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Emerging importance of nanotechnology-based approaches to control the COVID-19 pandemic; focus on nanomedicine iterance in diagnosis and treatment of COVID-19 patients

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ABSTRACT

The ongoing outbreak of the newly emerged coronavirus disease 2019, which has tremendously concerned global health safety, is the result of infection with severe acute respiratory syndrome of coronavirus 2 with high morbidity and mortality. Because of the coronavirus has no specific treatment, so it is necessary to early detection and produce antiviral agents and efficacious vaccines in order to prevent the contagion of coronavirus. Due to the unique properties of nanomaterials, nanotechnology appears to be a highly relevant discipline in this global emergency, providing expansive chemical functionalization to develop advanced biomedical tools. Fascinatingly, nanomedicine as a hopeful approach for the treatment and diagnosis of diseases, could efficiently help success the fight among coronavirus and host cells. In this review, we will critically discuss how nanomedicine can play an indispensable role in creating useful treatments and diagnostics for coronavirus.

1. Introduction

Following the identification of severe acute respiratory syndrome coronavirus (SARS-CoV) and middle east respiratory syndrome coronavirus (MERS-CoV), it was predicted that we would encounter another virus from the corona virus family that originates from common human and animal resources \([1]\). In late 2019, the first human cases of coronavirus (CoV) was identified in Wuhan/China. On March 11, 2020, the World Health Organization (WHO) describe the deployment of coronavirus disease 2019 (COVID-19) as a pandemic \([2]\). COVID-19 is the third largescale epidemic in human history, and the first pandemic caused by a coronavirus \([3]\). At the time of writing, September 24, 2021, more than 230,418,451 cases of coronavirus have been confirmed worldwide, of which 4,724,876 million have died (https://covid19.who.int/). With a total of 10,000 cases, the mortality rate of SARS and MERS were reported to be 10 and 37%, respectively. Nevertheless, the incidence of COVID-19 is nearly 90 times higher than that of SARS and MERS in total \([4]\). Considering the high transmissibility of COVID-19, secondary prevention measures in the form of timely diagnosis may contribute to the containment of the situation \([5]\). Scientists have made great efforts to propose an effective treatment for COVID-19 \([6]\).

Therefore, considering the increasing prevalence of this disease, it is a good time for all researchers to think about producing a quality detective tests and so new therapies without side effects and methods so they quickly sequenced the SARS-CoV-2 genome \([7]\). In current years, nanomedicine has provided hopeful solutions to surmount the curbs of
current diagnostics and treatments [8–11]. Highly sensitive immunological diagnostic assays are particularly efficacious for detection of viral antigens, particularly that of SARS-CoV-2 [12]. The lesser known “nano-based diagnostics” were also investigated in the case of major epidemics such as influenza [13] as reliable alternative solutions to conventional tests [14].

Traditional circulation-based delivery of drugs is not deemed to be an effective intervention, necessitating development of novel platforms for delivery of therapeutics to hard-to-reach tissues in human body. Today, several nanotechnology-based drug delivery platforms are available for experimental use against COVID-19 [15] in hopes of lowering the course of the disease [16].

This review critically argues various diagnostic and therapeutic strategies for CoVs, concentrating on nanomedical applications in COVID-19 and associated pathogenic CoVs (Graphical abstract).

2. COVID-19 characteristics

Coronavirus (CoVs), as a member of the coronaviruses family, has a single-stranded RNA genome of positive polarity that infect humans and animals [17]. Moreover, CoVs are enveloped and non-segmented RNA viruses with an asymmetric shape and surface spikes located so as to look like a crown [18]. Their genome size ranges from 28 to 32 kb, being the largest identified RNA virus. The structural proteins, which are encoded by 3’ terminus of SARS-CoV-2), consist of envelope (E), nucleocapsid (N), membrane (M) and spike (S) proteins [19] (Fig. 1. Modified from Ref. [20]).

CoVs are the second most widespread reason of the typical cold in humans and have been isolated from infants, humans, and animals in gastrointestinal infections and gastroenteritis [19]. There are four groups in this family: Alpha-CoV, beta-CoV, gamma-CoV, and delta-CoV. SARS-CoV-2 is classified in the beta-corona group of viruses [21]. COVID-19 was first reported in Hubei province, on December 31, 2019 and quickly outbreak all over China [22]. SARS-CoV was the cause of the Guangdong, china, outbreak in 2002, and MERS-CoV was first revealed in Saudi Arabia in 2012 and circulated along the Arabian Peninsula [23]. In general, these viruses attack the gastrointestinal and respiratory epithelial cells and can cause mild diseases in infants [24]. The virus is stable at low temperatures and at ambient temperatures for some time, but is similar to the Rabdo virus and is sensitive to light [25]. The most general signs contain fever, cough, and shortness of breath, extreme languor, digestive problems, and loss of sense of smell [26]. CoVs are most often transmitted through direct contact with a sick person [26]. The virus can also be spread by touching an infected surface and then touching the eyes, nose, mouth, and respiratory aerosols (droplets) [26,27]. CoVs attaches to host cell surface glycoproteins through connections between viral glycoprotein spikes [21,28]. Several CoVs bind to sialic acid glycoproteins and glycolipids via spike and/or hemagglutinin esterase glycoproteins [29]. Interactions between CoVs and host cell receptors determine the degree of specificity, tissue growth, and pathogenicity of the virus [28,29].

3. Therapeutic approaches

To date, no available methods are available to effectively treat the progression of COVID-19 [30]. Scientists have made great progress in repurposing of therapeutics for successful treatment of COVID-19 that include 1) drugs: old medicine (chloroquine phosphate), antiviral drugs (Lopinavir/ritonavir, leronimab, galidesivir, and arbidol (umifenovir)), renin–angiotensin-aldosterone system (RAAS inhibitors), 2)
Combination therapy, 3) Convalescent blood therapy, 4) Mesenchymal stem cell (MSC) therapy, 5) Psychological interventions [6] and 6) vaccines [31].

Owing to a shortage of appropriate vaccines and particular treatments preventive measures are currently effective for control [31]. Experts and governments are emphasizing the need for social distancing and quarantine to stop the spread of this contagious disease [32]. Currently, the most important concern for researchers around the world is to fight the CoVs is to develop a good vaccine [33].

3.1. Vaccines against CoVs

Certainly, the first part of the medicinal intermediation, is the elimination of the virus before it infected target cells or even be distributed throughout the body [34]. To date, the WHO has issued the first emergency authorization to use one of the vaccines against the Covid-19 pandemic [35]. Hence, the United Nations has agreed to make emergency use of Pfizer and BioNTech vaccines to prevent CoVs infection. But researchers are still trying to produce an efficient vaccine versus the SARS-CoV-2 to improve safety and decrease associated signs [36]. Table 1 displays various vaccine platforms utilized versus CoVs [37–52].

Vaccines basically introduce antigenic molecules to the body, which is generated in patients who have this illness, which in general can be said to be an assured procedure for the patient [53]. These antigens are present on the surface of dendritic cells and macrophages, known collectively as antigen presenting cells (APCs), as part of the major histocompatibility complex (MHC) I and II [54]. These antigens are pivotal for the function of adaptive immune system, which recognizes such antigens as antagonistic attackers and as well as generates antibodies or activate T cells to destroy the raider [55,56]. Furthermore, memory B cells progress virus particular antibodies on the outer area of the cell prompt a quick immune response to eliminate the infection of viral. Depending on the kind of infection, numerous different kinds of vaccines are presently in use, contain passive vaccines, conjugated vaccines, live attenuated vaccines, more newly DNA or RNA vaccines [57]. In spite of its presence for more than 20 years, because of side effects upon treatment or inadequacy of the vaccine, up to now no efficient vaccine against human CoVs could be developed, representing the need of a new approach to target CoVs. S protein as an important part of Co Vs considered a promising target in the development of vaccines [7]. The recently developed purified inactivated SARS-CoV-2 vaccine termed ‘PiCoVacc’ by Sinovac Biotech is currently in phase I clinical trials (Fig. 2. Modified from Ref. [20]).

