Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Process Biochemistry 118 (2022) 154–170

Contents lists available at ScienceDirect

Process Biochemistry

journal homepage: www.elsevier.com/locate/procbio

Clinical progress of therapeutics and vaccines: Rising hope against COVID-19 treatment

Ravi Bandaru [a], Smruti Rekha Rout [a], Omkar S. Kamble [a], Sangram K. Samal [b], Bapi Gorain [c], Amirhossein Sahebkar [d,e], Farhan J. Ahmed [f], Prashant Kesharwani [f,*], Rambabu Dandela [a,*]

[a] Department of Industrial and Engineering Chemistry, Institute of Chemical Technology, Indian oil Odisha Campus, Samantpuri, Bhubaneswar 751013, India
[b] Laboratory of Biomaterials and Regenerative Medicine for Advanced Therapies, Indian Council of Medical Research-Regional Medical Research Center, Bhubaneswar 751023, India
[c] Department of Pharmaceutical Sciences and Technology, Birla Institute of Technology, Mesra, Ranchi 835215, India
[d] Biotechnology Research Center, Pharmaceutical Technology Institute, Mashhad University of Medical Sciences, Mashhad, Iran
[e] Applied Biomedical Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
[f] Department of Pharmaceutics, School of Pharmaceutical Education and Research, Jamia Hamdard 110062, New Delhi, India

ARTICLE INFO

Keywords:
COVID-19
Clinical research
Repurposing
COVID-19 vaccines
SARS-CoV-2
Passive immunization
Hyper immune serum preparations

ABSTRACT

Cases of deaths due to COVID-19 (COrona VIrus Disease-19) infection are increasing gradually worldwide. Immense research is ongoing to control this pandemic condition. Continual research outcomes are indicating that therapeutic and prophylactic agents are the possible hope to prevent the pandemic from spreading and to combat this increasing death count. Experience gained from previous coronavirus infections (eg., SARS (Severe Acute Respiratory Syndrome), MERS (Middle Ease Respiratory Syndrome), accumulated clinical knowledge during this pandemic, and research helped to identify a few therapeutic agents for emergency treatment of COVID-19. Thereby, monoclonal antibodies, antivirals, broad-spectrum antimicrobials, immunomodulators, and supplements are being suggested for treatment depending on the stage of the disease. These recommended treatments are authorized under medical supervision in emergency conditions only. Urgent need to control the pandemic condition had resulted in various approaches of repurposing the existing drugs, However, poorly designed clinical trials and associated outcomes do not provide enough evidence to fully approve treatments against COVID-19. So far, World Health Organization (WHO) authorized three vaccines as prophylactic against SARS-CoV-2. Here, we discussed about various therapeutic agents, their clinical trials, and limitations of trials for the management of COVID-19. Further, we have also spotlighted different vaccines in research in combating COVID-19.

1. Introduction

The spreading of a novel strain of coronavirus, Severe Acute Respiratory Syndrome CoronaVirus-2 (SARS-CoV-2), has contributed to the outbreak of a new pandemic condition. The disease caused by this virus particle has been named COrona VIrus Disease-2019 or, in short, COVID-19 by the World Health Organization (WHO) [1]. Infection of this virus is known to cause an acute respiratory disease, which was first reported in Wuhan, Hubei province, China in December 2019 [2]. COVID-19 has been identified as a zoonotic disease and subsequent epidemiological studies suggested that the outbreak of the disease might be associated with a local seafood market in Wuhan [3,4]. Many of the scientific communities worldwide are pointing towards purposeful manipulation of the virus particle within the laboratory [1,5–7], with unknown motives. The etiological agent was isolated from the broncho-alveolar lavage fluid of the infected patients at the early stage of this pandemic spread and metagenomic analysis of the pathogen genome revealed that it is closely related to the *severe acute respiratory syndrome-related coronaviruses (SARS-CoV),* which belong to the family *Coronaviridae* [2–4]. The comparative sequence analyses of replicative proteins of the virus by the Coronaviridae study group, a research group of the International Committee on taxonomy of viruses, identified it as a new species of *SARS-CoV*. Sequential analysis at the whole-genome level of this novel Corona virus (CoV) showed 76.9% sequence identity with SARS-CoV.

* Corresponding authors.
E-mail addresses: prashantdops@gmail.com (P. Kesharwani), r.dandela@iocb.ictmumbai.edu.in (R. Dandela).

https://doi.org/10.1016/j.procbio.2022.04.011
Received 30 July 2021; Received in revised form 11 March 2022; Accepted 8 April 2022
Available online 14 April 2022

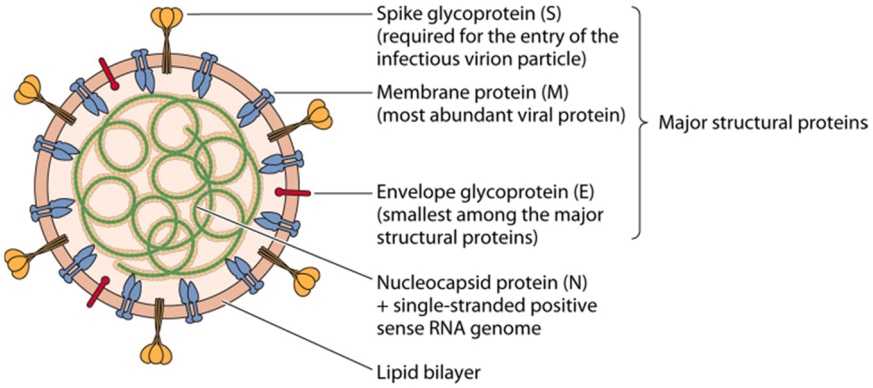

Fig. 1. Crown structure of Corona Virus [173].

Because of the similarity with SARS-CoV, this novel viral particle is designated as SARS-CoV-2. This virus belongs to the realm *Riboviria*, order *Nidovirales*, suborder *Cornidovirineae*, family *Coronaviridae*, genus *betacoronavirus*, and the subgenus *Sarbicovirus* [8]. SARS-CoV-2 is a positive-sense single-stranded RNA virus, which is round or oval and approximately 60–140 nm in size. It is the seventh coronavirus known to cause infection in human beings. The other six viruses are HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1, SARS-CoV and MERS-CoV. The last two viruses in the previously mentioned list are responsible for the 2002 and 2013 outbreaks, severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), respectively, whereas HCoV-229E, HCoV-OC43, HCoV-NL63 and HCoV-HKU1 are associated with mild symptoms in humans [1,9]. Spike proteins on the surface of the virus particles give the appearance of a crown under electron microscope (Fig. 1) [10]; hence it has been named coronavirus [1,11].

Since SARS-CoV-2 is a respiratory tract pathogen, the infection starts by inhaling virus-contaminated droplets released by an infected person through coughing or sneezing. The infection can also result through hands by touching contaminated areas and body parts, such as eyes, nose, mouth, etc. Spike proteins (S-protein) of the inhaled pathogens interact with angiotensin converting enzyme-2 (ACE2) receptors, which are highly expressed surface receptors on the respiratory epithelium, alveolar monocytes, vascular endothelium, intestine, and kidneys [4]. Interaction with the receptor followed by cell entry leads to replication of the virus inside the cell. After that, the virus particles are released from the infected cells in large numbers, which causes further infection to the other healthy cells to proliferate further. [3,12]. Incubation period of this virus in the human body is 14 days from the point of infection with an average of 3–7 days for the onset of symptoms. Based on severity of symptoms, the clinical presentation of SARS-CoV-2 infection can be classified into different categories such as uncomplicated illness, mild pneumonia, severe pneumonia, Acute Respiratory Distress Syndrome (ARDS), sepsis, and septic shock. Uncomplicated illness is characterized by non-specific symptoms like fever, headache, muscle pain, cough, sore throat, fatigue, loss of smell, etc. [13]. Clinical progression to severe conditions mainly depends on the association of comorbidities and risk factors [3,13]. According to the WHO report, 15% of the COVID-19 patients progress to severe stage for whom clinical assistance is needed. The severity of the disease is not only due to virus infection but also due to associated host responses. Infection, replication, and release of the virus (cytopathic pathogen) inside the alveolar cells have been shown to cause damage (pyroptosis) to the host cells, which triggers cytokines release, including IL-1, IL-18, GM-CSF, TNF, etc. [14]. Released cytokines induce inflammatory responses at the infection site, which leads to the killing of the infected cells and controlling the virus infection [15]. However, in some patients, uncontrolled release of inflammatory cytokines (dysfunctional immune system) leads to tissue damage, which increases disease severity [14,15]. Several risk factors contribute to clinical progressions of COVID-19, such as old age, diabetic condition, immunocompromised system, and other underlying co-morbidities. Some of the severe COVID-19 cases are further progressing to develop ARDS due to severe damage of the lungs within 8–9 days of symptom onset. ARDS is characterized by difficulty in breathing, thereby leading to low blood oxygen levels [16,17]. According to the literature, in 70% of the fatal cases, ARDS leads to respiratory failure and death, In 28% of the fatal cases, released cytokines induce sepsis and multiple organ failure, leading to death [17]. There is no compact explanation for the differences in the disease presentation among the infected individuals.

The current treatment for COVID-19 aims at symptomatic relief, treatment of underlying diseases, active monitoring and prevention of complications, maintaining the patient's homeostasis, and providing respiratory support whenever needed. Glucocorticoids are also being used in the treatment to a limited extent because continuous usage leads to immunodeficiency, leading to secondary infections [18].

Till now, there are no specific therapeutic agents available against COVID-19 [1,19]. Remdesivir is the only antiviral agent approved for the treatment of COVID-19 in emergency conditions under the supervision of physicians [20]. The increasing death toll worldwide indicates an urgent need for effective and safe therapeutic and prophylactic agents to grab the increasing claws for this viral particle. Developing new, specific therapeutic and prophylactic agents is a tedious and time-consuming process, so repurposing existing therapeutics for the treatment of COVID-19 is considered the best choice to counteract the consistent increase of infected people [1,21]. Many of clinical trials are in progress to establish the efficacy of the existing antivirals and other therapeutic agents in this pandemic scenario [1,4,9,22,23].

Recent news on new variants of SARS-CoV-2 is panicking people worldwide [24]. For example, a team of experts in the UK (United Kingdom) identified a new variant known as B.1.1.7, which increases the risk of death compared to the initial variant. Furthermore, this variant is known to spread more quickly than the other reported variants [25]. In addition, new strains of coronaviruses, such as N440K and E484K, have been detected in different parts of India. Therefore, to understand the potential of such variants, extensive genome surveillance is required to save humanity from this tiny danger [26]. Thus, in this review, we focused on recent advances in repurposed therapeutic agents and the current progress of vaccine development against COVID-19 to support future researchers with a background of research progress.

2. Recent advancements in therapeutics against COVID-19 in clinical research

SARS-CoV-2 contains non-segmented, single-stranded, positive-sense RNA as genetic material. The genome consists of 5'-terminal end, partially overlapping Open Reading Frames 1a and 1b (ORF 1a and 1b), region encoding structural and accessory proteins, and 3'-terminal.

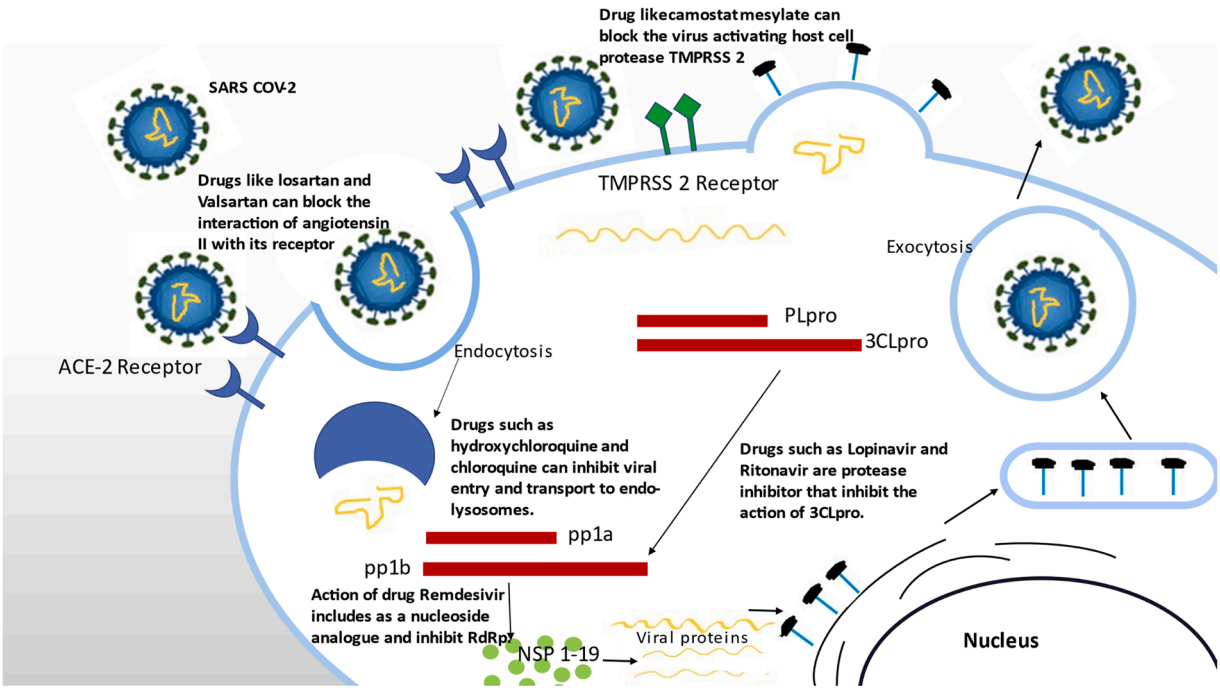

Fig. 2. Life cycle of Corona viruses and different targets for developing therapeutic agents.

