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RESEARCH PAPER

Treatment and Diagnosis Roles of Nanoparticles Against SARS-CoV-2

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ABSTRACT

In 2019, a new member of Coronavirus family, SARS-CoV-2, was appeared as a global pandemic and could infect 213 countries all over the world. Although some well-known companies have discovered SARS-CoV-2 vaccines, there is still not certain treatment in the world, especially for mutated species of this family. In addition of vaccine production, there are some antiviral or immunosuppression drugs that can reduce inflammation or interrupt one of the viral entrance steps to the cells. Now in this situation, nanoparticles because of their interesting features, such as the capability of being targeted to SARS-CoV-2 and the ultra-low detection limit can be considered as a novel treatment method of SARS-CoV-2 or even as reduction factors of SARS-CoV-2 infection rate. This review describes initially SARS-CoV-2 structure, internalization, and replication, along with its immunological responses and cell signaling that can be happened in the cells. Then, the role of nanotechnology in drug delivery toward SARS-CoV-2 and its detection are explained by gathering every research paper that studied SARS-CoV-2.

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INTRODUCTION

Coronaviruses from *Coronaviridae* family have been known as enveloped viruses with a positive-sense, single-stranded genomic RNA, and helical symmetry nucleocapsid. As reported by International Committee on Taxonomy of Viruses (ICTV), 2019 release, *Coronaviridae* family is divided into two subfamilies, *Letovirinae*, *Orthocoronavirinae*, and five genera, namely *Alphaletovirus*, *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus*, and *Deltacoronavirus*. It is noteworthy that *Alphacoronavirus* and *Betacoronavirus* can infect humans [1]. In details as shown by Fig. 1, there are six coronaviruses with human infection, including the alpha coronaviruses 229E and NL63 plus the beta coronaviruses HKU1, SARS-CoV, MERS-CoV, and SARS-CoV-2 as a recent global concern [2]. In December 2019, current pandemic was occurred because of the SARS-CoV-2 or Coronavirus infectious diseases 2019 (COVID-19) known as COVID-19 symptoms [3] in an exotic food market in Wuhan, China with more than 6.39 million death tolls and 574 million cases at the end of July 2022.

Besides, during recent decades nanotechnology has been emerged as a turning point in industry and accordingly in many facets of modern life with its revolutionary role. Nanoparticles has received much attention recently owing to some advantages, including rapid detection, ultra-low detection limit, low cost, easy surface functionalization, simple synthesis methods, low toxicity, and etc.

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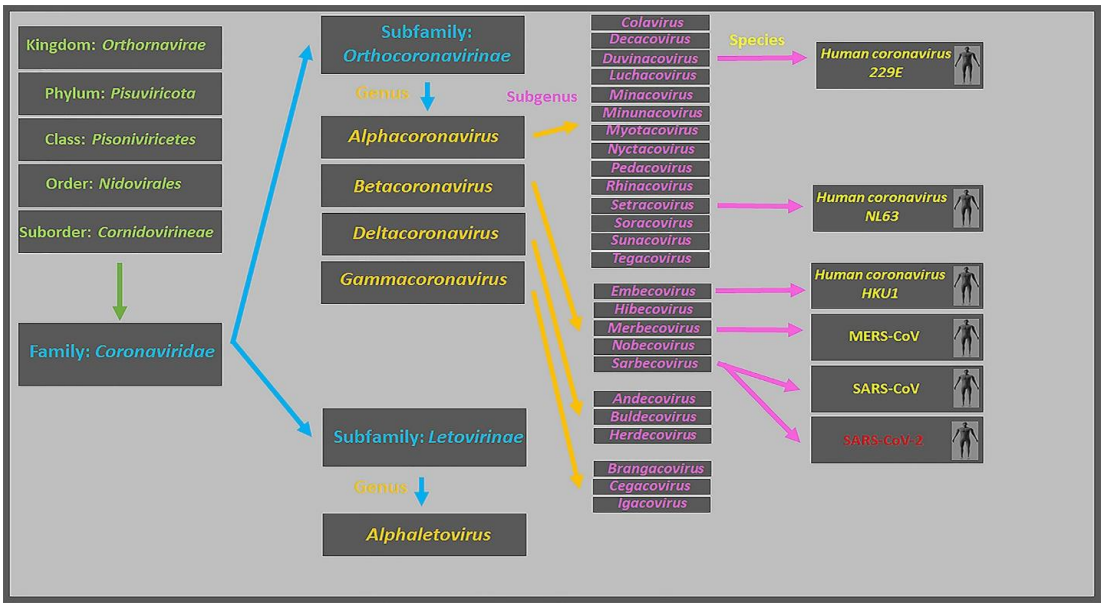

Fig. 1. Taxonomy of Coronavirus family by highlighting SARS-CoV-2

In addition of these features, nanoparticles can exhibit different chemical properties depend on their synthesis sources. For instance, some green nanoparticles can be synthesized from natural sources, such as fruits, vegetables, organic waste, and so on [4]. Because of their interesting features, nanoparticles can be applied into different applications like targeted drug delivery, disease diagnosis, biomedical imaging, and etc. Therefore, nanoparticles might be selected as a remarkable candidate to cope with current world wide crisis, COVID-19 pandemic, owing to same physical, chemical, and biological features, almost same size, and volume ratio between viruses and nanoparticles [5]. What is interesting is that in the umbrella term of COVID-19 there are many fields that nanotechnology can play a crucial role in them, from biomedical field that nanoparticles play a vital role as nanocarriers or adjuvants to industrial production realm, such as masks production, filtration, antiviral productions and washing abilities by nanofibers and nanoparticles [5].

In this review, a description about the structure of COVID-19 and its infectious instructions along with immunological responses are afforded. Then, for the first time the role of nanotechnology in therapeutic process and detection of COVID-19 are explained by gathering all of the suggested treatments or detection methods until now with mentioning every nanoparticle and its mechanism that can take part in tackling COVID-19 pandemic as a global problem.

STRUCTURE AND COMPOSITION OF COVID-19

As aforementioned, Coronaviruses generally have been known as enveloped viruses with helical nucleocapsid which was 9-11 nm in diameter and single-stranded RNA genome of 27-32 kilobases (kb) regarded as the largest genome among RNA viruses and polyadenylated at the 3’ end. Gene order for the proteins encoded by three high pathogenic Coronaviruses is illustrated by Fig. 2 (a). Generally, SARS-CoV-2 has 14 open reading frames (ORFs) encoding 27 proteins. ORF1ab and ORF1a at 5’ terminus encode pp1ab and pp1a proteins, respectively. These proteins together include 15 non-structural proteins (NSPs), namely NSP1 to NSP10 along with NSP12 to NSP16. Also, at 3’ terminus there are four structural proteins, S, E, M, and N plus eight accessory proteins, including 3a, 3b, 6, 7a, 7b, 8b, 9b, and orf14 [6].

SARS-CoV-2 as a member of Coronaviruses has a single stranded RNA genome of nearly 34 kb with 80% identical rate with SARS-CoV and 96% with Bat CoV RaTG13. Besides, the viral structural proteins of COVID-19 that like the proteins of other Coronaviruses members comprise: (i) Spike glycoprotein (S protein) plays a vital role in attachment and entering of virus

to host cells; (ii) Membrane glycoprotein (M protein) keeps the membrane integrity of the viral particle; (iii) Envelope protein (E protein) is the structural protein that takes part in assembly; (iv) Nucleocapsid protein (N protein) plays a supporting role in nucleocapsid formation (Fig. 2 (b)) [7].