### Table 1
Vaccine platforms for CoVs.

| Vaccine Platform                  | Target                                      | Product by                              | Virus          | Number of candidate vaccine | Ref.       |
|----------------------------------|---------------------------------------------|-----------------------------------------|----------------|-----------------------------|------------|
| Live-attenuated virus            | all proteins of the virus                   | eodagenix/serum institute of india      | CoVs          | 3                           | [37,38]    |
| Inactivated vaccines/ alum       | whole structural protein of the virus       | osaka university/sinovac biotech china   | CoVs          | 9                           | [39,40]    |
| RNA vaccines                     | SARS-CoV-2 spike protein                    | Moderna, Inc (USA), BioNTech/Fosun pharma/Pfizer (Germany, China, USA), CureVac(Germany) | SARS-CoV-2     | 16                          | [41]       |
| Virus-like particles             | unknown                                     | Doherty institute (Australia)           | CoVs          | 12                          | [42,43]    |
|                                  |                                             | Medicago Inc (Canada)                   |                |                             |            |
| DNA vaccines                     | s glycoprotein and subunit of sars-cov-2    | Saiba GmbH                              | CoVs containing SARS-CoV-2 | 11              | [44–46]   |
| Protein subunit                  | s glycoprotein and peptides/unknown         | Griffith University (Australia), Zydsus Cadila(india), Inovio pharmaceuticals (USA), Takara Bio (USA), BARDA and Sanofi pasteur(USA,France) | NVX-(COV2373)/ RSV | 49                          | [47,48]    |
| Recombinant protein vaccines     | Spike protein                               | Novavax, and Sanofi pasteur France, University of Queensland, (Australia), Vaxil Bio (Israeli), Emergent BioSolutions Inc(USA) | CoVs containing SARS-CoV-2 |                | [49–52]    |
|                                  | Nucleocapsid protein                        |                                         |                |                             |            |
|                                  | Membrane protein                            |                                         |                |                             |            |

3.1.1. DNA vaccine

A vaccine is a type of medicine that supplies active acquired immunity to a given infectious disease [58]. Nowadays, later than one year the find of SARS-CoV-2, antiviral drugs and vaccines are being established, with numerous treatment opportunities and vaccines in clinical studies around the world [59]. However, antiviral drugs are very important in modulating the existing pandemic disease, but effective vaccines are vital to control it [59,60]. The ability to stimulate the innate and acquired immune responses is the most important advantage of DNA vaccination [61]. A DNA vaccine designed to induce CD4+/CD8+ immune response by inducing the expression of SARS-CoV spike protein inside the host cells is currently being explored in a phase I clinical trial [62]. During antibody-dependent enhancement, in response to vaccines, the virus-specific antibodies facilitate viral entry and thus increase the incidence of infection [63]. Vaccines that stimulate an immune response against the S protein to prevent it’s attaching with the host angiotensin-converting enzyme 2 receptor, can be delivered as efficient vaccines against SARS-CoV-2 [64]. Presently, the INO-4800 structure (Fig. 2) is a DNA vaccine candidate matched to the SARS-CoV-2 S protein and developed by Inovio Pharma in a fashion similar to their previous MERS-CoV vaccine, which is presently undergoing clinical studies [46,65]. Moreover, a recombinant adenoviral vector-based vaccine for COVID-19 was reported to be safe and immunogenic in a first-in-human trial [66]. The vaccine developed by CanSino Biologics is the first candidate to be tested and has entered Phase II medical test [66]. The Shenzhen Immunogenic Medicine Institute of China is ensuing the COVID-19 vaccine and two global vaccine applicants for COVID-19 in the experimental stage, LV- SMENP-DC and pathogen-specific an APC (Fig. 2). Synthetic SARS-CoV-2 minigenes with certain modifications on conserved domains of the polyprotein protease and viral structural proteins and a have been investigated using an effective lentiviral vector system (NHP/TYF) to induce transcription of viral proteins to modulate the activity of dendritic and T cells.

3.1.2. mRNA vaccine

An RNA vaccine or mRNA (messenger RNA) vaccine is a novel kind of vaccine that work via introducing an mRNA sequence encoding a target antigen to incite an immune response [67]. mRNA vaccines are highly effective at inducing cellular immunity, since antigens are expressed inside the cell [68]. Over 150 COVID-19 vaccines are presently under progress via Biopharma Institute and investigation Governments in the globe [69]. Recently, Moderna partnered with researchers at the Vaccine Research Center (VRC) developed vaccine platforms against SARS-CoV-2 encoding for a prefusion fixation form of S protein through the use of mRNA-1273 [70]. Numerous studies are
currently simultaneously underway to improve mRNA vaccine versus SARS-CoV-2 [71]. In addition, administration of mRNA to encode antibody proteins is another similar approach for development of a COVID-19 vaccine.

### 3.1.3. Viral proteins

Subunit-based vaccines present an antigen lacking other viral elements to immune cells, via a specific, isolated protein of the pathogen [72,73]. Researchers have been able to determine the genetic sequence of the S protein and the baculovirus expression system is commonly used to produce recombinant proteins [74,75]. The foundation on the structure of coronavirus S protein, containing C-terminal, receptor-binding and N-terminal domains [76,77], and or fusion peptide [46], is considered as a vital target for the development of a vaccine versus SARS-CoV and MERS-CoV due to its capability to promote the immune response and deliver neutralizing antibodies [47,78,79]. At present, the most promising treatment Modality against COVID-19 is S-protein-based vaccines and up to now, many organizations and associations are paying close attention to this field. An alternative Covid-19 vaccine was generated via the combination of MERS-CoV-S1 and/or SARS-CoV-2-S1 immunoreactive epitopes with S-fold on trimerization region, reaching 27 lengths of amino acids, which was applicable to naïve viral structure. This complex had a unique affinity to the TLR on the cell surface and could trigger relevant signaling pathways [52]. It has been shown that the local introduction of target antigens could be done via the application of the novel delivery subcutaneous delivery system [52]. For instance, the microneedle patch system is a sophisticated delivery approach to release target antigens to the subcutaneous areas where local immune cells could appropriately respond to immuno-reactive molecules [80]. Via its patented Trimer-TagC knowledge, Clover Biopharmaceuticals Inc. has produced a vaccine via trimeric S protein that is analogous to the natural trimeric S protein of SARS-CoV-2 [51]. In addition, Dynavax is supplying CpG 1018, the adjuvant used in the FDA-approved HEPLISAV-B vaccine, to mediate the rapid development of COVID-19 Trimeric S protein vaccine [51]. Furthermore, a molecular clamp is a polypeptide used to preserve the shape of proteins in experimental vaccines [81]. According to conducted researches, the pre-fusion proteins available on the covid-19 surface are considered an ideal target for immune response [82]. Of note, it should be administered with other adjuvants’ therapy. Investigation of potential interactions among B and T cells and SARS-CoV S and N proteins (as protecting epitopes) in order to study vaccines epitopes are at the center of attention [83]. Due to some limitations including low-molecular-weight-related rare immunogenicity, it takes other adjuvants so as to increase its efficacy [82]. Notwithstanding its plenty in CoVs, N protein immunization did not persuade VN antibodies and provided no safety versus SARS-CoV [49]. However, it has been investigated that full-length M protein can induce effective neutralizing antibodies in SARS patients. Hence, it can be considered a candidate protein for designing SARS-CoV-2 vaccine [84,85].

### 3.1.4. Neutralizing antibodies

Antibodies can induce passive systemic anaphylaxis (PSA) through the low-affinity IgG receptor FcγRIII and platelet-activating factors in high antigenic environments [86]. The S protein is an important target for developing vaccines against coronavirus infections [31]. The inactivated SARS-CoV vaccine produces copious amounts of S protein-specific antibodies that inhibit receptor binding and viral entry. Fusion inhibitors target cellular receptors or viral epitopes to prevent the triad of binding, fusion, and virus entry [78,87,88]. Undoubtedly, Sui et al. developed a nonimmune human antibody library and recognized an anti-S1 human monoclonal antibody, 80R that can inhibit SARS-CoV entry by inhibiting S1 attachment to ACE2 receptors [78]. Soluble forms of angiotensin-converting enzyme 2 (ACE2) have lately been shown to prevent SARS-CoV-2 infection and could create long-lasting immunity for those who were previously infected [89].

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**Fig. 2.** The COVID-19 treatment by clinical phase vaccine candidates (modified from Ref. [20]).
3.2. COVID-19 ongoing vaccines

COVID-19 vaccines are perhaps the most rapidly developed in the history of vaccines [90]. Presently, there are over 180 vaccines being developed and 100 in clinical trials [91]. As of now, 18 different vaccines have been approved for public use against COVID-19 [91,92]. The COVID-19 vaccines can be classified in four major categories: (1) inactivated virus, (2) protein-based, (3) viral vector, and (4) nucleic acid [93]. Table 2 lists the characteristics of COVID-19 vaccines [90,91].

