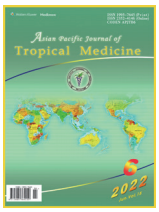

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Biopharmaceuticals for prevention of COVID-19: A scoping review

Afsaneh Farjami[1,2], Soheila Montazersaheb[3], Saiedeh Razi Soofiyani[4,5], Parvin Akbarzadehlaleh[6]✉, Sara Salatin[7]

[1]*Food and Drug Safety Research Center, Tabriz University of Medical Science, Tabriz, Iran*

[2]*Pharmaceutical Analysis Research Center, Tabriz University of Medical Science, Tabriz, Iran*

[3]*Molecular Medicine Research Center, Tabriz University of Medical Science, Tabriz, Iran*

[4]*Department of Molecular Medicine, Faculty of Advanced Medical Sciences, Tabriz University of Medical Sciences, Tabriz, Iran*

[5]*Clinical Research Development Unit Sina Educational, Research and Treatment Center, Tabriz University of Medical Sciences, Tabriz, Iran*

[6]*Department of Pharmaceutical Biotechnology, Faculty of Pharmacy, Tabriz University of Medical Science, Tabriz, Iran*

[7]*Neurosciences Research Center (NSRC), Tabriz University of Medical Sciences, Tabriz, Iran*

ABSTRACT

The COVID-19 epidemic caused by SARS-CoV-2 virus has turned into a worldwide pandemic. Therefore, health officials all around the world have strived for developing efficient preventive and treatment methods to deal with this global crisis. Amongst them, monoclonal antibodies, anti-TNFs, and convalescent plasma appear to be effective against this disease. In addition, clinical trials are currently being conducted for viral targeting vaccines. This review summarizes major advances using biopharmaceuticals in the treatment and prevention strategies against COVID-19 that have occurred in the global medicinal system from its introduction until March 2022.

Keywords: COVID-19; SARS-CoV-2; Biopharmaceuticals; Monoclonal antibodies; Anti-TNFs; Convalescent plasma; Vaccine

1. Introduction

COVID-19, a potentially lethal infection caused by the SARS-CoV-2 virus, is a serious global public health problem[1]. The SARS-CoV-2 virus enters the lower respiratory tract and causes pneumonia in humans, with symptoms that are milder than SARS or MERS, but eventually develops into a deadly hyperinflammation and respiratory dysfunction syndrome[2]. In March 2020, the WHO declared it a worldwide pandemic due to its fast spread all over the world[3,4]. SARS-CoV-2 is an enveloped positive-sense single-stranded RNA pathogenic virus, and its membrane envelope is covered with glycoprotein spikes that give the coronaviruses a crown-like appearance. Figure 1 schematically presents four main structural proteins of the virus: spike surface glycoprotein (S), membrane protein (M), an envelope protein (E), and nucleocapsid protein (N)[5]. The discovery of wide ranging antiviral compounds that target S proteins, which play a significant role in virus entrance and the viral replication cycle in the host cell[6]; or by employing particular therapeutic compounds capable of interrupting each phase of the viral life cycle (Figure 2); or deactivated receptor proteins found on host cells[7,8] has been a major research focus. Amongst treatment strategies, biopharmaceuticals such as monoclonal antibodies, anti-tumour necrosis factors (TNFs), and convalescent plasma are some of the most effective and indisputable options against COVID-19.

According to existing research, early administration of stimulating plasma or immunoglobulin overuse in patients with substantial antibody titers can result in a lower mortality[9,10]. The monoclonal antibody, designed to attach to a single substance in the body,

✉To whom correspondence may be addressed. E-mail: parvin.akbarzadeh@gmail.com; Akbarzadehp@tbzmed.ac.ir

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is a revolutionary way of preventing infectious diseases. This binding is highly adaptable, as it may imitate, inhibit, or create modifications to exact pathways, resulting in a highly successful therapeutic intervention with a specific therapy for disorders[11,12]. TNF is a pro-inflammatory cytokine that has elevated levels in COVID-19 patients' blood and tissues and is involved in excess inflammatory reactions and amplifying the inflammation process, which could predict their mortality. Therefore, anti-TNF agents are able to inhibit the progression of COVID-19 and reduce the need for intensive care unit (ICU) admission in hospitalized COVID-19 patients[13]. Despite vaccination efforts that have resulted in lower hospitalization and mortality rates in most countries, there is no definitive antiviral treatment for COVID-19 in infected patients, resulting in an increase in the number of infected people when new virus variants resistant to available vaccines emerge[14]. As a result, it is time to decide and describe the disease's treatment plans from several perspectives. This allows specialists in treatment and research fields to make more informed decisions about the best treatment method. Several review papers on the best treatment plan for COVID-19 have been published so far in various areas and have revealed some of its previously unknown secrets, and the number of these publications is growing every day. The expert panel advocated using promising therapies in the framework of a clinical trial where there was inadequate proof of benefit to warrant their usage and possible substantial risks or costs. These suggestions recognize the present "knowledge gap" and attempt to prevent making premature favorable recommendations for possibly ineffective or hazardous therapies. Despite the ongoing advancements in biotechnology techniques for the treatment of COVID-19, a thorough research is required to review the disease's triumphs and failures. The purpose of this study was to give a comprehensive overview of biopharmaceutical-based therapeutics including monoclonal antibodies, convalescent plasma, anti-TNFs and developed vaccines in treatment and prevention of COVID-19 infection.

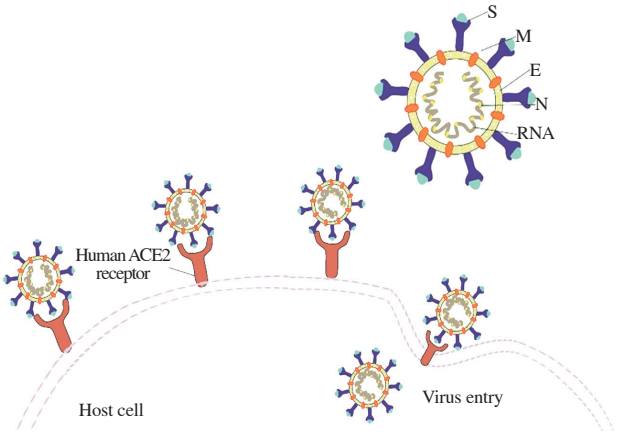

Figure 1. The structure of SARS-CoV-2. SARS-CoV-2 contains four structural proteins, that include spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins. S proteins play a significant role in virus entrance and the viral replication cycle in the host cell.

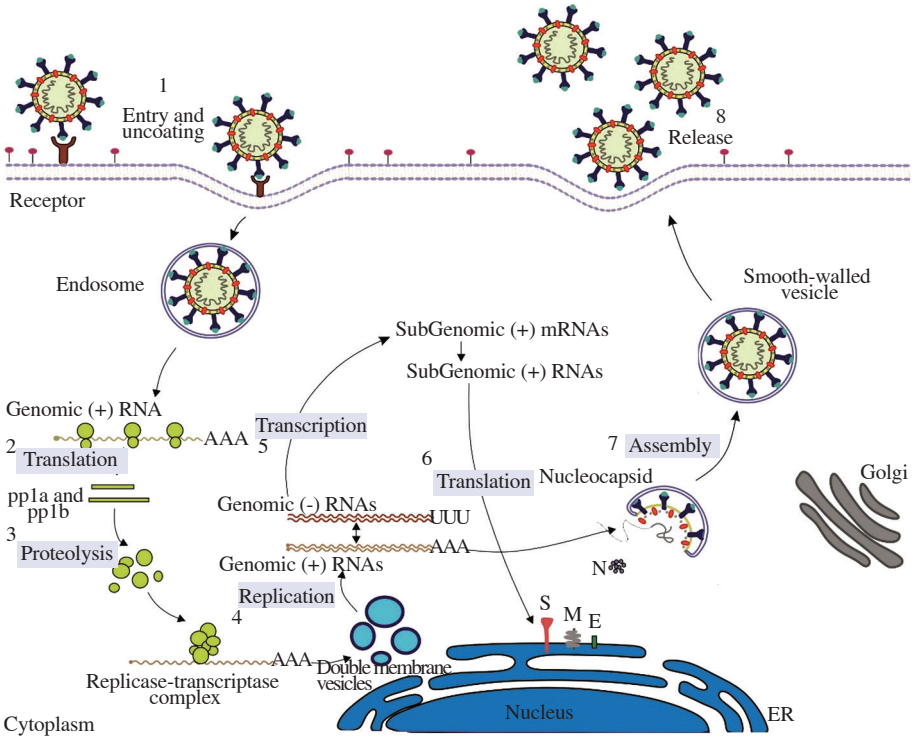

Figure 2. Viral life cycle. Multiple steps in the virus's life cycle are presented, including spike protein binding to receptor, membrane fusion between the virus and host cell, viral RNA release, translation of viral RNA, proteolysis of polyproteins (pp1a and pp1b), replication and translation, packaging and assembly of viral particles, and virion release.