The ORF 1a and 1b occupy two-thirds of the genome and encode Poly-Protein (PP) 1a (PP 1a) and PP 1ab (Fig. 2) [27]. The remaining genome encodes structural proteins, such as spike protein (S), envelop protein (E), membrane protein (M), nucleocapsid protein (N), and accessory proteins. The virion releases its genetic material into the cytoplasm upon entering the cell via endocytosis. After that, the ORF 1a and 1b are translated into PP 1a and PP 1ab, where these PP 1a and PP 1ab are cleaved by virus proteases, Papain-Like protease (PLpro), and 3C-like serine protease (3CLpro), to generate Non-Structural Proteins (NSPs). These NSPs include RNA-dependent RNA polymerase (RdRp) and helicase (Hel), which play a lead role in the transcription and replication of the virus genome inside the host cells [27,28]. SARS-CoV-2 shares 94.4% amino acid sequence identity with the *SARS-CoV* in the ORF 1ab region of the genome [19]. Thus, RdRp and helicase enzymes are highly conserved across the coronaviruses. Hence, broad-spectrum antivirals, which are capable of inhibiting these enzymes, can probably inhibit SARS-CoV-2. Repurposing of drugs is a better option to meet the global demand to fight against COVID-19. Therefore, WHO and other health agencies recommended repurposing drugs [29]. Therefore, nucleotide analogs (e.g., Favipiravir, Ribavirin, Remdesivir, Galidesivir) are known to inhibit the RdRp enzyme in a wide range of RNA viruses [30–33], several pieces of research are prompted to establish their efficacy.

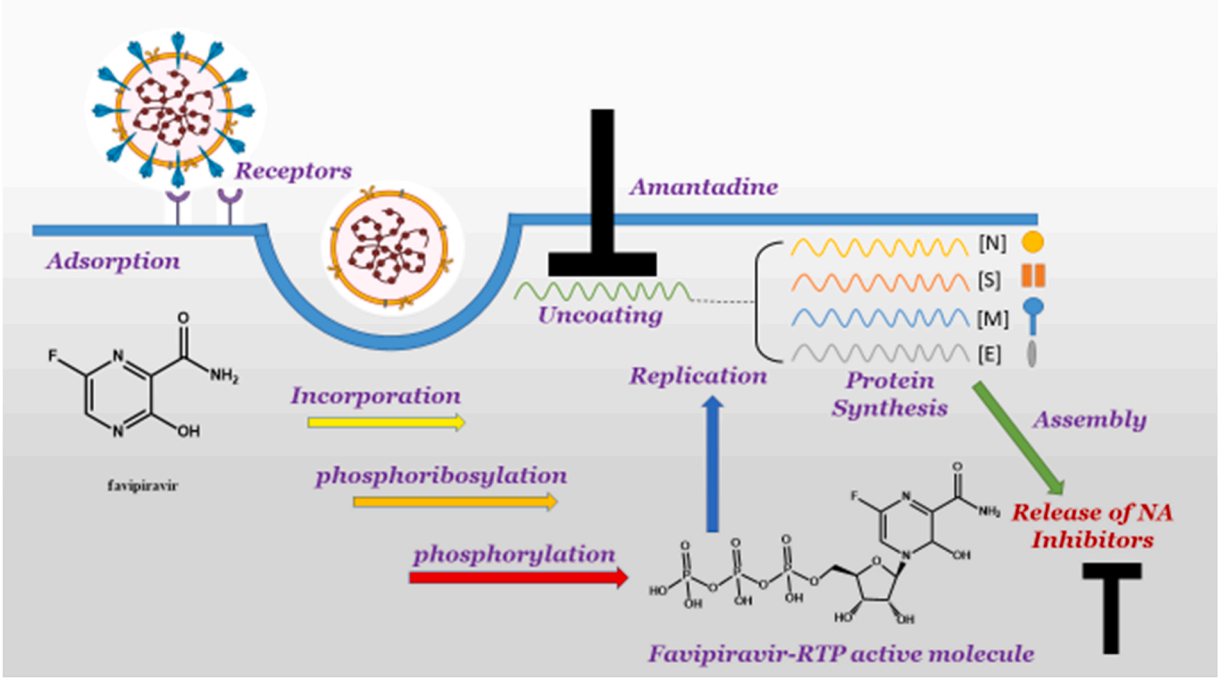

Fig. 3. Mechanism of antiviral action of Favipiravir indicating its role against COVID-19.

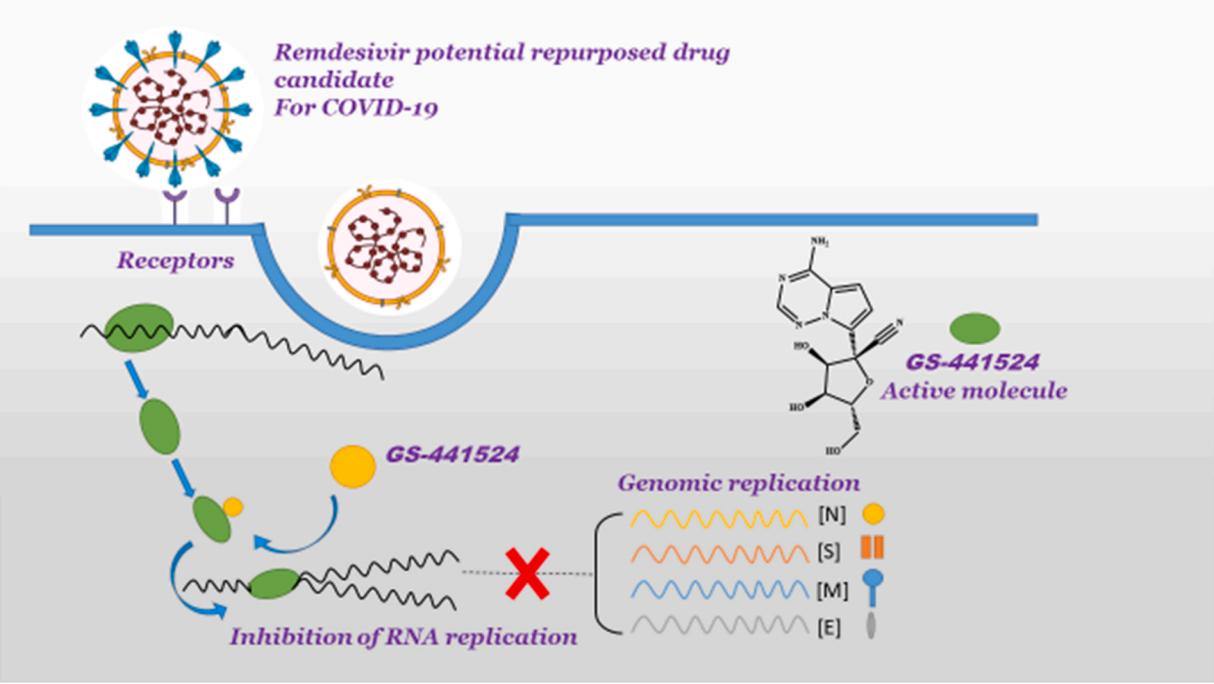

Fig. 4. Effective role of Remdesivir in the control of COVID-19.

Based on effective control of COVID-19 in clinical trials, Remdesivir was approved for emergency use for hospitalized patients by Food and Drug Administration (FDA) in October 2020 [20,34]. HIV protease inhibitors, Lopinavir, and Ritonavir were also considered to inhibit SARS-CoV-2 proteases (PLpro, 3CLpro), but WHO's solidarity clinical trials had shown that treatment with Lopinavir and Ritonavir was no better than standard treatment [35,36]. Other small molecules that were considered for repurposing are Chloroquine and HydroxyChloroquine. Although these treatments were initiated in emergency conditions, WHO's solidarity clinical trials concluded that Chloroquine and HydroxyChloroquine are not effective in reducing mortality [36]. Various types of existing pharmacological agents can be repurposed for the treatment of COVID-19. Apart from Remdesivir, other drugs were also considered, such as Favipiravir, Elbasvir, Cepharanthine; drugs acting on viral entry, such as Arbidol, Darunavir, Nafamostat; anti-inflammatory agents like Tocilizumab, Barcitinib for their efficacy against COVID-19 [29]. The following section of the article has been elaborated on different therapeutic agents in the management of COVID-19.

2.1. *Favipiravir*

It is a broad-spectrum antiviral agent known to inhibit viral RNA synthesis by impeding the RdRp enzyme of RNA viruses. *Favipiravir* is a prodrug that undergoes intracellular metabolism to transform to the active parent molecule triphosphate. RdRp identifies this triphosphate as a purine analog and includes it in the nascent viral RNA strand competitively with adenine and guanine. Inclusion of Favipiravir triphosphate into nascent RNA strand inhibits further growth of RNA strand [37].

It was originally developed to treat the influenza virus in Japan [37]. It was tested as a treatment option during 2013 against the SARS outbreak, and its therapeutic potential against SARS-CoV was established. Since SARS-CoV-2 conserves the RdRp enzyme, repurposing Favipiravir as a treatment for COVID-19 is justified (Fig. 3) [30]. Around the world, a considerable number (forty-eight, 48) of clinical trials are in progress to test the efficacy of this drug against COVID-19 (www.clinicaltrials.gov). However, the results of these clinical trials suggest that Favipiravir is not effective in critically ill patients, and there is no evidence that it can reduce the COVID-19 associated mortality [38]. Despite these results, India and Russia have approved this drug for emergency use against COVID-19 [39,40].

2.2. *Remdesivir in the treatment of COVID-19*

Remdesivir (GS-5734) was first developed by Gilead Sciences, USA, to treat ebolavirus disease [41]. It is a 1'-cyano substituted adenosine nucleotide prodrug, which interferes with the viral RNA replication catalyzed by RdRp in various RNA viruses like ebolavirus, respiratory syncytial virus (RSV), SARS, MERS, etc. Recent in vitro studies showed that it could inhibit the SARS-CoV-2 ($EC_{50} = 0.77$ μM in Vero cells) [42,43]. Another contemporary animal study on rhesus macaques showed that early administration of Remdesivir could prevent the advancement of the disease [44]. The mechanism of action of Remdesivir depicted that this antiviral agent can cause termination of premature RNA strands, which inhibits further replication of virus [45]. Similar to Favipiravir, this nucleotide analog also undergoes intracellular metabolism to form the triphosphate of the parent nucleoside. This Nucleoside TriPhosphate (NTP) is the pharmacologically active form that competes with Adenosine TriPhosphate (ATP) in RNA synthesis. Selectivity of ATP over NTP by RdRp is ~4 folds (Fig. 4) [43]. Incorporating NTP in the RNA chain does not affect the incorporation of immediately next nucleotide but leads to inhibition of the 5th nucleotide. This effect leads to the termination of the RNA progression. Hence, the mechanism of action of Remdesivir is considered delayed termination. The 1'-cyano group increases the selectivity towards viral RNA polymerase. Human mitochondrial RNA polymerase can efficiently distinguish between NTP and ATP. The selectivity of ATP over NTP is over 500 folds in the case of human RNA polymerase. Thus, Remdesivir does not interfere with human RNA polymerase [43].

Clinical trials are in progress to establish the efficacy of Remdesivir toward COVID-19 treatment. There are eighty-nine registered clinical trials to test the efficacy of Remdesivir against COVID-19. However, the results of the clinical trials are sometimes conflicting [46]. A preliminary data of a Chinese clinical trial reported that Remdesivir treatment is not better than a placebo. However, this clinical trial was not completed

because of difficulty in recruiting patients as the infection was subsided in China [47]. The preliminary results from a clinical trial of the National Institute of Allergy and Infectious Diseases (NIAID) showed a 31% faster recovery in Remdesivir treated patients compared to the placebo group. A compassionate study from Gilead Sciences showed a higher recovery rate (68%) in Remdesivir treated patients [48]. Recently, several clinical trials were conducted to evaluate the efficacy of Remdesivir when compared to standard care. The studies were conducted on moderate [49] (NCT04292730) as well as severe patients [50] (NCT04292899) of COVID-19 to study the anti-viral activity of Remdesivir. The findings from these clinical trials encounter several limitations, such as lack of uniformity in indexing the disease severity in the group. In contrast, some clinical trials had small sample sizes, some open-label studies, and some used concomitant medications. Despite these limitations, most clinical trials showed some improved efficacy against COVID-19 in hospitalized patients [51]. Moreover, there is no hard evidence that Remdesivir does not helpful in treating COVID-19. However, with the supporting evidence, US-FDA approved for emergency use authorization on 22nd October 2020 [20].

Use of Remdesivir is associated with adverse effects such as nausea, delayed blood clotting, increased transaminase level, and hypersensitive reactions in some. On the other hand, the patient's liver function and renal function of the patients should be closely monitored before and after administration. Thus, Remdesivir is not recommended for patients whose renal function is disturbed (glomerular filtration rate <30 mL/min) [52]. Co-administration of Chloroquine and HydroxyChloroquine had shown to reduce the antiviral activity of Remdesivir hence concomitant administration is not recommended [53]. Alternatively, co-administration of corticosteroids did not show any effect [51]. Remdesivir is primarily recommended to hospitalized patients who require supplementary oxygen without any inflammatory signs. The basis for this recommendation is to facilitate viral clearance, as this is important to prevent the disease from progressing to a severe inflammatory stage. Combination therapy of Remdesivir and Dexamethasone (corticosteroid) has been recommended for patients with inflammatory responses who require high flow oxygen support [51].

2.3. Use of monoclonal antibodies in COVID-19

Monoclonal antibodies are suggested for non-hospitalized patients with mild to moderate COVID-19 who are at high risk of progression to severe conditions. Currently, three monoclonal antibody therapies are approved on an Emergency Use Authorization (EUA) basis, including Bamlanivimab plus Etesevimab, Casirivimab plus Imdevimab, and Sotrovimab. This category of drugs plays a vital role in neutralizing SARS-CoV-2 by binding to the viral S-protein. However, supportive and symptomatic treatment was suggested for patients who were not hospitalized, devoid of any risk factors for progressing to severe conditions. However, not enough clinical data is available to support any specific treatment in this group of patients [51].