4. Antiviral compounds against CoVs

The manufacture of novel drugs and antiviral targets is time-consuming. To speed up the work process, it is essential to understand viral replication. An urgent demand to generate drugs to treat Covid-19 is vital. In this regard, using well-known drugs with approved efficacy and structure can be totally fruitful. Nucleoside and nucleotide analogs are commonly used in the therapy of cancer and viral infections [89,94,95]. They prevent virus replication by interfering with the cellular nucleotide synthesis. Remdesivir, a nucleotide analog produg, has broad-spectrum activity against viruses from multiple families. Remdesivir strongly binds the SARS-CoV-2 RNA-dependent RNA polymerase and Main Protease, and was recognized early as a promising therapeutic candidate against COVID-19 because of its capability to inhibit in vitro SARS-CoV infection. Several clinical experiments of favipiravir in combination with interferon have been performed in the therapy of COVID-19 in China [94,96,97]. Lopinavir is a new protease inhibitor (PI) established from ritonavir and stops the virus from replicating by attaching to viral proteases. Lopinavir is a new protease inhibitor (PI) developed from ritonavir and stops the virus from replicating by attaching to viral proteases and has been used for the treatment of SARS and MERS coronavirus infections and clinical trial versus SARS-CoV-2 has been started [98–100]. Antimalarial chloroquine is used for the therapy of immune-mediated diseases and neutralized by activating indolamine (2,3)-dioxegenase in PBMC and has been clinically tested versus COVID-19 the WHO suspends chloroquine-related clinical trials because of chloroquine ineffectiveness [94,101–104]. There are also other clinical trials for the therapy of COVID-19 worldwide like the neutralizing antibodies in patient sera, passive antibodies and Lastly, blocking factors that present affinity to attach to ACE2 receptor [105–109] and the use of cell-based methods such as mesenchymal stem cells MSCs are between the greatest commonly used cell kinds for regenerative medicine [110].

MSCs are attractive candidates for treating different diseases such as COVID19, largely since these cells showing several precautionary mechanisms to protect and repair pulmonary harm [111]. Besides, MSCs are considered suitable for anti-viral therapy as the safety and effectiveness of these cells have been mentioned in clinical studies of lung infections [112]. As well, that the use of Famotidine use is related to a decreased danger of clinical deterioration leading to intubation or mortality in patients who are hospitalized in COVID-19, according to a study published in Gastroenterology [113,114].

5. Nanotechnology in medicine; nanomedicine

Recently, many researchers have focused on nanomedicine and its advancement in the treatment and diagnosis of a wide range of diseases, such as cancers [115–117], inflammatory diseases [118], bacterial infections [119] as well as COVID19 [120].

Cancer, cirrhosis, viral and bacterial infections stand among the pathologies to have been detected by nanoscale diagnostics [121] before the onset of diseases. Furthermore, in vivo and in vitro studies demonstrated that drug-loaded nanocarriers are more effective than free drugs to treat such diseases [122–131].

Nanomaterial-based drug delivery platforms have improved efficiency of targeted drug delivery approach through sustained delivery of

| Vaccine platform | Type of vaccine | Developers | Phase |
|------------------|----------------|------------|-------|
| Viral vector     |                |            |       |
| (Non-replicating) |                |            |       |
| INO-4800 + EP   | International Vaccine | Phase | II/III |
| GRAV-COV2       | Institute + Inovio | Phase | IV |
| (Replication      | Pharmaceuticals + | Phase | II/III |
| defective          | Biopharmaceutical Co., Ltd |       |       |
| Simian Adeno (Grad encoding S) |       |       |       |
| Gam-COVID-Vac    | Gamaleya Research | Phase | III |
| Adeno-based (rAd26-S + rAd5.S) | Institute; Health Ministry of the Russian Federation |       |       |
| Ad26.COV2.S      | Janssen Pharmaceutical | Phase | III |
| ChAdOx1-S - (AZD1222) | University of Oxford | Phase | II/III |
| Recombinant nCoV vac. (Adeno type 5 vector) | AstraZeneca | Phase | IV |
| DNA based vaccine |                |            |       |
| AGO301-COVID19   | Takara Bio + ArGen + Osaka University | Phase | II/III |
| nCov vac.        | Zydus Cadila | Phase | III |
| Protein subunit  |                |            |       |
| SCB-2019 + AS03 or | Clover Biopharmaceuticals Inc./GSK/Dynavax | Phase | II/III |
| CpG 1018 adjuvant + alunm adjuvant (Native like Trimeric subunit S pro. vaccine) |       |       |       |
| MF59 adjuvanted SARS-CoV-2 Sclamp vac. | Seqirus + University of Queensland + CSL Ltd. | Phase | II/III |
| UB-612 (Multitope peptide based S1-RBD-protein based vac.) | Vaxxinity | Phase | II/III |
| SARS-CoV-2 rS/Matrix M1 adjuvant (Full length recombinant SARS-CoV-2 glycoprotein NP Vac. + Matrix M adjuvant) | Novavax | Phase | III |
| NVX-CoV2373      |                |            |       |
| Recombinant SARS-CoV-2 vac. (CHO Cell) | Institute of Microbiology, Chinese Academy of Sciences + Anhui ZhiLei Longcom | Phase | III |
| VAI00002: SARS-CoV-2 S protein + adjuvant | Biopharmaceutical GSK + Sanofi Pasteur | Phase | III |
| FINLAY-FR.2 anti-SARS-CoV-2 vac. (tetanus toxoid + RBD + adjuvant) | Instituto Finlay de Vacunas | Phase | III |
| EpiVacCorona (EpiVacCorona vac. + peptide antigens against COVID-19) | Federal Budgetary Research Institute | Phase | III |
| CIGB-66 (alumium hydroxide + RBD) | Center for Genetic Engineering and Biotechnology (CGB) | Phase | III |
| Virus like particle |                |            |       |
| Inactivated Virus |                |            |       |
| CoVLP COVID-19   | Medicago Inc. | Phase | II/III |
| COVID-19 inactivated vac. | Shifa Pharmed Industrial Co | Phase | II/III |
| Inactivated SARS-CoV-2 vac. (Vero cell) | Sinopharm + Wuhan Institute of Biological Products + China National Biotec Group Co. | Phase | III |
| Inactivated SARS-CoV-2 vac. (Vero cell) | Sinopharm + Beijing Institute of Biological Product + China National Biotec Group Co. | Phase | III |
| SARS-CoV-2 vac. (Vero cells) | Biopharmaceutical Co., Ltd | Phase | III |

(continued on next page)
SARS-CoV-2 involves mechanisms that might affect the entry of the virus [145]. The strategy of using nanoparticles (NPs) against several CoV-associated proposals have been introduced in the field of respiratory syncytial virus [143], and influenza virus [144]. Also, numerous infectious diseases consist of HBV [140], HIV-1 [141, 142], have been planning and established [139, 147]. Immunogens versus coronaviral infection, NP based delivery systems features, leading to favorable interactions of cell and impressive therapeutic teams and NPs high-level gives particular physicochemical into the host cell [146]. The Executive capability with a varied variety of mechanisms comes by reducing drug side effects [139].

Understanding the genetic mechanisms underlying the therapeutics via nanomaterials without causing significant toxicity [132,133]. Of note, the nanotechnology underlying the spread of novel viral outbreaks has mostly been made possible through nanotechnology [134].

Osteochondroplasty in medicine finds importance in several overlapping molecular technologies [133,135–138].

5.1. Nanomedicine and CoVs control

Following the emergence of the COVID-19 virus in early 2020, governments worldwide begin to implement measures to impede the expanse of the virus that became a universal pandemic. The application of nanotechnology for medical aims has been called nanomedicine, and is a multi-disciplinary approach, is the most interesting area for generating novel nanoproducts in biotechnology and biocompatible medicine [148,149]. One of the most important and well-known nanoproducts applied for medical purposes is nanoparticles (NPs) [150,151]. Currently, the ultimate goal for rapid control of the CoVs outbreak is vaccination. Administration of vaccine by NPs delivery systems can improved the efficacy and immunization of vaccine by protection of antigens degradation, controlled and sustained release as well as controlling cellular uptake and processing by APCs [152–154]. Table 2 summarizes the Nano-vaccines produced against the pathogenic CoVs [42,87,89,155–157].