COVID-19 REPLICATION AND INFECTIOUS PROCESS ALONG WITH IMMUNOLOGICAL RESPONSES

The angiotensin-converting enzyme 2 (ACE2) as the key receptor on the surface of human cells [8] and S protein of COVID-19 play a vital role in entry of viruses into human cells and produce more viruses due to the translation of viruses' RNA. According to Fig. 3, the S protein is performed by two subunits, S1and S2 proteins and S1 comprises the receptor binding domain (RBD) [9]. Concerning ACE2 structure, ACE2 is dimer of two units with

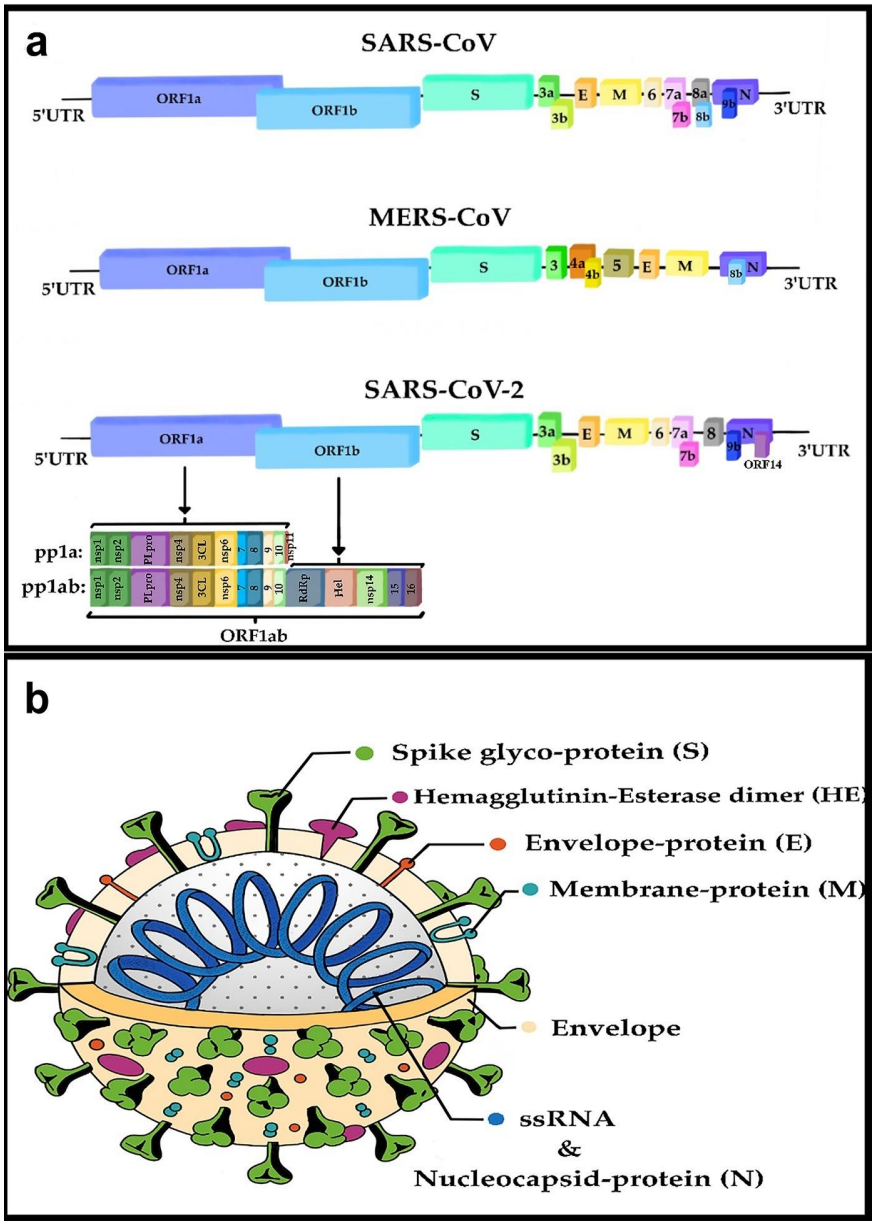

Fig. 2. (a) Genome sequence comparison of three high-pathogenic members of Coronavirus family. (b) Structure of SARS-CoV-2 virus

accommodations of RBD in its peptidase domain [10]. Furthermore, human airway trypsin-like protease (HAT) and transmembrane protease seine 2 (TMPRSS2) known as members of transmembrane serine protease (TTSPs) family facilitate SARS-CoV-2 activation by cleaving the S protein to their mentioned subunits during viral entry of viruses [11]. It should be mentioned that activation of S protein of SARS-CoV-2 by host cell proteases is essential for displaying their infection. In details, HAT and TMPRSS2 cleave the S protein by different mechanisms. HAT activates SARS-CoV-2 for cell-cell fusion but TMPRSS2 activates it for cell-cell and virus-cell fusion [12].

Given the surface of S protein that possesses sites for membrane fusion and recognition, during the interaction of ACE2 with viruses' S protein, this is split into S1 and S2 subunits. S1 subunit which contains RBD binds to peptidase domain of the ACE2 by polar interaction between the loop region of RBD of S proteins and arch-shaped helix of ACE2's peptidase domain although S2 subunit