BLAZE-1 is a placebo-controlled, double-blind, randomized clinical trial to evaluate the efficacy of Bamlanivimab plus Etesevimab in non-hospitalized patients with high-risk factors. Surprisingly, this study showed a 70% relative reduction in the incidence of hospitalization or death. However, the results of the study were neither peer-reviewed nor published. Alternatively, the dose of Bamlanivimab plus Etesevimab utilized in this trial was 2800 mg, and 2800 mg, respectively, which were much higher than that of EUA approved dose (700 mg and 1400 mg, respectively). Additionally, in vitro study results demonstrated that Bamlanivimab possesses less neutralizing activity toward variants that exhibit E484K mutation. However, till now, no variants showed reduced susceptibility towards the combination of Bamlanivimab plus Etesevimab, and the clinical impact of this mutation is not identified [54].

R10933–10987-COV-2067 is another randomized placebo-controlled, parallel study to test the safety and efficacy of Casirivimab plus Imdevimab in non-hospitalized patients with high-risk factors. Data from this study showed a 71% relative reduction in hospitalization or death in the Casirivimab plus Imdevimab treated patients compared to the placebo group. However, because of its parallel assessment design, the study design possesses some limitations, and thus, the study results are neither peer-reviewed nor published [55].

Sotrovimab was a recently (on May 26, 2021) approved anti-SARS-CoV-2 monoclonal antibody under EUA by USFDA. It targets highly a conserved epitope of the receptor-binding domain (RBD) of SARS-CoV-2. Interestingly. This epitope is not a part of mutation sites of SARS-CoV-2 variants. *In vitro* studies on Sotrovimab showed neutralizing activity against B.1.1.7 (alpha), B.1.351 (beta), P.1 (gamma), B.1.427/429 (epsilon), and B.1.526 (iota) variants. The evidence for approving Sotrovimab under EUA was documented via the COMET-ICE trial (NCT04545060). COMET-ICE is a phase 3 randomized, placebo-controlled clinical trial to test the efficacy of Sotrovimab against COVID-19 in non-hospitalized patients with high-risk factors. The study showed an 85% relative reduction in the hospitalization or death of the patients [56,57].

Studies comparing the efficacies between monoclonal antibodies are not done yet. Hence one of the above monoclonal antibodies is suggested for treatment against COVID-19 in non-hospitalized patients with high-risk factors. The criteria of considering risk factors is not uniform in the above-mentioned clinical trials; hence it is difficult to compare these treatment methods. Treatment with monoclonal antibodies is not recommended hospitalized patients due to the severity of COVID-19 [51].

2.4. Dexamethasone against COVID-19

Dexamethasone is a corticosteroid, which has been approved and enlisted by WHO as an essential medicine for its immunosuppressant and anti-inflammatory properties [58]. Usually, Dexamethasone is used to treat conditions like rheumatism, allergies, skin problems, respiratory issues, ulcerative colitis, cancer, liver fibrosis, etc. [59,60]. As COVID-19 is affecting the lives of a large population, Dexamethasone has shown the potential to rescue the lives of some critically ill patients. A clinical study at Oxford University, UK, "RECOVERY" (Randomized Evaluation of COVid 19 thERapY) had established the promising role of Dexamethasone. In the study, patients treated with Dexamethasone and standard treatment were compared with the outcome of patients who received only standard care [61,62]. From the reported results of the clinical trial, it was demonstrated that the co-treatment of Dexamethasone and standard treatment to the patients on ventilator resulted in the reduction of mortality rate to one-third compared to the patients who received standard care. On the other hand, the mortality was reduced to one-fifth in patients who required oxygen support [61]. The results are quite promising to incorporate in reducing the death toll due to COVID-19 infection.

Moreover, Dexamethasone is inexpensive and can be easily accessible worldwide. However, it is not suitable for asymptomatic patients with mild symptoms [62]. Dexamethasone exhibits high affinity towards glucocorticoid receptors [63,64]. This binding inhibits the enzyme phospholipase A2, which, in turn, is responsible for preventing the secretion of arachidonic acid. Such action of Dexamethasone further suppresses the formation of cytokines [65]. It has been well documented that increased production of cytokines results in 'cytokine storm,' which can affect healthy cells leading to inflammation [66]. Mortality in COVID-19 is due to the uncontrolled inflammatory response of the immune system [67]. Concurrently, another randomized trial of this drug was performed comparing with and without standard intensive care. This clinical trial revealed the reduction in duration of mechanical ventilation in patients with COVID-19 [22]. Dexamethasone can suppress immune responses in critically ill patients. Thus, it is being repurposed as a treatment option for hospitalized COVID-19 patients.

Furthermore, the dosing regimen of this corticosteroid is highly essential. A high dose of this corticosteroid can cause harm to the patient

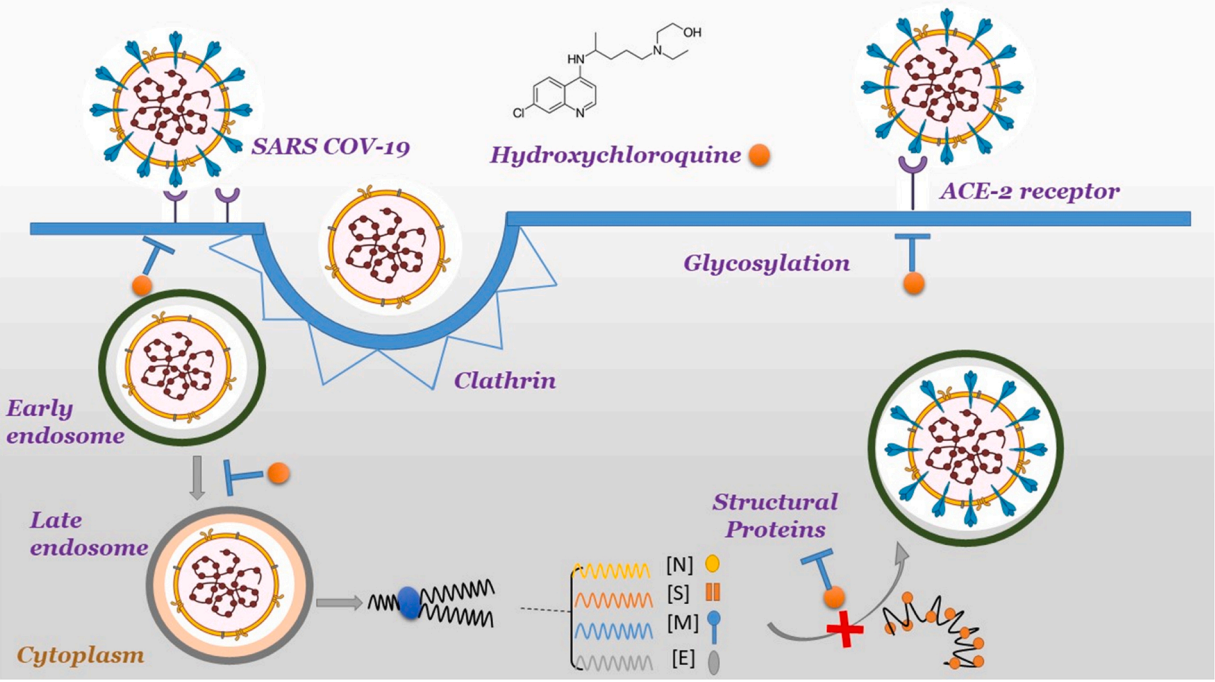

Fig. 5. The inhibiting role of HydroxyChloroquine towards ACE2 glycosylation, early endosome into late endosome and formation of autophagosome.

rather than a beneficial deed. The usage of this drug can be fatal if there is a low level of inflammation and replication of the virus is fast [68]. Patients receiving the dose of a corticosteroid (e.g., Dexamethasone) may face minor risks of secondary infections, including invasive fungal and bacterial infection or worsening the pre-existing condition [69].

A total of fifty-five clinical trials are registered (www.clinicaltrials.gov) to establish the efficacy of Dexamethasone in COVID-19, where a few of the studies are already completed. Most of the studies are at recruiting stage of COVID-19 patients in establishing its positive potential. To specify, these studies are primarily conducted on moderate to severe cases of COVID-19 cases (NCT04603729) [70] or in conditions with ARDS (NCT04395105) [71]. Furthermore, clinical trials using different doses of Dexamethasone are also performed with standard intensive care. According to the study, the dosage of Dexamethasone should be high (20 mg) during the initial five days and low (10 mg) during the next five days, which could shorten the duration of respiratory system failure, hence, can be used for the treatment of SARS-CoV2 [72]. Also, investigation on this steroidal agent is ongoing in severe hypoxic patients at a lower dose to establish its prominent role (NCT04509973) [73].

Based on various clinical trials, WHO and National Institute of Health (NIH) have encouraged and appreciated the use of Dexamethasone alone or combined with Remdesivir to treat COVID-19 [58]. There is a rationale for suggesting the combination of Remdesivir and Dexamethasone. Corticosteroid delays the viral clearance; hence if Dexamethasone alone was administered it would take long time for viral clearance. Thus, co-administration of Remdesivir is suggested. However, for critically ill patients, Dexamethasone is only suggested [51]. One of the subgroup in clinical trials RECOVERY and ACTT-2 tested the efficacy of Barcitinib and Remdesivir and Tocilizumab and Remdesivir combination therapies instead of Dexamethasone on a small subgroup of patients who were hospitalized and receiving oxygen therapy [74]. Study results showed the benefit of using Barcitinib and Tocilizumab. However, these studies are underpowered. Hence, there is insufficient data to suggest Barcitinib and Tocilizumab in the treatment of COVID-19. Some experts suggested useing of Barcitinib and Tocilizumab when Dexamethasone is contraindicated, where these drugs should be given with Remdesivir [51]. For critically ill patients, Dexamethasone might be the only therapeutic option because corticosteroids play an important role in suppressing the body's inflammatory responses.

2.5. HydroxyChloroquine against COVID-19

Although WHO has declared through the solidarity clinical trials that HydroxyChloroquine is unable to produce benefits in terms of reducing mortality, however, there are two hundred sixty-two studies registered for human trials. Amongst, ten studies were suspended, fourteen were terminated, and nineteen were withdrawn due to safety reasons. Around one hundred seventy-nine studies are in the active stage of recruiting or will be recruiting.

HydroxyChloroquine is a USFDA approved drug for treating malaria, rheumatoid arthritis, and lupus. It was initially thought to be a treatment option for patients with COVID-19. This agent's predicted mechanism of action to control COVID-19 demonstrated an increase in endosomal pH to restrict fusion of the viral particle to the cells at the respiratory epithelium (Fig. 5) [75–77]. It has also been reported that the endocytosis of the SARS-CoV-2 could be interfered by the action of this agent [78], and also known to block sialic acid receptors and finally prevent the formation of cytokine storm. The major limitation of this agent includes QT interval prolongation, retinopathy, and gastrointestinal complications [76]. Some clinical studies were carried out that raised the question of the efficacy of HydroxyChloroquine in COVID-19 (NCT04340544) [79,80]. After observing a large group of randomized clinical trials and retrospective observational studies, NIH (National Institute of Health) suggested that Chloroquine and HydroxyChloroquine are not recommended for the treatment of COVID-19 patients either alone or in combination with Azithromycin [51,81].

2.6. Other agents

Clinical progress towards the treatment of COVID-19 has not been limited to the above-mentioned therapeutics. Several other therapeutic agents have also been considered for clinical research. A recent study started recruiting patients in October 2020 to evaluate the efficacy of immune modulators in combating COVID-19 [82]. It has been shown positive response in controlling pathological immune response in

patients. It has been reported that administration of Infliximab to COVID-19 patients with concomitant inflammatory bowel disease had shown marked improvement in the symptoms associated with COVID-19 [83,84]. Thus, clinical trials are in the process of recruiting patients to establish the efficacy of Infliximab in COVID-19 [82]. Baricitinib, a Janus kinase (JAK) inhibitor, is also known to suppress immune responses. The clinical trial data [74,85] of this drug showed that it is effectively reduces mortality in hospitalized patients who require non-invasive ventilation. US-FDA issued a EUA for this agent. Furthermore, NIH recommended Barcitinib or Tocilizumab (JAK inhibitors) in combination with Remdesivir when corticosteroids are contraindicated [51,86].

Several study reports demonstrate the efficacy of the combination of baricitinib and Remdesivir in the treatment of COVID-19. The clinical outcome of combination therapy in patients has revealed better results than the patients who received Remdesivir alone. Reduction in recovery time was observed when the combination of these two drugs was used [87]. Thus, combination drug therapy is being encouraged to increase the effectiveness of individual drugs. Therefore, the combination of HydroxyChloroquine and nitazoxanide is also expected to have efficacy against COVID-19. Hence, clinical trials are in progress to test the efficacy of this combination [88,89].

Patients infected with SARS-CoV-2 face several other complications, such as gut microbiota dysbiosis, pulmonary fibrosis, venous thromboembolism (VTE), etc. [90,91]. A meta-analysis report depicted a 14.1% prevalence of VTE in hospitalized COVID-19 patients. COVID-19 associated VTE is characterized by an increase in fibrin and fibrin degradation products, D-dimers in the blood. Based on the meta-analysis of pooled data and results obtained from randomized clinical trials, NIH recommended using a prophylactic dose of anticoagulation therapy for hospitalized and critically ill COVID-19 patients [51,92].

