Review Article

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Efficacious nanomedicine track toward combating COVID-19

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Abstract: COVID-19 outbreak has become one of the catastrophic health emergencies that could threaten public health worldwide through several hospitalizations and thousands of deaths, leading to boosting global concern intensive precautionary measurements. The clinical and research trials are ongoing for developing several diagnostic tools, antiviral therapeutics, and vaccines *versus* COVID-19 infectiousness. This review argues the recent nanomedical progress and efficient nanomedicine applications and highlights relevant challenges and considerations of nano-based materials for combating COVID-19 infectiousness and severity. Eventually, we also provide futuristic avenues and perspectives paving the way to explore outstanding solutions for SARS-CoV-2 control and eradication.

Keywords: COVID-19, nanomedical diagnostics, nano-based therapeutics and vaccines

1 Introduction

The first identification of SARS-CoV-2 took place in December 2019, which belonged to Coronaviridae family and encompassed a massive variety of regularly widespread viruses in animals and humans. The major manifestations in humans are a mild respiratory or digestive disturbance [1]. Otherwise, minor coronaviruses have dense and severe respiratory

disorders leading to lethal outbreaks [2,3]. Comparable to SARS-CoV-1 and MERS-CoV, SARS-CoV-2 possesses characteristic features of rapid transmission among human beings to be categorized as the largest global public health menacing to humanity in this century [4]. As the majority of patients with COVID-19 are asymptomatic, the transmission of COVID-19 among persons is glaringly high [5]. Basically, the critical step of COVID-19 pathogenesis is SARS-CoV-2 intracellular entry through binding of S protein to angiotensin-converting enzyme (ACE) surface receptors that are specific receptors facilitating SARS-CoV-2 invasion of the host and then endosomal encapsulation and eventually the lysosomal and viral membrane fusion [6,7]. The spike proteins could stick tightly to glycans of mucins in the mucus that line the airway epithelium; hereby SARS-CoV-2 possesses the capability to remain in the airways (Figure 1). Based on the significance of S protein, effective targeting by inhibition of its activity exhibits one of the targeting options of COVID-19 cures displaying SARS-CoV-2 viral blockage [8,9]. The M protein is classified as a transmembrane glycoprotein type III, the most common protein predominating on the surface of SARS-CoV-2 [10]. M protein could organize the viral assembly during its binding to N protein for the nucleocapsid. The virion stabilization and M protein also regulate the interaction with other structural proteins [11–13]. The N protein is a remarkable protein in the SARS-CoV-2 genome that plays a fundamental role in the formation of nucleocapsids *via* supporting the viral genome conjugation with arginine and lysine amino acids [14,15]. Moreover, several studies have reported that the high expression of N protein is correlated with significant boosting in the viral-like particles (VLPs) production and assembly leading to maturation of formed virion [16,17]. Eventually, the smallest protein is E protein, a 10–74 kDa molecular weight. Higher E protein expression within host cells has been noticed during the viral life cycle, whereas a little fraction is integrated into the package of the mature virion [18–20].

In March 2020, The World Health Organization endorsed that the COVID-19 outbreak had become a pandemic due to a massive number of infectious cases with an accelerated mortality rate. Fever, cough, and tiredness are the

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Figure 1: SARS-CoV-2 structure and mechanism for remaining in the airways *via* spike protein.

main symptoms and shortness of breath, headache, and loss of smelling or/and tasting sensation are the less common symptoms of COVID-19. Moreover, elevated blood pressure and coronary heart disease may present in case of severe cases [21,22].

2 Nanomedicine track against COVID-19 infectiousness

Nanotechnology applications have become a pillar part of industrial and translational researches these few years. To be more specific, the nanomedicine term is carefully designed for nanomedical purposes, such as diagnosis, prevention, and therapy of diseases [23]. As demonstrated in Figures 2 and 9, nanomaterials or nanoparticles provide a wide variety of approaches in the manufacture of diagnostic kits and in the ongoing development of antiviral therapeutics and vaccines. Ameliorative modification in physicochemical characterizations, lower adverse effects, higher drug delivery efficiency, and higher bioavailability have been provided as outstanding advantages for recruiting nanomaterials against COVID-19 [24]. These unique features of nanomaterials could enable them to easily overlap with viral entry or host cell receptor attachment [25]. Below, we will manifest an overview of nanomaterials along

with their clinical applications in COVID-19 diagnosis, vaccination, and treatment.

2.1 Nanoparticles for diagnosis of COVID-19

Currently, the RT-PCR test and serologic diagnostic test are widely harnessed in the detection and screening of the virus in specimens. The detailed steps in the RT-PCR test procedure are illustrated in Figure 3.

Cellex Inc had manufactured a new rapid test as a serological immunodetection, qSARS-CoV-2 IgG/IgM rapid test (Figure 4), which has been recently approved by the FDA [26].

The ongoing progress on conventional tools for the diagnosis of COVID-19 by researchers to tackle their various limitations, for instance, false-negative results, longer evaluation time, and lack of sensitivity and specificity [27,28]. Harnessing quantum dot nanocrystal, magnetic and metal nanoparticles, ranged from 2 to 60 nm for conducting rapid COVID-19 detection.