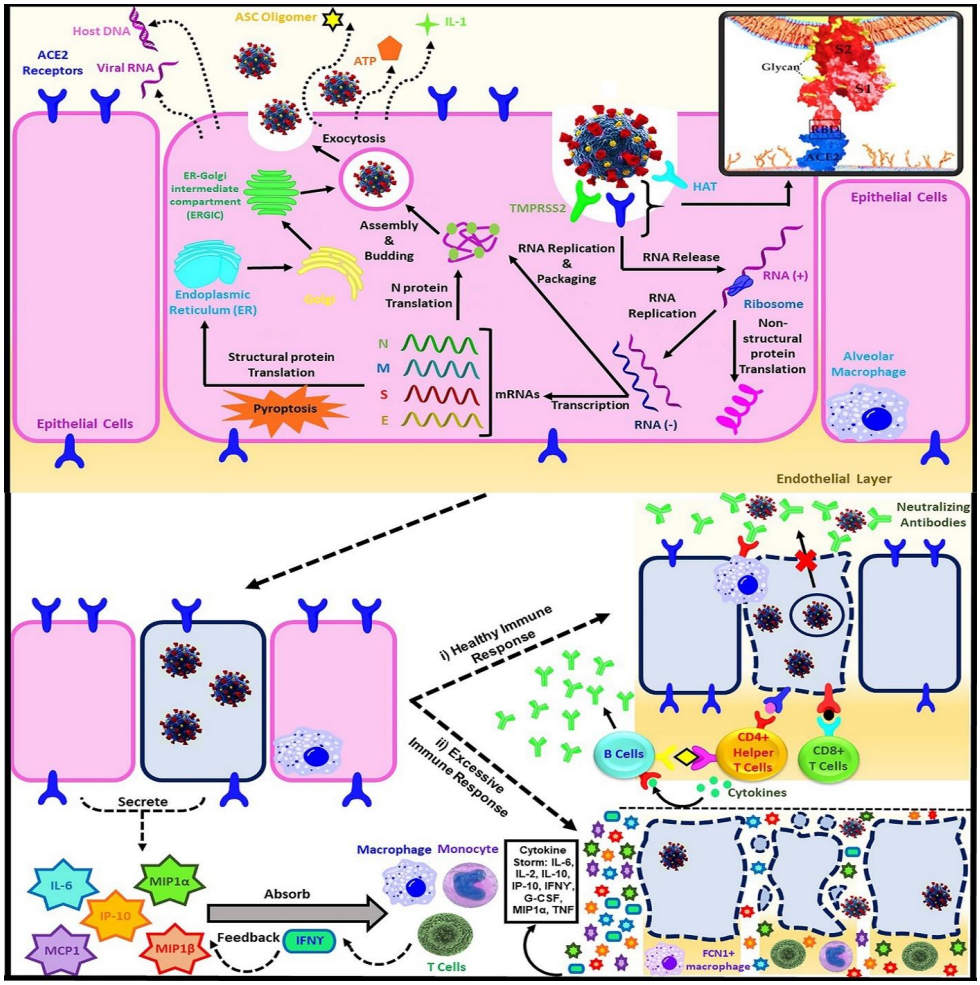

Fig. 3. The entrance process and lifecycle of SARS-CoV-2 along with immunological responses that might be occurred. After the connection between the ACE2 as human receptor and the S protein of SARS-CoV-2, viruses' entrance and RNA release are happened. As a next step, RNA replication is occurred. Then, transcription and translation as two main steps are happened. It should be mentioned that translation of N protein plays an important role in RNA packaging. Eventually, the last step is devoted to budding and assembly process. After that, exocytosis of viruses and damage associated molecular patterns, including nucleic acids, ASC oligomer, ATP, and IL-1 are happened. After viruses' entrance into the epithelial cells, some chemokines, such as IL-6, MIP1α, IP-10, MCP1, and MIP1β are secreted. These chemokines absorb macrophages, monocytes, and T cells. After that, two states can be occurred; i) healthy immune response and ii) excessive human response that second state causes chemokines storm and most of the time this state is considered as one of the reasons of human death by SARS-CoV-2.

helps membrane fusion [13]. After the connection between the ACE2 and S protein of SARS-CoV-2, viruses enter human cells and RNA release along with nucleoprotein uncoating are occurred. Accordingly, non-structural protein translation along with replication happened by RNA-dependent RNA polymerase (RdRp) and replicase are occurred as next step. Then, two detailed facts might be going on, transcription along with RNA replication and packaging. After both of them, assembly and exocytosis of more viruses from human cells are happened [14]. Generally, it can be mentioned that virus release by host cells and active replication are occurred during pyroptosis and release damage associated molecular patterns, comprising nucleic acids, apoptosis-associated speck-like protein containing a CARD (caspase recruitment domain) (ASC) oligomer, and ATP. These are acquainted by nearing epithelial cells, endothelial cells, and alveolar macrophages. This function can provoke pro-inflammatory cytokines and chemokines production, including inter lunkin-6 (IL-6), macrophage inflammatory protein 1α (MIP1α), MIP1β, monocyte chemoattractant protein-1 (MCP1), and interferon gamma-induced protein 10 (IP-10) [15]. These mentioned proteins absorb macrophages, monocytes, and T cells to the infection site. A cycle of pro-inflammatory feedback is initiated by interferon γ (IFNγ) released by T cells [16]. After this stage, two situations can be occurred: i) healthy immune response and ii) defective or excessive immune response. In first one, as aforementioned cytokines and chemokines secretions absorb monocytes and T cells to infection site for inhibition of virus spread. $CD8^+$ T cells can directly kill infect cells whereas $CD4^+$ T cells help $CD8^+$ T cells and have significant role in cytokine production along with B cells provocation and neutralizing antibodies secretion. It should be mentioned that neutralizing antibodies can block individually viral infection. Alveolar macrophages also recognize and remove neutralized viruses and apoptotic cells by phagocytosis. Second situation known as dysfunctional immune responses lead to further accumulation of immune cells in appropriate organ that in this case is lungs. This function leads to over production of pro-inflammatory cytokines, including IL-2, IL-7, IL-10, IP-10, MCP1, MIP1α, granulocyte colony-stimulating factor (G-CSF), and tumor necrosis factor (TNF) that these cytokines finally damage the lung infrastructure

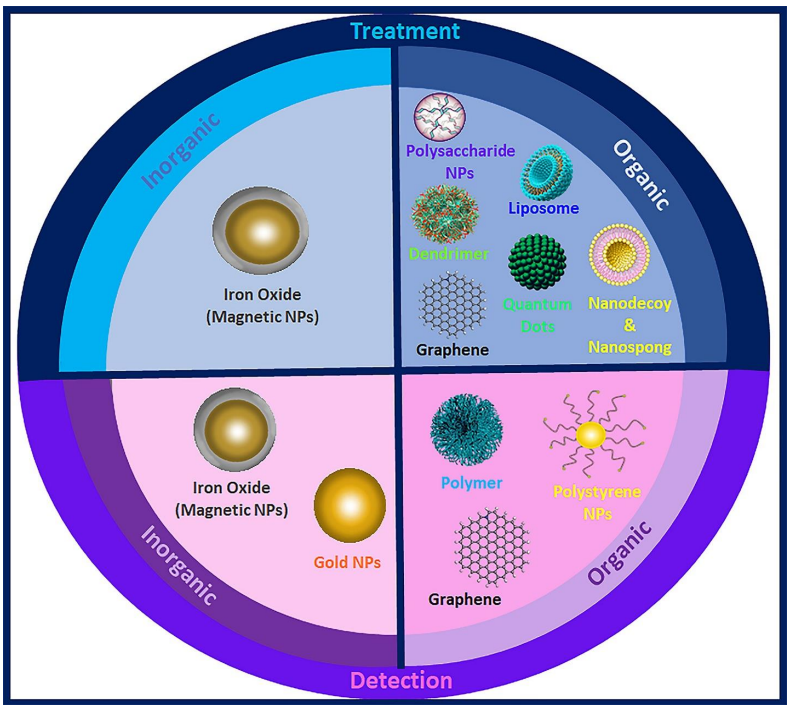

Fig. 4. Nanoparticles that have role in detection or treatment of SARS-CoV-2 by inorganic or organic category.

[17]. Even, cytokines storm can result multi-organ damage. There is also a high level of inflammatory monocyte-derived $FCN1^{+}$ macrophages in this second situation. Additionally, non-neutralizing antibody secretion by B cells may increase SARS-CoV-2 infection during antibody-dependent enhancement (ADE). This function has harmful role in multi-organ damage. It is noteworthy that high-level of pyroptosis with associated vascular leakage is occurred in airway epithelial cells by viral infection and replication (Fig. 3). Generally, it can be mentioned that second situation has been seen in SARS-CoV-2 patients [16].