2. Monoclonal antibodies against COVID–19

The aim of using monoclonal antibodies (mAbs) in viral infection therapy is to decrease the viral load by interfering with the virus' entry into the host cell through binding to the viral spike proteins and preventing virus attachment to the host cell surface receptors. Thus, the host cells binding sites become un-accessible to the virus. In other words, mAbs act as immunosuppressive agents by suppressing immune-mediated damages[15,16]. Following the virus' entry into the body, the naive immune system response is activated, and the acquired immune system response is activated a few days later. The clinical phases of COVID-19 infection can be divided into the viremia phase, the acute phase, and the severe or recovery phase. Recent studies demonstrated that the inflammation in local tissues and systemic cytokine storm is directly responsible for developing sepsis caused by COVID-19 infection. Deregulated host immune response can result in pneumonitis, inflammatory lung damage, respiratory failure, shock, organ failure, and death in the high-risk group infected by COVID-19[17–20]. Based on their mechanism of action, the mAbs are used in the treatment of COVID-19. The SARS-CoV-2 virus uses trimeric spike (S) glycoproteins on its surface to enter the host cells and infect them. Therefore, targeting the S glycoproteins specific by monoclonal antibodies can neutralize the virus. The spike proteins of SARS-CoV-2 (Wuhan-Hu-1 strain) and SARS-CoV (Urbani strain) have 77.5% similarity in the primary amino acid sequences, and they attach to the angiotensin-converting enzyme two protein on the surface of the host cells[21]. Recently, some unique humanized or engineered mAbs can target different parts of spike protein SARS-CoV-2's have been registered in clinical trials. Casirivimab and imdevimab (REGN-COV2) are the types of mAb cocktail therapy that bind to no overlapping epitopes of the spike protein receptor-binding domain (RBD) of SARS-CoV-2. Accordingly, the virus cannot bind to the angiotensin-converting enzyme 2 receptor[22].

The mAb cocktail therapy is recommended for patients with mild and moderate COVID-19, as well as those with a high possibility of developing severe COVID-19. But the COVID-19 patients who were hospitalized and needed oxygen therapy or those with previous underlying co-morbidity were excluded from receiving the mAb cocktail therapy[23].

2.1. Monoclonal antibodies against IL–6

Tocilizumab, siltuximab, and sarilumab are commercially available mAbs against IL-6. Tocilizumab, a recombinant humanized mAb, and sarilumab, fully human immunoglobulin G1 monoclonal can interact with the membrane and soluble form of the IL-6 receptor. Tocilizumab is an food and drug administration-approved anti-IL-6 receptor antibody used for treating different inflammatory and autoimmune diseases[24]. Tocilizumab was used to treat moderate and severe COVID-19 patients besides standard treatment protocols[23].

Tocilizumab is now recommended for COVID-19 patients with warning signs of hyperinflammation[25]. Aziz *et al*. reported that the patients with COVID-19 who received tocilizumab had a better survival rate. A severe COVID-19 patient may be presented with overexpressed IL-6, which can bind to IL-6 receptors and activates vascular endothelial growth factor and reduce E-cadherin expression, leading to an increased vascular permeability, shock, and multiorgan dysfunction. The better outcome of patients treated with tocilizumab can be attributed to its effectiveness in alleviating cytokine release syndrome (CRS)[26–28]. In fact, tocilizumab exerts its effects by breaking this cycle through suppressing both membrane and soluble IL-6 binding receptors as well as suppressing both initial and consequent CRS stages. Meanwhile, as tocilizumab suppresses the immune system and may increase the risk of infection, there is no reservation in using that liberally[29]. Siltuximab, a chimeric human-murine immunoglobulin mAb that has binding affinity greater than tocilizumab, can interact with the human IL-6-R. In this regard, siltuximab can be used to treat COVID-19 patients who are especially resistant to tocilizumab and steroids[30]. As a treatment option for COVID-19 patients with high levels of IL-6, siltuximab inhibits the interaction of IL-6 by its both soluble and membrane receptor; therefore, no signaling results from the interaction of ligand and receptor. According to the reports by Palanques-Pastor *et al*., COVID-19 patients tolerate siltuximab well[31]. The recommended dose of siltuximab is 11 mg/kg over 1 hour given intravenously every 3 weeks. As the half-life of siltuximab is (16.3±4.2) days and COVID-19 infection is a severe process, a single dose would be sufficient to downregulate IL-6 levels[31]. Because siltuximab can cause analytical alterations, it is essential to confirm that the absolute neutrophil count is $\geqslant 1\times 10^9$/L, the platelet count is $\geqslant 75\times 10^9$/L and hemoglobin is <170 g/L before administration[31]. In addition, the efficacy of siltuximab can be evaluated indirectly by C-reactive protein suppression (CRP) levels[32]. Sarilumab is a fully-humanized antibody against the IL-6 receptor that binds specifically to both soluble and membrane-bound IL-6 receptors, suppressing signaling pathways. The affinity of sarilumab for the IL-6 receptor is higher and its half-life is longer than that of tocilizumab, however, their efficacy and safety seem to be comparable[30]. Della-Torre *et al*. showed that IL-6 blockade with sarilumab was safe and associated with a low mortality rate. Although treatment

with sarilumab was not related to improved MV-free survival or hospitalization duration, but the mAb was associated with faster recovery in a subset of patients with minor lung consolidation at baseline[33]. A primary study of the trial showed that the sarilumab was effective in critically ill COVID-19 patients who required mechanical ventilation or high-flow oxygenation, or who needed treatment in an intensive care unit, but not those who were severely ill (*i.e.* not requiring mechanical or high-flow oxygenation)[34]. The 200 mg intravenous dose of sarilumab that was administered to severely infected COVID-19 patients has been withdrawn from the manufacturer-sponsored trials based on primary documents, but the 400 mg *i.v.* dose is still being evaluated for the treatment of critically hospitalized patients[35].

2.2. Human IL-1 receptor antagonist protein

There is growing evidence that members of the IL-1 family are major mediators of inflammation. Among them, IL-1α and IL-1β both act as typical pro-inflammatory cytokines[36]. It has been demonstrated that IL-1 as a pleiotropic cytokine, plays an essential role in COVID-19, and the elevated level of IL-1 is detectable in the lung of patients with the disease. A massive amount of IL-1α is released upon necrotic cell death mediated by virus infection. IL-1α binds to its receptor, as IL-1β does, and triggers identical pro-inflammatory responses. In other words, IL-1α and IL-1β are the main mediators orchestrating inflammatory reactions in response to tissue injury[37]. According to the previous sections, severe form and advanced stages of COVID-19 disease can cause a life-threatening hyperinflammatory state characterized by widespread epithelial and endothelial damage to the lung tissue[38]. The release of IL-1α by epithelial cells leads to a variety of events, including sensing inflammatory myeloid cells and inflammasome activation, resulting in the stimulation of the inflammatory cascade. As a result of these alterations, COVID-19 pathogenesis is thought to be attributed to IL-1α-induced inflammation[39]. Based on this evidence and the IL-1-mediated hyper-inflammatory reactions in severe COVID-19 patients, it is hypothesized that inhibiting IL-1 may have some benefits in these patients. Indeed, immunomodulatory agents are supposed to abrogate the dysfunction of the immune system in hyperinflammatory status in COVID-19 patients, so they are currently being scrutinized in various clinical trials. Anakinra is a recombinant human IL-1 receptor antagonist that blocks both IL-1α and IL-1β signaling pathways. This natural regulatory agent has been reported to be safe and effective for treating autoinflammatory diseases and rheumatoid arthritis at a dose of 100 mg daily *via* a subcutaneous route. It has been revealed that intravenous administration of anakinra at a dose of 5 mg/kg twice a day decreased systemic inflammation, respiratory dysfunction, and mortality in 29 patients with acute respiratory distress syndrome (ARDS) as compared to standard care management[40]. Anakinra has a half-life of about 3-4 hours. This short half-life quickly stops the adverse effects or secondary infections caused by this drug. The inhibition of IL-1 also reduces the endothelial dysfunction and microvascular changes, which are critical in COVID-19-related thromboembolic events[41]. A cohort study of moderate-to-severe ARDs patients with COVID-19 and hyperinflammation showed that administration of high-dose anakinra intravenously was safe and accompanied by clinical improvement in 72% of the patients[42,43]. Pontali *et al*. showed that the administration of high intravenous doses of anakinra in severe or moderate COVID-19 patients with pulmonary involvement led to a notable improvement in respiratory parameters in the patients[44]. Navarro-Millán *et al*. proposed that anakinra could be effective in COVID-19 patients with cytokine storm syndrome when initiated early after the onset of acute hypoxic respiratory failure[45]. Studies indicate that anakinra may be a promising treatment option for severe COVID-19, primarily through the inflammasome pathway[41,43]. Moreover, a growing number of independent studies have reported that anakinra administration reduced mortality and the need for invasive mechanical ventilation[46,47]. Jamil *et al*.[48] reported that invasive mechanical ventilation is related with worse outcomes, presumably because of ventilator-induced lung damage. It is noteworthy to highlight that there is a bi-directional link between IL-1-mediated inflammatory responses and the coagulation cascade; thereby IL-1 blockade with anakinra might reduce thromboembolic complications and thrombo inflammatory states in COVID-19[49]. Giulio Cavalli *et al*. conducted a retrospective cohort study in 29 patients with COVID-19 ARDS and hyperinflammation status (CRP$\geqslant$100 mg/L), receiving a high dose of anakinra (5 mg/kg twice a day). At the 21th day, the survival rate of those who were treated with high-dose anakinra was 90% as compared with patients who received the standard treatment (56%). Besides, 21 (72%) patients had a reduction in serum level of CRP, exhibiting significant clinical improvement in respiratory function. The results inferred that high-dose intravenous anakinra could dampen systemic inflammation. Furthermore, the results indicated that high-dose anakinra was well tolerated, and its withdrawal did not lead to relapses in respiratory dysfunction and systemic inflammation[50]. In a single-center, observational study in Italy, IL-1 and IL-6 inhibitors were compared in COVID-19 patients with respiratory insufficiency and hyperinflammation. Among the 392 patients, 275 did not receive cytokine inhibitors, 62 patients were treated with anakinra, and 55 received IL-6 inhibitors (tocilizumab