Infectious pathogens possessing advanced nanosensing characteristics were primarily detected *via* versatile quantum dot nanocrystals. The most common commercial nanocrystals, the MHC-Ig avidin-biotin tagged coupling and the complex anti-CD28 antibodies on the top of a polymer-coated quantum point have readily constituted

Figure 2: Nano-sized materials utilized in diagnosing, fighting, and preventing COVID-19.

a quantum dot artificial antigen-presenting cell (aAPC). The incidence of CD28 T cells proliferation, once the exposure of antigen-presenting cells induced by quantum dot aAPCs, is higher 15 times than controls [29]. Fluorescent quantum dots can also be used to detect coronaviruses. One of the major steps of COVID infection is S protein receptor attachment to the host cell ACE2 receptors on the plasma membrane. Now, the recombinant spike receptor is conjugated with quantum points to synthesize multilateral imaging probe. The specific diagnostic reaction was regarded as neutralization of anticörper and human recombinant ACE2 blocked quenching. The additional function of this unique nanoparticle-based probe has obviously demonstrated in the validated identification of S protein and ACE2 receptor attachment inhibitors [30]. Quantum dot-tagged RNA aptamer particularly for the SARS-CoV N protein was tremendously susceptible for immobilized protein detection of virus [31]. For swift screening and detection of IgG antibodies generating against COVID-19, immunoassay strips are widely utilized [32]; for instance, a concise IgM antibodies detection relied on versatile colloidal gold nanoparticle

(Au-NP) multilateral flow assay [33] or double-functional photothermal biodetectors for coronaviruses [34].

Iron oxide nanoparticles (IO-NPs) are the popularly used magnetic-based nanoparticles, characterized with marvelous magnetic efficiency [35]. There are a variety of important applications recruiting these nanoparticles, such as newly developed Cdn detectors in coronaviruses similarly to harnessing silica nanoparticles in PCR assays [36]. In this assay, magnetic-bonded dsDNA conjugates are regularly synthesized, and also nontargeted cDNA is easily identified through the reaction of oligonucleotide probes with silica-encapsulated superparamagnetic nanoparticles. The magnetoplasmonic nanoparticles were additionally utilized to ameliorate the diagnostic RT-PCR method of SARS-CoV-2 when entered in a combination with poly(aminoester) and carboxyl groups. This pattern uses probe-functionalized magnetoplasmonic nanoparticles to enhance the viral RNA targeting [37]. Furthermore, the interesting advantages of biomimetic-functionalized magnetoplasmonic nanoparticles, such as smaller size, tremendous magnetic features, and saving biodetection

Figure 3: The diagnostic steps in PCR test for the COVID-19 detection. Procedures include the collection of samples and viral RNA extraction. By reverse transcription process, cDNA will be generated to obtain the amplification plot. A fluorescent signal is readily used to detect the viral cDNA.

Figure 4: Serological immunoassay of qSARS-CoV-2 IgG/IgM rapid test for the detection of COVID-19 antibodies.

time, have basically acquired them valuable preference for their multiple applications, especially in the detection of various pathogens.

Nanopore target sequencing, as shown in Figure 5, which has been developed by Oxford Nanopore Technologies, Oxford Science Park, UK is recently utilized for COVID-19 detection. This novel technique is based on the amplification and sequencing of 11 virulent and specific SARS-CoV-2 genome fragments (ORF1ab) [38] along with encoding other structural parts, for example, ORF7a, ORF8, S, E, M, N, ORF3a, and ORF10.

Surface plasma resonance represents a characteristic property of metal nanoparticles, such as copper, gold, and silver, which could govern the size modification of these nanoparticles depending on their morphology [39]. Au-NPs are the most functionalized metal nanoparticles used for the detection of coronaviruses. The antisense oligonucleotides targeted the N gene is utilized in a combination with Au-NP to detect the viral N gene resulting in high aggregation of Au-NPs [40,41]. Furthermore, silver nanoparticles (Ag-NPs) were also mainly used for MERS-CoV detection by a color change in the colorimetric assay method for the rapid estimation of viral target cDNAs.

There is a modern study focusing on nano-based diagnosis of SARS-CoV-2 with poly carboxyl-functionalized magnetic nanoparticles. This trend has offered promising outcomes through 20 min working time and the highest detection sensitivity (even ten copies) for COVID-19 molecular diagnosis [42]. The diverse applications of nanomedicine are not limited only to PCR figuring but also in further techniques, such as reverse transcription loop-tagged isothermal amplification and enzyme-linked immunosorbent assay [43]. For example, Zhu and colleagues also reported the nanoparticle-related biosensor platform for COVID-19. This platform is a simple track showing a one-step reaction procedure for an hour of result delivery [44]. Eventually, Mertens exhibited a recent method based on silver Respi-Strip diagnostic assay [45]. Recently, protein corona sensor technique and magnetic levitation assay have been proposed as multidisciplinary nanotechnology-based diagnostic methods for the detection of high-risk individuals at the early phase of COVID-19 infection [30,46], thus, prioritizing the proper patients, and evaluating plasma protein and biomolecule patterns, as well as minimizing the economic and social pressure leading to lowering the mortality rate among high-risk

Figure 5: Nanopore SARS-CoV-2 genome target sequencing consists of the preparation of clinical samples for RNA extraction and cDNA synthesis for PCR implementation, rapid barcoding, and genome sequencing.