Nano-vaccines are made by loading CoVs antigen into nanocapsules or locating them on NPs surface, fabricating NPs of similar immunological conformation. S protein is an important binding factor and immunodominant antigen in the coronavirus and is the main Nano-based vaccine candidates. The most common process for developing and producing corona viral Nano-based vaccines is structure-based assembly. The assembly pattern is important for controlling the thermodynamic consistency of assembled NPs and for preventing aggregation. S protein trimmers in SARS-CoV can be assembled with the removal of a non-ionic purifier versus the filtration process to form NPs. Vaccination of mice through these NPs prompts the production of neutralizing antibodies, which are enhanced by the use of aluminum hydroxide nanoparticles and the development of composite adjuvants. At prompt, a high level of neutralizing antibodies, vaccine mice with NPs is also remarkably augmented with adjuvants such as or M1 matrix (68-fold) and aluminum hydroxide (15-fold) [157]. Adjuvants may well also ameliorate safety and immunity with the MERS-CoV vaccine [175]. In addition, virus-like particles (VLPs) have a multi-protein structure and are fundamentally analogous to viral particles, except that they lack a viral genome and are potential candidates for vaccine production [176, 177]. MERS-CoV VLPs (MERS-CoV-LPs) are made in insect cells by expressing S, M, and E proteins [178]. With a slight correction of these NPs with S protein SARS-CoV, it causes the NP proteins to bind to the ACE2 receptor, thereby strengthening and stimulating the immune system. The structural gene of VP2 canine parvovirus is integrated with RBD MERS-CoV, it can Self-assemble into chimeric [158]. Therefore, RBD-Dedicated safety responses induced by mice vaccination and anti-sense can preserve cells from MERS-CoV entry. Bacterial expression systems due to affordable, fast breeding speed, easiness of culture, and production of high-yield recombinant proteins that can be used in nano-vaccine assembly processes. Using ferritin as a molecular scaffold in bacterial systems, self-assembled NPs of MERS-CoV antigens can be formed. Fusion of RBD with bacteriophage and RNA-interaction domain to be expressed in a soluble form in Escherichia coli. In addition, chaperones immunize mice versus CoV via intervening with RBD binding to the DPP4 receptor. Bacteriophythin (Bfr) is an oligomer protein that contains both dual-core iron centers and Heme B, which prevents accumulation during the assembly of viral antigens. SARS B cell epitopes of HRC1 protein S have been activated with self-assembled polypeptide NPs (25 nm) to produce tridimensional indigenous compounds and to produce highly particular antibodies [179]. Gold nanoparticles (AuNPs) are generally used in Nano-vaccines because by incite antigen-presenting cells and ensuring control of the release of antigen they can be used to increase the quality and effectiveness of vaccines. VLPs can be created via incubating AuNPs as a core with CoVs protein which automatically functionalizes the surface (S-AuNPs).

Moreover, nanoencapsulation of antimicrobial drugs may be rather effective in activating intracellular mechanisms and may contribute to the development of safe treatments for COVID-19 and other viral diseases. Table 2. Nanoparticles-based vaccination against.

### 5.1.1 Therapy

#### 5.1.1.1 NPs-based vaccines against CoVs

Nanotechnology, as an interdisciplinary approach, is the most interesting area for generating novel nanoproducts in biotechnology and biocompatible medicine [148,149]. One of the most important and well-known nanoproducts applied for medical purposes is nanoparticles (NPs) [150,151]. Currently, the ultimate goal for rapid control of the CoVs outbreak is vaccination. Administration of vaccine by NPs delivery systems can improved the efficacy and immunization of vaccine by protection of antigens degradation, controlled and sustained release as well as controlling cellular uptake and processing by APCs [152–154]. Table 2 summarizes the Nano-vaccines produced against the pathogenic CoVs [42,87,89,155–157].

| Vaccine platform | Type of vaccine | Developers | Phase |
|------------------|----------------|------------|-------|
| mRNA-1273        | mRNA-2 CoV vac. | Moderna + National Institute of Infectious Diseases (NIAID) | Phase IV |
| BNT162b2 (3LN     | mRNA-2 CoV vac. | Pfizer/BioNTech + Fosun Pharma | Phase IV |
| mRNA, or 'Comirnaty' | mRNA-2 CoV vac. | BioNTech + Pfizer | Phase IV |
| mRNA-1273        | mRNA-2 CoV vac. | Moderna + National Institute of Infectious Diseases (NIAID) | Phase IV |
| BNT162b2 (3LN     | mRNA-2 CoV vac. | Pfizer/BioNTech + Fosun Pharma | Phase IV |
| mRNA, or 'Comirnaty' | mRNA-2 CoV vac. | BioNTech + Pfizer | Phase IV |

**Adeno or Ad: Adenovirus, CoVLP: CoV-like particle, EP: Electroporation, nCoV: novel CoV, NP: Nanoparticle, S pro: Spike Protein, Vac: Vaccine.**
S-AuNP-based vaccines which used versus other severe pneumonia-related CoVs can increase lymphatic antigen transmission and humoral and cellular immune responses compared to free antigens. Although, this vaccine prompted an antigen-dependent IgG response, it is defective in stimulating protective antibodies and limiting the infiltration of eosinophils into the lungs. Thus, an in-depth and effective study of the S-AuNPs concentration and size are needed for promising CoVs vaccines [87].

5.1.2. Diagnosis

5.1.2.1. NPs-based diagnosis of CoVs. Common diagnostic assays for detection of SARS-CoV-2 adopt nucleic acid-based testing procedures, the most prominent of which is the RT-PCR technique [183,184]. Rapid diagnostic tests and identification for infectious diseases is the foremost method to contain epidemics, and this is difficult with common detection manner due to inaccessibility to tool, as well as the requirement for technological experience. Given the importance of prompt, sensitive, and cost-effective COVID-19 detection, nanotechnology holds enormous potential in the identification, treatment, and prevention of COVID-19, and can use NP-based electrical, mechanical, and magnetic attributes. Exact analyses need effective and sufficient isolation of RNA from samples to prevent infection or false-negative results. Table 4 provide a summary of the NPs used in the diagnostic detection of CoVs [185–190]. Magnetic NPs (MNPs) can be adopted for separation of nucleic acids. Fig. 4 represents the nanoparticle-based assays for CoVs (modified from Refs. [20,191]). For example, an investigation [189] reported successful extraction of SARS-CoV-2 RNA by means of specialized MNPs with poly (amino ester) with carboxyl groups (pcMNPs) coatin agent. These purified nucleic acids (NA), in the presence of an external magnetic field, are released from the surface of MNPs. The pcMNPs-briefed rapid extraction of RNA molecules is possible due to the strong interaction between the host cells via S2 subunit prompted membrane fusion [180]. Compared with PIH alone, PIH-modified gold nanorods Increase inhibitory activity, HR1 inhibitor can prevent membrane fusion as a result of HR1/HR2 complex (6-HB) formation and inhibit MERS-CoV infections [180]. PIH-AuNR with enhanced potential biocompatibility and biostability. Using molecular dynamics simulations, we have shown that a peptide inhibitor, which is elicitation from ACE2 creates very Promising routes for SARS-CoV-2 blockage [181]. The essential method of action of boric acid-functionalized CQDs is interference with protein S and prevention of HCoV-229E entry, it can also simply enter cells and inhibit the virus from replicating [182].

ACE: Angiotensin-converting enzyme, Ad5: Adenovirus serotype 5, AuNPs: gold nanoparticles, CD4+: Cluster of differentiation 4, CD8+: Cluster of differentiation 8, IFN: Interferon, IgA: Immunoglobulin A, IgG: Immunoglobulin G, IL-2, Interleukin-2, GM-CSF: Granulocyte/Macrophage Colony Stimulating Factor, MERS-CoV: Middle East Respiratory Syndrome Coronavirus, N pro: nucleocapsid N, NPs: nanoparticles, RBD: Receptor-binding domain, SARS-CoV: Severe acute respiratory corona viral entry. Fig. 3 illustrates a number of well-known nano products. Thus, NPs are often designed to block S protein and prevent CoVs vaccines [87].

S-AuNP-based vaccines which used versus other severe pneumonia-related CoVs can increase lymphatic antigen transmission and humoral and cellular immune responses compared to free antigens. Although, this vaccine prompted an antigen-dependent IgG response, it is defective in stimulating protective antibodies and limiting the infiltration of eosinophils into the lungs. Thus, an in-depth and effective study of the S-AuNPs concentration and size are needed for promising CoVs vaccines [87].