and sarilumab with the same mechanism of action). Compared with patients treated with only conventional care, those who received anakinra had a significant reduction in mortality risk, whereas those treated with anti-IL-6 did not. Inhibition of IL-6 only showed efficacy in a subgroup of COVID-19 patients with a high level of CRP. This scenario can be due to the important mechanistic role of IL-6 in inducing the production of CRP by the liver during the acute phase response. Interestingly, both antagonists of IL-1 and IL-6 exhibited effectiveness in patients with a low level of lactate dehydrogenase[51]. The effectiveness of IL-1 inhibition compared to IL-6 may be attributed to the endotheliopathy of COVID-19 which releases IL-1α. Given this fact, IL-1 is an upstream mediator of the IL-6-mediated signaling pathway; accordingly, blocking of IL-1 signaling can indirectly block IL-6-mediated activity. Indeed, effective inhibition of IL-1 may suppress IL-6 expression. Such a mechanistic relationship might account for developing IL-1 antagonists for a subset of COVID-19 patients with CRS to benefit from this strategy[52]. Noteworthy, anakinra has a remarkable safety potential, including lower rate of opportunistic infections, short half-life, and prompt clearance as compared with 2-3 weeks' half-life of IL-6 inhibitors[53]. Despite being very effective in alleviating CRS, inhibiting the IL-1-mediated activity may be accompanied by some safety concerns and warning issues, such as the risk of serious infection. However, the incidence of serious infection from IL-1 inhibitors is very low, which promotes to development of targeted therapy in an active infection. Moreover, anakinra may lead to neutropenia, so a blood neutrophil count should be measured before starting the treatment[54].

Given the pivotal role of IL-1β in the pathogenesis of COVID-19, blocking this cytokine is a promising therapeutic strategy in this regard. Canakinumab is a high-affinity monoclonal antibody designed to block the binding of IL-1β to its receptors, thus neutralizing the cytokine's activity. Canakinumab can be used as a therapeutic agent for a subgroup of patients with severe COVID-19[55,56]. Canakinumab acts in a specific manner and blocks only IL-1β that is produced within the inflammasome and does not react with other cytokines or the other members of the IL-1 family[56]. Based on the data from Katia *et al*'s cohort study, canakinumab therapy leads to a considerable and rapid improvement in respiratory failure and blood parameters in comparison to the group receiving standard therapy. Besides, canakinumab was able to reduce the inflammation indices and oxygen flow as compared to the standard care group[57]. Similarly, data from Generali *et al*. provided evidence about canakinumab treatment in 48 patients with moderate COVID-19-associated pneumonia. Among them, 33 patients received canakinumab and 15 patients received only standard care and served as a control group. Canakinumab administration resulted in faster hospital discharge of treated patients (63%) compared to the control group (0%) as well as improved ventilation regimes and lung damage. Furthermore, canakinumab significantly reduced the number of white blood cells, platelets, and neutrophils, but increased the number of lymphocytes. With regards to inflammatory states, administration of canakinumab led to a prompt reduction in CRP. These data implied that canakinumab treatment could restore normal oxygen levels, diminish the need for invasive mechanical ventilation, and improve the clinical symptoms in COVID-19 patients[58]. However, canakinumab therapy has been reported to cause hematological disorders such as leukopenia, thrombocytopenia, neutropenia, and elevated liver enzyme levels. Collectively, blockade of the CRS *via* canakinumab treatment can be a therapeutic option to prevent the clinical deterioration of COVID-19 patients, exhibiting a better prognosis[54].

2.3. Monoclonal antibodies against vascular endothelial growth factor

Bevacizumab is a recombinant humanized mAb that blocks vascular endothelial growth factor (VEGF) by specifically binding to both circulating and soluble forms of VEGF[59]. Bevacizumab competes with VEGF receptors on the surface of the endothelial cells for VEGF binding and suppresses the effects caused by binding to its receptor[60]. Previous studies showed that VEGF expression is significantly up-regulated in the plasma of patients with ARDS. Also, VEGF induces vascular permeability. In ARDS, increased pulmonary vascular permeability makes the lung vulnerable to edema[61]. Pang *et al*. indicated that a single-dose of bevacizumab could significantly improve oxygen levels in COVID-19 patients compared to standard treatment[62]. Therefore, bevacizumab might be a promising therapeutic approach for ARDS, one of the severe complications of COVID-19[20]. Due to bevacizumab's ease of administration and patient toleration, it may offer more promising results. The main reported side effects of bevacizumab were associated with hypertension, thromboembolism, proteinuria, and a persistent elevation of arterial blood pressure, causing cardiovascular complications, bleeding, delayed wound healing, and gastrointestinal events[63,64]. Islam *et al*. reported that a single treatment with a single dose of bevacizumab resulted in 92% survival benefit[65]. Also, Pang *et al*. showed that treatment of patients with severe COVID-19 by bevacizumab plus standard care improved oxygenation and reduced oxygen-support requirements[62]. Given its potentially serious side effects, bevacizumab was limited for adminstration to COVID-19 patients[59].

2.4. Monoclonal antibodies against granulocyte-macrophage colony-stimulating factor receptor

Mavrilimumab is a monoclonal antibody against the granulocyte-macrophage colony-stimulating factor (GM-CSF) receptor. Increased level of GM-CSF may lead to hyperinflammation in COVID-19 patients as it is high in bronchoalveolar lavage in ARDS-patients with COVID-19[66,67]. It has been revealed that GM-CSF is significantly up-regulated in the serum of individuals who died from COVID-19. GM-CSF is also the major pro-inflammatory cytokine response regulator in the lung. It can stimulate alveolar macrophages and promotes clearance of respiratory microbes *via* pro-inflammatory cytokines, but the further inflammatory loop might induce the damage[68]. In previous studies, immunosuppression with dexamethasone reduced the mortality rate in severe or critical COVID-19 patients, supporting the significance of hyperinflammation in adverse outcomes. Observational studies have proposed a probable advantage of GM-CSF antagonism in COVID-19 patients[50, 69]. Although mavrilimumab administration did not reduce the oxygen supplement therapy at day 14 among severe or critical COVID-19 patients with hypoxemia, a positive result was seen in those patients treated with mavrilimumab. By day 28, patients who were treated with mavrilimumab were more likely to be alive and not have respiratory failure[70]. The mavrilimumab was intravenously injected once daily for 14 days at a dosage of 250 μg/m^2[71].

3. Anti-TNF agents

TNF is a pro-inflammatory cytokine that is involved in excess inflammatory reactions. COVID-19 patients have elevated levels of TNF in their blood and tissues, which could predict their mortality. TNF is involved in almost all acute inflammatory responses, amplifying the inflammation process. Therefore, anti-TNF agents may be able to inhibit the progression of COVID-19 and reduce the need for ICU admission in hospitalized COVID-19 patients. This immunomodulatory approach holds a great promise for COVID-19 treatment. Anti-TNF has been administered to millions of patients over many years for various clinical indications. Moreover, TNF plays a crucial role in the pathophysiology of COVID-19, particularly in the initiation of inflammatory cascades. As TNF levels are elevated in the early stages of the disease, early treatment may be more beneficial for patients than treatment at a later stage. In other words, TNF coordinates responses to infections and facilitates the recruitment of a variety of cells by regulating numerous chemokines and adhesion molecules[13]. It has been shown that anti-TNF treatment could reduce the production of some pro-inflammatory cytokines such as IL-1 and IL-6. Therefore, it can be assumed that blocking TNF-mediated effects can reduce the production of pathogenic cytokines. Though there are many potential drugs for treating inflammation in COVID-19 patients, only a few are potentially effective. Anti-TNF antibodies such as infliximab or adalimumab have clinically met safety and efficacy profiles for the treatment of COVID-19 patients. Researchers have shown that blockade of TNF can reduce both GM-CSF and VEGF expression in patients with rheumatoid arthritis (RA), suggesting that anti-TNF may help decrease the COVID-19-derived capillary leak, the main factor affecting COVID-19 lung function[72]. The antiviral effect of TNF has also been demonstrated. However, it is unclear whether anti-TNF therapy will interfere with antiviral activity. In light of these concepts, using powerful anti-inflammatory agents should be undertaken with more caution because of the possibility of increasing viral replication. Furthermore, there is a huge immune response against virus-induced lung infections, thereby a moderate reduction in inflammation may be helpful[73]. It has also been reported that anti-TNF had efficacy in several infections, with no evidence of a decline in antiviral immunity. A large number of observational studies have shown that anti-TNF agents may be effective in the treatment of COVID-19 patients. There is a recruiting trial of infliximab in hospitalized COVID-19 patients in the United Kingdom in the CATALYST phase Ⅱ trial (ISRCTN40580903)[72]. Infliximab is a chimeric monoclonal antibody that specifically targets TNF and blocks its binding to the corresponding receptors. This can prevent TNF-mediated signaling cascades and subsequent gene expression. Observational research conducted by Farrokhpour in 104 patients with severe COVID-19 admitted to the ICU, receiving standard care regimens based on the local protocol (Tehran, Iran). Among them, 43 cases served as the control group and the remaining 61 cases were in three groups receiving infliximab (n=27), intravenous gammaglobulin (n=23), and combination of infliximab and gammaglobulin therapy (n=11), respectively. Gammaglobulin is prepared from human serum, which contains a large number of polyclonal antibodies. The survival was as follows: 63% of infliximab-treated patients, 9% of intravenous gammaglobulin-treated, 54.5% in combination therapy, and 37.2% in the control group, indicating the effectiveness of infliximab on the patient's outcomes[74].