Interferons (alfa, beta) are a group of cytokines that show antiviral properties. These were also tested in various clinical trials for their efficacy against COVID-19 in hospitalized and critically ill patients. Some clinical trials [93] showed a reduction in the severity of COVID-19 disease but the sample size of the study was not sufficient to derive a clinical conclusion. In contrast, an opposite outcome was reported based on another study's clinical trial data [94]. Furthermore, another clinical study showed the benefit of survival using interferon. However, the interferon utilized in that study was not USFDA approved [95]. Hence, there is no sufficient data suggesting interferons as a treatment option for COVID-19. Moreover, interferons produce toxic effects when administered in high doses [51].

It has been well understood that the severe stage of COVID-19 includes an unregulated immune response which may cause inflammation and sepsis. Interleukin inhibitors are a group of immunosuppressants, prone to suppress interleukins (1 and 6). Interleukin-1 (IL-1) inhibitor (Anakinra) was tested for its efficacy against COVID-19 in hospitalized patients with inflammatory indications. According to NIH, clinical data is not sufficient to recommend Anakinra as a treatment option because of the poor design of clinical trials [51,96,97]. As discussed earlier, Tocilizumab is an anti-IL-6 receptor monoclonal antibody, approved by the FDA for rheumatoid arthritis and other immune-related disorders. This was also tested as a treatment option for COVID-19 in combination with corticosteroid (Dexamethasone) in hospitalized patients with inflammatory indications. Data from clinical trials indicated that Tocilizumab in combination with Dexamethasone effectively reduces mortality. Hence, this combination treatment was recommended by NIH to treat COVID-19 in hospitalized patients [29,98,99].

Along with the antiviral and immunomodulatory agents, other adjunctive therapeutic agents like vitamins (C and D) [100–102] and minerals (Zinc) [103] are also considered for the treatment against COVID-19. Clinical trials to test the efficacy of these adjunctive agents are mostly open-label, small sample size, heterogeneous study population. Hence there is no rigorous evidence to suggest them as a treatment option for COVID-19 [51]. Therefore, many clinical trials are in progress to establish the efficacy of those agents.

An antiparasitic drug, ivermectin, was also thought to be a possible treatment for COVID-19. It is an FDA-approved antiparasitic drug for helminthiasis, onchocerciasis, and scabies. Despite its in vitro evidence, ivermectin was not approved for treatment against COVID-19 because of the high dose requirement. Based on in vitro studies, the effective dose to achieve antiviral activity is 100 fold more than the safe dose prescribed in humans. In addition, the clinical trials that investigated the efficacy of ivermectin are poorly designed, i.e., low sample size, administration of different doses of ivermectin, open-label studies, concomitant medications, etc. [51,104,105].

Lopinavir/Ritonavir are retroviral protease inhibitors, which were also investigated for COVID-19 treatment. The clinical trial data [35,106,107] from the solidarity trial and RECOVERY trial [108] revealed that these drugs are ineffective in reducing the mortality or progression to severe disease. A pharmacodynamic study demonstrated that the plasma concentration of these drugs achieved through oral administration is very low compared to in vitro concentration required to inhibit SARS-CoV-2 [109] effectively. Hence, Lopinavir and Ritonavir are not recommended for the treatment against COVID-19.

Overall, scientists worldwide are in search of therapeutic agents against this pandemic causing viral particles to save humanity. Connecting section of the review has been focused on the progress of vaccines against this coronavirus.

3. Vaccines for COVID-19

A *vaccine* is a preparation that induces an immune response towards a particular disease-causing pathogen by exposing specific antigens to the body's adaptive immune system. After that the adaptive immune system develops antigen-specific immune responses, such as cell mediate, and anti-body-mediated immune responses. These responses protect the person from future infection of that particular pathogen [110]. Generally, vaccines are prophylactic agents, where vaccination is considered the best strategy to stop a pandemic from spreading, particularly when there are no specific therapeutic agents available [111]. Nevertheless, vaccine development includes a wide range of research and evaluation, which normally takes years for a single vaccine as COVID-19 is spreading like wild blaze around the world, developing the vaccine in the middle of the pandemic was a real challenge. With the concepts of developing a vaccine against coronavirus or other viruses, certain vaccines have already been authorized for protecting mankind from this SARS-CoV-2. Recently, WHO approved using a viral vector vaccine called ChAdOx1-S developed by AstraZeneca-SKBio (republic of Korea) and Serum Institute, India which has proved to show the efficacy of 63.09% [112]. COVAXIN is another vaccine of Indian origin, developed by Bharat Biotech in collaboration with the Indian Council of Medical Research, India, and the National Institute of Virology. This vaccine is done in various countries such as Srilanka, Myanmar, Bahrain, Oman, etc. [113]. Apart from the vaccines mentioned above, certain vaccines were approved in other countries as well. Comirnaty (BNT162b2) is an m-RNA based vaccine (nucleoside-modified) developed by Pfizer/BioNTech in the US and Germany. After testing into several subgroups, the efficacy of this vaccine was estimated to be in the range of 91.2–100%. The shelf life of this vaccine at − 90 °C to − 60 °C is 6 months and is stable up to 5 days after removing from freezer and kept at 2–8 °C [114]. Different country's National Regulatory Authorities approved 19 vaccines based on EUA against COVID-19; however, out of those 19, WHO authorized only 6 vaccines [115]. Those WHO-recommended vaccines are Pfizer/BioNTech BNT162b2 vaccine, Moderna's mRNA-1273 vaccine, Johnson & Johnson's Ad26. COV2. S vaccine, AstraZeneca's AZD1222, Sinopharm COVID-19 vaccine, and Sinovac COVID-19 vaccine.

During the spreading of this pandemic since December 2019, a total of 17 different variants (clads) of SARS-CoV-2 were identified around the world [24]. On 14th December 2020, a new variant (B.1.1.7) of

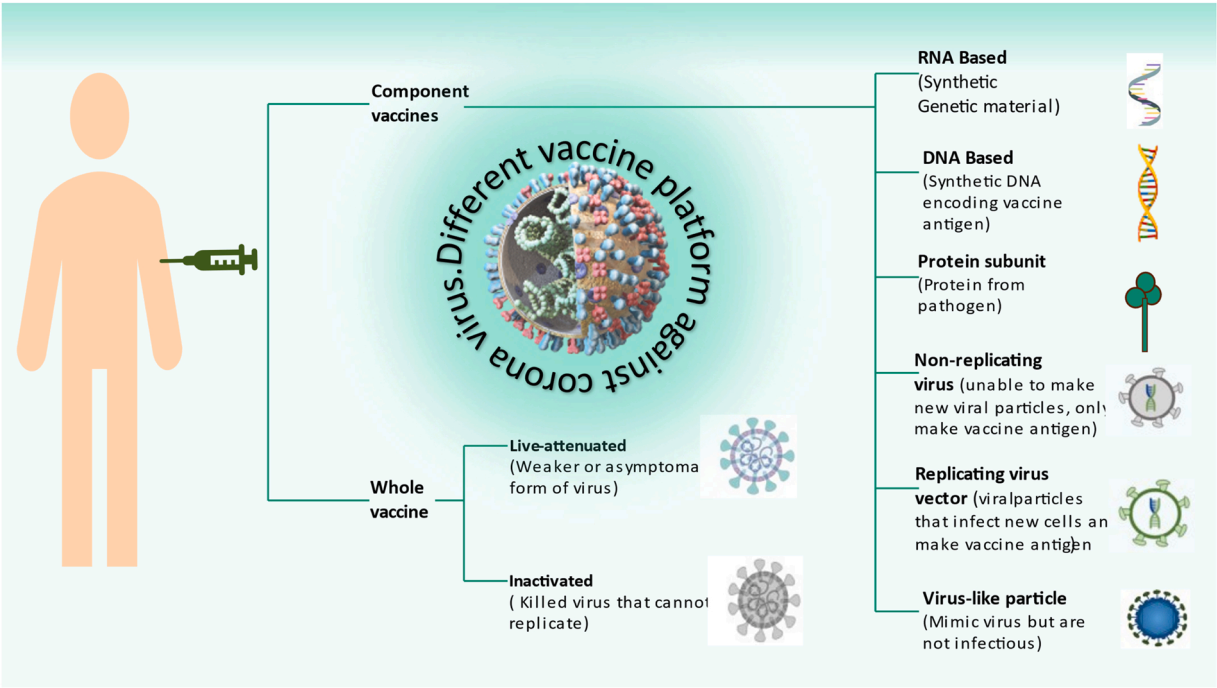

Fig. 6. Various vaccine platforms which are under development for COVID-19.

SARS-COV-2 was identified in the UK, and later, it was found that this variant is more transmissible and causes less severe disease [116]. All the variants exhibit mutations in different regions of the viral genome. Most mutations are observed in the spike protein region [24]. Variants present a challenge to vaccines and therapeutic agents for their prevention and efficacy against this viral particle. It is uncertain that the approved vaccines will show their effectiveness towards the new mutants or variants. However, continuous research is going on to test the efficacy of these vaccines against new variants.

Around 120 vaccine candidates have been proposed worldwide for COVID-19 [117]. These vaccine candidates are based on different approaches; some are conventional, whereas some are relatively new. Fundamentally, vaccines can be classified into 4 categories virus-based, viral-vector based, nucleic-acid based, and protein-based [118]. We have summarized different categories of vaccines hereafter.

3.1. *Virus based vaccines*

This type of vaccine utilizes an inactivated or weakened (attenuated) pathogen (SARS-CoV-2), with no disease-causing ability. It keeps antigenic properties to stimulate the immune system once injected into the biological system (Fig. 6). Polio and measles vaccines were developed by this approach [118]. This is a conventional approach for developing vaccines, where the virus particle is inactivated or killed by applying of heat, solvent treatments (formaldehyde), acidic pH, steam, or a combination of these [119]. Alternatively, the virus can be weakened by passing through animal or human cells to pick up mutations, which makes the virus's genome weak enough that it would not be able to cause the disease anymore. Table 1 shows the virus-based vaccine candidates under different phases of clinical trials.

Five inactivated virus-based vaccine candidates crossed preclinical and clinical studies and have been approved for emergency use in different countries. Sinovac, a Chinese biopharmaceutical company, is developing an inactivated virus-based vaccine candidate named CoronaVac. CoronaVac has already passed phase III clinical trials, and efficacy was found to be 91.25% and was approved for commercial production in China. In February 2021, CoronaVac was used in Brazil, Turkey and Chile under EUA [120]. Sinopharm-BBIBP has been developed by the China National Pharmaceutical Group and the Beijing Institute of Biological Products. Bharat Biotech, India has developed Covaxin. Sinopharm-WIBP has been developed by the China National Pharmaceutical Group and the Wuhan Institute of Biological Products. Alternatively, Covivac was developed by the Russian Academy of Sciences, Russia. These are some other virus-based vaccines progressed so far to combat this pandemic situation [119].

The main advantage of the virus-based vaccine candidates is to mass production of the vaccine upon successful completion of clinical trials. This is possible because of the existing infrastructure as they are licensed platforms for vaccine production. However, the production of inactivated or weakened virus particles requires many pathogenic virus clones. Extensive safety testing is required before the approval of this type of vaccine candidates [121].

3.2. *Viral vector vaccines*

Developing vaccines based on other vaccine platforms, such as viral vector-based, nucleic acid-based, and protein-based vaccines requires complete knowledge of SARS-CoV-2 genome. The genome carries all the information of the proteins that make up the virus particle in a coded form. The complete genetic sequence of the etiological agent (SARS-CoV-2) was made available by the middle of January 2020 (GenBank: MN908947.3) [122]. The viral genome is around 30k nucleotides long and encodes structural and NSPs, whereas the structural proteins include S, E, M and N. Non-structural proteins include 3CL pro, PLpro, helicase, and RdRp. NSPs play an important role in the transcription and translation of the viral genome inside the host cell. Among the structural proteins, S protein facilitates the infection and entry into host cells by ACE2 host receptors. Therefore, S protein and NSPs can be used as targets for vaccine development [123]. Most vaccine candidates are using spike protein as an antigen to stimulate adaptive immune system.

Viral vectors are genetically modified viral particles, which can produce SARS-CoV-2 proteins inside the host cells [124–132]. These viral vectors are non-pathogenic that carry the particular SARS-CoV-2 gene (mostly S-protein gene) to produce the protein in the host cells. These vectors can be replicating or non-replicating in nature (Fig. 6). According to WHO, three non-replicating viral vector-based vaccine

Table 1
Inactivated virus vaccine candidates in clinical trials [174,175].

