peroxide, which ruptures the virus's envelope [138]. Meanwhile, it is almost always hard to sanitise surfaces; hence, the researchers aim to create a surface coating that utilizes active compounds to immobilise viral nucleotides and spike glycoproteins.

Personal Protective Equipment (PPE): Nanoparticles incorporated in textiles have been extensively investigated. NPs enhance the physicochemical characteristics of fabrics, including UV protection, fire retardancy, antibacterial capabilities etc. [139-140]. Mao Ningtao (2019) evaluated the application of nanotechnology in safety gear, such as aprons, facemasks, and lab coats [141]. Furthermore, Libertino et al. (2018) reported that smart wearables and sensor-based electronics have been investigated, notably for health-based solutions [142]. According to Jayathilaka et al. (2019), wearable fabrics might be employed for therapeutic delivery [143]. Bhattacharjee et al. (2019) demonstrated that graphene oxide loaded with metallic NPs may be

utilised to coat personal protective equipment (PPE) [144]. As a result, the combination of graphene oxide and metal NPs such as Zn, Fe, Cu, and Ag can shield PPE from viral infection. Balagna et al. (2020) investigated the anti-viral activity of a silver nanocluster/silica nanocomposite coated on a Filtering Facepiece-3 (FFP3) facial mask against SARS-CoV-2 [145]. This antiviral coating is suitable for use on filtering media as well as on glass, polymeric or metallic surfaces and it can suppress the SARS-CoV-2 titer. Thus, silver nanocluster coating offers protection in populated environments including marketplaces, schools and hospitals.

Surface coatings: Nanomaterials-based coatings are now being employed in various applications, notably metallic elements like bismuth, titanium, silver or copper [146-147]. Furthermore, because of the nanoscale topographical arrangement, nanostructured surfaces can physically limit pathogen adhesion [148] and even destroy pathogen structure [149]. Nanomaterials are being incorporated in coatings or paints for handled surfaces, such as railings or doorknobs, walls, and surgical instruments, to restrict the spread and survivability of viruses and other disease-causing organisms. Rai et al. (2020) highlight numerous nano-coatings and their possible usage in public settings to reduce pathogen prevalence [150]. CuNPs and other metal NPs derived from polymers can be employed as a virucidal coating that can be sprayed or deposited on surfaces [151]. The antiviral coating can also be employed to reduce coronavirus transmission [152]. Interestingly, coupling CuNPs with quaternary ammonium shell has virucidal action [153].

Disinfectants and cleaning measures: Silver salts are now employed in disinfectants [154], as Ag is considered safe for sanitising applications [155]. Sanitizing with nanotechnology-based solutions in clinical environments might reduce viral existence on frequently contacted surfaces and keep them virus-free for extended periods.

Current and prospective applications: Nanomaterials can be utilized to enhance the efficiency of air filters in healthcare organizations or other areas using recirculated air. It can minimise viral particle distribution and eliminate viruses and pathogens from water [156]. Nanotechnology has been extensively researched for application in manufacturing wound dressings due to its capability to guard against infections and accelerate healing. New progress might involve the creation of enhanced detection kits, which have been identified as a critical requirement for existing viral management and monitoring efforts. Hameed et al. (2018) highlight the importance of nanotechnology in evolving pathogen identification [157]. Aside from identification, there have been significant breakthroughs in nanotechnology-based smart packaging to restrict viruses [158]. Though Zhong et al. (2020) and Hameed et al. (2018) evaluations emphasise on food-related aspects, they can also be employed in the medical environment.

Conclusion

The advent of virulent infections has always represented a burden in regulating the global transmission of lethal contagious diseases. As evidenced by the recent COVID-19 outbreak, the higher requirement of PPE, inadequate hospital amenities, and delays in medicine and vaccine research all had a detrimental impact on the community. The appearance of new strains and the consequences of the extended shutdown and the pandemic risk tend to influence socio-economic status. As a result, the research community must focus more on biosafety components to

generate technologies that could be employed to tackle future pandemics more effectively. Learning and knowledge from the COVID-19 pandemic are vital in this respect, as it is necessary to establish standard protocols or appropriate sterilising technologies for the reusability of PPEs that are freely available not just in health centres but also to the normal community. Computational research can help to accelerate the testing and screening of these therapies [159]. The widespread quest for advanced technologies to prevent COVID-19 has prompted industry and academics to switch away from old-fashioned ways and move towards innovative, smarter technology, i.e. nanotechnology [160]. Through effective management, therapy and diagnostics capabilities, nanotechnology has supported the comprehensive and integrated approach to the global COVID-19 outbreak. Nanoparticles based detection technologies have enabled quick, accurate and cost-effective infection screening, guiding public health campaigns. The potential of nanotechnology-driven detection to control COVID-19 and other possible viral infections may be researched further. Nanotechnologies offer prospects for optimal collaboration among healthcare providers, scientists and policymakers in tackling the continuing challenges posed by SARS-CoV-2 and future viral pandemics.

Abbreviations

ACE-2: Angiotensin-converting enzyme 2; acpcPNA: a cationic pyrrolidiny peptide nucleic acid; AMP: Antibody mimic proteins; APCs: Antigen-presenting cells; AuNPs: Gold nanoparticles; COVID-19: Coronavirus Disease 2019; CRISPR: Clustered Regularly Interspaced Short Palindromic Repeats; CuNPs: Copper nanoparticles; DNPs: Dendrimer nanoparticles; FCoV: Feline Coronavirus; FDA: Food and Drug Administration; FeO: Iron oxide; FF-3: Filtering facepiece-3; GO: Graphene Oxide; HIV: Human Immunodeficiency Virus; ICT: Immunochromatographic test; ISGs: Interferon-stimulating genes; LNPs: Lipid nanoparticles; MERS: Middle East Respiratory Syndrome coronavirus; NFC: Near Field Communication; NO: Nitric oxide; NPs: Nanoparticles;

PAD: Paper-Based Analysis Device; PCR: Polymerase Chain Reaction; PoC: Point-of-care; PPE: Personal Protective Equipment; RdRP: RNA-dependent RNA polymerase; RT-PCR: Reverse Transcription Polymerase Chain Reaction; S1: Spike protein; SARS: Severe Acute Respiratory Syndrome; TMPRSS: Transmembrane protease serine 2; USB: Universal Serial Bus; VEEV: Venezuelan Equine Encephalitis Virus; VLNPs: Virus-Like nanoparticles; WHO: World Health Organization; Zr: Zirconium.

Author Contributions: Zeeshan Arif, conceptualized, compiled, performed the study, figures preparation, and wrote the manuscript draft. The work was edited, and compiled by Habiba Khan. The published version of the work was approved by all authors after it was reviewed.

Conflict of interests: The authors declare that they have no conflicts of interest.

Acknowledgements: The authors thank the Council of Scientific & Industrial Research (CSIR), New Delhi, India and the Computational Toxicology Facility at CSIR-Indian Institute of Toxicology Research, Lucknow, Uttar Pradesh for providing computational support. The authors are also thankful to the Department of Zoology, University of Lucknow for providing research facilities.

Funding: No external funding was received for this research.

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