4. Convalescent plasma as a potential strategy

To date, there are only a few available antiviral treatments with limited efficacy for COVID-19 disease and, more importantly, the

Table 1. Characteristics of COVID-19 vaccines in phase Ⅲ and Ⅳ trials according the WHO's draft landscape of COVID-19 candidate vaccines[88].

Vaccine platform	Registered name	Dose number	Dose interval	Administration route	Developer	Phase
mRNA vaccines	BNT162b2,4	2	0+21	IM	BioNTech and Pfizer	Ⅳ
	MRNA-1273	2	0+28	IM	Moderna and NIAID	Ⅳ
	mRNA-1273.351	3	0+28+56	IM	Moderna + National Institute of Allergy and Infectious Diseases (NIAID)	Ⅳ
	CVnCoV	2	0+28	IM	CureVac AG	Ⅲ
	ARCoV	2	0+14 or 0+28	IM	Walvax Biotechnology, Suzhou Abogen Biosciences	Ⅲ
	ARCT-154		0+28	IM	Arcturus Therapeutics, Inc.	Ⅲ
DNA based vaccine	ZyCoV-D	3	0+28+56	ID	Zydus Cadila	Ⅲ
	INO-4800	2	0+28	ID	Inovio Pharmaceuticals + International Vaccine Institute + Advaccine	Ⅲ
Viral vector (Non-replicating)	Ad26.COV2.S	1-2	0 or 0+56	IM	Janssen Pharmaceutical Johnson & Johnson	Ⅳ
	Gam-COVID-Vac	2	0+21	IM	Gamaleya Research Institute; Health Ministry of the Russian Federation	Ⅲ
	AZD1222	2	0+28	IM	AstraZeneca + University of Oxford	Ⅳ
	AD5-nCOV	1	0	IM	CanSino Biological Inc./Beijing Institute of Biotechnology	Ⅳ
Inactivated virus	Coronavac	2	0+14	IM	Beijing-based biopharmaceutical company Sinovac	Ⅳ
	BBV152	2	0+14	IM	Bharat Biotech International Limited	Ⅲ
	BBIBP-CorV	2	0+21	IM	Beijing Institute of Biological Products, China	Ⅳ
	WIBP COVID-19 vaccine	2	0+21	IM	Wuhan Institute of Biological Products, China	Ⅳ
	KCONVAC	2	0+28	IM	Shenzhen Kangtai Biological Products	Ⅲ
	VLA2001	2	0+21	IM	French biotechnology company Valneva SE in collaboration with American company Dynavax Technologies	Ⅲ
	TURKOVAC	2	0+21	IM	Health Institutes of Turkey and Erciyes University	Ⅲ
	SARS-CoV-2	2	0+28	IM	Institute of Medical Biology + Chinese Academy of Medical Sciences	Ⅲ
	QazCovid-in®	2	0+21	IM	Research Institute for Biological Safety Problems, Rep of Kazakhstan	Ⅲ
Live attenuated virus	COVI-VAC	1-2	0 or 0+28	IN	Codagenix/Serum Institute of India	Ⅲ
R\\ecombinant protein-based	NVX-CoV2373	2	0+21	IM	Novavax	Ⅲ
	ZF2001	2-3	0+28 or 0+28+56	IM	Anhui Zhifei Longcom Biopharmaceutical + Institute of Microbiology, Chinese Academy of Sciences	Ⅲ
	VAT00002	2	0+21	IM	Sanofi Pasteur + GSK	Ⅲ
	FINLAY-FR-2	2	0+28	IM	Instituto Finlay de Vacunas	Ⅲ
	EpiVacCorona	2	0+21	IM	Federal Budgetary Research Institution State Research Center of Virology and Biotechnology "Vector"	Ⅲ
	RBD	2	0+28	IM	West China Hospital + Sichuan University	Ⅲ
	CIGB-66	3	0+14+28 or 0+28+56	IM	Center for Genetic Engineering and Biotechnology in Cuba	Ⅲ
	Nanocovax	2	0+21	IM	Nanogen Pharmaceutical Biotechnology JSC	Ⅲ
	MVC-COV1901(Beta)	2	0+28	IM	Medigen Vaccine Biologics + Dynavax + National Institute of Allergy and Infectious Diseases (NIAID)	Ⅳ
	CpG 1018 (SCB-2019)	2	0+21	IM	Clover Biopharmaceuticals Inc./Dynavax	Ⅲ
	SPIKOGEN®	2	0+21	IM	Vaxine Pty Ltd./CinnaGen Co.	Ⅲ
	BECOV2	2	0+28	IM	Biological E. Limited	Ⅲ
	GBP510	2	0+28	IM	SK Bioscience Co., Ltd. and CEPI	Ⅲ
	Razi Cov Pars	3	0+21+51	IM and IN	Razi Vaccine and Serum Research Institute	Ⅲ
	Noora Vaccine		0+21+35	IM	Bagheiat-allah University of Medical Sciences/AmitisGen	Ⅲ

IM: Intramuscular; IN: Intranasal; ID: Intradermal.

current treatment schemes failed to successfully reduce mortality. Meanwhile, historical and classical interventions have emerged as therapeutic options for the treatment of COVID-19. A literature search has indicated that convalescent plasma (CP) has been used as a passive immunization strategy for hindrance and management of various infectious diseases since the early 20th century[75]. CP is collected using apheresis in patients who have survived infections and developed antibodies against the infectious agents. Given its rapid preparation, CP has been used as a useful intervention for over 100 years in various pandemics infections with viral etiology such as SARS-CoV, West Nile virus, Spanish flu, and Ebola virus. Several lines of evidence revealed that CP therapy at the early stages and after the onset of the symptoms could reduce mortality in most of the above-mentioned diseases, as compared with the placebo group[76]. Typically, viremia peaks within the first week of infection, and immune responses are usually developed in the second week following the onset of symptoms. Indeed, the induced immune response more likely leads to CRS as a lethal status in affected patients[77]. In the apheresis process, neutralizing antibodies (NAbs), anti-inflammatory cytokines, natural antibodies, clotting factors, and many other elements are obtained from survived donors[78]. The collected cp is anticipated to include sufficiently high antibody titers against the pathogen of illness, which might neutralize the targeted pathogen in recipients following transfusion, resulting in disease eradication and a favorable clinical outcome[79,80]. With such an over-activation of the immune system and subsequent systemic hyperinflammation in COVID-19, CP therapy offers a therapeutic approach in COVID-19 patients. a meta-analysis found that the administration of CP, hyperimmune globulin, or serum to patients with severe respiratory problems is a safe and effective approach[81]. Clinical studies have found several efficacies of CP administration, and more importantly, no adverse effects in recipients were noted so far. However, CP administration has its latent risk, for instance, worsening hyperimmune attacks. It is attributed to passive immunity of CP therapy and delivery of specific antibodies to those infected patients. In this context, CP fusion may be more effective in an earlier stage of infection[75]. Considering these factors, the optimal time for CP therapy must be carefully considered. The consolidated results from five studies of 27 COVID-19 patients suggest that in addition to standard care programs, CP therapy could be an effective therapeutic approach with favorable clinical outcomes. Based on these findings, CP administration results in various beneficial effects in virtually all affected patients, including a reduction in mortality, an increase in neutralizing antibodies titer and a disappearance of virus RNA. These results showed the safety and effectiveness of CP therapy in COVID-19-infected patients[82]. It is of crucial importance to note that the therapeutic efficacy of CP against COVID-19 is attributed to the level of neutralizing antibody titer.

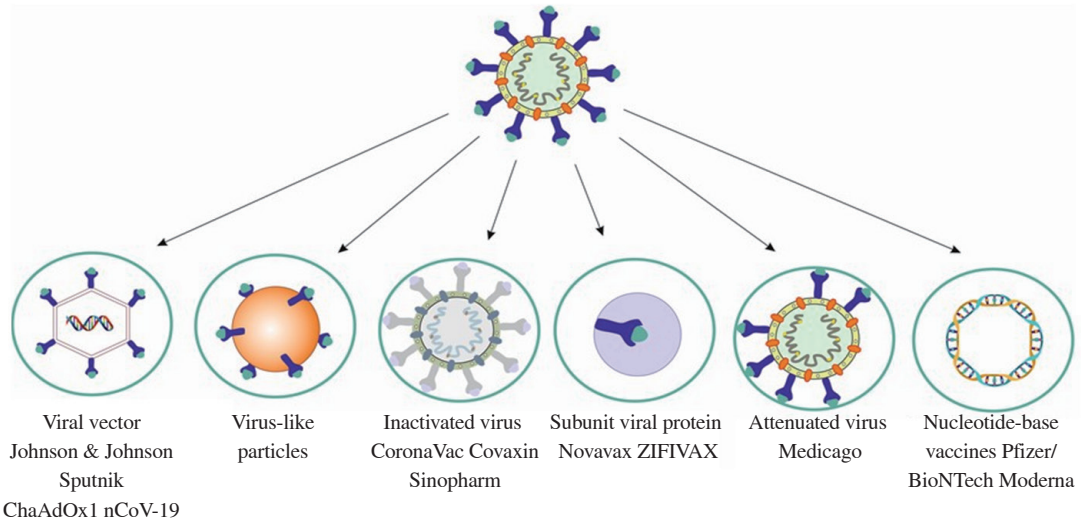

Figure 3. COVID-19 vaccine platform. Viral vector platform: Applying recombinant viral vectors which cause incompetent replication is the basis of non-replicating viral vector vaccines. These vectors are adequate to trigger an immune response in the vaccine recipient but are disabled to replicate within host cells. Virus like particle (VLP) vaccine platform: VLPs contain recurrent, dense presentations of conformational viral epitopes that evoke potent T cell and B cell immune responses. VLPs are a safer alternative to attenuated viruses due to their inability to replicate. Inactivated virus vaccine platform in which SARS-CoV-2 vaccine seed is produced (scaled up) in Vero E6 cells, chemically inactivated, and then synthesized with a particular adjuvant. Protein subunit platform in which full or portions of spike proteins, such as the receptor-binding domain, are expressed in mammalian, insect, or yeast cells, purified, and then combined with a particular adjuvant. Live-attenuated vaccine platform in which SARS-CoV-2 is engineered by reverse genetics to produce modified vaccine seed that is utilized for vaccine production in susceptible cells such as Vero E6 cells. Nucleotide base vaccine platform that instructs the cells to produce a protein or a piece of protein that triggers an immune response to produce antibodies that fight infection when a real virus enters the body.