S. No.	Vaccine	Developer	Current status
1.	CoronaVac (Inactivated + alum)	Sinovac	Phase 3 clinical trial in Hong Kong, Indonesia, Brazil, Turkey, China and Chile. It is approved in 32 countries. Validated by WHO for emergency use [176].
2.	Inactivated (Vero Cells)	Wuhan Institute of Biological Products/ Sinopharm	Approved use in China [177] and phase 3 clinical trial in many countries such as UAE, Peru, Bahrain, Egypt, Jordan, Morocco.
3.	BBIBP-CorV	Beijing Institute of Biological Products/ Sinopharm	Phase 3 clinical trial in UAE, Peru, Bahrain, Egypt, Jordan, China and Argentina. It is approved in 53 countries. ChiCTR2000034780 NCT04612972 NCT04510207
4.	COVAXIN Whole-virion inactivated	Bharat Biotech	Phase 3 clinical trial in India. Approved to use in India [113] and other 8 countries. NCT04641481
5.	Inactivated (Vero Cells)	Institute of Medical Biology, Chinese Academy of Medical Sciences	Phase 3 Clinical trial in Brazil and Malaysia. It is not approved in other countries. NCT04659239 NCT04412538
6.	KoviVac	Chumakov Federal Scientific Center for Research and Development	Phase 1/2 clinical trial by Russian Federation and approved to be used in Russian federation. 502
7.	QazVac	Research Institute for Biological Safety Problems, Kazakhstan	Phase 3 Clinical trial in Kazakhstan and approved to be used in Kazakhstan. NCT04691908
8.	SARS-CoV-2 Vaccine (Vero Cells)	Minhai Biotechnology Co.	Phase 3 clinical trial in China and approved to be used in China. NCT04852705
9.	COVID-19 Inactivated Vaccine	Shifa Pharmed Industrial Co	Phase 2/3 clinical trial in Iran and approved to be used in Iran. IRCT20201202049567N3
10.	VLA2001	Valneva	Phase 3 clinical trial in UK and North Ireland and not approved in any country yet. NCT04864561
11.	KD-414	KM Biologics Co Ltd	Phase 1/2 clinical trial in Japan and not approved in any country yet. jRCT2071200106
12.	ERUCOV-VAC	Health Institutes of Turkey	Phase 1 and 2 clinical trial in Turkey and not approved yet. NCT04824391 NCT04691947
13.	FAKHRAVAC (MIVAC)	Organization of Defensive Innovation and Research	Phase 1 Clinical trial in Iran. IRCT20210206050259N1
14.	Recombinant NDV Vectored Vaccine	Laboratorio Avi-Mex	Phase 1 clinical trial in Mexico. NCT04871737
15.	Koçak-19 Inaktif Adjuvanlı COVID-19 Vaccine	Kocak Farma	Phase 1 clinical trial in Turkey. NCT04838080
16.	Adjuvanted Inactivated Vaccine	The Scientific and Technological Research Council of Turkey	Phase 1 clinical trial in Turkey. NCT04866069

Table 2
Non-replicating viral vector based vaccine candidates that are approved and in clinical trials [174,175].

S. No.	Vaccine	Developer	Current status in development
1.	Ad5-nCoV	CanSino Biologics	Phase 3 Clinical trial in Russia, Moscow NCT04540419. Approved in 8 countries.
2.	Ad26. COV	Janssen (Johnson & Johnson)	Phase 3 in South Africa and other countries. NCT04838795 NCT04614948 Approved in 52 countries
3.	Adeno-based SPUTNIK-V	Gamaleya Research Institute	Phase 3 clinical trial in UAE and Russia NCT04656613 NCT04741061 Approved in 68 countries
4.	AZD1222	Oxford/AstraZeneca	Phase 3 clinical trial in many countries and approved in 115 countries. NCT04864561 NCT04800133 NCT04536051
5.	Covishield	Serum Institute of India	Phase 2/3 clinical trial in India and approved 43 countries. CTRI/2020/08/027170
6.	GRAd-COV2	Rei Thera and Lazzaro Spallanzani national institute of infectious diseases	Phase 2/3 clinical trial in Italy and other countries. It has not been approved in any country yet. NCT04791423
7.	MVA-SARS-2-ST	Universitätsklinikum Hamburg-Eppendorf (UHE)	Phase 1/2 clinical trial in Germany and not approved by in any country yet. NCT04895449
8.	COVIVAC	Institute of Vaccines and Medical Biologicals	Phase 1/2 clinical trial in Vietnam and not approved yet. NCT04830800
9.	LV-SMENP	Shenzhen Geno-Immune Medical Institute	Phase 1/2 clinical trial in China and not approved in any country yet. NCT04276896
10.	hAd5-Covid-19	ImmunityBio Inc	Phase 1/2 clinical trial in America and south-Africa. Not approved in any country. NCT04845191 NCT04710303
11.	AdCOVID	Altimmune Inc	Phase 1 clinical trial in US NCT04679909
12.	BBV154	Bharat Biotech	Phase 1 clinical trial in India. NCT04751682
13.	SAM-LNP-S	National Institute of Allergy and Infectious Diseases (NIAID)	Phase 1 clinical trial in US. NCT04776317
14.	ChAdV68-S	NIAID	Phase 1 clinical trial in US. NCT04776317
15.	VXA-CoV2–1	Vaxart (American biotechnology company)	Phase 1 clinical trial in US. NCT04563702
16.	Ad5-nCoV	Institute of Biotechnology, Academy of Military Medical Sciences, China	Phase 1 clinical trial in China. NCT04552366
17.	SC-Ad6–1	Tetherex Pharmaceuticals Corporation	Phase 1 clinical trial in Australia. NCT04839042
18.	MVA-SARS-2-S	UHE	Phase 1 clinical trial in Germany. NCT04569383

Table 3
Nucleic acid based vaccines under clinical trials [174,175].

S. No.	vaccine candidate	Developer	Current status in the development
1.	mRNA-1273 (RNA - LNP-encapsulated mRNA) mRNA-1283 mRNA-1273.351	Moderna/NIAID	Phase 3 clinical trial in US, Canada and Switzerland. It is approved to be used in 53 countries. NCT04805125 NCT04470427 NCT04806113 Phase 1 clinical trial in US and not approved. NCT04813796 Phase 1 clinical trial in US and approved. NCT04785144
2.	BNT162b2(RNA - 3 LNP-mRNAs)	BioNTech/Fosun Pharma/Pfizer	Phase 3 clinical trial in Switzerland, Hong Kong and US. It is approved in 89 countries. NCT04805125 NCT04800133 NCT04713553
3.	CVnCoV (RNA – mRNA)	Curevac	Phase 3 Clinical trial in Germany, Argentina, Columbia and Peru. It is not approved in any countries. EUCTR2020-004066-19, NCT04674189 NCT04848467
4.	Covigenix VAX-001	Entos Pharmaceuticals Inc	Phase 1/2 clinical trial in Canada and not approved yet. NCT04591184
5.	GLS-5310 (DNA based)	GeneOne Life Science Inc	Phase 1/2 Clinical trial in Republic of north Korea and not approved yet. NCT04673149
6.	COVID-eVax (DNA based)	Takis	Phase 1/2 Clinical trial in Italy and not approved yet. EUCTR2020-003734-20, NCT04788459
7.	GX-19(DNA - DNA Vaccine)	Genexine Consortium	Phase 1/2 clinical trial in Republic of Korea and not approved. NCT04445389
8.	LUNAR-COV19/ ARCT-02(RNA – mRNA)	Arcturus Therapeutics Inc	Phase 2 Clinical trial in Singapore, US. NCT04668339 NCT04728347
9.	DS-5670a	Daiichi Sankyo Co Ltd	Phase ½ Clinical trial in Japan and not approved yet. NCT04821674
10.	mRNA vaccine (RNA - mRNA)	People's Liberation Army (PLA) Academy of Military Sciences/ Walvax Biotech.	Phase 3 and 2 clinical trial in China but not approved in any countries. ChiCTR2100041855 NCT04847102
11.	TAK-919	Takeda	Phase 1/2 clinical trial in Japan, Approved in Japan. NCT04677660
12.	BNT162b1	Pfizer/BioNTech	Phase 2/3 clinical trial in Argentina, Brazil, Germany, South Africa, Turkey and US. It is not approved in any countries. NCT04368728

candidates are in various stages of clinical trials and another twenty are in the pre-clinical stage [117,133]. The University of Oxford in partnership with AstraZeneca PLC, has developed a non-replicating viral vector-based vaccine candidate for the management of COVID-19, named ChAdOx1 nCoV-19 (AZD1222) [117]. They have chosen genetically modified chimpanzee adenovirus as a vector, which carries the whole SARS-CoV-2 spike protein gene. The reason behind choosing chimpanzee adenovirus as a vector is based on their previous experience on MERS vaccine which was developed using the same adenovirus as a vector with the MERS spike gene. However, the vaccine development was not progressed as the infection subsided by the time it reaches phase-I clinical trials. On 28 January 2021, FDA approved ChAdOx1-S [recombinant] under EUA [134]. The severity of COVID-19 is particularly high in old and immunocompromised people. Therefore, a non-replicating adenovirus vector is a good choice for immunogenicity.

Table 3 (*continued*)

S. No.	vaccine candidate	Developer	Current status in the development
13.	ChulaCov19	Chulalongkorn University	Phase 1/2 clinical trial in Thailand and not approved. NCT04566276
14.	BNT162a1 BNT162b3	Pfizer/BioNTech	Phase 1/2 clinical trial in Germany and not approved yet. EUCTR2020-001038-36, NCT04380701 NCT04537949, EUCTR2020-003267-26-DE
15.	Elixirgen Therapeutics Inc	EXG-5003	Phase 1/2 clinical trial in Japan and not approved yet. NCT04863131
16.	MRT5500	Sanofi Pasteur	Phase 1/2 clinical trial in US and not approved yet. NCT04798027
17.	HGCO19 (RNA based)	Gennova Biopharmaceuticals Limited	Phase1/2 clinical trial in India and not approved yet. CTRI/2021/04/032688
18.	PTX-COVID19-B (RNA based)	Providence Therapeutics Holdings Inc	Phase 1 clinical trial in Canada and not approved. PRO-CL-001, NCT04765436
19.	CoV2 SAM (LNP) (RNA based)	GlaxoSmithKline	Phase 1 clinical trial in US and not approved. NCT04758962
20.	AG0302-COVID19 (DNA based)	AnGes	Phase 2/3 clinical trial in Japan and not approved. NCT04655625
21.	ZyCoV-D (DNA-DNA Plasmid vaccine)	Zydus Cadila	Phase 3 clinical trial in India and not approved. CTRI/2021/01/030416
22.	INO-4800 (DNA - DNA plasmid vaccine with electroporation)	Inovio	Phase 2/3 clinical trial in US and Phase 2 in China. It is not approved it. NCT04642638 ChiCTR2000040146
23.	CORVax12 (DNA based)	Providence Health & Services	Phase 1 clinical trial in US and not approved. NCT04627675
24.	COVIGEN (DNA based)	University of Sydney	Phase 1 clinical trial in Australia and not approved. NCT04742842
25.	bacTRL-Spike	Symvivo	Phase 1 clinical trial Australia and not approved. NCT04334980

However, booster shots are required to induce long-lasting immunity [135]. CanSino Biological Inc. and Beijing Institute of Biotechnology are jointly developing a COVID-19 vaccine using adenovirus type 5 as a vector. This vaccine candidate has been reached in phase 1/2 clinical trial [117]. This platform has been previously explored to develop a vaccine against the Ebola virus [117,136]. Similarly, Gamaleya Research Institute is also developing an adenovirus-based vaccine candidate, where they are using human adenovirus types 5 and 26 as vectors [137]. However, this platform is not licensed. A few of the non-replicating viruses, which are at the clinical progress are mentioned in Table 2. Alternatively, Ad26. COV2. S is a recombinant viral vector vaccine developed by Johnson & Johnson, which WHO has approved. This vaccine uses non-replicating human adenovirus type Ad26 as a vector and expresses SARS-CoV-2 spike protein. This vaccine is administered as a single dose intramuscular injection [138].

According to the WHO, 17 replicative viral vector-based vaccine candidates are in pre-clinical evaluation for COVID-19. Attenuated measles virus, influenza virus, horsepox virus etc. are being used as vectors to carry SARS-CoV-2 whole S-gene or the RBD of SARS-CoV-2 [117]. The disadvantage of the viral-based vaccines observed in a person having existing immunity for the vector, which may suppress the immunogenicity of the vaccine [118].

3.3. Nucleic acid-based vaccines

This vaccine platform uses nucleic acids (RNA or DNA), which encode pathogen (SARS-CoV-2) proteins. These nucleic acids induce the production of pathogen proteins in vivo, which stimulate the adaptive immune system. This platform is relatively new and currently, a few of these vaccines are licensed based on this technology [128,131, 139–143]. This technology allows the rapid development of vaccines because millions of copies of protein-specific nucleic acids can be generated from a template using the polymerase chain reaction (PCR) technique. According to WHO, nine nucleic acid-based vaccine candidates are in different stages of clinical trials. Among these, five are RNA-based vaccine candidates, and the remaining are DNA-based vaccine candidates.

Moderna and Inovio are the main players in the development of nucleic acid-based vaccines. Moderna's messenger-RNA (mRNA) vaccine [144] (mRNA-1273) encodes prefusion stabilized form of SARS-CoV-2 spike protein [145]. Moderna's vaccine (mRNA-1273) was developed in collaboration with the US National Institute of Allergy and Infectious Diseases. It has shown 94% efficacy to treat patients of COVID-19 [146]. As cells do not accept mRNA, lipid nanoparticles (LNP) are used to deliver the mRNA inside the cells [145]. Few nucleic acid-based vaccines are presented in Table 3, which are at different stages of clinical research. Similarly, Pfizer-BioNTech has also developed another mRNA vaccine, BNT162b2. It is also LNP formulated nucleoside modified mRNA vaccine encoding PS2 spike protein of SARS-CoV-2. In the preclinical trials, the vaccine showed a good cell-based immune response. The results of conducted clinical trials showed safety and immunogenicity in humans [147]. BNT162b2 and mRNR-1273 are now WHO-approved mRNA vaccines.

Inovio's DNA vaccine candidate, INO-4800, uses the entire S protein gene of SARS-CoV-2 [118,148]. This S protein gene is introduced into an optimized plasmid, where these plasmids would be introduced into the host cell by electroporation [118,149]. This DNA will trigger the cell to synthesize virus spike protein, which will act as an antigen to stimulate the immune system (Fig. 6).

3.4. Protein-based vaccines

Protein-based vaccines are of two types, protein subunit vaccines and virus-like particles (VLP) (Fig. 6). Protein subunit vaccines use a virus protein, which is specific to the pathogenic virus or a subunit of a protein (epitope) as an immune-stimulating antigen. These proteins can be

Table 4
Protein based vaccines in clinical trials and approved [174,175].