Table 1: Characterizations of different types of nanoparticles used for COVID-19 diagnosis

Types	Examples	Size (nm)	Composition	Surface charge	Biodeceptor type	Ref.
Inorganic nanoparticles	Quantum dots	2–10	Composed of Hg, Pb, Zn, and Cd, e.g., CdSe, CdTe	+ /or –	Electrochemical and optical	[29,30]
	Magnetic nanoparticles (IO-NPs, zinc oxide NPs)	2–20	Fe ₂ O ₃ , γ-Fe ₂ O ₃ , Fe ₃ O ₄ , and ZnO	+ /or –	Electrochemical	[35]
	Metal nanoparticles (gold, silver, copper NPs)	1–60	Au, Ag, and Cu	+ /or –	Electrochemical and optical	[39–41,64]
Organic nanoparticles	Graphene oxide (GO) NPs	40–200	GO	–	Electrochemical and optical	[35]

patients due to serious COVID-19 complications, for example, sudden blood clots. Table 1 summarizes the main features of different types of nano-based materials used for COVID-19 diagnosis.

2.2 Nanoparticles in COVID-19 therapy

Several studies have discussed the use of different nano-materials as facilitators or carriers of treatment patterns for greater antiviral effectiveness in combating COVID-19 infectiousness. One of these examples, lipid-based carriers for salinomycin intrapulmonary delivery in COVID-19 infected patients. Many researchers have argued this drug in COVID-19 infection as a result of the supposed relationship of COVID-19 severity with dietary styles and commensal microbiome *via* designing efficacious foods and smart therapeutics for targeting problematic pathogens in the intestinal gut as a sort of supplementary agent for COVID-19 [47,48].

As revealed in Figure 6, salinomycin is a potential antiviral agent, works on the interference with S protein of SARS-CoV-2 for ACE2 receptors binding on the surface of host cells in a pH-dependent manner, thus preventing the viral fusion with the host cell membrane to release viral genetic material into the cytoplasm leading to hindering viral entry without induction of viral infection [49,50]. Due to its good physicochemical properties of salinomycin, it could be aerosolized efficiently by droplets to obtain good adherence of the lung’s mucosal surface and for prolongation of release time to be considered as a prospective therapeutic nanomedicine-based potential against SARS-CoV-2 infection [51]. The encapsulation of salinomycin by using lipid-based nanostructures as a nanocarrier pattern because of their extraordinary aerodynamic characterizations led to gradually boosting the absorption of salinomycin in the lung of infected patients [52].

A recent *in vitro* study by Zhang *et al.* harnessed the plasma membrane of human cells for synthesis of two forms of nanosponges, for example, alveolar epithelial cells and macrophages to induce SARS-CoV-2 neutralization [53]. Moreover, these nanosponges revealed higher binding and attaching to SARS-CoV-2 to optimize the neutralization than displayed in ACE2 receptors overexpressed on the outer surface of host cells, therefore, blocking the viral-cellular entry. Another report conducted by Ting *et al.* successfully cultured the Vero cells to experimentally investigate the porcine epidemic diarrhea virus (PEDV) as a similar pattern to those of SARS-

Figure 6: Lipid-based nanoparticles for pulmonary salinomycin delivery in the treatment of COVID-19 infected patient.

CoV through curcumin (CCM) delivery by stable carbon dot encapsulation of CCM for delivery using these intelligent nanomaterials [54]. The resultant findings of this study suggested that these carbon dots inhibited both ROS accumulation induced by PEDV and viral RNA synthesis and budding, thus altering the uniform shape of SARS-CoV-2 surface proteins and eventually hampered its entry for host cell infection. This inhibition of ROS accumulation in host cells assisted in limited SARS-CoV-2 expansion and is expected to damage DNA, which could lead to down-regulation of a set of cellular apoptotic pathways, inflammatory cytokine production, and interferon-stimulating genes [55,56]. A further similar study that discussed different nanomaterials, silver sulfide-loaded glutathione nanoclusters, have been examined for efficient delivery of glutathione as a powerful antioxidant to host cells exhibiting promising outcomes for the suppression of SARS-CoV-2 replication [57]. Opposing stable carbon dots, this research reported that this type of nanomaterials positively overexpressed inflammatory cytokines and interferon-stimulating genes, hence causing innate immunity activation against the virus. Considering together, these promotive findings indicate the significant role of various inorganic nanoformulations as fundamental contributors in the suppression of SARS-CoV-2 viral proliferation and replication for combating its infectiousness. Additionally, Chen and coauthors utilized GO sheets-coupled Ag-NPs to suppress feline coronaviruses, approximately 25% infection inhibition in cell culture [58]. GO bound to feline CoV lipophilic tails, whereas Ag-NPs attached to thiol group in E protein of