NANOTECHNOLOGY

During recent years, theranostic nanoparticles have accounted for the largest proportion in medicine field for treatment of multitudes of diseases [18]. This has been afforded due to some merits, such as chemical modification capabilities, minuscule size, suitable surface charge, and low toxicity for most of the nanoparticles [19]. Utilizing of nanotechnology in therapeutic fields has been preferred because of the capability of overcoming some limitations, for instance low bioavailability and poor aqueous solubility are some difficulties that can be tackled by nanocarrier based drug delivery [20].

Concerning the role of nanotechnology in COVID-19 treatment or reducing infection rate of COVID-19, it was scrutinized that nanoparticles can play a crucial role as carriers for delivery of drugs [21], siRNA [22], peptide inhibitors [23], and so on plus an impressive factor for inhibition of virus penetration to human cells by blocking the S protein of COVID-19 [24]. In addition, the role of nanotechnology in COVID-19 diagnosis was investigated too. In this inquiry, aforementioned facets of nanotechnology will be investigated with example works relating COVID-19. Regarding aforementioned aspects, all utilized nanoparticles in COVID-19 treatment and diagnosis included polymer nanoparticles [25], lipid nanoparticles like liposome [26], extracellular vesicles such as nanodecoys [27] and nanosponges [28], polysaccharide nanoparticles [29], polystyrene nanoparticles [30], dendrimer nanoparticles [31], magnetic nanoparticles (iron oxide) [32], gold nanoparticles [33], quantum dots (QDs) [34], and graphene [35] were illustrated by Fig. 4.

ROLE OF NANOTECHNOLOGY IN COVID-19 TREATMENT

DRUG DELIVERY

As WHO (World Health Organization) proposed, there are five targets for drug development for COVID-19, namely i) attack to the virus with plasma that obtained from recovered patient and monoclonal antibodies. ii) inhibition of ACE2 by drugs. iii) inhibition of endocytosis by appropriate drugs. iv) inhibition of proteolysis of polypeptides. v) inhibition of RNA polymerization.

As mentioned above, nanocarriers have some bright sides in medical fields. It is patently obvious that active targeted nanocarriers suggest more opportunities for overcoming some biological barriers [36,37]. The cargo of these nanocarriers can be drugs [26], RNA [22], inhibitor peptides [32], proteins [28], and so forth [38]. One of the important parts that has been attracted adequate attention is nanocarrier selection. By choosing suitable nanocarrier, multitudes of barriers in delivery field are tackled [39]. What is noteworthy is that one of the feasibilities of COVID-19 treatment is combination drug therapy [39]. It should be noted that a wide range of nanocarriers have been expanded for co-encapsulation of both hydrophilic and hydrophobic drugs. According to pathophysiology of COVID-19 some nanocarriers can be provided targeted to COVID-19 by ACE2 expressing cells or cathepsin binding sites or even S protein's domain [40].

Particularly, some nanoparticles have could play an effective role in COVID-19 treatment that these nanoparticles with their specific mechanisms of COVID-19 treatment are illustrated by Fig. 5 and Table 1. As displayed by Fig. 5, it was reported that lipid-based nanocarriers, like liposome, were utilized to transfer a mix of micro RNAs (miRNAs) to myriads of regions on COVID-19 open reading frame (ORF) and 3' UTR in order to inhibit translation and transcription processes of some parts of SARS-CoV-2 genes (Fig. 5) [22]. Dexamethasone liposome is also another candidate for COVID-19 infection by inhibiting macrophage mediated inflammation or immune cells accumulation in the lung and accordingly avoiding long-term lung damage (Fig. 5) [41]. Additionally, liposomes have been used as a carrier for propolis and remdesivir delivery with anti-viral activity against COVID-19 (Fig. 5). As exhibited by Fig. 5, remdesivir inhibits the viral RNA synthesis of SARS-CoV-2 by blocking RNA dependent RNA polymerase (RdRp) [42]. It is noteworthy that among all aforementioned

researches that are relevant to targeted drug delivery toward SARS-CoV-2 by nanoparticles, just dexamethasone liposome is a nanoparticle which is in clinical phase, especially recovery in the post-ICU phase. Others are still in preclinical phase and need more investigations. All of the cargos of liposomes have an inhibition role in translation or transcription processes of SARS-CoV-2 genes. However, dexamethasone liposome has impact on immune cells.

It is abundantly patent that the binding of normal cells receptors to viral particles, leading viral particles entry. As aforementioned, in COVID-19, the attachment mechanism is devoted to the S glycoprotein of virus and its receptor, ACE2 [43]. As a consequence, blocking this attachment mechanism can be considered as a strategy for drug development. Concerning this of course, some nanoparticles were reported by other studies that by displaying their either cargos, ligands or receptors can play a key role in inhibition of virus penetration to human cells. For instance, as exhibited by Fig. 5, utilizing of astodrimer sodium which is a dendrimer with a wide range of antimicrobial activities as a kind of nanoparticles in inhibition of COVID-19 replication in Vero E6 cells by binding to virus and blocking infection was reported [31]. Another group of nanoparticles reported as a decisive factor in COVID-19 treatment is carbon-based nanoparticles, such as graphene and quantum dots (QDs) by using docking and molecular dynamics simulations studies. It should be mentioned that QDs can interact with S protein of COVID-19 and hamper genomic replication of