S. No.	vaccine candidate	Developer	Current status in development
1.	RBD-Dimer (Protein subunit – Adjuvanted recombinant Protein)	Anhui Zhifei longcom Biopharmaceutical/ Institute of Microbiology, Chinese Academy of Sciences	Phase 3 Clinical trial China, Ecuador, Indonesia, Pakistan and Uzbekistan. Approved in China and Uzbekistan. ChiCTR2000040153, NCT04646590 NCT04445194
2.	(NVX-CoV2373) Protein subunit – Full length recombinant SARS-CoV-2 glycoprotein nanoparticle vaccine adjuvanted with Matrix M	Novavax	Phase 3 Clinical trial in United Kingdom of Great Britain, Northern Ireland, Mexico and Puerto Rico. EUCTR2020-004123-16, NCT04583995 NCT04611802
3.	KBP-201 (Protein subunit – RBD based)	Kentucky Bioprocessing, Inc.	Phase 1/2 Clinical Trial in US. NCT04473690
4.	(SCB-2019) Protein subunit – Native like Trimeric subunit spike protein vaccine	Clover Biopharmaceuticals Inc./GSK/Dynavax	Phase 2/3 Clinical trial in Belgium, Brazil, Colombia, Dominican Republic, Germany, Nepal, Panama, Philippines and Poland. It is not approved yet. NCT04672395 PHRR210209-003334
5.	(COVAX-19) Protein subunit – Recombinant spike protein with Advax adjuvant	Vaxine Pty Ltd/ Medytox	Phase 2 and Phase 1 clinical trial in Iran and Australia respectively. It is not approved yet. IRCT20150303021315N23 NCT04453852
6.	UB-612 (Protein Subunit)	COVAXX	Phase 2 Clinical trial in Taiwan. NCT04773067
7.	MVC-COV1901 (Protein subunit – S-2 P protein + CpG 1018)	Medigen Vaccine Biologics Corporation/NIAID/ Dynavax	Phase 2 clinical trial in Taiwan and Vietnam. NCT04695652 NCT04822025
8.	QazCoVac-P (Protein Subunit)	Instituto Finlay de Vacunas, Cuba	Phase 1 IFV/COR/04
9.	EpiVacCorona (Protein subunit – Peptide)	FBRI SRC VB VECTOR, Rospotrebnadzor, Koltsovo	Phase 3 clinical trials in Russian Federation. It is approved in Russian Federation and Turkmenistan. NCT04780035
10.	Protein subunit – RBD (baculovirus production expressed in Sf9 cells)	West China Hospital, Sichuan University	Phase 3 and 2 Clinical trials in China but not approved yet. NCT04887207 NCT04904471 ChiCTR2000039994, NCT04640402
11.	COVOVAX	Serum Institute of India	Phase 2/3 Clinical trials in India and not approved. CTRI/2021/02/031554
12.	CIGB-66 CIGB-669	Center for Genetic Engineering and Biotechnology (CIGB)	Phase 3 Clinical trial in Cuba and not approved. RPCEC00000359 Phase 1/2 clinical trial in Cuba and not approved yet. RPCEC00000345
13.	Recombinant Protein	Sanofi/GSK	Phase 3 Clinical trial in US and Kenya. It is not approved yet. NCT04904549 PACTR202011523101903
14.		Nanocovax	

(continued on next page)

Table 4 (*continued*)

S. No.	vaccine candidate	Developer	Current status in development
	Nanogen (Protein Subunit)		Phase 3 Clinical Trials in Vietnam and not approved yet. NCT04922788 NCT04683484
15.	FINLAY-FR-1A (Protein subunit – RBD + Adjuvant)	Instituto Finlay de Vacunas Cuba	Phase 3 Clinical trials in Cuba and not approved yet. IFV/COR/09
16.	EuCorVac-19 (protein subunit)	EuBiologics Co Ltd	Phase 1/2 Clinical trials in Republic of Korea and not approved yet. NCT04783311
17.	GBP510 (protein subunit)	SK Bioscience Co Ltd	Phase 1/2 clinical trial in Republic of Korea and not approved yet, NCT04742738 NCT04750343
18.	S-268019	Shionogi	Phase 1/2 clinicals trial in Japan and not approved yet. jRCT2051200092
19.	QazCoVac-P	Research Institute for Biological Safety Problems	Phase 3 clinical trial in Kazakhstan and not approved yet. NCT04930003
20.	Razi Cov Pars	Razi Vaccine and Serum Research Institute	Phase 2 clinical trial in Iran and not approved yet. IRCT20201214049709N2
21.	Recombinant SARS-CoV-2 Vaccine (CHO Cell)	National Vaccine and Serum Institute	Phase 1/2 clinical trial in China and not approved yet. NCT04869592
22.	IVX-411	Icosavax	Phase 1/2 Clinical trial in Australia and not approved yet. ACTRN12621000738820
23.	V-01	Livzon Mabpharm Inc	Phase 2 clinical trial in China and not approved yet. ChiCTR2100045107
24.	AKS-452	University Medical Center Groningen	Phase 1/2 clinical trial in Netherlands and not approved yet. NCT04681092
25.	COVAC-2	University of Saskatchewan	Phase 1/2 clinical trial in Canada and not approved yet. NCT04702178
26.	TAK-019	Takeda	Phase 1/2 clinical trial in Japan and not approved yet. NCT04712110
27.	BECOV2A BECOV2D	Biological E Limited	Phase 1/2 Clinical trial in India and not approved yet. CTRI/2020/11/029032 Phase 1/2 Clinical trial in India and not approved yet. CTRI/2020/11/029032
28.	AdimrSC-2f	Adimmune Corporation	Phase 1 Clinical trial in Taiwan. NCT04522089
29.	ReCOV	Jiangsu Rec-Biotechnology Co Ltd	Phase 1 Clinical trial in New Zealand. NCT04818801
30.	SpFN COVID-19 Vaccine	US Army Medical Research and Development Command	Phase 1 Clinical trial in US. NCT04784767
31.	CoVac-1	Tuebingen	Phase 1 Clinical trial in Germany. NCT04546841
32.	NBP2001	SK Bioscience Co Ltd	Phase 1 clinical trial in Republic of Korea. NCT04760743
33.	CoVepiT	OSE Immunotherapeutics	Phase 1 clinical trial in Belgium. NCT04885361
34.	CoV2-OGEN1	VaxForm	Phase 1 clinical trial in US. NCT04893512

produced by recombinant technology [150–155]. These protein subunit vaccines need adjuvants for better immunogenicity and multiple doses must be administered [156,157]. According to WHO (7th July 2020), three protein subunit-based vaccine candidates are in clinical trials and 51 are in pre-clinical evaluation. All the subunit vaccines in clinical trials use SARS-CoV-2 spike protein or RBD of spike protein [158–162].

VLPs are multi-protein structures similar to native virus particles except that they lack genetic material, so they cannot replicate. VLPs can stimulate strong immune responses because the protein structure of VLPs mimics the native virus particle. Therefore, when these are introduced into the body, they can stimulate strong immune responses [163]. These vaccine candidates are safe because of the lack of genetic material thereby they cannot cause any disease; however, these are difficult to manufacture [118]. Medicago Inc. is developing a VLP vaccine, which is currently in phase I clinical trials, where these VLPs are plant-based [164]. Other protein-based vaccines are listed in Table 4.

4. Significance of considering SARS-CoV-2 spike protein as an antigen in vaccine development

Being S protein is a structural component of the SARS-CoV-2 virus particle, it enables the virus to infect the host cells by latching with the ACE2 receptor of host cells. Similarly, the SARS virus also uses the same receptor; however, SARS-CoV-2 S protein shares only 73% similarity with SARS [165], and the binding affinity of SARS-Cov-2 S protein with ACE2 receptor is more than that of SARS S protein [166]. Immunogenic experiments in mice had revealed that the S protein of both SARS-CoV-2 and SARS are known to trigger the immune system to generate specific antibodies. SARS-CoV-2 S protein-specific antibodies and SARS S protein-specific antibodies did not exhibit any cross neutralization [167]. This lack of cross-neutralization between the two spike protein-specific antibodies indicates that SARS-CoV-2 spike protein has unique antigenic properties [167]. Hence, it is justified to consider SARS-CoV-2 spike protein as a specific antigen for vaccine development.

5. Passive immunization

Persons, who recovered from COVID-19 disease, exhibit SARS-CoV-2 specific antibodies in their plasma. Passive immunization injects the plasma of recovered patients to those critically ill or those with a high chance of infection [168]. Passive immunization is an age-old practice. This practice was followed in 1918 for the H1N1 influenza virus pandemic. During the outbreak of SARS in 2002-03, this approach was evaluated [169]. Passive immunization is mainly prophylactic rather than a therapeutic option. Convalescent plasma therapy may be effective for those in the early stages of infection or those susceptible to infection [1,4,168,170]. This approach might not provide a good prognosis for those already critically ill. Mechanism of action of passive immunization includes neutralization of virus particles by convalescent antibodies and induction of antibody-dependent cellular cytotoxicity [168]. Serum containing high titer virus-neutralizing antibodies can be administered prophylactically to prevent infection in vulnerable individuals, including healthcare providers susceptible individuals (e.g., hospital staff), or can be used in patients with mild conditions to reduce symptoms and mortality [168].

The advantage of passive immunization includes ready availability [168]. On the other hand, risks of passive immunization include the possibility of other infections that can be transferred via plasma constituents, immunological reactions such as serum sickness, transfusion-elated acute lung injury (TRALI), and antibody-dependent disease enhancement (ADE). ADE is a condition in which antibodies fail to neutralize the virus and facilitate disease enhancement; however, there is no evidence for this until now [168]. According to FDA and NIH guidelines, only high titer convalescent plasma therapy is suggested for non-hospitalized patients based on randomized clinical trials, but these clinical trials had some limitations such as small sample size and poor

Table 5
VLP based vaccine in clinical trials [175].

S. No	Vaccine candidate	Developer	Status of development.
1.	Plant-based VLP	Medicago	Phase 2/3 clinical trial in Canada and US. NCT04636697 NCT04450004
2.	RBD SARS-CoV-2 HBsAg VLP	SpyBiotech	Phase 1/2 clinical trial in Australia. ACTRN12620000817943
3.	VBI-2902a	VBI Vaccines Inc	Phase 1/2 clinical trial in Canada. NCT04773665
4.	SARS-CoV-2 VLP Vaccine	The Scientific and Technological Research Council of Turkey	Phase 1 clinical trial in Turkey. NCT04818281
5.	ABNCoV2	Radboud University	Phase 1 clinical trial in Netherland. NCT04839146

design [51].

6. Hyperimmune serum preparations (hyper-immune globulin, H-Ig preparations)

Plasma contains several components along with various antibodies. Hyperimmune serum preparations contain polyclonal SARS-CoV-2 specific immuno-globulins derived from the convalescent plasma [171]. Plasma-derived therapies help treat rare, life-threatening, complex genetic diseases. Convalescent plasma from patients with mild symptoms is collected and tested for adequate titers of virus-neutralizing antibodies [172]. However, the large-scale production of H-Ig preparations is complicated. Till now no hyperimmune serum preparations are available for COVID-19 treatment [51]. Table 5 presents some of the products which are in the developmental stage.

7. Conclusion

Overall, it can be concluded that the research progress to combat this pandemic situation has brought several leads for different stages of the disease condition. The monoclonal antibodies are essential tools to reduce the clinical progress of COVID-19 to severe conditions in non-hospitalized patients with high-risk factors. At the same time, Remdesivir in combination with Dexamethasone could be recommended for hospitalized patients with standard oxygen therapy. Alternatively, Dexamethasone and other immunomodulators could be recommended for severely ill patients in intensive care. All the recommended drugs are authorized on an emergency basis only and should be administered under medical supervision. Alternatively, different approaches have been made to develop vaccines against COVID-19 where different categories are associated with advantages and limitations. So far, 19 vaccines have been developed by scientists around the globe; only 6 out of them are authorized by WHO to vaccinate people to protect them against this harmful disease. Continuous research is ongoing to evaluate the efficacy of these vaccines towards newly emerging variants; however, nothing has nothing been reported yet. However, most of the vaccines are sufficiently effective against known variants. Present understanding of these therapeutic agents and vaccines gives hope to the world to get rid of the pandemic soon.

Declaration of Competing Interest

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

Acknowledgment

The authors acknowledge ICT-IOC, Bhubaneswar for providing necessary support. Rambabu Dandela thanks DST-SERB for Ramanujan fellowship (SB/S2/RJN-075/2016), Core research grant (CRG/2018/000782) and ICT-IOC start-up grant.