Duan *et al*. showed that in addition to standard supportive care and antiviral drugs, one dose of CP transfusion (200 mL) in 10 patients with severe COVID-19 significantly improved clinical symptoms in terms of rapid neutralization of viremia and enhancement of oxyhemoglobin saturation. Obtained CP from recovered patients who developed humoral response/immunity against COVID-19 had a huge amount of Nabs (⩾1: 640). After the transfusion of CP, SARS-CoV-2 RNA becomes negative for all investigated patients, accompanied by an improvement in the lymphocyte counts, oxygen saturation, liver function, and CRP level. The results implied that well-tolerated antibodies of CP could potentially neutralize and eradicate SARS-CoV-2 from blood and pulmonary tissues, as well as an attenuating immune overreaction and inflammatory responses in affected patients[83]. A similar study was conducted by Shen *et al*., who investigated five patients with laboratory-confirmed COVID-19 and ARDS. The patients were treated with CP from recovered patients, containing SARS-CoV-2-specific antibodies with a titer of 1.800 up to 16.200 and the range of NAbs titers was 80 up to 480. Collecting plasma from donors and transfusing it at the same day could reduce viral loads and improve clinical status for the affected patients. Moreover, CP transfusion increased IgG and IgM titers in a time-dependent manner. It can be inferred that Nabs of CP have a vital effect on recipients and have the ability to eradicate viral infection. Being tolerable, safe, and potentially effective[84], CP therapy might be a good treatment and control method to reduce mortality and morbidity of COVID-19. Aside from the CP's importance in saving affected patients, plasma transfusion can lead to various immune-related adverse events, such as anaphylactic and hemolytic reactions, as well as transfusion-related acute lung injury. In addition, circulatory fluid overload may occur following CP infusion[85].

5. COVID–19 vaccines

The devastating consequences emphasized the emergent need to introduce effective vaccines to prevent COVID-19 and protect the high-risk population from related complications. Despite the rigorously applying control strategies such as contact tracing, testing, and isolation for symptomatic and exposed persons, wearing a mask, and social distancing to limit the transmission of the virus, it is still insufficient to prevent the spread and infection of COVID-19. Given this background, vaccines are required to decrease the morbidity and mortality caused by COVID-19[86]. Vaccine side effects are mild and affect only a small percentage of recipients. Parvej *et al*.[87] reported that socio-demographic and health-related variables impact vaccination acceptability. People are not frightened of vaccines if they experience modest side effects. These results may help governments establish efficient immunization programs[87]. According to the WHO's draft landscape of COVID-19 candidate vaccines as of mid-December 2020, among 349 COVID-19 vaccine candidates, 153 are in the clinical phase and 196 are in the preclinical phase[88]. The COVID-19 vaccines are categorized into four classes based on different platforms: 1) Nucleic acid vaccines (DNA and RNA based, 2) Protein-based vaccines (protein subunit and virus-like particle(, 3) viral vector vaccines (replicating and non-replicating), and 4) whole virus vaccines (attenuated or inactivated form)[89]. Figure 3 is schematically representing four mentioned platforms of COVID-19 vaccines. Table 1 contains all developed COVID-19 vaccines which are in phase Ⅲ and Ⅳ trials up to March 2022. In this section, we reviewed developed COVID-19 vaccines whose efficacy and safety have been proved in published data.

5.1. Nucleic acid–based vaccines

The nucleic acid-based vaccine is a new generation of vaccines that instructs the cells to produce a protein or a piece of protein that triggers an immune response to produce antibodies that fight infection when a real virus enters the body. Currently, there are six mRNA-based and two DNA-based COVID-19 vaccines in phases Ⅲ and Ⅳ (Table 1).

5.1.1. mRNA–based vaccines

5.1.1.1. Pfizer/BioNTech vaccine–BNT162b2, 4

Development of BNT162b2 by BioNTech and Pfizer was begun on January 10, 2020, when the genetic sequence of SARS-CoV-2 was released for control and prevention of the disease. It is a nucleoside-modified RNA, also known as Comirnaty[90]. This vaccine is formulated as a lipid nanoparticle[91] and encodes the full-length spike of SARS-CoV-2. Two proline mutations were modified to lock it in the prefusion conformation[20]. The protein production in cells is carried out by highly unstable mRNA. The injection of laboratory-made mRNA into cells can result in the production of pieces of proteins. Proteins leaving the cells can stimulate the body to elicit an immune reaction. Pfizer/BioNTech vaccine is developed using this approach[92]. A study performed in Germany and the United States showed that injection of 30 μg doses of BNT162b2 could elicit the production of high titer of SARS-CoV-2 neutralizing antibody, $CD8^+$, and Th1-type $CD4^+$ T-cell responses. Also, short-term local responses at the injection site and systemic responses were observed in the reactogenicity profile of BNT162b2. Assessment of efficacy, immunogenicity, and safety

of BNT162b2 in phase Ⅱ/Ⅲ of the clinical trial represented that a BNT162b2 in a two-dose regimen 21 days apart was safe with 95% efficacy against COVID-19 in recipients 16 years of age or older. While in the interval between two doses, the efficacy of the vaccine was 52%, and it reached 91% seven days after the second dose[93]. Furthermore, a low level of neutralizing antibodies was detected in people ⩾80 years as compared with the younger people[94], emphasizing the need for earlier revaccination of this group to create significant immunity against disease[95]. Polyethylene glycol was assumed to be a candidate allergen in the BNT162b2 vaccine which resulted in 2 cases of anaphylaxis on the first days of vaccination during the clinical trials[96]. Shipping and long-term storage of this vaccine require a very cold temperature, but it remains stable for up to 5 days at a standard refrigerator temperature[97].

5.1.1.2.Moderna-mRNA-1273

mRNA-1273 was developed by Moderna and the Vaccine Research Center at the National Institute of Allergy and Infectious Diseases[98]. It is an mRNA vaccine formulated as a lipid-nanoparticles expressing the prefusion-stabilized spike glycoproteins. The phase Ⅲ trial of MRNA-1273 was conducted in July 2020 at 99 centers across the United States with 30 420 volunteers who received randomly either a placebo or vaccine (1:1 ratio). The findings of this study revealed that receiving two doses of the mRNA-1273 vaccine (100 μg) 28 days apart resulted in 94.1% efficacy in preventing COVID-19 infection. Among the 30 cases of severe infection with coronavirus, one death was reported, but all of them had been given a placebo. Frequent short-term and moderate responses and rare serious adverse effects were observed in the reactogenicity profile of the mRNA-1273 vaccine. Apart from the temporary local and systematic responses, the vaccine was overall safe[86]. Although it was found that the mRNA-1273 vaccine was safe and effective, its efficacy against the rising variants of SARS-CoV-2 should be investigated[99]. This vaccine requires to be stored in refrigerated condition; however, it is stable at room temperature up to 8 hours before injection[86].

5.1.1.3. mRNA-1273.351.

mRNA-1273.351 is a new lipid nanoparticle (LNP)-encapsulated mRNA-based vaccine encoding for a full-length, prefusion-stabilized S protein of the SARS-CoV-2 B.1.351 variant. It was developed by Moderna and the Vaccine Research Center at the National Institute of Allergy and Infectious Diseases. Neutralizing antibody titers against B.1.351 variant were lowered 2.1 to 8.4-fold in eight mRNA-1273 phase Ⅰ study subjects. A protective antibody titer threshold for SARS-CoV-2 in humans is unclear. Reduced in vitro neutralizing antibody titers against variations compared to the wild-type D614G virus enhances the likelihood of breakthrough infections and fading vaccination effectiveness. To address this concern, updated versions of the prototype mRNA-1273 vaccine with the variant S protein's genetic sequence were developed with the name of mRNA-1273.351. Variant vaccinations activate an immune response against changed neutralizing sites on the S protein of variant viruses and, in the event of a multivalent vaccine, the wild-type strain. Data from an exploratory interim analysis of the preliminary safety and immunogenicity of single booster doses of modified mRNA-1273.351 (25 μg) revealed that it was safe and well-tolerated and increased neutralization titers against B.1.351variant[100].