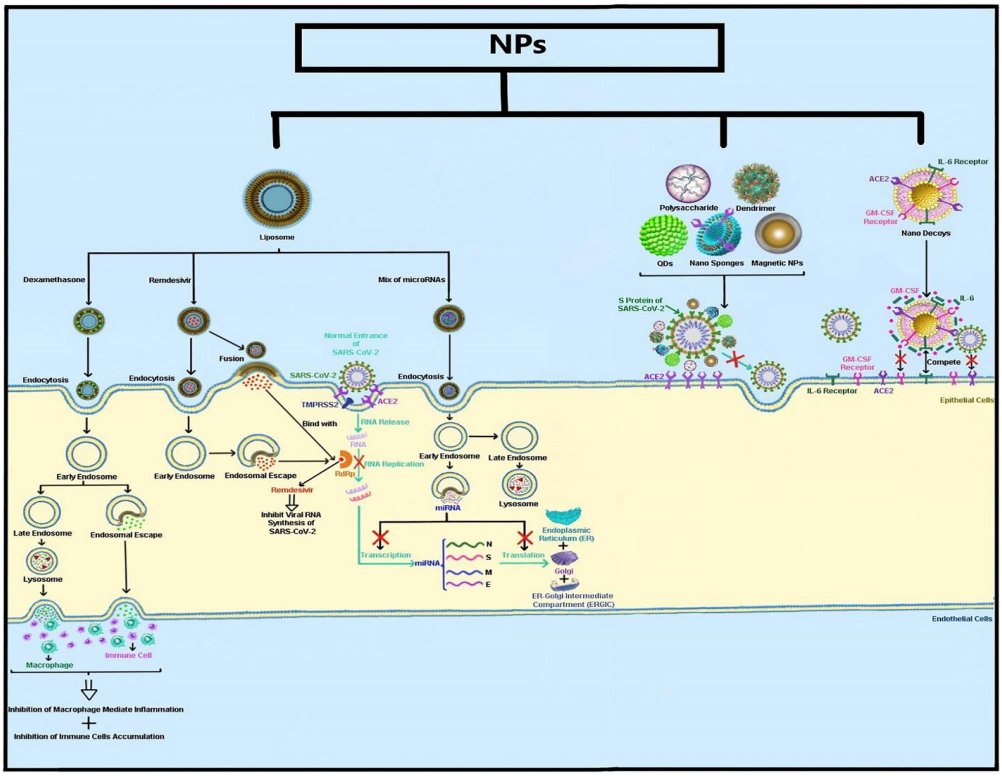

Fig. 5. The mechanism of nanoparticles that have the key roles in SARS-CoV-2 treatment by different interruption processes of SARS-CoV-2 entrance into the cells. Generally, nanoparticles (NPs) can be classified into three categories, including i) Liposomes that mix of microRNAs along with two drugs, such as remdesivir, and dexamethasone are encapsulated via them and liposomes enter into the cells by endocytosis or fusion as two ways for epithelial cells entrance. Dexamethasone inhibits macrophage mediate inflammation and immune cells accumulation. Remdesivir inhibits viral RNA synthesis of SARS-CoV-2. Mix of microRNAs inhibit transcription or translation parts of SARS-CoV-2. ii) Polysaccharides/ Dendrimer/ QDs/ Nano sponges/ Magnetic NPs which block the S proteins of SARS-CoV-2 and accordingly inhibit the virus entrance. iii) Nano decoys which display epithelial receptors compete with epithelial cells in making connection with SARS-CoV-2 and this function can reduce the percentage of SARS-CoV-2 entrance into the cells.

Table 1. Nanoparticles which are involved in SARS-CoV-2 treatment with different mechanisms

Nanocarrier	Cargo	Mechanism of COVID-19 treatment	*In vitro* Tests	*In vivo* Tests	Condition	Ref.
Liposome	Dexamethasone	inhibiting macrophage mediated inflammation or immune cells accumulation	-	Syngeneic and xenograft mouse model	Acute and intermediate phase/ more rapid recovery in the post-ICU phase	[41]
Liposome	Remdesivir	RNA dependent RNA polymerase (RdRp) inhibitor	3CL-protease inhibition test + RT-PCR for evaluation of anti-viral effect + *In vitro* release study	-	Preclinical studies	[42]
Liposome	Mix of microRNAs	Inhibition of translation and transcription of SARS-CoV-2 genes	RT-PCR	-	Preclinical studies	[22]
Dendrimer	-	binding to virus and blocking infection	Virus-induced cytopathic effect inhibition assay + Virucidal assay + MTT assay + Time of addition assay (TOA) +	-	Preclinical studies	[31]

			Virus yield reduction assay			
QDs	-	interaction with S protein of COVID-19 and hampering genomic replication of viral RNA	CCK-8 assay + Plaque assay + RT-PCR + ROS determination by a confocal laser scanning microscope	-	Preclinical studies	[44]
Iron oxide	-	interaction with S protein of COVID-19	-	-	Preclinical studies (Docking studies by software)	[32]
Nanodecoy	-	displaying ACE2 and IL-6 receptors and compete with host cells	Flowcytometry + Immunofluorescence + Western blotting + Luciferase assay + Viral nucleoprotein immunofluorescence + qRT-PCR for viral genes copies +	Fluorescence bioimaging + Staining with hematoxylin and Eosin	Preclinical studies	[27]

			IL-6 or GM-CSF ELISA kit			
Nanosponge	-	binding to virus receptors and blocked virus entry	Wester blotting + Fluorescent labeled antibodies analysis	Staining with hematoxylin and Eosin + Histopathological analysis	Preclinical studies	[28]

viral RNA (Fig. 5) [34]. Moreover, there are some features of quantum dots that make this targeting better, such as size range of quantum dots reported 1-10 nm and their shapes that can penetrate to COVID-19 with size range of 60-140 nm. Another property of cationic quantum dots is their positive surface charge that can disable the S protein of COVID-19 [44]. Additionally, this type of quantum dots can interact with negative RNA strand of the virus [45]. Iron oxide is another nanoparticle in inorganic category that has impact on process of COVID-19 treatment. The interaction of iron oxide nanoparticles with S protein receptor binding domain (S1-RBD) of COVID-19 as an inhibition way of entry was depicted by mentioned paper (Fig. 5) [32]. In addition, another inhibition method by nanoparticles that has received much focus in COVID-19 treatment is nanodecoys as cell-derived vesicles. For example, it was reported that some cellular membrane nanovesicles derived from 293T/ACE2 and THP-cells. These nanodecoys compete with host cells by displaying ACE2 and IL-6 receptors on their surface and have protection ability against COVID-19 penetration (Fig. 5) [27]. Another inhibition method in COVID-19 treatment is devoted to cellular nanosponges. For instance, it was reported that two types of cellular nano sponges were created from plasma membranes derived from human lung epithelial type II cells and human macrophages. These created nanosponges exhibited same receptors that have key role in cellular COVID-19 entry. Accordingly, cellular nanosponges bound to viruses receptors and blocked viruses entry (Fig. 5) [28]. In addition, there are some studies that measured the interaction between some polysaccharides like heparin, Chinese herbal polysaccharides, etc. and S1 protein receptor binding domain of COVID-19. This interaction can prevent virus-host cell connection and viral entry [46,47]. Generally, it can be resulted that polysaccharides nanoparticle can change the affinity between COVID-19 and heparan sulfate proteoglycan (HSPG) receptors or change the structure of RBD protein of COVID-19. It should be mentioned that polysaccharide nanoparticles can ameliorate immune responses against COVID-19 viruses as adjuvants in vaccine (Fig. 5) [48]. In this section, as illustrated by Table 1, all of studies are in preclinical phase. Moreover, *In vivo* studies also were recorded for two kinds of aforementioned nanoparticles, nanodecoys and nanosponges and it can be mentioned that one of the most complete *In vitro* and *In vivo* studies were done for nanodecoys compared with other researches.

Eventually, it can be resulted that nanotechnology has a crucial influence on the process of COVID-19 treatment and can be considered as a great candidate in coping with this global problem. More information about candidate drugs delivery to SARS-CoV-2 by nanocarriers are presented by (Table 2). As displayed by Table 2, the most efficiency rate of drugs is devoted to favipiravir (IC_{50}= 0.022 µg/mL) which is delivered by protein-lipid nanovesicles.