References

[1] B. Gorain, H. Choudhury, N. Molugulu, R.B. Athawale, P. Kesharwani, Fighting strategies against the novel coronavirus pandemic: Impact on global economy, Front. Public Heal. 8 (2020) 800, https://doi.org/10.3389/FPUBH.2020.606129.
[2] F. Wu, S. Zhao, B. Yu, Y.M. Chen, W. Wang, Z.G. Song, Y. Hu, Z.W. Tao, J.H. Tian, Y.Y. Pei, M.L. Yuan, Y.L. Zhang, F.H. Dai, Y. Liu, Q.M. Wang, J.J. Zheng, L. Xu, E. C. Holmes, Y.Z. Zhang, A new coronavirus associated with human respiratory disease in China, Nature 579 (2020) 265–269, https://doi.org/10.1038/s41586-020-2008-3.
[3] P. Zhou, X.-L. Yang, X.-G. Wang, B. Hu, L. Zhang, W. Zhang, H.-R. Si, Y. Zhu, B. Li, C.-L. Huang, H.-D. Chen, J. Chen, Y. Luo, H. Guo, R.-D. Jiang, M.-Q. Liu, Y. Chen, X.-R. Shen, X. Wang, X.-S. Zheng, K. Zhao, Q.-J. Chen, F. Deng, L.-L. Liu, B. Yan, F.-X. Zhan, Y.-Y. Wang, G.-F. Xiao, Z.-L. Shi, A pneumonia outbreak associated with a new coronavirus of probable bat origin, Nature 579 (2020) 270–273, https://doi.org/10.1038/s41586-020-2012-7.
[4] E. Shirbhate, J. Pandey, V.K. Patel, M. Kamal, T. Jawaid, B. Gorain, P. Kesharwani, H. Rajak, Understanding the role of ACE-2 receptor in pathogenesis of COVID-19 disease: a potential approach for therapeutic intervention, Pharmacol. Rep. 1 (2021) 3, https://doi.org/10.1007/s43440-021-00303-6.
[5] K.G. Andersen, A. Rambaut, W.I. Lipkin, E.C. Holmes, R.F. Garry, The proximal origin of SARS-CoV-2, Nat. Med. 26 (2020) 450–452, https://doi.org/10.1038/s41591-020-0820-9.
[6] S. Mule, A. Singh, K. Greish, A. Sahebkar, P. Kesharwani, R. Shukla, Drug repurposing strategies and key challenges for COVID-19 management, J. Drug Target. (2021) 1–17, https://doi.org/10.1080/1061186X.2021.2013852.
[7] M. Agrawal, S. Saraf, S. Saraf, U.S. Murty, S.B. Kurundkar, D. Roy, P. Joshi, D. Sable, Y.K. Choudhary, P. Kesharwani, A. Alexander, In-line treatments and clinical initiatives to fight against COVID-19 outbreak, Respir. Med. (2020), 106192, https://doi.org/10.1016/j.rmed.2020.106192.
[8] A.E. Gorbalenya, S.C. Baker, R.S. Baric, R.J. de Groot, C. Drosten, A.A. Gulyaeva, B.L. Haagmans, C. Lauber, A.M. Leontovich, B.W. Neuman, D. Penzar, S. Perlman, L.L.M. Poon, D.V. Samborskiy, I.A. Sidorov, I. Sola, J. Ziebuhr, The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2, Nat. Microbiol. 5 (2020) 536–544, https://doi.org/10.1038/s41564-020-0695-z.
[9] M. Agrawal, S. Saraf, S. Saraf, U.S. Murty, S.B. Kurundkar, D. Roy, P. Joshi, D. Sable, Y.K. Choudhary, P. Kesharwani, A. Alexander, In-line treatments and clinical initiatives to fight against COVID-19 outbreak, Respir. Med. (2020), 106192, https://doi.org/10.1016/j.rmed.2020.106192.
[10] Coronavirus: severe Covid-19 can damage the brain, preliminary study finds | South China Morning Post, (n.d.).
[11] P. Yang, X. Wang, COVID-19: a new challenge for human beings, Cell. Mol. Immunol. 17 (2020) 555–557, https://doi.org/10.1038/s41423-020-0407-x.
[12] M. Hoffmann, H. Kleine-Weber, N. Krüger, M. Müller, C. Drosten, S. Pöhlmann, The novel coronavirus 2019 (2019-nCoV) uses the SARS-coronavirus receptor ACE2 and the cellular protease TMPRSS2 for entry into target cells, BioRxiv (2020), https://doi.org/10.1101/2020.01.31.929042.
[13] Y. Shi, Y. Wang, C. Shao, J. Huang, J. Gan, X. Huang, E. Bucci, M. Piacentini, G. Ippolito, G. Melino, COVID-19 infection: the perspectives on immune responses, Cell Death Differ. 27 (2020) 1451–1454, https://doi.org/10.1038/s41418-020-0530-3.
[14] D. McGonagle, K. Sharif, A. O'Regan, C. Bridgewood, The role of cytokines including interleukin-6 in COVID-19 induced pneumonia and macrophage activation syndrome-like disease, Autoimmun. Rev. 19 (2020), 102537, https://doi.org/10.1016/j.autrev.2020.102537.
[15] W. Cao, T. Li, COVID-19: towards understanding of pathogenesis, Cell Res. 30 (2020) 367–369, https://doi.org/10.1038/s41422-020-0327-4.
[16] P.G. Gibson, L. Qin, S.H. Puah, COVID-19 acute respiratory distress syndrome (ARDS): clinical features and differences from typical pre-COVID-19 ARDS, Med. J. Aust. 213 (2020) 54–56.e1, https://doi.org/10.5694/mja2.50674.
[17] M.Z. Tay, C.M. Poh, L. Rénia, P.A. MacAry, L.F.P. Ng, The trinity of COVID-19: immunity, inflammation and intervention, Nat. Rev. Immunol. 20 (2020) 363–374, https://doi.org/10.1038/s41577-020-0311-8.
[18] C. Strehl, L. Ehlers, T. Gaber, F. Buttgereit, Glucocorticoids—all-rounders tackling the versatile players of the immune system, Front. Immunol. 10 (2019) 1744, https://doi.org/10.3389/FIMMU.2019.01744.
[19] P. Zhou, X. Lou Yang, X.G. Wang, B. Hu, L. Zhang, W. Zhang, H.R. Si, Y. Zhu, B. Li, C.L. Huang, H.D. Chen, J. Chen, Y. Luo, H. Guo, R. Di Jiang, M.Q. Liu, Y. Chen, X.R. Shen, X. Wang, X.S. Zheng, K. Zhao, Q.J. Chen, F. Deng, L.L. Liu, B. Yan, F.X. Zhan, Y.Y. Wang, G.F. Xiao, Z.L. Shi, A pneumonia outbreak associated with a new coronavirus of probable bat origin, Nature 579 (2020) 270–273, https://doi.org/10.1038/s41586-020-2012-7.
[20] FDA Approves First Treatment for COVID-19 | FDA, (n.d.).

[21] S. Mule, A. Singh, K. Greish, A. Sahebkar, P. Kesharwani, R. Shukla, Drug repurposing strategies and key challenges for COVID-19 management, J. Drug Target. 0 (2021) 1–17, https://doi.org/10.1080/1061186x.2021.2013852.

[22] G. Zhaori, L. Lu, C. Liu, Y. Guo, Progresses in clinical studies on antiviral therapies for COVID-19—Experience and lessons in design of clinical trials, Pediatr. Investig. 4 (2020) 263–274, https://doi.org/10.1002/PED4.12227.

[23] S. Singh, A. Numan, D. Sharma, R. Shukla, A. Alexander, G.K. Jain, F.J. Ahmad, P. Kesharwani, Epidemiology, virology and clinical aspects of hantavirus infections: an overview, Int. J. Environ. Health Res. (2021) 1–13, https://doi.org/10.1080/09603123.2021.1917527.

[24] CoVariants, (n.d.).

[25] About Variants of the Virus that Causes COVID-19 | CDC, (n.d.).

[26] Govt confirms two new strains of Covid-19 in India. Here is all you need to know - Coronavirus Outbreak News, (n.d.).

[27] A. Zumla, J.F.W. Chan, E.I. Azhar, D.S.C. Hui, K.Y. Yuen, Coronaviruses-drug discovery and therapeutic options, Nat. Rev. Drug Discov. 15 (2016) 327–347, https://doi.org/10.1038/nrd.2015.37.

[28] R. Thakare, P. Kesharwani, A. Dasgupta, N. Srinivas, S. Chopra, Antibiotics: past, present, and future, Drug Discov. Target. Drug-Resist. Bact. (2020) 1–8, https://doi.org/10.1016/B978-0-12-818480-6.00001-1.

[29] T.U. Singh, S. Parida, M.C. Lingaraju, M. Kesavan, D. Kumar, R.K. Singh, Drug repurposing approach to fight COVID-19, Pharmacol. Rep. 72 (2020) 1479–1508, https://doi.org/10.1007/s43440-020-00155-6.

[30] G. Li, E.De Clercq, Therapeutic options for the 2019 novel coronavirus (2019-nCoV), Nat. Rev. Drug Discov. 19 (2020) 149–150, https://doi.org/10.1038/d41573-020-00016-0.

[31] M. Malani, P. Salunke, S. Kulkarni, G.K. Jain, A. Sheikh, P. Kesharwani, J. Nirmal, Repurposing pharmaceutical excipients as an antiviral agent against SARS-CoV-2, J. Biomater. Sci. Polym. Ed. (2021), https://doi.org/10.1080/09205063.2021.1975020.

[32] V. Kakoty, S. K C, S.K. Dubey, C.H. Yang, P. Kesharwani, R. Taliyan, Lentiviral mediated gene delivery as an effective therapeutic approach for Parkinson disease, Neurosci. Lett. 750 (2021), 135769, https://doi.org/10.1016/j.neulet.2021.135769.

[33] V. Srivastava, A. Singh, G.K. Jain, F.J. Ahmad, R. Shukla, P. Kesharwani, Viral vectors as a promising nanotherapeutic approach against neurodegenerative disorders, Process Biochem. 109 (2021) 130–142, https://doi.org/10.1016/J.PROCBIO.2021.07.002.

[34] J.H. Beigel, K.M. Tomashek, L.E. Dodd, A.K. Mehta, B.S. Zingman, A.C. Kalil, E. Hohmann, H.Y. Chu, A. Luetkemeyer, S. Kline, D. Lopez de Castilla, R. W. Finberg, K. Dierberg, V. Tapson, L. Hsieh, T.F. Patterson, R. Paredes, D. A. Sweeney, W.R. Short, G. Touloumi, D.C. Lye, N. Ohmagari, M. Oh, G.M. Ruiz-Palacios, T. Benfield, G. Fätkenheuer, M.G. Kortepeter, R.L. Atmar, C.B. Creech, J. Lundgren, A.G. Babiker, S. Pett, J.D. Neaton, T.H. Burgess, T. Bonnett, M. Green, M. Makowski, A. Osinusi, S. Nayak, H.C. Lane, Remdesivir for the treatment of Covid-19 — Final report, N. Engl. J. Med. (2020), https://doi.org/10.1056/nejmoa2007764.

[35] B. Cao, Y. Wang, D. Wen, W. Liu, J. Wang, G. Fan, L. Ruan, B. Song, Y. Cai, M. Wei, X. Li, J. Xia, N. Chen, J. Xiang, T. Yu, T. Bai, X. Xie, L. Zhang, C. Li, Y. Yuan, H. Chen, H. Li, H. Huang, S. Tu, F. Gong, Y. Liu, Y. Wei, C. Dong, F. Zhou, X. Gu, J. Xu, Z. Liu, Y. Zhang, H. Li, L. Shang, K. Wang, K. Li, X. Zhou, X. Dong, Z. Qu, S. Lu, X. Hu, S. Ruan, S. Luo, J. Wu, L. Peng, F. Cheng, L. Pan, J. Zou, C. Jia, J. Wang, X. Liu, S. Wang, X. Wu, Q. Ge, J. He, H. Zhan, F. Qiu, L. Guo, C. Huang, T. Jaki, F.G. Hayden, P.W. Horby, D. Zhang, C. Wang, A trial of lopinavir–ritonavir in adults hospitalized with severe covid-19, N. Engl. J. Med. (2020), https://doi.org/10.1056/nejmoa2001282.

[36] Solidarity clinical trial for COVID-19 treatments, 2020.

[37] Y. Furuta, T. Komeno, T. Nakamura, Favipiravir (T-705), a broad spectrum inhibitor of viral RNA polymerase, Proc. Jpn. Acad. Ser. B Phys. Biol. Sci. 93 (2017) 449–463, https://doi.org/10.2183/pjab.93.027.

[38] C. Chen, Y. Zhang, J. Huang, P. Yin, Z. Cheng, J. Wu, S. Chen, Y. Zhang, B. Chen, M. Lu, Y. Luo, L. Ju, J. Zhang, X. Wang, Favipiravir versus arbidol for COVID-19: a randomized clinical trial, MedRxiv (2020), https://doi.org/10.1101/2020.03.17.20037432.

[39] Favipiravir in Hospitalized COVID-19 Patients (FIC), (n.d.).

[40] U. Agrawal, R. Raju, Z.F. Udwadia, Favipiravir: a new and emerging antiviral option in COVID-19, Med. J. Armed Forces India 76 (2020) 370–376, https://doi.org/10.1016/j.mjafi.2020.08.004.

[41] R.T. Eastman, J.S. Roth, K.R. Brimacombe, A. Simeonov, M. Shen, S. Patnaik, M. D. Hall, Remdesivir: A review of its discovery and development leading to emergency use authorization for treatment of COVID-19, ACS Cent. Sci. 6 (2020) 672–683, https://doi.org/10.1021/acscentsci.0c00489.

[42] M. Wang, R. Cao, L. Zhang, X. Yang, J. Liu, M. Xu, Z. Shi, Z. Hu, W. Zhong, G. Xiao, Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro, Cell Res. 30 (2020) 269–271, https://doi.org/10.1038/s41422-020-0282-0.

[43] E.P. Tchesnokov, J.Y. Feng, D.P. Porter, M. Götte, Mechanism of inhibition of ebola virus RNA-dependent RNA polymerase by remdesivir, Viruses 11 (2019), https://doi.org/10.3390/v11040326.

[44] B.N. Williamson, F. Feldmann, B. Schwarz, K. Meade-White, D.P. Porter, J. Schulz, N. van Doremalen, I. Leighton, C.K. Yinda, L. Pérez-Pérez, A. Okumura, J. Lovaglio, P.W. Hanley, G. Saturday, C.M. Bosio, S. Anzick, K. Barbian, T. Cihlar, C. Martens, D.P. Scott, V.J. Munster, E. de Wit, Clinical benefit of remdesivir in rhesus macaques infected with SARS-CoV-2, Nature 585 (2020) 273–276, https://doi.org/10.1101/2020.04.15.043166.