5.1.1.4. CureVac-CVnCoV

CVnCoV vaccine was developed by a German biopharmaceutical company, CureVac AG, using mRNA-based technology and formulated as lipid nanoparticles. Despite hopeful consequences of phase Ⅰ and Ⅱ, insufficient results (only 47% efficacy) were achieved in phase Ⅲ in Europe and Latin America[101]. According to the European Medicines Agency statements, at least 50% efficacy is needed for a developed vaccine[102].

5.1.1.5.Walvax COVID19-ARCoV

The first mRNA-based vaccine was developed in China by Walvax Biotechnology, Suzhou Abogen Biosciences known as Walvax COVID-19 vaccine. This product is formulated as a liquid nanoparticle that is stable in refrigerated conditions for six months. However, the Abogen Company also produces solid lipid nanoparticles to facilitate transportation. According to the findings of phase Ⅰ clinical trials, ARCoV was safe and well-tolerated, inducing strong humoral and cellular immune responses that supported large-scale evaluations of safety and efficacy. Phase Ⅲ trial was started in May 2021 in Mexico with more than 6 000 participants. This phase's efficacy data has not yet been released[103].

5.1.1.6. ARCT-154

ARCT-154, also known as VBC-COV19-154 in Vietnam, is a COVID-19 vaccine candidate. Vinbiocare, a Vietnamese company, helped Arcturus with manufacturing and clinical trials. This self-amplifying mRNA vaccine needs two doses, 28 days apart. The vaccine candidate can be prepared as a lyophilized powder and kept between 2-8 ℃. Phase Ⅲ placebo-controlled vaccination efficacy research included 16 000 participants. The trial fulfilled its main aim of preventing virologically proven COVID-19 illness. In an analysis of COVID-19 cases collected between 7 and 56 days following a

two-dose vaccination series, two 5-μg doses of ARCT-154 exhibited 55% vaccine efficacy for protection against COVID-19[104].

5.1.2. DNA-based vaccines

5.1.2.1. ZyCoV-D

The first DNA-based vaccine against COVID-19 is ZyCoV-D developed by Zydus Cadila in India. Applying the SARS-CoV-2 virus gene containing non-integrating and non-replicating plasmid in its formulation has made it safe. ZyCoV-D is a three-dose vaccine designed to apply intradermally using PharmaJet® needle-free system that significantly reduces side effects[105]. The vaccines produced using DNA-based platforms are known to be more stable with no need for special cold chain requirements. Phase Ⅰ-Ⅱ study occurred in India in July-October 2020. Healthy persons aged 18 to 55 were successively recruited and assigned to one of four treatment arms [Arm 1 (1 mg: Needle), Arm 2 (1 mg: Needle-Free Injection System (NFIS), Arm 3 (2 mg: Needle), and Arm 4 (2 mg: NFIS)] in a dose-escalation manner. Each patient was monitored for 28 days after the third vaccination dosage to assess safety and immunogenicity. According to the results of phase Ⅰ part of the phase Ⅰ-Ⅱ study, ZyCoV-D vaccine was safe, well-tolerated, and immunogenic and no fatalities or significant adverse events were reported[105]. In addition, the effectiveness of the ZyCoV-D vaccination was determined to be 66% in phase Ⅲ clinical studies including 600 participants aged 12 to 17 years and 60 years or older. At the data cutoff, two fatalities were recorded; none of these were deemed to be connected to the research therapies[106]. The developed vaccine remains stable at 2-8 ℃ and even at room temperature for at least three months. The thermal stability of ZyCoV-D facilitates its transportation and minimizes vaccine wastage due to a breakdown in the cold chain[105].

5.1.2.2. INO-4800

Inovio Pharmaceuticals has developed the Inovio COVID-19 vaccine with the code name of INO-4800. It is a DNA vaccine that encodes the SARS-CoV-2 S-protein and administered intradermally using the CELLECTRA® electroporation delivery technology, and it promotes a balanced immune response including T and B cells. In April 2020, the company initiated phase Ⅰ safety trials on humans for its lead vaccine in the United States. The findings of the phase Ⅰ clinical study demonstrated that the vaccine was safe and well-tolerated, with only grade 1 adverse event recorded and no increase in adverse events after dose two. Two doses of INO-4800 result in a heightened immunological response without further reactogenicity. After receiving the second vaccination dosage, all volunteers developed an anti-spike immune response[107]. Inovio teamed with South Korea, Seoul National University, and International Vaccine Institute to further human research on INO-4800 in a phase Ⅰ-Ⅱ safety and efficacy study on 120 individuals. It was found that INO-4800 at 1.0 mg and 2.0 mg dosages in a 2-dose regimen was safe and well-tolerated in all adult ages. Comparative immunogenicity favors INO-4800 2.0 mg dosage for phase Ⅲ efficacy investigation[108]. Inovio INO-4800 was the first DNA vaccination launched in the biggest vaccine trial in history. Philippines, Mali and Colombia declared participation, with many more to be named. The WHO directly funds this study as a global COVID-19 trial called the Solidarity Trial Vaccines. Andrade *et al*. observed INO-4800 immunization elicited neutralizing antibodies against all variants tested, with lower levels against B.1.351. Interferon gamma (IFN-γ) T cell responses were maintained against all variations tested[109].

5.2.Viral vector-(non-replicating) vaccines

Applying recombinant viral vectors which cause incompetent replication is the basis of non-replicating viral vector vaccines. These vectors are adequate to trigger an immune response in the vaccine recipient but are disabled to replicate within host cells[89]. There are currently four non-replicating viral vector COVID-19 vaccines in phases Ⅲ and Ⅳ which are described as follows:

5.2.1. Johnson & Johnson/Janssen (J&J)-Ad26.COV2.S

American company Johnson & Johnson developed a viral vector vaccine named Johnson & Johnson COVID-19 vaccine which is also called Janssen COVID-19 vaccine. Its platform is based on a modified human adenovirus, containing genes to produce the SARS-CoV-2 spike protein, to which the immune system produces antibodies. According to the data of phase Ⅲ trials on January 2021, one dose of vaccine has 64% and 81.7% effectiveness to prevent moderate and severe/critical COVID-19 at least 28 days after administration, respectively. Mild to moderate adverse reactions with Johnson vaccine was higher than placebo[110]. Some reports of cerebral venous sinus thrombosis with thrombocytopenia have been received after the vaccineation[111], which is associated with IgG antibodies that recognize PF4 and activate platelets through their Fcγ receptors[112]. It is a one-dose regimen vaccine and is stable in refrigerated conditions[113]. Currently, the vaccine is in phase Ⅳ of the clinical trial for further assessment.

5.2.2. Sputnik V- Gam-COVID-Vac

Gamaleya Research Institute of Epidemiology and Microbiology of the Russian Federation developed a combined vector vaccine

against COVID-19 named Sputnik V, in which V stands for victory against COVID-19. On 11 August 2020, it was registered as Gam-COVID-Vac by the Russian Ministry of Health[114]. Gam-COVID-Vac is a two-vector adenovirus vaccine consisting of recombinant replication-deficient adenovirus types 26 and 5 containing the genes that encodes full-length glycoprotein S of SARS-CoV-2. Among the developed viral vector vaccines to date, only Gam-COVID-Vac uses the different serotypes in each dose; others use the same one in both doses and need to be injected in a 21-day interval[115]. Adenoviral vector-delivered antigens mediate both humoral and cellular immunity, therefore, they can be used as an urgent tool for the prevention of COVID-19. In addition, long-term immunity was achieved by the two-dose regimen. The results of the phase Ⅰ/Ⅱ clinical trials revealed that the vaccine highly stimulated immunogenic response and was well-tolerated in healthy volunteers. Furthermore, the results were obtained from placebo-controlled, double-blind, and randomized phase Ⅲ trials conducted at 25 hospitals and polyclinics in Moscow, Russia with 21 977 participants aged 18 years or older to evaluate the efficacy and safety of this vaccine. According to their results, a robust cellular and humoral immunity along with 91.6% efficacy to prevent COVID-19 disease is achieved by two doses of vaccination (0.5 mL/dose). Asthenia, headache, injection site reactions and flu-like illness were the prevalent reported adverse events. A total of 0.3% of participants (in both placebo and vaccine groups) reported serious adverse events with a need for hospital admission, and four deaths (in placebo and vaccine groups) with no relation to the vaccine[116]. Although storage and distribution of the vaccine is required to be performed at –18 ℃, the Ministry of Health of the Russian Federation approved refrigerated conditions for global distribution of the vaccine[115].