RECOMBINANT VACCINES

The growing number of COVID-19 cases and death has been created an immense pressure on researchers, clinicians, and some organizations like Food and Drug Administration (FDA) and WHO to allotted “emergency use authorization (EUA)” certification to some types of vaccines, such as mRNA and DNA-based vaccines, subunit

Table 2. Drugs candidates for SARS-CoV-2 treatment

Drug Name	Nanocarrier	Classification	Action Site of Drugs	IC_{50} in Cell Culture	Drugs Concentration for Human	Ref.
Remdesivir	Liposome	Antiviral drugs	Translation & Replication	IC_{50} = 1.183 ± 0.06 µM	-	[42]
Remdesivir	Aerosolized Liposome	Antiviral drugs	Translation & Replication	IC_{50}>17.6 µM	100-200 mg	[49]
Remdesivir	Poly [lactic-co-glycolic) acid [PLGA)	Antiviral drugs	Translation & Replication	IC_{50} = 0.77 µM	200 mg first day/ 100 mg for each subsequent day	[50]
Remdesivir	Carbon nanotube	Antiviral drugs	Translation & Replication	-	-	[51]
Dexamethasone	Liposome	Antiinflammation	-	-	6 mg/day	[41]
Ivermectin	Poly [lactide-co-glycolide)-*b*-polyethylene glycol NPs	Anti-parasite modalities	Reduced inhibition of the antiviral responses	IC_{50} = 1-10 mM	150 µg/kg	[52]
Favipiravir [Avigan)	Protein-lipid nanovesicles	Antiviral drugs	Translation & Replication	IC_{50} = 0.022 µg/mL	-	[53]
Tocilizumab	Protein-lipid nanovesicles	Immunosuppressive drugs	-	-	-	(53]

vaccines, and viral vector-based vaccines. Because of the same scale of nanoparticles and viruses and reproduction of the structural and functional properties of viruses by nanoparticles, they can be considered as a powerful tool in vaccines development and immunoengineering. Due to applying nanotechnology into contemporary vaccines, a wide range of candidate vaccines in clinical trials were existed [54].

Concerning mRNA and DNA vaccines, the part of SARS-CoV-2 genes are carried by these kinds of vaccines which synthesize a harmless protein as normal cells receptor for spike peptide of SARS-CoV-2. After that, as aforementioned in previous parts, immune responses by generating of B and T lymphocytes are started. BNT 162b2 (Pfizer-BioNTech Ltd., USA) and mRNA-1273 (Modema TX, Inc., USA) with efficacy rate of 94-95% are mRNA vaccines approved from FDA. In addition, protein subunit vaccines trigger immune response to some purified and harmless protein fragments of the viral pathogen. NVX-CoV2373 (Novavax and

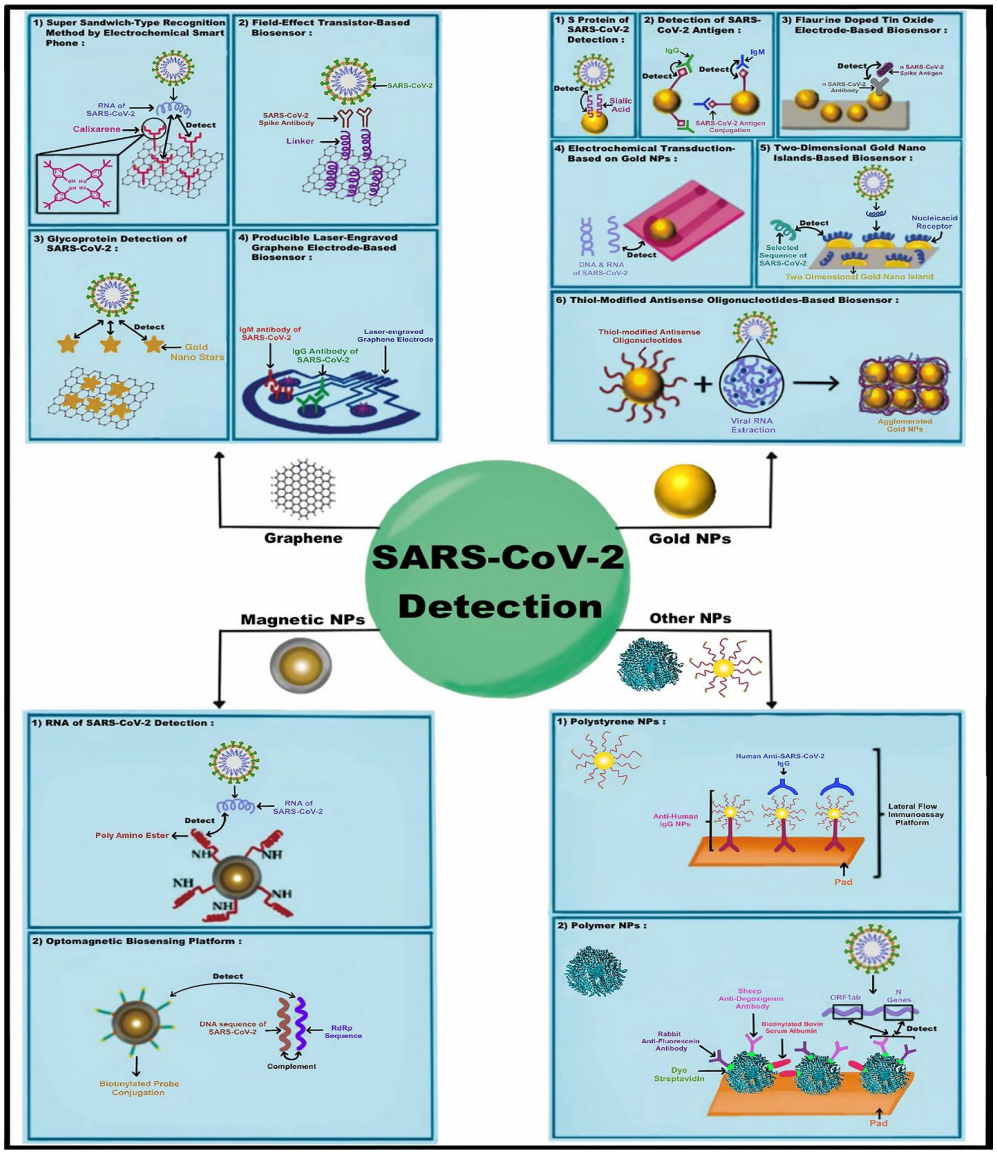

Fig. 6. Different mechanisms of all biosensors using nanoparticles for detection of SARS-CoV-2 that have been produced until now. SARS-CoV-2 detection can be classified into four categories, including graphene, gold nanoparticles, magnetic nanoparticles, and other nanoparticles, such as polystyrene and polymer nanoparticles. By using graphene four biosensors are created, namely 1) super sandwich-type recognition method by electrochemical smartphone to detect RNA of SARS-CoV-2. 2) Field-effect transistor-based biosensors to detect S protein of SARS-CoV-2 by conjugated SARS-CoV-2 spike antibody on it. 3) Graphene biosensor based on the glycoprotein detection of SARS-CoV-2 by conjugated gold nano stars on it. 4) Producible laser-engraved graphene electrode-based biosensor which detects IgM and IgG antibodies of SARS-CoV-2. Another nanoparticle is gold NPs that six biosensors are designed by them. 1) Conjugated gold nanoparticles with sialic acid to detect S protein of SARS-CoV-2. 2) Conjugated gold nanoparticles with SARS-CoV-2 antigen to detect IgG and IgM antibodies. 3) Flaurine doped tin oxide electrode-based biosensor to detect n SARS-CoV-2 spike antigen by conjugated n SARS-CoV-2 antibody on the gold NPs. 4) Electrochemical transduction-based on the gold NPs to detect DNA and RNA of SARS-CoV-2. 5) Two-dimensional gold nano islands-based biosensor to detect selected sequence of SARS-CoV-2 by nucleocapsid receptor. 6) Thiol-modified antisense oligonucleotides-based biosensor to detect viral RNA extract of SARS-CoV-2. Third category is devoted to the magnetic NPs. 1) Conjugated magnetic NPs with poly amino ester to detect RNA of SARS-CoV-2. 2) Optomagnetic biosensing platform to detect RdRp sequence of SARS-CoV-2. Other NPs as a fourth group comprises polystyrene NPs to detect human anti-SARS-CoV-2 IgG by lateral flow immunoassay platform and polymer NPs to detect N genes and ORF1ab of SARS-CoV-2 RNA by sheep anti-degoxigenin antibodies and rabbit anti-fluorescein antibodies.