the virus, thus resulting in subsequent aggregation and rupture. This platform seemed to be considered in clinical practice to generate frontier effects for presenting new therapeutic nano-based modality along with intrasuppressive features in relevance for combating SARS-CoV-2 infection [59,60]. Peptide-mediated lipid nanoparticles (LNPs) represented one of the most common nanostructures functionalized for antivirals or vaccines delivery against COVID-19; for example, Ansari and colleagues have published a study emphasizing the use of lipid-based nanoparticles for improving the effectiveness of repurposed therapeutics against the virus [61]. Due to its biocompatibility and cell penetrability plus its high stability and capacity to customize it for cinematically accurate and long-term release of drugs, peptide-mediated LNPs had been taken into consideration to create state-of-the-art bioengineered systems possessing attractive characterizations for life-threatening health hazards specifically in the emergent of COVID-19. Interestingly, there is a current direction of mesenchymal stem cell transplantation for the treatment of infected patients with COVID-19 [62]. A recent study reported the importance of exosomes synthesized from mesenchymal stem cells in comparison with other fabricated nano-derived vesicles [63]. Safety, high biocompatibility, and lack of immunogenic levels are a variety of characterized merits for cellular targeting and fighting the COVID-19 crisis. Weiss *et al.* have focused in detail on the antiviral efficacies of some metal nanoparticles, involving copper and silver [64]. Mechanistically, SARS-CoV might be subjected to similar antiviral activity as a role of

ROS and the toxicity of Ag⁺ emissions of Ag-NPs to virus's species, encompassing HIV and HBV. Briefly, it was claimed that ionic species could link to surface proteins of the virus resulting in viral damage and accumulation as well as blocking viral replication [65,66], thereby enhancing the reaction with intracellular enzymes, influenza A virus (H9N2), herpes simplex virus, and orthopoxvirus [67,68]. Although the antiviral efficacy attributed in these sheets' virus binding and shielding potential because of their intensive edges and attaching supported by the electrostatic attractiveness between the positive charge of nucleocapsid shell of viral particles and the negative charge on the surface of GO [69,70]. Moreover, a study published recently that displayed the inactivation effect of titanium apatite filter on SARS-CoV by S protein damaging during 6 h exposure to UV light and further constricting the viral infectiousness [71]. Therefore, it demonstrated tremendously futuristic functions in advanced drug design as well as nano-based vaccines for SARS-CoV-2 control and eradication.

As demonstrated in Figure 7 and Table 2, we overview current nanoparticles that have been utilized for the treatment of COVID-19 along with highlighting their therapeutic points of intervention. Due to higher biocompatibility and water solubility, silicon nanoparticles (SiNPs) are much more applicable and approachable. SiNPs inhibit viral attachment to host cells through strong viral binding by hydrophilic or hydrophobic bonds exerting scavenger activity of the virus, for example, mesoporous-SiO₂ (mSiO₂) NPs [72]. A further model of this mode of action is cationic chitosan, which prevents S protein of SARS-CoV-2 binding to ACE2 receptors on the surface of host cells *via* the interaction of polysaccharide chain of cationic chitosan with SARS-CoV-2 S protein [73]. A new study in 2021 has suggested that the fabricated titanium oxide nanoparticles (TiO₂-NPs) nanotubes have considerable *in vitro* inhibitory effects on SARS-CoV-2 at lower concentrations (IC₅₀ = 568.6 ng/mL) along with weak adverse effects on the host cells, thereby they recommend the use of these interesting nanotubes *in vitro*

Figure 7: The life cycle of SARS-CoV-2 and its replication within the host cell and the therapeutic points of intervention. Viral attachment and entry through endocytosis may represent the most important point for blocking. Nanoparticles could target SARS-CoV-2 cellular entry, viral replication, and viral packaging and assembling besides their capability to act as carriers for antiviral delivery in host cells.

Table 2: Proposed mechanism of action of nanoparticles used in COVID-19 therapy

Types	Examples	Mechanism of action
Therapeutics	Cationic carbon dots encapsulated CCM	Blocking viral entry and cell attachment <i>via</i> altering the uniform shape of SARS-CoV-2 surface proteins
	Au-NPs	Blocking viral entry and cell attachment <i>via</i> complex with receptor binding domain (RBD) of SARS-CoV-2 than ACE2 on cell surface of the host
	Ag-NPs	Blocking viral entry and cell attachment <i>via</i> inhibiting the entry of virion inside the host by interaction with SARS-COV-2 surface
	IO-NPs	Blocking viral entry and cell attachment <i>via</i> interactions with S1-RBD) of SARS-CoV-2
	Zinc oxide NPs	Blocking viral entry and cell attachment <i>via</i> inhibition of binding of ACE2 on cell surface of the host to S-protein SARS-CoV-2
	TiO ₂ -NPs	Blocking viral entry and cell attachment <i>via</i> inhibition of binding of ACE2 on cell surface of the host to S-protein SARS-CoV-2
	Silicon NPs (SiNPs) and mSiO ₂ NPs	Blocking viral entry and cell attachment <i>via</i> inhibition of binding of ACE2 on cell surface of the host to S-protein SARS-CoV-2
	GO and its derivatives	Blocking viral entry and cell attachment <i>via</i> inhibition of binding of ACE2 on cell surface of the host to S-protein SARS-CoV-2
	Nanosponges	Blocking viral entry and cell attachment <i>via</i> inhibition of binding of ACE2 on cell surface of the host to S-protein SARS-CoV-2
	Au-NPs, Ag-NPs, and glutathione-capped silver sulfide nanoclusters	Interfering with DNA polymerase activity of the virus leading to inhibition of viral replication
	LNPs	Pulmonary salinomycin delivery for preventing the viral fusion with host cell membrane and thus hindering viral entry without induction of viral infection
	Ag-NPs	Artemisinin and artesunate delivery for interactions between negative charges of oxygen atoms of drugs with Ag surface
	Polymeric NPs	Ribavirin delivery for RNA-dependent RNA polymerase (RdRp) targeting
	PLGA-loaded NPs	Remdesivir delivery for RdRp targeting

and for sterilization approaches particularly in the wall coatings [74].