5.2.3. ChAdOx1 nCoV-19 vaccine-AZD1222

The ChAdOx1 nCoV-19 vaccine was developed at Oxford University with the code name AZD1222. It is composed of a replication-deficient chimpanzee adenoviral vector ChAdOx1, containing the full-length SARS-CoV-2 structural surface glycoprotein (spike protein; nCoV-19) gene. To assess the efficacy of the developed vaccine, four controlled trials were conducted in the UK, South Africa, and Brazil with 11 636 participants, indicating that two-dose regimen of the vaccine was 70.4% effective against COVID-19[116]. Also, data from the phase Ⅰ/Ⅱ trial of the ChAdOx1 nCoV-19 vaccine was conducted on 1 077 participants aged 18-55 years. All participants received (1:1) either ChAdOx1 nCoV-19 or meningococcal conjugate vaccine (MenACWY) as control. The achieved data showed that injection of two doses of the vaccine with a 28-day interval led to an increase in anti-spike IgG responses following the second dose. In addition, 91% and 100% of participants were found to have neutralizing antibody responses, as measured by MNA80 (micro-neutralization test) and plaque-reduction neutralization test (PRNT50), respectively. Furthermore, neutralizing activity was detected in all participants after the second dose. The ChAdOx1 nCoV-19 research team found that paracetamol can prevent some local and systematic adverse events after vaccination, including headache, muscle ache, chills, feeling feverish, pain, and malaise. Severe adverse events have not been reported yet. Induction of humoral and cellular immunity as well as acceptable safety profile, support large-scale evaluation of ChAdOx1 nCoV-19 in phase Ⅲ trial in three groups: participants in the age of 18-55, 56-69, and ≥70 years, with an emphasis on safety and immunogenicity evaluation in older adults (above 70 years) who are more at the risk of serious diseases and even death[117]. The data revealed that although the frequency of systemic and local adverse effects in participants ≥56 years was less than in younger participants, similar titers of neutralizing antibody were observed after a second dose across all age groups. Neutralizing antibody responses were detected in >99% of participants after 14 days of second dose injection. Furthermore, T-cell responses increased to a maximum level 14 days after a single dose of AZD1222. Among 13 serious adverse events reported, none were related to the vaccination[118]. It should be noted that receiving two doses of the vaccine in COVID-19 infected patients will not protect against B.1.351 variant, which is recognized in South Africa with three mutations in the receptor-binding domain and five mutations in the *N*-terminal domain[116].

5.2.4. Convidecia-AD5-nCOV

Convidecia, with the registered name of AD5-nCOV (adenovirus type 5 vector) is a single-dose, viral vector-based vaccine developed by CanSino Biologics in China. It was safe and triggered a significant immunity level according to phase Ⅱ trial's data. Severe adverse effects were observed in only 1% of participants in the vaccine-receiving group, and no serious adverse events were recorded in this regard[119]. According to data from the phase Ⅲ trials in February 2021, the vaccine was 65.7% effective in preventing moderate symptoms against COVID-19, and 91% effective in preventing severe disease. AD5-nCOV is now in phase Ⅳ clinical trial for further evaluation[119].

5.3. Inactivated virus

Inactivated vaccines contain the destroyed genetic material of viruses which can trigger an immune response but are disabled to

replicate and infect the cells[89]. There are currently six inactivated COVID-19 virus vaccines in phases Ⅲ and Ⅳ:

5.3.1. CoronaVac

CoronaVac is an inactivated SARS-COV-2 vaccine (Vero cell) developed by Beijing-based biopharmaceutical company Sinovac. Intramuscular injection of Coronavac (in a two-dose regimen) at a concentration of either 3 μg or 6 μg created moderate immune responses in volunteers aged 18-59 years. The rate of adverse events in various dosage groups (3 μg or 6 μg) was similar, suggesting no dose-related safety risk. Moreover, most adverse responses were minor and temporary, and injection site pain was the most reported symptom[119]. According to the pre-clinical results, the safety of the developed vaccine in phase Ⅰ (vaccine produced using a cell factory process) and phase Ⅱ (vaccine produced using a bioreactor process) was similar, while much better immunity was achieved in phase Ⅱ as compared with phase Ⅰ. More than 90% seroconversion rate was recorded in phase Ⅱ for both concentrations (3 μg and 6 μg) in volunteers in both age groups (18-59 and older than 60 years). Considering acceptable immunogenicity, safety, and production capacity, Coronavac vaccine containing 3 μg in inactivated viruses was selected for large-scale efficacy assessment in phase Ⅲ trial in China, Brazil, Indonesia, and Turkey[120]. The vaccine efficacy in the range of 50.4% to 91.25% was recorded following phase Ⅲ clinical trials in Brazil, Indonesia, and Turkey[121]. Furthermore, according to the study conducted with 550 participants, there were no safety concerns for children aged 3-17 years[122].

5.3.2.Covaxin–BBV152

Baharat Biotech used traditional techniques to develop inactivated virus-based vaccine named Covaxin registered with the codename of BBV152. For this purpose, large amounts of the SARS-CoV-2 were grown by Vero cells using isolated samples of the virus. Beta-propiolactone was applied to bind the virus genes and deactivate them and other particles of the virus left intact. An aluminum-based adjuvant that generates a response in bias to T-helper-2 is used to mix with the obtained inactivated viruses. It should be noted that induction of T-helper-1 response by any vaccine against COVID-19 such as BBV152 is a favorable feature[123]. According to the findings of phase Ⅰ trial, among three initial formulations including 3 μg with Algel-IMDG, 6 μg with Algel-IMDG, or 6 μg with Algel, injection of two doses of both Algel-IMDG formulation with a 14-day interval could highly stimulate immunogenic response and also were well tolerated, thus selected for phase Ⅱ clinical trial in which two doses of selected formulation were injected with a 28-day interval[123]. Titers of neutralizing antibodies and rates of seroconversion (at least four-fold higher post-vaccination titer than baseline titer) after 56 days of second dose injection were measured by plaque-reduction neutralisation test (PRNT50) and the microneutralisation test (MNT50) and was recorded as primary outcomes of vaccination by BBV152. The findings showed that the geometric mean titers (GMTs) based on PRNT50 and MNT50, as well as seroconversion based on PRNT50 and MNT50, in the 6 μg with Algel-IMDG group were greater than those in the 3 μg with Algel-IMDG group. However, the rate of local or systemic adverse events had no significant difference in both groups. Furthermore, it was observed no serious adverse effects in the study. Enhanced cellular and humoral immunity and better safety and reactogenicity consequences in the phase Ⅱ trial of the BBV152 vaccine were obtained compared with the phase Ⅰ trial. The phase Ⅲ efficacy trial was conducted with the 6 μg with Algel-IMDG formulation as the selectedformulation[123]. The developed vaccine remained stable at refrigerated conditions (2-8 ℃) compatible with the immunization system of most countries.

5.3.3. Sinopharm– BBIBP–CorV

Beijing Institute of Sinopharm in China developed a vaccine named BBIBP-CorV manufactured using the whole inactivated virus. This vaccine is made by similar technology with Covaxin and Coronavac and is called Sinopharm COVID-19 vaccine. Along with BBIBP-CorV development, Wuhan Institute of Biological Products Co., Ltd. developed another chemically-inactivated whole virus vaccine for COVID-19, both belong to Sinopharm. Clinical trials of both Sinopharm vaccines were approved in April 2020. The data of phase Ⅰ and Ⅱ of clinical trials performed on October 2020 with 192 and 448 participants, respectively, revealed that all examined doses of BBIBP-CorV vaccine were safe and well-tolerated. Moreover, titers of SARS-CoV-2 neutralizing antibodies were evoked in adults older than 60 after 42 days of vaccination. On August 2020, phase Ⅰ and Ⅱ clinical studies of the first Sinopharm vaccine demonstrated adequate immunogenicity and low adverse effects. Further efficacy evaluation in phase Ⅲ was completed in United Arab Emirates, Peru, Pakistan, Morocco, Egypt, Bahrain, and Argentina with more than 60 000 vaccine recipients. In December 2020, it was announced by Sinopharm that the efficacy of Sinopharm's first vaccine was 79%, according to the results of phase Ⅲ trials. At the same time, its efficacy was reported about 86% by the United Arab Emirates. Sinopharm also announced that the efficacy of the second vaccine is slightly lower (about 72.5%)[121]. Although the efficacy of BIBP-CorV is lower than mRNA vaccines such as BNT162b2,4 and mRNA-1273 (their efficacy was >90%), it can be stored and distributed in normal refrigerated conditions without the need to

freeze or deep-freeze facilities. Therefore, BIBP-CorV can be a favorable vaccine option in the developing world[17,121].

5.3.4. Minhai COVID-19 vaccine-KCONVAC

Shenzhen Kangtai Biological Products Co., Ltd. developed a fourth inactivated Chinese vaccine named Minhai COVID-19 vaccine with the trade-mark of KCONVAC®. The phase Ⅰ clinical trial conducted with adults aged 18 to 59 years revealed that all reported adverse events were grade 1 or 2. One case of foot fracture was also observed in the phase Ⅰ trial. Also, the vaccine elicited a significant level of T-cell response 14 days after the second shot in participants receiving 5 μg or 10 μg vaccine representative of positive interferon-γenzyme-linked immunospot responses. Based on acceptable safety, tolerability, and immunogenicity of KCONVAC, phase Ⅲ clinical trial of this vaccine has been begun in Malaysia at eight research centers with over 3 000 participants aged ≥18 years old[124].

5.3.5.Valneva-VLA2001/VLA2101

Another inactivated COVID-19 virus vaccine was developed by French biotechnology company Valneva SE in collaboration with American company Dynavax Technologies named Valneva with the code name of VLA2001 and VLA2101. It was manufactured using inactivated-virus technology in which virus is grown using the Vero cell line, inactivated with beta-propiolactone. CpG 1018 and aluminum were used as two adjuvants in its formulation. Phase Ⅰ/Ⅱ trials were successfully undergone in the United Kingdom and the vaccine efficacy, safety, and immunogenicity were verified. The phase Ⅲ trials of the vaccine were commenced On August 2021 for further assessment[125].

5.3.6. WIBP COVID-19 vaccine

One of the two inactivated viral COVID-19 vaccines created by Sinopharm is the WIBP COVID-19 vaccine, commonly known as WIBP-CorV. Another COVID-19 vaccine developed by Sinopharm (BBIBP-CorV), is much more effective. Both vaccines are chemically-inactivated whole viral vaccines for COVID-19. On August 13, 2020, the Wuhan Institute of Biological Products announced interim phase Ⅰ (96 participants) and phase Ⅱ (224 participants) clinical study data. The vaccination exhibited a low rate of adverse reactions and showed immunogenicity, In May 2021, peer-reviewed findings of phase Ⅲ studies in United Arab Emirates and Bahrain indicated the vaccination is 72.8% effective against symptomatic cases and 100% effective against severe cases[126].