Coalition for Epidemic Preparedness Innovation (CEPI)) is a kind of subunit and viral vector-based vaccines with efficacy rate of 89%. Viral vector-based vaccines employ live viruses to convey DNA into host cells for antigenic proteins synthesis. JNJ-78436735 (Johnson & Johnson's-Janssen pharmaceuticals, USA), AZD1222 (Covishield-India and Vaxzevria-Europe) (Oxford-AstraZeneca, USA and Serum Institute, India), and Sputnik V (Gamaleya Research Institute, Russia) can be considered as examples of this kind of vaccine with efficacy rate of 75%, 64%, and 92%, respectively [55]. Eventually, research and clinicians' findings justify that nanotechnology have a significant effect on vaccines development in the curb of global COVID-19 crisis.

ROLE OF NANOTECHNOLOGY IN COVID-19 DIAGNOSIS

During past decades, detection of different analytes from pollutant analytes, such as pesticides [56,57], heavy metals [58], and etc. in environment and agriculture products to specific elements of appropriate diseases, such as antibodies, particular part of viruses or cells have been detected by different nanoparticles [59]. Most *in vitro* detections even cell imaging [60] have been devoted to nanoparticles maybe owing to their low cytotoxicity [61].

One of the crucial factors in COVID-19 pandemic is rapid COVID-19 detection tests with due attention to fast propagation of this virus [62]. COVID-19 detection can be classified into three categories, namely SARS-CoV-2 RNA detection, SARS-CoV-2 antigen detection, and SARS-CoV-2 antibodies detection [63,64]. The current and common test for COVID-19 detection usually is reverse transcription polymerase chain reaction (RT-PCR). This test requires trained operators at every step of this method and specific equipment. Moreover, this test takes hours for analyzing and it is included as high-cost tests. Whereas, in current pandemic we need fast and cost-effective detection test without experts or special equipment [65]. In this situation, electrochemical and optical properties of nanosensors can receive adequate focus (Fig. 6) [35]. All of the nanoparticles' examples utilized for COVID-19 detection are illustrated by Fig. 6 and Table 3 to display their detection mechanisms. For instance, it has been reported that one of the studies utilized calixarene functionalized graphene oxide to detect RNA of COVID-19 by super sandwich-type recognition method. It should be mentioned that this method detects RNA of COVID-19 by electrochemical smart phone instead of nucleic acid amplification (Fig. 6 part 1 of graphene) [66]. Seo et al. have reported that graphene has been functionalized by COVID-19 spike antibody and after that substrates have been modified by functionalized graphene. Eventually, this nanosensor has permitted the evaluation of the field-effect transistor biosensing response to different samples, namely COVID-19 antigen, COVID-19 culture, and real clinical samples with different detection limits (Fig. 6 part 2 of graphene) [67]. It can be concluded that graphene which is coated by calixarene can be considered more accurate and sensitive detection device compared to field-effect transistor biosensor. Although both of these nanobiosensors have been designed as electrochemical biosensors which were based on a chip, detection process of coated graphene by calixarene have been performed by a smartphone. Another common denominator between both nanobiosensors is RT-PCR and ELISA measurements during their detection process. As discussed by Zhao et al., coated graphene with calixarene equipped with a smart phone is a low-cost, user friendly, and simple method than others methods [66]. Hashemi et al. have reported an electrochemical kit consists of electrodes activated upon a layer of graphene oxide with sensitive chemical compounds and gold nanostars. This nanosensor has detected viral glycoproteins of COVID-19 or other viruses at different voltage by different detection limits (Fig. 6 part 3 of graphene) [68]. In another same study about COVID-19, mass producible laser-engraved graphene electrode has been used for viral antigen nucleocapsid protein, IgM and IgG detection in wireless electrochemical platform (Fig. 6 part 4 of graphene) [69]. Both of these electrochemical biosensors which are based on graphene are able to record low detection limits. However, graphene which is coated by gold nanostars displays lower detection limit (1.68×10^{-22} μg/mL) than laser-engraved electrode. As reported by Hashemi et al., the possible detection mechanism of viral glycoproteins was studied by CV measurement which is one of the most common diagnostic methods in assessment of electrochemical mechanism of chemical reactions. Nonetheless, another one is designed as a wireless electrochemical RapidPlex platform. Moreover, both of nanobiosensors were applied toward

Table 3. Nanoparticles which are involved in SARS-CoV-2 detection with different mechanisms

Nanoparticle	Coated factor	Detected Analyte	Detection Limit	Detection Mechanism	Ref.
Graphene	Calixarene	RNA of SARS-CoV-2	200 copies/mL (1 copy of SARS-CoV-2 = 5µL)	Super sandwich-type recognition method by electrochemical smart phone	[66]
Graphene	Linker	SARS-CoV-2 spike antibody	1.6 × 10 pfu/mL	Field-effect transistor-based biosensor	[67]
Graphene	Gold nano stars	viral glycoproteins of SARS-CoV-2	1.68×10^{-22} µg/mL	Glycoprotein detection	[68]
Graphene	Viral antigen nucleocapsid protein	IgM and IgG antibodies of SARS-CoV-2	IgM: 500 pg/mL IgG: 250 ng/mL	Electrochemical detection by laser-engraved electrode	[69]
Gold Nanoparticle	Sialic acid	SARS-CoV-2 spike protein	8 µg./mL	Spike protein of SARS-CoV-2 detection in a lateral flow point of care diagnostic device	[70]
Gold Nanoparticle	SARS-CoV-2 antigen	IgM and IgG antibodies of SARS-CoV-2	-	Rapid IgM-IgG combined antibody test	[33]
Gold Nanoparticle	n SARS-CoV-2 antibody	n SARS-CoV-2 spike antigen	90-120 fM	Fluorine doped tin oxide electrode-based biosensor	[71]
Gold Nanoparticle	-	DNA and RNA of SARS-CoV-2	-	Electrochemical transduction-based on gold nanoparticles	[72]

Gold nano island	Nucleic acid receptor	Selected sequence of SARS-CoV-2	0.22 pM	Two-dimensional gold nano islands-based biosensor	[73]
Gold Nanoparticle	Thiol-modified antisense oligonucleotides	Viral RNA extraction	0.18 ng/µL	Thiol-modified antisense oligonucleotide-based biosensor	[74]
Magnetic Nanoparticle	Poly amino ester	RNA of SARS-CoV-2	10 copies of pseudo virus	RNA of SARS-CoV-2 detection	[75]
Magnetic Nanoparticle	Biotinylated probe	RdRp sequence	0.4 fM	Optomagnetic biosensing platform	[76]
Polystyrene Nanoparticle	Anti-human IgG	Human anti-SARS-CoV-2 IgG	-	Lateral flow immunoassay platform	[30]
Polymer Nanoparticle	Rabbit anti-fluorescein antibody + Sheep anti-digoxigenin antibody + Dye streptavidin + Biotinylated bovine serum albumin	N genes and ORF1ab gene of SARS-CoV-2	12 copies per reaction	Nanoparticle-based lateral flow biosensor	[77]

SARS-CoV-2 detection in real human samples using RT-PCR evaluation [68].