2.3 Nanoparticles for COVID-19 vaccines

Viruses are nanoscale objects and can thus be considered natural nanomaterials; inactivated vaccines, live attenuated vaccines, DNA-based vector vaccines are, according to this definition, nano-based technologies. Viruses and nanoparticles manipulate at the same length, and that is why vaccine development and immunoengineering approaches in nanotechnology are extremely robust. Nanoparticles, synthetic or natural, mimic the viral structural features while biotechnology, chemical biology, and nanochemistry enable the revolutionary design of next-generation vaccine technologies. A recent review has suggested that it is the ideal time for the application of novel approaches and technologies in vaccine evolutions to generate efficacious impact in various clinical phase trials for the first time [75].

Peptide-based vaccines have been regarded as the simplest form of readily designed vaccines, rapidly validated and manufactured [76]. These sorts of vaccines are

fabricated either as peptides with adjuvant mixtures or peptides-loaded nanocarrier or encoding nucleic acid vaccine structures. Most of the peptide-based vaccines and peptide-based nanoparticles are evaluated by *in vitro* and *in vivo* experimental tests to extend for clinical phases testing and development especially in cancer and chronic diseases [77,78]. In addition to the peptide-based COVID-19 vaccines development, academic and industrial efforts leverage foretold B-cell and T-cell epitopes in their subunit vaccines *versus* SARS-CoV-2; for instance, EpiVacCorona vaccine [79] (clinical trial number NCT04780035), which has been developed by the Vektor State Research Center of Virology and Biotechnology in Russia on the basis of chemically fabricated peptide antigens of viral proteins and adsorbed on an aluminum-containing adjuvant after conjugation with a carrier protein. From our view, the use of aluminum hydroxide as an adjuvant represents a hazardous limitation in vaccine manufacture and development due to some serious endogenous signals and diseases related to the existence of excess aluminum quantities in the body.

Nanoparticles have basically offered both peptide-based vaccines-dependent factors for effectiveness, namely

adjuvants and delivery systems. By engaging emerging plans for targeting cellular subsets and subcellular locations or lymph nodes, the immune profiles of nanoparticle vaccines tailored to attack specific location of diseases, and their efficacies could be ameliorated. For example, the exploitation of natural trafficking capability of albumin to lymph nodes by the state-of-the-art strategy of albumin hitchhiking [80]. Currently, nanoparticle-adjuvanted potency to address particular subsets of macrophages and lymph node-settled dendritic cells was recruited for the design and shape of a dual-targeting HBV vaccine. In a chronic HBV mouse model, the noticeable immune responses initiated *via* these specific subsets resulted in a stimulated activity of HBV viral clearance [81]. Vaccine design markers such as embedded antigens *versus* surface-presented antigens administer the presentation and processing of the antigen. Although the former demands the nanocarrier degradation or disassembly, and therefore resembles viral infection for the cellular immune response, the latter leads essentially to the humoral immune response created *via* the extrinsically presented viral proteins [82]. Moreover, polymeric micelle nanocarriers that switch antigenic peptides configuration to simplify cytosolic delivery could be reliably utilized for antigen-displaying cell uptake, antigen cross-presentation, and lymph nodes targeting [83].

VLPs are recent technology represented as one of peptide-guided nanotechnologies which were generated from bacteriophages, mammalian and insect viruses for innovative applications of various immunotherapies and vaccines [84]. There is a close similarity between VLPs and diseased pathogens in the molecular and pathological behaviors for much more visible to the immune system. Furthermore, VLP delivery platforms also are of service as adjuvants for effective amplifiers and activators of the antigen-specific immune response; hence, the variety of VLP nanostructures is in the stage of development, and some of them are in the pipeline of clinical trials [85]. Subunit vaccine candidates represent minimal constructions of SARS-CoV-2, which can induce protective immune responses when codelivered with some molecular adjuvants for triggered immunogenicity. For instance, SARS-CoV-2 subunit vaccine candidates are either S1/S2 subunits or fully length S protein formulations combined with adjuvants. In May 2020, the Novavax vaccine has been developed and entered a phase I/II trial [86]. Moreover, the most outstanding examples are COVAX-19, NVX-CoV2373, and VAT00002, which have been developed by Vaxine, Novavax, and Sanofi Pasteur/GSK along with noticeable progress in clinical outcomes either in phase II or phase III [87,88]. The recombinant expression method has been used to produce VLP vaccines undergoing genetic engineering for the integration of immunomodulators, ligands,

and targeting molecules. Both self-assembled VLPs and protein nanoparticles exhibit extremely monodisperse and stable vaccine platforms. Alongside the production of protein nanoparticles from subunits of antigens, their presentation and expression on proteinaceous bioengineered scaffolds, for example, encapsulin, bacteriophage, and ferritin VLPs have also been used to accomplish multivalent antigen displaying for augmented immunogenicity [75,89]. Eventually, subunit vaccines can outline the viral proteins combined with fabricated protein cages, VLPs and nano-based materials, which are recruited as delivery vehicles and/or adjuvants, plus rewarding additional benefits inveterate to every nanopatform [90,91]. CoVLP vaccine has been regarded as one of VLPs candidates for SARS-CoV-2, passed to Phase 3 clinical trials and developed by Canada-based Medicago introducing the prefused stable nanostructure of the S protein on self-assembling VLPs surface [92].