5.4. Protein-based vaccines

Subunit and virus-like particle vaccines are two types of protein-based vaccines. Protein subunit vaccines are composed of antigenic components of a pathogen that trigger an immune response and may be manufactured by recombinant protein techniques. Although compared with whole virus vaccines, this type of vaccine is relatively safe, well-tolerated, and easy to manufacture, yet they are more expensive due to the requirement for specific adjuvants to improve immunogenicity[89]. In this case, empty virus shells are used to produce virus-like particles that are similar to the coronavirus structure without genetic material so they are noninfectious[127]. The protein subunit and virus-like particle COVID-19 vaccines in phase Ⅲ and Ⅳ are as following:

5.4.1. Protein subunit vaccines

5.4.1.1. Novavax COVID-19- NVX-CoV2373

Novavax Company developed recombinant protein-based vaccines named Novavax COVID-19 vaccine with the registered name of NVX-CoV2373. It is formulated using the full-length SARS-CoV-2 glycoprotein nanoparticle, adjuvanted with matrix M and is stable in refrigerated conditions. It was reported that a two-dose regimen of the vaccine had 89.7% effectiveness to prevent SARS-CoV-2 infection[128], and it alsodemonstrated high efficacy against the B.1.1.7 variant[128]. Regarding accepted safety and efficacy in phases Ⅰ and Ⅱ, phase Ⅲ was initiated in the US and Mexico with participants aged ≥18 years on December 2020. On May 2021, the phase Ⅲ clinical trial was conducted with 3 000 participants aged 12-17 years.

5.4.1.2. ZIFIVAX- ZF2001

A protein-based vaccine named RBD-Dimer or ZIFIVAX was developed by Anhui Zhifei Longcom Biopharmaceutical in collaboration with the Institute of Microbiology, Chinese Academy of Sciences with the codename of ZF2001. It encodes the SARS-CoV-2 RBD in a dimeric form as the antigen and was produced in the Chinese hamster ovary (CHO) cell lines. ZIFIVAX is the three-dose regimen vaccine manufactured as the liquid formulation adjuvanted with aluminum hydroxide. Considering its significant safety, efficacy, and immunogenicity data from phase Ⅰ and Ⅱ trials, it is under large-scale evaluation in phase Ⅲ in China, Ecuador, Malaysia, Pakistan, and Uzbekistan[129].

5.4.1.3. FINLAY-FR-2

The Finlay Institute, a Cuban epidemiological research institute, in cooperation with the Pasteur Institute of Iran, produced Soberano 02 (Soberana 2) with the technical name FINLAY-FR-2. It is a conjugate vaccine in which the RBD of SARS-CoV-2 spike protein (produced in Chinese hamster ovary cell) is chemically attached to the tetanus toxoid plus adjuvant. Since October 30, 2020, the

clinical trials of the vaccine have been started. According to the obtained results, injection of two doses created 62% efficacy, and efficacy of 91.2% was achieved after injection of a booster dose. Iranian officials from the Pasteur Institute supervised the second phase, and phase Ⅲ is currently being undergone in Iran in 8 centers with a sample size of 24 000 people. Protective and long-lasting immunity is the remarkable advantage of conjugated polysaccharide vaccines such as Soberana 02 especially in the population under two years old who showed poor immune response after injection of unconjugated polysaccharide vaccines. Therefore, based on phase Ⅰ/Ⅱ trial results, the emergency use of Soberena 02 was requested for vaccination of the population between 3 and 18 years of age on August 27, 2021. On September 5, 2021, the vaccination of this age group began in the province of Cienfuegos, Cuba[130].

5.4.1.4. EpiVacCorona

EpiVacCorona is a protein subunit vaccine developed by the Federal Budgetary Research Institution State Research Center of Virology and Biotechnology "Vector" in Russia. It contains three synthetic peptides (small fragments of SARS-CoV-2 spike protein) conjugated to a carrier protein and adsorbed on aluminum hydroxide[131]. The results of phase Ⅰ/Ⅱ clinical trials conducted with 14 participants aged 18-30 years in phase Ⅰ and 86 participants aged 18-60 years in phase Ⅱ showed that the intramuscular injection of two doses with a 21-day interval induced the antibody production in response to the vaccines antigens and seroconversion with a neutralizing antibody titer ⩾1:20 in 100% of the participants. The vaccine was also reported safe, and only mild local reactions such as mild injection-site pain were observed. on November 2020, the phase Ⅲ clinical trials were initiated with more than 3 000 participants[132].

5.4.1.5. Nanocovax

Nanogen Pharmaceutical Biotechnology JSC in Vietnam developed a recombinant protein subunit COVID-19 vaccine named Nanocovax consisting of full-length prefusion spike glycoproteins (S-2P) of SARS-CoV-2 with an aluminum adjuvant. Phase Ⅰ and Ⅱ clinical trials conducted with 60 and 480 volunteers showed limited grade 1 adverse events disappearing in less than 3 days. The robust anti-S-IgG response was induced as injection of two doses of vaccine (25 μg). It was reported the vaccine had more than 90% efficacy to prevent SARS-CoV-2 infection 42 days after the first dose and 14 days after the second dose. Phase Ⅲ of clinical trials began in June 2021 with 13 000 participants in both Vietnam and other Asian countries[133].

5.4.2. Virus-like particle

5.4.2.1. Medicago-CoVLP

A virus-like particle (VLP) of the coronavirus was developed by Medicago Biopharmaceutical Company. The genetic sequence of the SARS-CoV-2 encoding the spike protein was inserted into Agrobacterium, a soil phytopathogen that naturally infects plants. The infected plants produce VLP containing the spike protein of COVID-19. Nicotiana benthamiana plant was used by Medicago Inc. to generate the SARS-CoV2 virus VLPs. The VLPs possess a similar shape and size with the real virus without nucleic acid and, therefore, are noninfectious[134]. Phase Ⅰ clinical trials of Medicago have been completed successfully, and phase Ⅱ/Ⅲ of the clinical development was started on November 12, 2020 to complete the development program founded by the Canada government. According to obtained results, CoVLP demonstrated excellent safety and tolerability and was immunogenic. According to Health Canada's National Advisory Committee on Immunization, CoVLP showed 69.5% effectiveness against laboratory-confirmed, symptomatic SARS-CoV-2 infection commencing at least seven days following the second dose of the vaccine[135]. The cost of producing a plant-made vaccine based on VLPs is a small fraction compared to its conventional counterpart[134].

6. Limitations of this review

The review is not a systematic review and is susceptible to selection bias. Numerous new and diverse trials are listed in the paper. However, insufficient risk-benefit data could not be collected for them. The majority of the suggested therapeutic approaches are also not standardized. Furthermore, only four groups, including monoclonal antibodies, anti-TNFs, convalescent plasma, and vaccines, were reviewed among the various biopharmaceuticals used in the treatment and prevention of COVID-19 virus infection. These groups included cytokines (interferons, interleukins, colony-stimulating factors, tumour necrosis factors), erythropoietins, plasminogen activators, blood plasma factors, growth hormones and growth factors, insulins. Additionally, developed COVID-19 vaccines in phases Ⅲ and Ⅳ were reviewed among the 349 COVID-19 vaccine candidates in clinical and preclinical trials.

7. Conclusions

The devastating consequences of COVID-19 infection emphasized the need for using antiviral agents to treat outpatients at the initial stage of the disease. It was found that the administration of CP to

patients with severe respiratory problems is a safe and effective approach. IL-6 inhibitor mAbs such as sarilumab were effective in critically COVID-19 ill patients. There have been a growing number of independent studies reported that the administration of human IL-1 receptor antagonist protein such as anakinra reduced mortality and the need for invasive mechanical ventilation. Anti-TNF antibodies such as infliximab and adalimumab clinically met the safety and efficacy profiles for the treatment of hospitalized COVID-19 infected patients. However, up to now, no large-scale randomized placebo-controlled studies have introduced safe and effective antiviral agents to fight against the disease. It is strongly recommended to avoid the use of antiviral agents until their safety and efficacy are completed and analyzed in the clinical trial evaluations as some of them such as anti-cytokine treatment could be potentially harmful during the stage of viral replication. Also, the production scale of these biopharmaceuticals can not meet the need for all patients. So, treatment of outpatients with mild symptoms at the initial stage of COVID-19 infection seems necessary. In 2021, the approval of the vaccines against COVID-19 was hopeful to prevent the spread of the disease all over the world. However, the efficacy of developed vaccines against various variants of SARS-CoV-2 is challenging[136,137]. At this time, the best option currently is fast and universal vaccination along with further studies to develop effective vaccines against new generations of variants. To stop SARS-CoV-2, solely hope for mass vaccination is unwise. Besides, rigorous applying control strategies such as contact tracing, testing and isolation for symptomatic and exposed persons, wearing a mask, and social distancing, maintaining the maximum standard of health and hygiene, and educating people about the hazards of the disease are necessary methods to limit the transmission of the virus.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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Authors' contributions

A.F. writing original draft, review & editing; S.M. writing original draft, investigation; S.R.S. writing original draft, investigation; P.A. conceptualization, review & editing, supervision; S.S. writing original draft. The manuscript has been read and approved by all the authors.

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