Concerning gold nanoparticles, it has been reported that Baker et al. synthesized multivalent gold nanoparticles bearing sialic acid to detect the spike glycoprotein of COVID-19 as a colorimetric detection by nanoparticles. In mentioned paper explained that α,N-acetyl neuraminic acid binds to the S protein of COVID-19 (Fig. 6 part 1 of gold NPs) [70]. Another study about gold nanoparticles is devoted to Li et al. that synthesized gold nanoparticles with COVID-19 antigen conjugation. This nanoparticle has detected IgM and IgG antibodies against SARS-CoV-2 in human blood (F. 6 part 2 of gold NPs) [33]. It has been reported by other same studies that gold nanoparticles have been synthesized with fluorine doped tin oxide electrode and were immobilized with n SARS-CoV-2 monoclonal antibody for detection of n SARS-CoV-2 spike antigen (Fig. 6 part 3 of gold NPs) [71]. Label-free electrochemical transduction based on gold nanoparticles as transducing

elements for RNA and DNA detection of SARS-CoV-2 has been presented by this mentioned example (Fig. 6 part 4 of gold NPs) [72]. Qiu et al. have designed a dual-functional plasmonic biosensor which is combination of plasmonic photothermal effect and localized surface plasmon resonance sensing. In this platform, they synthesized the two-dimensional gold nanoislands functionalized by DNA receptors for detection of selected sequence of COVID-19 through nucleic acid hybridization (Fig. 6 part 5 of gold NPs) [73]. Another study reported gold nanoparticles which capped with thiol-modified antisense oligonucleotides to detect isolated RNA samples of COVID-19. As colorimetric detection by nanoparticles, change in gold nanoparticles surface plasmon resonance and absorption band confirms detection process (Fig. 6 part 6 of gold NPs) [74]. Generally, it can be mentioned that two kinds of aforementioned nanobiosensors which are based on gold nanoparticles can be considered as electrochemical biosensors that in this group fluorine-doped tin oxide electrode-based biosensor has ultra-low detection limit of 90-120 fM. Another nanobiosensor which is based on gold nanoislands can be considered as a dual-functional plasmonic biosensor combining the plasmonic photothermal effect on a cost-effective chip. This kind of nanobiosensor with the sensitive detection limit of 0.22 pM can put pressure on PCR-based tests. Among other nanobiosensors based on gold nanoparticles, thiol-modified antisense oligonucleotide-based biosensor has the lowest detection limit of 0.18 ng/µL which make it a great candidate for biosensors based on only gold nanoparticles. Furthermore, almost all of mentioned papers in this section, detection by gold nanoparticles, have declared that their designed detection devices are cost-effective and cheap for users, except conjugated gold nanoparticle with SARS-CoV-2 antigen for IgM and IgG detection [74].

Another study has reported COVID-19 detection by magnetic nanoparticles. They have synthesized poly (amino ester) with carboxyl groups-coated magnetic nanoparticles that leads to SARS-CoV-2 RNA extraction. Accordingly, its RNA detection has been occurred by these nanoparticles. It should be noted that RNA molecules have been attracted into nanoparticles owing to a strong interaction between the nucleic acids and carboxyl groups (Fig. 6 part 1 of magnetic NPs). The detection limit reported in Zhao et al. paper is 10 copies of pseudo virus and they reported the conventional RT-PCR use in their nanobiosensor synthesis process [75]. The inquiry of Tian et al. devoted to magnetic nanoparticles has reported that iron oxide nanoparticles have been synthesized with biotinylated probe conjugation for detection RdRp sequence which is a complementary DNA sequence of SARS-CoV-2 by optomagnetic biosensing platform (Fig. 6 part 2 of magnetic NPs). It should be mentioned that the reported ultra-low detection limit for this biosensor is 0.4 fM. Moreover, some crucial tests like feasibility tests, quantitative detection in real sample, and specificity tests have been done for confirmation of sensitivity and accuracy of this designed nanobiosensor [76]. Although these reported magnetic nanoparticles have a vital role in COVID-19 diagnosis, aforementioned nanoparticles can be utilized in different biosensor devices and can report some information more accurate and clearer. Probably, these designed biosensor devices have been found more possible than other nanoparticles which are in preclinical studies to COVID-19 diagnosis and treatment.

Chen et al. have detected the anti-SARS-CoV-2 IgG in human serum by lanthanide-doped polystyrene nanoparticles in lateral flow immunoassay platform which can be considered as a kind of colorimetric detection by nanoparticles (Fig. 6 part 1 of other NPs). The advantage of Chen et al. project is their investigation in reproducibility and clinical sample tests of their cost-effective device [30]. Next nanoparticle that has been investigated by Zhu et al. is polymer nanoparticles coated with dye streptavidin which immobilized by rabbit anti-fluorescein antibody, sheep anti-digoxigenin antibody, and biotinylated bovine serum albumin for ORF1 ab and N genes detection of SARS-CoV-2 (Fig. 6 part 2 of other NPs). It was reported by Zhu et al. that their designed biosensor is cost-effective and its price is established $5.5 USD per disposable. Furthermore, sensitivity and specificity assay of COVID-19 along with its application assay in clinical samples with detection limit of 12 copies per reaction were investigated during their paper [77]. What is noteworthy is that these papers can confirm the crucial role of nanotechnology in SASRS-CoV-2 detection during current pandemic and even can be industrialized in future.

A novel treatment and diagnostic technology

can be developed into four phases, including i) design and verification of treatment method or synthesis a specific device; ii) clinical testing in small patient cohorts; iii) clinical trial in large patient cohorts; and iv) commercialization for patient use. Passing these four phases play a vital role in making a new technology popular and common in a population. These phases have a significant effect on SARS-CoV-2 treatment and diagnosis in future [78]. Absolutely, one of the techniques that have very significant effect on the control of SARS-CoV-2 pandemic is vaccine development which really boost humanity medical knowledge. Health organizations like WHO can find it possible to produce kinds of vaccines, such as mRNA and DNA vaccines that have never been taken into practice in large scale. Furthermore, a wide range of diagnostic devices have been producing that dramatically change the future perspective of public health [54].

CONCLUSION

COVID-19 or SARS-CoV-2 as a worldwide problem with high mortality rate significantly affect mankind's life. In this situation that there is no exact and assured treatment of COVID-19, nanotechnology can be considered as a vital field in declining infection rate of COVID-19 or in the best case of scenario, treatment of COVID-19. It can be resulted that nanoparticles can play a crucial and impressive role in tackling SARS-CoV-2 problem by controlling the inflammatory responses or interruption of different steps of SARS-CoV-2 entrance into the cells or detection glycoprotein and nucleic acid parts of SARS-CoV-2. These nanoparticles roles are recognized by investigation of SARS-CoV-2 structure, replication and infection mechanism, immunological responses, and pathophysiology features along with the ability of nanoparticles in appropriate drugs delivery against SARS-CoV-2 and the capability of nanoparticles to design different biosensors for SARS-CoV-2 detection.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

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