Nucleic acid-based vaccines are a promotive substitute to traditional vaccine strategies addressed to deliver the genetic material for *in situ* viral proteins production. Both mRNA and DNA vaccines represent this type of category in terms of COVID-19 fighting. Although these forms of vaccines are fascinating in the range of scalability, stability, and safety, there is a higher proportion of failure for undergoing clinical trial developments as shown finally with other modern technologies [93]. The induction of both CD4+ and CD8+ T cell responses has offered the most powerful advantage of this type of vaccine for virus control and elimination [94,95]. mRNA-1273 (clinical trial number NCT04792567) and BNT162b2 (clinical trial number NCT04780659) vaccines as shown in Figure 8, are the current examples of mRNA-based technology vaccines, have been developed by Moderna and BioNTech-Pfizer pharmaceuticals, respectively [96,97]. BNT162b2 vaccine for emergency use in preventing COVID-19 infection has recently been moved to be fully approved by the FDA in USA.

Harnessing nanoparticle-based encapsulation in mRNA-1273 and BNT162b2 vaccines has essentially offered a critical impact on half-life prolongation and stability increment because mRNA has a very short onset duration with immunogenetic mutations [98]. Furthermore, ARCT-021 vaccine developed by Arcturus Therapeutics is a good example for shaping self-amplifying RNA technology to extend the half-life of the RNA and thereby increase S protein expression levels [99]. Nanotechnology-based trends provide extraordinary solutions for challenges related to delivery by trafficking and addressing the vaccine to proper cellular populations and subcellular sites. Although formulated nanocarriers involving polymeric nanoparticles and cationic liposomes have enormously been utilized for DNA vaccine delivery across cell membranes, targeted nanoconstructs could further boost nuclear translocation of the plasmid DNA [100].

Figure 8: mRNA-1273 and BNT162 vaccines for COVID-19 infection.

2.3.1 Currently active and recruiting nanoparticles in clinical pipelines for COVID-19 vaccines

We are still awaiting approximately ten innovative technologies for nanoparticles in COVID-19 combating that have started since 2019. Table 3 overviews these novel nanoparticle technologies. Most of these technologies are based on protein subunits and LNPs utilized for nucleic acid-based vaccines particularly mRNA-based vaccines.

2.3.2 FDA approved nanoparticles for the production of COVID-19 vaccines

There are two FDA approved nano-based vaccines demonstrating the continued progress of nanoparticles to be introduced into the market and the clinic. Table 4 summarizes these approved nanoparticles by FDA for use for successful protection from COVID-19.

3 Concurrent nanomedicine challenges

Alveolar fluids and mucus may primarily constitute the main physiological barriers for reticuloendothelial and intranasal structures in systemic nanodelivery. Biodegradability and the ability to provide the preferred cell type along with

persistent drug delivery are required to maximize the endogenous efficacy of nanoparticles. In addition, nanoparticles should acquire intrinsic strength for overcoming cellular degradation processes [101,102]. However, studies showed that those procedures could cause severe damage to the air locations and extensive disturbance in the functions of lung. Nanoparticles of delivery methods established showed significant potential applications. Oxidative stress, genotoxicity, fibrosis, and inflammation are four pathobiological adverse effects that should be fully considered in associated methods for the production of nanoparticle perspectives [103]. There is no evidence for achieving mucosal immunity prolongation, safety, and full protection *versus* the virus by whether oral or nasal nano-based vaccines. Moreover, the correlation between different administration routes of variable age groups and generation of appropriate protection is still mysterious [104,105]. Sekimukai and coauthors discussed the massively allergic inflammation, which induced failure of protein-loaded Au-NPs to boost vaccine efficacy besides the occurrence of declining eosinophilic infiltration and triggering IgG reaction [106]. However, once nano-based medicines were diluted, they would lose their efficacies due to the disassociation of the compound–virus complex leading to virus liberation and restoration of viral replication, hence hampering their clinical translation success [107,108]. Nanoparticle-induced oxidative stress is owing to cellular ROS production or interference with mitochondrial respiration leading to prospective toxicities. Several types of researches have studied the intratracheal

Polymeric nanoparticles	Inorganic nanoparticles	Lipid-based nanoparticles	Organic nanoparticles
<p>Polymersome Dendrimer</p> <p>Polymer micelle Nanosphere</p>	<p>Silica nanoparticle Quantum dot Inorganic nanotubes</p> <p>Iron oxide nanoparticle Gold nanoparticle Silver nanoparticle</p>	<p>Liposome Lipid nanoparticle</p> <p>Emulsion</p>	<p>Carbon nanotubes Graphene oxide nanosheets</p>
Advantages <ul style="list-style-type: none"> • Precise control of particle characteristics • Payload flexibility • Easy surface modification Disadvantages <ul style="list-style-type: none"> • Possibility of aggregation and toxicity 	Advantages <ul style="list-style-type: none"> • Unique electrical, magnetic, optical properties • Variability in size, structure, geometry • Suited for theranostic applications Disadvantages <ul style="list-style-type: none"> • Solubility limitations • Toxicity limitations 	Advantages <ul style="list-style-type: none"> • Formulation simplicity • High bioavailability • Payload flexibility Disadvantages <ul style="list-style-type: none"> • Low encapsulation efficiency 	Advantages <ul style="list-style-type: none"> • Unique electrochemical and optical properties • High sensitivity and selectivity • High surface area • Size controllability Disadvantages <ul style="list-style-type: none"> • High cost production • High toxicity