### Table 3

| Platform | Antigenic component | virus | Approach and result | Ref. |
|----------|---------------------|-------|---------------------|------|
| AuNPs   | S pro               | SARS-CoV | Stimulation of IgG response | [87,89,173] |
| Ferritin-based NPs | MERS-CoV (RBD antigen) | MERS | Stimulation of CD4+ T cells and IFN-TNF- responses | [155] |
| VLPS from MERS-CoVs protein | Ad5/MERS, alun | MERS | CD8+ T cell response; IL-2, TNF-a, GM-CSF, and IFN-c responses; higher with Ad5/MERS | [156] |
| VLPS from SARS-CoV & MERS-CoVs protein (full) | alun, Matrix M1 | SARS, MERS | Antibody titers is high against homologous virus virus-specific vaccine | [156,157] |
| RBD-displaying VLPS | Gene of RBD of S pro | MERS-CoV | Preserving the host cells from CoV infection through persuade RBD- specific immune responses Antisera | [158] |
| Hollow polymeric NPs | MERS-CoV (RBD antigen) | MERS-CoV | Stimulate more levels of humoral responses and IgG2a antibodies without induction of lung eosinophilic immunopathology | [156,159] |
| Chitosan NPs | SARS-CoV N pro | SARS | Intramuscular, Intranasal, dendritic cell targeting. | [160] |
| S-AuNPs | S pro | SARS | Strong CD4+ response, high titers of IFN-γ, IgA and IgG (including IgG1, IgG2a, IgG2b) | |
| Lipid NPs | RNA vaccine (Phase III) ModernaTX, Inc. | SARS-CoV-2 | Acts as mRNA carrier for efficient/safe transport in vivo | [161] |
| | mRNA vaccine (Phase I/II/III) | SARS-CoV-2 | mRNA carrier for efficient/safe transport in vivo | [162–164] |
| | BioNTech/Fourn Pharma/Pfizer | SARS-CoV-2 | mRNA carrier for efficient/safe transport in vivo | [165,166] |
| | mRNA vaccine (Phase I/II) Arcturus Therapeutics Ltd | SARS-CoV-2 | mRNA carrier for efficient/safe transport in vivo | [166–168] |
| | mRNA vaccine (Phase III) CureVac AG | SARS-CoV-2 | mRNA carrier for efficient/safe transport in vivo | [166,169,170] |
| Novel lipid NPs | RNA vaccine (Phase I) Chulalongkorn University | SARS-CoV-2 | Thermostable, with higher binding affinity toward the human ACE2 receptor, considerable neutralizing of virus infection | |
| VLPs | Protein subunit Vaccine (Phase I/II) Novavax | SARS-CoV-2 | | |

S-AuNP-based vaccines which used versus other severe pneumonia-related CoVs can increase lymphatic antigen transmission and humoral and cellular immune responses compared to free antigens. Although, this vaccine prompted an antigen-dependent IgG response, it is defective in stimulating protective antibodies and limiting the infiltration of eosinophils into the lungs. Thus, an in-depth and effective study of the S-AuNPs concentration and size are needed for promising CoVs vaccines [87].
with various moieties, for instance, antigens and antibodies [193, 194]. AuNPs have been extensively used in colorimetric hybridization assays, the disulfide bond-based colorimetric assay designed by Kim et al. is a good example of which [185]. The specific thiolated probes form the complementary single-stranded deoxyribonucleic acid (ssDNA) with the target sites of MERS-CoV and, through continuous disulfide bond formation, make a disulfide-induced long self-assembled hybrid complex [195]. This structure protects citrate ion-headed AuNPs from the salt-persuaded assembly. Nonetheless, in the absence of a target gene, this protection will no longer exist, resulting in the accumulation of AuNPs. The same dependable colorimetric hybridization method of SARS-CoV was planned via particular hybridization of ssDNA-AuNPs and target DNA sequence, leading to accumulation and color alteration (Fig. 4A) [187]. AuNPs based elementary electrochemical hybridization methods have been described with a gene-sensor, which includes thiolated-DNA comb immobilized on AuNPs carbon terminal to hydrolyze biotinylated target DNA of SARS-CoV (Fig. 4B) [196].

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Table 4

| NP-based detection       | Target                           | virus     | Notes                                                                 | size  | Ref. |
|--------------------------|----------------------------------|-----------|----------------------------------------------------------------------|-------|------|
| AuNP-based colorimetric assay | Upstream of E pro gene and ORF-1a | MERS-CoV  | Visual detection Inexpensive, fast (10 min) LOD: 1 pmol/μl            | -     | [185]|
| SFNPs                    | Target cDNA                      | SARS-CoV-2| Quick technique, High specificity and sensitivity association of AuNPs via the formation of dsDNA, |
| AuNPs                    | viral RNA                        | MERS-CoV  | cDNAs inhibiting aggregation of AgNPs prompted via acpcPNA, high |
|                          | viral cDNA Upstream of envelope | MERS, MTB | quality detection, cost-effective, fast (10 min), LOD: 1 pmol/μl     | 19 nm | [186, 187, 188, 190]|
|                          | protein gene and ORF-1A          | MERS-CoV  | Detection kit; COVID-19 point-of-need diagnostic test (Mologic Ltd) |
|                          | N/A                              | SARS-CoV-2| Detection kit; COVID-19 Rapid Test Cassette (SureScreen Diagnostics Ltd) |
|                          | N/A                              | SARS-CoV-2| Detection kit; COVID-19 Rapid POC high sensitivity and reliability of |
|                          | N/A                              | SARS-CoV-2| visual detection, applied in point-of-care tests (NanoComposix)      |       | -    |
| AuNRs                    | N/A                              | SARS-CoV-2| Detection kit; Lateral flow (Sona Nanotech, Inc.)                     | [189] |
| MNPs                     | Viral RNA                        | SARS-CoV-2| One-step, easy, sensitive, great paramagnetic characteristic, numerous |
|                          |                                  | SARS-CoV-2| purity, and fecundity, no toxic reagents                             |       | -    |

acpcPNA: Anthraquinone-labeled pyrrolidinyl peptide nucleic acid, AgNPs, Silver nanoparticles, AuNPs: gold nanoparticles, AuNRs: Au NanoRods, Cdna: Complementary DNA, dsDNA: double strand DNA, E pro: Envelope protein, LOD: Limit of Detection, MNPs: Magnetic Nanoparticles, N/A: not applicable, MERS-CoV: Middle East Respiratory Syndrome Coronavirus, NP: nanoparticles, ORF: Open Reading Frame, POC: Point-of-care, SARS-CoV: Severe acute respiratory syndrome coronavirus, SFNPs: Silk fibroin nanoparticles.
Fig. 4. Nanoparticle-based assays for CoVs. a) Colorimetric hybridization assays, b) Electrochemical hybridization assays, c) electrochemical immunosensor assay (modified from Refs. [20,191]).

Fig. 5. Emerging tests for SARS-CoV-2 detection. C: Control well; G: Conjugate pad; S: Sample well; T: Testing well (modified from Ref. [20]).
procedure, any of CaAuNPs and QDs were electrostatically conjugated to two various target virus targeted antibodies. In the attendance of the target virus, a nano-sandwich configuration is generated, bringing about superior plasmonresonance coupling with QD beta particles [197]. AuNPs can also be used for identification of CoVs-specific antibodies [198] through an electromagnetic immunosensor assay containing a chip and a-termin that include a variety of AuNPs to recognize CoV-special antibodies [199]. This particular approach was taken for detection of antibody-immobilized MERS-CoV proteins across AuNPs anodes, leading to emulsion of free viruses in the prototype with immobilized MERS-CoV protein [200]. A ferrocyanide probe was used for electrochemical measurement. This chip was used for multiplexed identification together through velocity terminals on the same chip, with every electrode attached to distinct viral antigens [201]. According to recent investigations, NP-based flow detection strips are perhaps are sufficient antibodies [199]. This particular approach was taken for detection chip and a C-terminal that include a variety of AuNPs to recognize CoV-RT-LAMP and bound to streptavidin-AuNP conjugates via fluorescein [198] through an electromagnetic immunosensor assay containing a very Controversial to securely translate NPs from lab novation to the viral infections. However, notwithstanding of interferences, it this yet 10 min [203]. immobilized anti-FITC antitoxin on a strip and delivering a color line in well-known color line [202]. This FITC-labeled complex is prepared via an anti-FITC antibody immobilized a strip, producing a well-known color line [202]. This FITC-labeled complex is prepared via immobilized anti-FITC antitoxin on a strip and delivering a color line in 10 min [203].