Figure 9: Advantages and disadvantages of major classes of nanoparticles used for combating COVID-19 infectiousness.

uptake of TiO_2 -NPs during 90 days of administration in mice models and demonstrated remarkable antioxidant levels, ROS and inflammatory cytokines generation due to the nanoparticle accumulation in the lungs of mice along with a tremendous elevation of the AP-1 transcription factor (activator protein 1), which negatively affects the processes of transcription in the cells [109,110]. One of the harmful effects of nanoparticles is the endogenous interaction with DNA resulting in extensive genotoxicity, for example, carbon nanotubes which can cause fibrosis and pneumonia in experimental mice models, thereby it is essential to estimate such intrinsic factors before nanoparticle harnessing in clinical use [111,112]. The deep study of nanoparticle behaviors postexposure inside the human body has become a huge concern toward clinical practice. In this context, platinum-containing therapies such as cisplatin and carboplatin are among the most potent and used cancer chemotherapeutics for the treatment of several solid cancers [113]. Nephrotoxicity and off-targeting to normal tissues are major arising side effects of utilizing platinum-based therapeutic drugs [114]. Nano-based chemotherapeutics has possessed the potential tool in order to ameliorate the characterization of drug delivery as well as get rid of this challenge. However, the rapid reticuloendothelial clearance of nano-based therapeutic drugs might represent the main limitation for clinical settings, thus maximizing serious toxicities and lowering curative efficacy on off-target organs and tissues such as kidney, liver, and

spleen [115–117]. *In vitro* and *in vivo* experiments of IO-NPs have exhibited ROS production as a harmful adverse reaction [118,119]. To avoid this, surface coating of IO-NPs by using inert polymers gradually recovers cell viability to be one of the available solutions for the improvement of nanoparticle deficiencies [120]. The profound level of inflammatory cytokines in the human body is generally correlated to the sharpness of several infections. The exaggerated release of these components is popularly named as cytokine storm, caused by uncontrolled reactions of our immune system as a result of severe pathogenic infections [121,122]. Macrophages and monocytes in the immune system have been regarded as a fundamental cornerstone for curbing these extensive inflammatory responses and controlling the adaptive and innate immune reactions [123]. In case of SARS-CoV-2 infection, this storm boosts the severity of symptoms in most infected patients, which mimic those that happened in macrophage stimulating syndrome incorporating with dysfunction of macrophage [124]. Immunosuppressive agents such as methylprednisolone have been prescribed as a potent treatable approach against cytokine storms in severe cases of COVID-19. The regulated modulation of factors governing innate and adaptive immune responses at COVID-19 infected patients is also recently under consideration. Unfortunately, this activation is still not adequately enough for the resultant pathological effects of cytokine storms. Targeting primary immune cells promoting

Table 3: Currently active and recruiting nanoparticles in clinical pipelines that have been used for the production of COVID-19 vaccines

Name and nanoparticles	Type and payload	Developer	Route	Dose number	Clinical studies status
NVX-CoV2373 (Covovax [®] , Nuvaxovid [®]) SARS-CoV-2 rS/Matrix-M1 adjuvant	Protein subunit (recombinant S protein)	Novavax	IM	2 (day 0 + 21)	Phase 3 recruiting NCT04611802, NCT04583995, and NCT04533399
VAT00002 and VAT00008 (Vidprevryn [®]) SARS-CoV-2 rS/AS03 adjuvant	Protein subunit (recombinant S protein)	Sanofi Pasteur & GSK	IM	2 (day 0 + 21)	Phase 3 recruiting NCT04904549
COVAX-19 (Spikogen [®]) SARS-CoV-2 rS/Advax adjuvant	Protein subunit (recombinant S protein)	South Australian-based biotech (Vaxine)	IM	2 (day 0 + 21)	Phase 1 recruiting NCT04453852 Phase 2 recruiting NCT04944368 Phase 3 recruiting NCT05005559
GBP510	Protein subunit (recombinant S protein, RBD)	SK Bioscience	IM	2 (day 0 + 21)	Phase 1/2 recruiting NCT04742738, NCT04750343
Self-assembled protein nanoparticle immunogen					Phase 3 recruiting NCT05007951
CoVLP virus like particle based on Australian weed, Nicotiana benthamiana	Plant-based SARS-CoV-2 spike protein (CoVLP)	Canada Medicago	IM	2 (day 0 + 21)	Phase 1 recruiting NCT04450004 Phase 1/2 recruiting NCT05065619 Phase 2/3 recruiting NCT04636697 Phase 3 recruiting NCT05040789
mRNA-1283 LNPs	RNA-based vaccine (mRNA)	ModernaTX, Inc.	IM	2 (day 0 + 28)	Phase 1 recruiting NCT04813796 Phase 2 recruiting NCT05137236
DS-5670a, LNPs	RNA-based vaccine (mRNA)	Daiichi Sankyo Co., Ltd.	IM	2 (day 0 + 21)	Phase 1/2 recruiting NCT04821674
CVnCoV LNPs	RNA-based vaccine (mRNA)	CureVac AG	IM	2 (day 0 + 28)	Phase 3 recruiting NCT04674189, NCT04838847, and NCT04860258
ARCT-021/LUNAR-COVID19	RNA-based vaccine (mRNA)	Arcturus therapeutics	IM	2 (day 0 + 28)	Phase 2 recruiting NCT04728347 and NCT04480957
Lipid-enabled nucleomonomer moiety mRNA					