6. Challenges & limitations

Nanotechnology propose in the field of vaccination, innovative steps to detects, molecular diagnosis, and Countless opportunities against coronaviral infections. However, notwithstanding of interferences, it this yet very Controversial to securely translate NPs from lab novation to the infarmary. The main challenge and obstacles in various levels, from beginning to realize the viruses genomic and proteomic compound to clinical translation. Whereas SARS-CoV-2 genomic and proteomic studies were rapidly recognition to help scheme and expand NP-based Performance against the virus, the number of multiple mutations and genetic diversity more still remains an obstacle for successful treatment. In the case of NP-based RBD vaccines, RBD is a changed segment in the CoV genome [204]. In addition, it is not yet known which amino acids in the S protein of SARS-CoV-2 might induce hepatotoxicity [46,175]. So, full-length S protein may encounter immune problems when used as an antigen [46]. Viruses are simply targeted without influence host cells and Viruses do not have their own metabolism and need host cells to produce new products. Therefore, we can study the weaknesses of the virus and the vulnerability of infected cells to allow us to scheme solutions for particular ligands that can utilize the functional NPs of the virus surface and life cycle. SARS-CoV-2 is emerging as a coronavirus, which first appeared in China in late 2019 and causes a respiratory disease called “Coronavirus 2019 (COVID-19)”. The virus does not have enough animal models. Which is needed for clinical trials. While the behavior of each virus is different, they all have the same goal, and the host response to SARS-CoV-2 is needed to better understand the illness pathogenesis. In this regard, it is necessary to produce new nano-drugs with higher quality and safety because this virus has a great spread due to the disappointing slow production of drugs across the globe. In this regard, it is necessary to produce new nano-drugs with higher quality and safety because this virus has more and more spread due to the disappointing slow production of drugs around the world.

7. Conclusion & future perspective

Coronavirus the COVID-19 virus is a major global crisis and the greatest challenge we have faced since World War II [205]. The Corona virus epidemic (COVID-19) 2019 is a major disaster that has also disrupted health, human casualties and many more. Despite many efforts by all the countries of the world with many studies and also with the beginning of many clinical experiments, but no treatment has yet been proven to control the coronavirus. As well as an important role of Nano medicine to the novel SARS-CoV-2, this study highlights various customary treatment methods. Replacement of drugs, for example remdesivir and chloroquine, is a quick method to Achieving secure treatments and the relevant experimental studies have unfolded the Successful evidence against COVID-19. Furthermore, one of the scientific solutions used to decrease viral load is nano-metal vaccines, which are mostly basis on the antigenic attributes of protein S. However, a large number of studies provide evidence to support NP-based diagnostic and therapeutic tools, which have been reported for SARS-CoV-2. Therefore, it is necessary for all researchers from all over the world to expand their research in the arena of NP-based therapy. The important thing is that in order to prevent and treat the correct COVID-19 or any viral pandemic, we must have enough information about the virus’s virulence and transmission. This will enable us to identify various encoded unstructured proteins, enzymes, and functional mechanisms, and most importantly, to understand the transmission of the virus between species. Therefore, we can identify and target therapeutic goals using functional level NPs. Therefore, if we have sufficient and appropriate information about the virus life cycle and host answer, it will allow us to start a clinical trial to create an efficient Nano-vaccine. According to studies by researchers conducted by scientists around the world, we expect to be able to develop a universal NP-based vaccine that has effective immunogenicity in the near future. Microfluidics has the advantages of fast detection and portability Therefore, our prediction is that they can perform a significant part in the diagnosis of CoV [206].

Declaration of competing interest

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

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References

[1] Y.-Z. Zhang, E.C. Holmes, A genomic perspective on the origin and emergence of SARS-CoV-2, Cell 181 (2020) 223–227.
[2] J.R. Koo, A.R. Cook, M. Park, Y. Sun, H. Sun, J.T. Lim, C. Tam, B.L. Dickens, Interventions to mitigate early spread of SARS-CoV-2 in Singapore: a modelling study, Lancet Infect. Dis. 20 (2020) 678–680.
[3] T.G. Kizirian, D. Erdman, C.S. Goldsmith, S.R. Zaki, T. Peret, S. Emery, S. Tong, C. Urbani, J.A. Comer, W. Lim, A novel coronavirus associated with severe acute respiratory syndrome, N. Engl. J. Med. 348 (2003) 1953–1966.
[4] D. Mahade, Coronavirus: Covid-19 has killed more people than SARS and MERS Combined, Despite Lower Case Fatality Rate, British Medical Journal Publishing Group, 2020.
[5] A. Taghi-zadeh, H. Mikaelli, M. Ahmadi, H. Valizadeh, Acute kidney injury in pregnant women following SARS-CoV-2 infection: a case report from Iran, Respiratory medicine case reports 30 (2020) 101909.
[6] R. Sheervoilou, M. Shirvailou, N. Dadashzadeh, S. Shirvailou, O. Shahrahi, Y. Pilevher-Soltanahmadi, H. Ghanzavi, S. Khoei, Z. Nazarloo, COVID-19 under spotlight: a close look at the origin, transmission, diagnosis, and treatment of the 2019-nCoV disease, J. Cell. Physiol. 235 (2020) 8928–8926.
[7] M. Ghaebi, A. Osali, H. Valizadeh, L. Roshangar, M. Ahmadi, Vaccine development and therapeutic design for 2019-nCoV/SARS-CoV-2: challenges and chances, J. Cell. Physiol. 235 (2020) 9098–9109.
[8] R. Sheervoilou, M. Shirvailou, S. Sargazi, S. Shirvailou, O. Shahrahi, Y. Pilevher-Soltanahmadi, A. Sarhadi, Z. Nazarloo, H. Ghaznavi, S. Khoei, Application of nanobiotechnology for early diagnosis of SARS-CoV-2 infection in the COVID-19 pandemic, Appl. Microbiol. Biotechnol. (2021) 1–10.
B. Hashemi et al.

Journal of Drug Delivery Science and Technology 67 (2022) 102967

P. Gentile, A. Sterodimas, J. Pizzicannella, C. Calabrese, S. Garcovich, Research on onslaught of extracellular vesicles from human MSCs, in: D.T. Corporation (Ed.), Clover Biopharmaceuticals Announce progress on mesenchymal stem cells (MSCs), adipose-derived mesenchymal stem cells (AD-MSCs), drugs, and vaccines in inhibiting COVID-19 disease, Aging and Progression (2020) 104422.

S. Tahmasebi, B.Q. Saeed, E. Temirgalieva, A.V. Yumashev, M.A. El-Esawi, J. Nejati, M. Dadashpour, T. Gharibi, H. Mellatyar, A. Akbarzadeh, Biomedical applications of functionalized gold nanoparticles: a review, J. Cluster Sci. (2021) 1–16.

S. Tahmasebi, S. Karami-Mohammadi, M. Dadashpour, H. Mellatyar, A. Akbarzadeh, M. Dadashpour, T. Gharibi, H. Mellatyar, A. Akbarzadeh, Biomedical applications of functionalized gold nanoparticles: a review, J. Cluster Sci. (2021) 1–16.

S. Tahmasebi, A. Sadeghi, M. Nouri, Y. Panahi, The role of extracellular vesicles from human MSCs, in: D.T. Corporation (Ed.), Clover Biopharmaceuticals Announce progress on mesenchymal stem cells (MSCs), adipose-derived mesenchymal stem cells (AD-MSCs), drugs, and vaccines in inhibiting COVID-19 disease, Aging and Progression (2020) 104422.

S. Tahmasebi, B.Q. Saeed, E. Temirgalieva, A.V. Yumashev, M.A. El-Esawi, J. Nejati, M. Dadashpour, T. Gharibi, H. Mellatyar, A. Akbarzadeh, Biomedical applications of functionalized gold nanoparticles: a review, J. Cluster Sci. (2021) 1–16.

S. Tahmasebi, A. Sadeghi, M. Nouri, Y. Panahi, The role of extracellular vesicles from human MSCs, in: D.T. Corporation (Ed.), Clover Biopharmaceuticals Announce progress on mesenchymal stem cells (MSCs), adipose-derived mesenchymal stem cells (AD-MSCs), drugs, and vaccines in inhibiting COVID-19 disease, Aging and Progression (2020) 104422.

S. Tahmasebi, B.Q. Saeed, E. Temirgalieva, A.V. Yumashev, M.A. El-Esawi, J. Nejati, M. Dadashpour, T. Gharibi, H. Mellatyar, A. Akbarzadeh, Biomedical applications of functionalized gold nanoparticles: a review, J. Cluster Sci. (2021) 1–16.

S. Tahmasebi, A. Sadeghi, M. Nouri, Y. Panahi, The role of extracellular vesicles from human MSCs, in: D.T. Corporation (Ed.), Clover Biopharmaceuticals Announce progress on mesenchymal stem cells (MSCs), adipose-derived mesenchymal stem cells (AD-MSCs), drugs, and vaccines in inhibiting COVID-19 disease, Aging and Progression (2020) 104422.

S. Tahmasebi, B.Q. Saeed, E. Temirgalieva, A.V. Yumashev, M.A. El-Esawi, J. Nejati, M. Dadashpour, T. Gharibi, H. Mellatyar, A. Akbarzadeh, Biomedical applications of functionalized gold nanoparticles: a review, J. Cluster Sci. (2021) 1–16.

S. Tahmasebi, A. Sadeghi, M. Nouri, Y. Panahi, The role of extracellular vesicles from human MSCs, in: D.T. Corporation (Ed.), Clover Biopharmaceuticals Announce progress on mesenchymal stem cells (MSCs), adipose-derived mesenchymal stem cells (AD-MSCs), drugs, and vaccines in inhibiting COVID-19 disease, Aging and Progression (2020) 104422.

S. Tahmasebi, B.Q. Saeed, E. Temirgalieva, A.V. Yumashev, M.A. El-Esawi, J. Nejati, M. Dadashpour, T. Gharibi, H. Mellatyar, A. Akbarzadeh, Biomedical applications of functionalized gold nanoparticles: a review, J. Cluster Sci. (2021) 1–16.

S. Tahmasebi, A. Sadeghi, M. Nouri, Y. Panahi, The role of extracellular vesicles from human MSCs, in: D.T. Corporation (Ed.), Clover Biopharmaceuticals Announce progress on mesenchymal stem cells (MSCs), adipose-derived mesenchymal stem cells (AD-MSCs), drugs, and vaccines in inhibiting COVID-19 disease, Aging and Progression (2020) 104422.

S. Tahmasebi, B.Q. Saeed, E. Temirgalieva, A.V. Yumashev, M.A. El-Esawi, J. Nejati, M. Dadashpour, T. Gharibi, H. Mellatyar, A. Akbarzadeh, Biomedical applications of functionalized gold nanoparticles: a review, J. Cluster Sci. (2021) 1–16.

S. Tahmasebi, A. Sadeghi, M. Nouri, Y. Panahi, The role of extracellular vesicles from human MSCs, in: D.T. Corporation (Ed.), Clover Biopharmaceuticals Announce progress on mesenchymal stem cells (MSCs), adipose-derived mesenchymal stem cells (AD-MSCs), drugs, and vaccines in inhibiting COVID-19 disease, Aging and Progression (2020) 104422.

S. Tahmasebi, B.Q. Saeed, E. Temirgalieva, A.V. Yumashev, M.A. El-Esawi, J. Nejati, M. Dadashpour, T. Gharibi, H. Mellatyar, A. Akbarzadeh, Biomedical applications of functionalized gold nanoparticles: a review, J. Cluster Sci. (2021) 1–16.

S. Tahmasebi, A. Sadeghi, M. Nouri, Y. Panahi, The role of extracellular vesicles from human MSCs, in: D.T. Corporation (Ed.), Clover Biopharmaceuticals Announce progress on mesenchymal stem cells (MSCs), adipose-derived mesenchymal stem cells (AD-MSCs), drugs, and vaccines in inhibiting COVID-19 disease, Aging and Progression (2020) 104422.

S. Tahmasebi, B.Q. Saeed, E. Temirgalieva, A.V. Yumashev, M.A. El-Esawi, J. Nejati, M. Dadashpour, T. Gharibi, H. Mellatyar, A. Akbarzadeh, Biomedical applications of functionalized gold nanoparticles: a review, J. Cluster Sci. (2021) 1–16.

S. Tahmasebi, A. Sadeghi, M. Nouri, Y. Panahi, The role of extracellular vesicles from human MSCs, in: D.T. Corporation (Ed.), Clover Biopharmaceuticals Announce progress on mesenchymal stem cells (MSCs), adipose-derived mesenchymal stem cells (AD-MSCs), drugs, and vaccines in inhibiting COVID-19 disease, Aging and Progression (2020) 104422.

S. Tahmasebi, B.Q. Saeed, E. Temirgalieva, A.V. Yumashev, M.A. El-Esawi, J. Nejati, M. Dadashpour, T. Gharibi, H. Mellatyar, A. Akbarzadeh, Biomedical applications of functionalized gold nanoparticles: a review, J. Cluster Sci. (2021) 1–16.

S. Tahmasebi, A. Sadeghi, M. Nouri, Y. Panahi, The role of extracellular vesicles from human MSCs, in: D.T. Corporation (Ed.), Clover Biopharmaceuticals Announce progress on mesenchymal stem cells (MSCs), adipose-derived mesenchymal stem cells (AD-MSCs), drugs, and vaccines in inhibiting COVID-19 disease, Aging and Progression (2020) 104422.

S. Tahmasebi, B.Q. Saeed, E. Temirgalieva, A.V. Yumashev, M.A. El-Esawi, J. Nejati, M. Dadashpour, T. Gharibi, H. Mellatyar, A. Akbarzadeh, Biomedical applications of functionalized gold nanoparticles: a review, J. Cluster Sci. (2021) 1–16.

S. Tahmasebi, A. Sadeghi, M. Nouri, Y. Panahi, The role of extracellular vesicles from human MSCs, in: D.T. Corporation (Ed.), Clover Biopharmaceuticals Announce progress on mesenchymal stem cells (MSCs), adipose-derived mesenchymal stem cells (AD-MSCs), drugs, and vaccines in inhibiting COVID-19 disease, Aging and Progression (2020) 104422.

S. Tahmasebi, B.Q. Saeed, E. Temirgalieva, A.V. Yumashev, M.A. El-Esawi, J. Nejati, M. Dadashpour, T. Gharibi, H. Mellatyar, A. Akbarzadeh, Biomedical applications of functionalized gold nanoparticles: a review, J. Cluster Sci. (2021) 1–16.

S. Tahmasebi, A. Sadeghi, M. Nouri, Y. Panahi, The role of extracellular vesicles from human MSCs, in: D.T. Corporation (Ed.), Clover Biopharmaceuticals Announce progress on mesenchymal stem cells (MSCs), adipose-derived mesenchymal stem cells (AD-MSCs), drugs, and vaccines in inhibiting COVID-19 disease, Aging and Progression (2020) 104422.
[93] A. Nagy, B. Alhalmi, An overview of current COVID-19 vaccine platforms, Vaccine 37 (2019) 700–708.

[94] M.R. Hamilton, A.M. Watanabe, H.A. Pizzato, M.R. Thompson, C. Bradshaw, C.C. Weinkauf, C. Bime, Orthogonal SARS-CoV-2 serological assays enable surveillance of low-prevalence communities and reveal durable humoral immunity, Immunity 53 (2020) 925–933, e924.

[95] K.J. Flanagan, J. Kwan, L.E. Crawford, A. Gold, C.A. Rice, J. Aikens, E. Vail, B. MacNamey, F. Russell, B.W. Teh, S.C. Wen, Progress and pitfalls in the quest for effective SARS-CoV-2 (COVID-19) vaccines, Front. Immunol. 11 (2020) 2410.

[96] F. Wang, R.M. Kream, G.B. Stefano, An evidence-based perspective on mRNA-SARS-CoV-2 vaccine development. Med. Sci. Mon. Int. Med. J. Exp. Clin. Res. - Int. Med. J. Exp. Clin. Res. 26 (2020) e294700-294701.

[97] F. Oroojalian, A. Haghighi, B. Baradaran, N.M. Hemat, N. Gharibian, A. Mokhtarzadeh, M.H. Baghi, A. Mokhtarzadeh, M.R. Hamblin, Novel insights into the treatment of SARS-CoV-2 infection: an overview of current clinical trials, Int. J. Biol. Macromol. 2020.

[98] R.L. Graham, E.F. Donaldson, R.S. Baric, A decade after SARS: strategies for controlling emerging coronaviruses, Nat. Rev. Microbiol. 11 (2013) 836-848.

[99] N.M. Oiko, V.S. Raj, B.L. Haagmans, Middle East respiratory syndrome coronavirus vaccines: current status and novel approaches, Current opinion in virology 2017 (2017) 49-58.

[100] S. Fukushima, A. Fukuma, T. Kurosu, S. Watanabe, M. Shimohiro, K. Shirato, N. Iwata-Yoshitaka, N. Nagata, K. Ohishi, Characterization of novel monoclonal antibodies against the MERS-coronavirus spike protein and their application in species-independent antibody detection by competitive ELISA, J. Virol Methods 251 (2018) 22-29.

[101] A. Fukuma, H. Morita, Y. Ishigaki, M. Shimohiro, M. Saijo, S. Fukushima, Inability of rat DPP4 to allow MERS-CoV infection revealed by using a VSV pseudotype bearing truncated MERS-CoV spike protein, Arch. Virol. 160 (2015) 2293-2300.

[102] Y. Chen, S. Lu, H. Jia, Y. Deng, J. Zhou, B. Huang, Y. Yu, J. Lan, W. Wang, Y. Lou, A novel neutralizing monoclonal antibody, MERS015, against the MERS-CoV N-terminal domain of the MERS-CoV spike protein, Emerg. Microb. Infect. 6 (2017) 1-7.