Table 4: Currently FDA approved nanoparticles that have been used for the production of COVID-19 vaccines

Name and nanoparticles	Type and payload	Developer	Route	Dose number	Clinical studies status
mRNA-1273 (Spikevax®) LNPs	RNA-based vaccine (mRNA)	Moderna & National Institute of Allergy and Infectious Diseases	IM	2 (day 0 + 28)	Phase 1 NCT04283461 Phase 2 NCT04405076 Phase 3 NCT04470427, NCT04760132, NCT04792567, and NCT04885907 FDA, emergency use authorization (2020)
Tozinameran/BNT162b2 LNPs	RNA-based vaccine (mRNA)	Pfizer/BioNTech	IM	2 (day 0 + 21)	Phase 1/2 NCT04380701 Phase 2/3 NCT04368728 Phase 3 NCT04760132, NCT04780659, NCT04775069, NCT04852861, and NCT04878211 FDA, emergency use authorization (2020)

cytokine storm progression through utilizing therapeutic patterns could contribute as an alternative option in terms of remedy of severe COVID-19 cases [125,126]. Earlier results have revealed that the depletion of liposome-associated macrophages might play a curative function of limiting the generation of cytokines at infectious and autoimmune diseases [127,128]. The surface functionalization with targeted ligands and peptides of nano-based therapeutics for efficient attachment to major extracellular factors of macrophage membrane with higher affinity can readily enhance their particular uptake for alleviating macrophage dysfunctional responses [129,130]. As shown in Figure 9, we summarize the major advantages and disadvantages of several nanoparticles that have substantially participated in the eradication of COVID-19 infectiousness.

4 Future outlooks

Massive advancements harnessing nanotechnology-based approaches will be fulfilled in COVID-19 diagnosis and therapy in the upcoming future. Not only exploitation of these nano-based tools in this issue, but also in a broad area of protruding pathogens. Furthermore, efficient delivery of active constituents using nano-based vaccines and monoclonal antibodies toward infected locations accelerates precise virus detection. Eventually, the capability of nano-materials for undergoing clinical translation and enhancing their scalability in production remains a big obstacle to ongoing development and progress. Mesenchymal stem cell secretome exhibits one of the recent regenerative nanomedicine options for COVID-19. Mesenchymal stem cells play critical functions in acute respiratory distress syndrome remedy particularly against fibrosis through secretion of VEGF, hepatocyte growth factor, and IL-10 for repairing and regenerating excessive damage in the lung [131]. Moreover, these stem cells can cause inhibition of the irregular employment of macrophages and T lymphocytes, inducing their proper differentiation into anti-inflammatory macrophages and T regulatory subsets. All of these significant functions of mesenchymal stem cells enable them a great opportunity to be one of the optimum therapeutic preferences among further cellular therapeutics for COVID-19 treatment [132]. Exosomes are tiny packs, initiated by stem cells and encapsulated with nucleic acid materials and cellular proteins [133], characterized by their immune-modulatory functions, anti-inflammatory activities, and regenerative assimilation likely mimic to those of their ancestors, mesenchymal stem cells [134,135]. Consequently, exosomes have represented futuristic therapeutic regimens for COVID-19 eradication.

5 Conclusion

This review has briefly argued the COVID-19 pathophysiological causes and the role of nanomedicine approach toward its combating. We have summarized a remarkable progression of the development of nano-based diagnostic, therapies, and vaccines against COVID-19. Nanotherapeutics (nanovaccines and nanoparticle-based therapeutics), single and combined antiviral therapies along computational-based methods are innovative tracks for designing novel drug discovery for fighting COVID-19. Nanoparticles of delivery methods established showed significant potential applications. Oxidative stress, genotoxicity, fibrosis, and inflammation are four pathobiological adverse effects that should be fully considered in associated methods for the production of nanoparticle perspectives. Nanoparticle-induced oxidative stress is due to cellular ROS production or interference with mitochondrial respiration leading to prospective toxicities. One of the harmful effects of nanoparticles is the endogenous interaction with DNA resulting in extensive genotoxicity; for example, carbon nanotubes that can cause fibrosis and pneumonia in experimental mice models, thereby it is essential to estimate such intrinsic factors prior to nanoparticle harnessing in clinical use. All of these drawbacks are not neglectable in rational engineering and design, still remain unclear leading to several difficulties to accomplish an efficient clinical practice and translation. Finally, Mesenchymal stem cells and exosomes might offer promising tools for the treatment of COVID-19 in the near future.

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