[103] L. Jiaming, Y. Yanfeng, D. Yao, H. Baoying, Y. Jinghua, G. Xiao, Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro, Cell Res. 35 (2020) 269–271.

[104] M.M. Holdhus, C. Delagrange, L. Seng, J. Faye, D. Tally, H. Slama, E. Cassir, C. Spitters, K. Ericson, S. Wilkerson, A. Laval, First Case of 2019 Novel Coronavirus in the United States, New England Journal of Medicine, 2020.

[105] A. Zamba, J.F. Chan, E.L. Ashar, D.S. Hui, K.-Y. Yuen, Coronaviruses—drug discovery and Therapeutic development, Nat. Rev. Drug Discov. 15 (2016) 342-347.

[106] J.A. Al-Tawfiq, H. Momman, Z. Bim, A.Z. Memish, Ribavirin and interferon therapy in patients infected with the Middle East respiratory syndrome coronavirus: an observational study, Int. J. Infect. Dis. 20 (2014) 42-46.

[107] C.-Y. Wu, J.-T. Jan, S.-H. Su, C.-J. Kao, H.-Y. Juan, Y.-S.E. Cheng, H.-H. Hsu, H.-W. Hwang, C.-H. Huang, D. Wu, A. Brik, Small molecules targeting severe acute respiratory syndrome coronavirus human, Proc. Natl. Acad. Sci. Unit. States Am. 101 (2004) 109-11017.

[108] C. Chu, V. Cheng, I. Hung, M. Wang, K. Chan, K. Chan, R. Kao, L. Poon, C. Wang, Y. Guan, Role of lopinavir–ritonavir in the treatment of SARS: initial virological and clinical findings, Thorax 59 (2004) 256-252.

[109] B. Cao, Y. Wang, D. Wen, W. Liu, J. Wang, G. Fan, L. Buan, Y. Cai, M. Wei, A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19, N. Engl. J. Med. 2020.

[110] J.-M. Rollain, P. Colson, D. Raufel, Recycling of chloroquine and its hydroxy analogue to face breaking down of viral infections in the 21st century, Int. J. Antimicrob. Agents 30 (2007) 297–308.

[111] M.J. Vincent, E. Bergeron, S. Benjannet, B.R. Erickson, P.E. Rollin, T.G. Ksiazek, N.G. Seidt, S.T. Nichol, Chloroquine is a potent inhibitor of SARS coronavirus for neutralization in vitro, J. Virol. 75 (2001) 1-6.

[112] Y. Yan, Z. Zou, Y. Sun, X. Li, K.-F. Xu, Y. Wei, N. Jin, C. Jiang, Anti-malaria drug chloroquine is highly effective in treating avian influenza A H5N1 virus infection in an animal model, Cell Res. 13 (2003) 300-302.

[113] A. Savarino, L. Di Triai, L. Cauzas, C. Cassone, New insights into the antiviral effects of chloroquine, Lancet Infect. Dis. 6 (2006) 67–69.

[114] W. Li, J.M. Moore, N. Vasiliou, J. Sui, S.K. Wang, M.A. Berne, M. Somasundaran, J.L. Sullivan, K. Luzuriaga, T.C. Greenough, Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus, Nature 432 (2004) 485–487.

[115] P. Zhou, X.-L. Yang, X.-G. Wang, B. Hu, L. Zhu, Z. Wang, H.-R. Si, Y. Zhu, B. Li, C.-L. Huang, A pneumonia outbreak associated with a new coronavirus of probable bat origin, Nature 579 (2020) 270-273.

[116] R. Lu, X. Zhao, J. Li, W. Hu, Y. Niu, H. Wang, B. Huang, N. Zhu, Genomic characterization and epidemiology of 2019 novel coronavirus infections for virus origins and receptor binding, Lancet 395 (2020) 565-574.

[117] U. Karakus, M.O. Foll, S. Stertz, Breaking the convention: sialoglycan variants, upregulators, and alternative receptors for influenza A virus entry, J. Virol. 94 (2020).

[118] X. Xu, P. Chen, J. Wang, J. Feng, H. Zhou, X. Li, W. Zhong, P. Hao, Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission, Sci. China Life Sci. 63 (2020) 457–460.

[119] L. Orioles, H. is Vice, L. Manchikanti, Expanded umbilical cord mesenchymal stromal cells (UCMSCs) as a therapeutic strategy in managing critically ill COVID-19 patients: the case for compassionate use, Pain Physician 23 (2020) E71–E83.

[120] D.J. Weiss, I. Bertoncello, Z. Borok, A. Panoskaltsis-Mortari, S. Reynolds, M. Rojas, B. Stripp, D. Warburton, D.J. Prokop, Stem cells and cell therapies in lung injury and disease, Ann. N. Y. Acad. Sci. 1225 (2022) 223–372.

[121] J. Aljituras-Reig, E. Esteva-Valverde, C. Belzina, A. Selva-O Callaghan, J. Pardos-Go, A. Quintero-González, A. Mekinaín, A. Amatriain-Amatriain, F. Miró-Mur,}
[186] M.B. Buschmann, M.J. Carrasco, S. Alshetty, M. Paige, M.G. Alameh, D. Weissman, Nanomaterial delivery systems for mRNA vaccines, Vaccines 9 (2021) 65.

[187] Cg.Ast.tes.tia.o.v.C.i.ha.i.Gf. COVID-19, I.N. https://clinicaltrials.gov/ct2/show/NCT04674189.

[188] L.U., Acuitas Therapeutics, 2020.

[189] Cg.C.m.v.ha.i.N. NCT04566276, https://clinicaltrials.gov/ct2/show/NCT04566276.

[190] G.S.G. WO2020219941, 2020.

[191] Cg.E.o.t.s.a.i.o.a.S.-C.r.n.v.w.w. Matrix-M, a.I.N. http://www.clinicaltrials.gov/ct2/show/NCT04566276.

[192] S.R. Ahmed, A. Laromaine, L. Koh, M. Murugesan, R.V. Ulijn, M.J. Stevens, Protease-triggered dispersion of nanoparticle assemblies, J. Am. Chem. Soc. 129 (2007) 4156–4157.

[193] S.A. Lim, T.H. Lim, A.N. Ahmad, The Applications of Biosensing and Artificial Intelligence Technologies for Rapid Diagnosis and Detection of COVID-19 in Remote Setting, Diagnostics Strategies for COVID-19 and Other Coronaviruses, Springer, 2020, pp. 109–134.

[194] G. Martinez-Paredes, M.B. Gonzalez-Garcia, A. Costa-Garcia, Genosensor for SARS virus detection based on gold nanostructured screen-printed carbon electrodes, Anal. Chem. 89 (2017) 4084–40857.

[195] I.U., Acuitas Therapeutics, 2020.

[196] T. Kato, Y. Takami, V.K. Deo, E.Y. Park, Preparation of virus-like particle mimetic nanovesicles displaying the S protein of Middle East respiratory syndrome coronavirus using insect cells, J. Biotechnol. 306 (2019) 177–184.

[197] S.H. Radwan, H.M. Azzazy, Gold nanoparticles for molecular diagnostics, Expert Rev. Mol. Diagn. 9 (2009) 511–524.

[198] P. Gong, X. He, K. Wang, W. Tan, W. Xie, P. Wu, H. Li, Combination of functionalized nanoparticles and polymerase chain reaction-based method for SARS-CoV gene detection, J. Nanosci. Nanotechnol. 8 (2008) 293–300.

[199] S.A. Lim, T.H. Lim, A.N. Ahmad, The Applications of Biosensing and Artificial Intelligence Technologies for Rapid Diagnosis and Detection of COVID-19 in Remote Setting, Diagnostics Strategies for COVID-19 and Other Coronaviruses, Springer, 2020, pp. 109–134.

[200] K.E. Pascal, C.M. Coleman, A.O. Mujica, V. Kamat, A. Badithe, J. Fairhurst, Nanoengineering of virus detection based on gold nanostructured screen-printed carbon electrodes, Microchemia Acta 186 (2019) 1–10.

[201] Y. Wang, Z. Fan, L. Shao, X. Kong, X. Hou, D. Tian, Y. Sun, L. Xiao, Y. Nanobody-derived nanobiotechnology tool kits for diverse biomedical and biotechnology applications, Int. J. Nanomed. 11 (2016) 3287.

[202] Z. Zhao, H. Cui, W. Song, X. Ru, W. Zhou, X. Yu, A Simple Magnetic Nanoparticles-Based Viral RNA Extraction Method for Efficient Detection of SARS-CoV-2, 2020. BioRxiv.

[203] D. Weissman, Nanomaterial delivery systems for mRNA vaccines, Int. J. Nanomed. 11 (2016) 3287.