[45] T.K. Warren, R. Jordan, M.K. Lo, A.S. Ray, R.L. Mackman, V. Soloveva, D. Siegel, M. Perron, R. Bannister, H.C. Hui, N. Larson, R. Strickley, J. Wells, K.S. Stuthman, S.A. Van Tongeren, N.L. Garza, G. Donnelly, A.C. Shurtleff, C.J. Retterer, D. Gharaibeh, R. Zamani, T. Kenny, B.P. Eaton, E. Grimes, L.S. Welch, L. Gomba, C.L. Wilhelmsen, D.K. Nichols, J.E. Nuss, E.R. Nagle, J.R. Kugelman, G. Palacios, E. Doerffler, S. Neville, E. Carra, M.O. Clarke, L. Zhang, W. Lew, B. Ross, Q. Wang, K. Chun, L. Wolfe, D. Babusis, Y. Park, K.M. Stray, I. Trancheva, J.Y. Feng, O. Barauskas, Y. Xu, P. Wong, M.R. Braun, M. Flint, L.K. McMullan, S.-S. Chen, R. Fearns, S. Swaminathan, D.L. Mayers, C.F. Spiropoulou, W.A. Lee, S.T. Nichol, T. Cihlar, S. Bavari, Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys, Nature 531 (2016) 381–385, https://doi.org/10.1038/nature17180.

[46] J.D. Goldman, D.C.B. Lye, D.S. Hui, K.M. Marks, R. Bruno, R. Montejano, C. D. Spinner, M. Galli, M.-Y. Ahn, R.G. Nahass, Y.-S. Chen, D. SenGupta, R. H. Hyland, A.O. Osinusi, H. Cao, C. Blair, X. Wei, A. Gaggar, D.M. Brainard, W. J. Towner, J. Muñoz, K.M. Mullane, F.M. Marty, K.T. Tashima, G. Diaz, A. Subramanian, Remdesivir for 5 or 10 days in patients with severe covid-19, N. Engl. J. Med. 383 (2020) 1827–1837, https://doi.org/10.1056/nejmoa2015301.

[47] Y. Wang, D. Zhang, G. Du, R. Du, J. Zhao, Y. Jin, S. Fu, L. Gao, Z. Cheng, Q. Lu, Y. Hu, G. Luo, K. Wang, Y. Lu, H. Li, S. Wang, S. Ruan, C. Yang, C. Mei, Y. Wang, D. Ding, F. Wu, X. Tang, X. Ye, Y. Ye, B. Liu, J. Yang, W. Yin, A. Wang, G. Fan, F. Zhou, Z. Liu, X. Gu, J. Xu, L. Shang, Y. Zhang, L. Cao, T. Guo, Y. Wan, H. Qin, Y. Jiang, T. Jaki, F.G. Hayden, P.W. Horby, B. Cao, C. Wang, Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial, Lancet 395 (2020) 1569–1578, https://doi.org/10.1016/S0140-6736(20)31022-9.

[48] J. Grein, N. Ohmagari, D. Shin, G. Diaz, E. Asperges, A. Castagna, T. Feldt, G. Green, M.L. Green, F.-X. Lescure, E. Nicastri, R. Oda, K. Yo, E. Quiros-Roldan, A. Studemeister, J. Redinski, S. Ahmed, J. Bernett, D. Chelliah, D. Chen, S. Chihara, S.H. Cohen, J. Cunningham, A. D'Arminio Monforte, S. Ismail, H. Kato, G. Lapadula, E. L'Her, T. Maeno, S. Majumder, M. Massari, M. Mora-Rillo, Y. Mutoh, D. Nguyen, E. Verweij, A. Zoufaly, A.O. Osinusi, A. DeZure, Y. Zhao, L. Zhong, A. Chokkalingam, E. Elboudwarej, L. Telep, L. Timbs, I. Henne, S. Sellers, H. Cao, S.K. Tan, L. Winterbourne, P. Desai, R. Mera, A. Gaggar, R. P. Myers, D.M. Brainard, R. Childs, T. Flanigan, Compassionate use of remdesivir for patients with severe Covid-19, N. Engl. J. Med. 382 (2020) 2327–2336, https://doi.org/10.1056/nejmoa2007016.

[49] Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734TM) in Participants With Moderate Coronavirus Disease (COVID-19) Compared to Standard of Care Treatment - Full Text View - ClinicalTrials.gov, (n.d.).

[50] Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734TM) in Participants With Severe Coronavirus Disease (COVID-19) - Full Text View - ClinicalTrials.gov, (n.d.).

[51] COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health., (n.d.).

[52] M.L. Adamsick, R.G. Gandhi, M.R. Bidell, R.H. Elshaboury, R.P. Bhattacharyya, A. Y. Kim, S. Nigwekar, E.P. Rhee, M.E. Sise, Remdesivir in patients with acute or chronic kidney disease and COVID-19, J. Am. Soc. Nephrol. 31 (2020) 1384–1386, https://doi.org/10.1681/ASN.2020050589.

[53] HIGHLIGHTS OF PRESCRIBING INFORMATION - VEKLURY (Remdesivir), (n.d.).

[54] R.L. Gottlieb, A. Nirula, P. Chen, J. Boscia, B. Heller, J. Morris, G. Huhn, J. Cardona, B. Mocherla, V. Stosor, I. Shawa, P. Kumar, A.C. Adams, J. Van Naarden, K.L. Custer, M. Durante, G. Oakley, A.E. Schade, T.R. Holzer, P.J. Ebert, R.E. Higgs, N.L. Kallewaard, J. Sabo, D.R. Patel, P. Klekotka, L. Shen, D. M. Skovronsky, Effect of bamlanivimab as monotherapy or in combination with etesevimab on viral load in patients with mild to moderate COVID-19: a randomized clinical trial, J. Am. Med. Assoc. 325 (2021) 632–644, https://doi.org/10.1001/jama.2021.0202.

[55] COV-2067 PHASE 3 TRIAL IN HIGH-RISK OUTPATIENTS SHOWS THAT REGEN-COV TM (2400 MG AND 1200 MG IV DOSES) SIGNIFICANTLY REDUCES RISK OF HOSPITALIZATION OR DEATH WHILE ALSO SHORTENING SYMPTOM DURATION, (n.d.).

[56] VIR-7831 for the Early Treatment of COVID-19 in Outpatients - Full Text View - ClinicalTrials.gov, (n.d.).

[57] Fact sheet for healthcare providers. Emergency use authorization of Sotrovimab, (n.d.).

[58] WHO welcomes preliminary results about dexamethasone use in treating critically ill COVID-19 patients, (n.d.).

[59] K. Dubois-Camacho, P.A. Ottum, D. Franco-Muñoz, M. De La Fuente, A. Torres-Riquelme, D. Díaz-Jiménez, M. Olivares-Morales, G. Astudillo, R. Quera, M. A. Hermoso, Glucocorticosteroid therapy in inflammatory bowel diseases: From clinical practice to molecular biology, World J. Gastroenterol. 23 (2017) 6628–6638, https://doi.org/10.3748/wjg.v23.i36.6628.

[60] Dexamethasone, oral tablet, 2020. (n.d.).

[61] Low-cost dexamethasone reduces death by up to one third in hospitalised patients with severe respiratory complications of COVID-19 | University of Oxford, (n.d.).

[62] Corticosteroids | COVID-19 Treatment Guidelines, (n.d.).

[63] COVID-19: What is dexamethasone and how does it work?, Wire Sci. (2020).

[64] H. Brotherton, E. Usuf, B. Nadjm, K. Forrest, K. Bojang, A.L. Samateh, M. Bittaye, C.A. Roberts, U. d'Alessandro, A. Roca, Dexamethasone for COVID-19: data needed from randomised clinical trials in Africa, Lancet Glob. Heal. 8 (2020) e1125–e1126, https://doi.org/10.1016/S2214-109X(20)30318-1.

[65] U.N. Das, Bioactive lipids in COVID-19-further evidence, Arch. Med. Res. (2020), https://doi.org/10.1016/j.arcmed.2020.09.006.

[66] R.J. Jose, A. Manuel, COVID-19 cytokine storm: the interplay between inflammation and coagulation, Lancet Respir. Med. 8 (2020) e46–e47, https://doi.org/10.1016/S2213-2600(20)30216-2.
[67] T.M.C. de Lucena, A.F. da Silva Santos, B.R. de Lima, M.E. de Albuquerque Borborema, J. de Azevêdo Silva, Mechanism of inflammatory response in associated comorbidities in COVID-19, Diabetes Metab. Syndr. Clin. Res. Rev. 14 (2020) 597–600, https://doi.org/10.1016/j.dsx.2020.05.025.
[68] M.H. Ahmed, A. Hassan, Dexamethasone for the treatment of coronavirus disease (COVID-19): a review, SN Compr. Clin. Med. 2 (2020) 2637–2646, https://doi.org/10.1007/s42399-020-00610-8.
[69] M. Rafiullah, K. Siddiqui, Corticosteroid use in viral pneumonia: experience so far and the dexamethasone breakthrough in coronavirus disease-2019, J. Comp. Eff. Res. 9 (2020) 1247–1254, https://doi.org/10.2217/cer-2020-0146.
[70] Comparison of Efficacy of Dexamethasone and Methylprednisolone in Moderate to Severe Covid 19 Disease - Full Text View - ClinicalTrials.gov, (n.d.).
[71] Dexamethasone for COVID-19 Related ARDS: a Multicenter, Randomized Clinical Trial - Full Text View - ClinicalTrials.gov, (n.d.).
[72] J. Villar, C. Ferrando, D. Martínez, A. Ambrós, T. Muñoz, J.A. Soler, G. Aguilar, F. Alba, E. González-Higueras, L.A. Conesa, C. Martín-Rodríguez, F.J. Díaz-Domínguez, P. Serna-Grande, R. Rivas, J. Ferreres, J. Belda, L. Capilla, A. Tallet, J.M. Añón, R.L. Fernández, J.M. González-Martín, J. Álvarez, J.M. Añón, M. J. Asensio, J. Blanco, M. Blasco, L. Cachafeiro, R. del Campo, J.A. Carbonell, N. Carbonell, A. Cariñena, D. Carriedo, M. Chico, L.A. Conesa, R. Corpas, J. Cuervo, F.J. Díaz-Domínguez, C. Domínguez-Antelo, L. Fernández, R. L. Fernández, E. Gamboa, R.I. González-Luengo, J.M. González-Martín, R. Ortiz Díaz-Miguel, R. Pérez-González, A.M. Prieto, I. Prieto, L. Rojas-Viguera, M. A. Romera, J. Sánchez-Ballesteros, J.M. Segura, A. Serrano, R. Solano, J.A. Soler, M. Soro, Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial, Lancet Respir. Med. 8 (2020) 267–276, https://doi.org/10.1016/S2213-2600(19)30417-5.
[73] Higher vs. Lower Doses of Dexamethasone for COVID-19 and Severe Hypoxia - Full Text View - ClinicalTrials.gov, (n.d.).
[74] A.C. Kalil, T.F. Patterson, A.K. Mehta, K.M. Tomashek, C.R. Wolfe, V. Ghazaryan, V.C. Marconi, G.M. Ruiz-Palacios, L. Hsieh, S. Kline, V. Tapson, N.M. Iovine, M. K. Jain, D.A. Sweeney, H.M. El Sahly, A.R. Branche, J. Regalado Pineda, D.C. Lye, U. Sandkovsky, A.F. Luetkemeyer, S.H. Cohen, R.W. Finberg, P.E.H. Jackson, B. Taiwo, C.I. Paules, H. Arguinchona, N. Erdmann, N. Ahuja, M. Frank, M. Oh, E.-S. Kim, S.Y. Tan, R.A. Mularski, H. Nielsen, P.O. Ponce, B.S. Taylor, L. Larson, N.G. Rouphael, Y. Saklawi, V.D. Cantos, E.R. Ko, J.J. Engemann, A.N. Amin, M. Watanabe, J. Billings, M.-C. Elie, R.T. Davey, T.H. Burgess, J. Ferreira, M. Green, M. Makowski, A. Cardoso, S. de Bono, T. Bonnett, M. Proschan, G. A. Deye, W. Dempsey, S.U. Nayak, L.E. Dodd, J.H. Beigel, Baricitinib plus remdesivir for hospitalized adults with covid-19, N. Engl. J. Med. 384 (2021) 795–807, https://doi.org/10.1056/nejmoa2031994.
[75] J. Gao, Z. Tian, X. Yang, Breakthrough: chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies, Biosci. Trends (2020), https://doi.org/10.5582/bst.2020.01047.
[76] S. Satarker, T. Ahuja, M. Banerjee, V.B. E, S. Dogra, T. Agarwal, M. Nampoothiri, Hydroxychloroquine in COVID-19: potential mechanism of action against SARS-CoV-2, Curr. Pharmacol. Rep. 6 (2020) 203–211, https://doi.org/10.1007/s40495-020-00231-8.
[77] R. Shah, T. Soni, U. Shah, B.N. Suhagia, M.N. Patel, T. Patel, G.A. Gabr, B. Gorain, P. Kesharwani, Formulation development and characterization of lumefantrine nanosuspension for enhanced antimalarial activity, J. Biomater. Sci. Polym. Ed. (2020), https://doi.org/10.1080/09205063.2020.1870378.
[78] T.Y. Hu, M. Frieman, J. Wolfram, Insights from nanomedicine into chloroquine efficacy against COVID-19, Nat. Nanotechnol. 15 (2020) 247–249, https://doi.org/10.1038/s41565-020-0674-9.
[79] B.S. Abella, E.L. Jolkovsky, B.T. Biney, J.E. Uspal, M.C. Hyman, I. Frank, S. E. Hensley, S. Gill, D.T. Vogl, I. Maillard, D.V. Babushok, A.C. Huang, S.D. Nasta, J.C. Walsh, E.P. Wiletyo, P.A. Gimotty, M.C. Milone, R.K. Amaravadi, Efficacy and safety of hydroxychloroquine vs placebo for pre-exposure SARS-CoV-2 prophylaxis among health care workers: a randomized clinical trial, JAMA Intern. Med. 181 (2021) 195–202, https://doi.org/10.1001/jamainternmed.2020.6319.
[80] Hydroxychloroquine for the Treatment of Mild COVID-19 Disease - Full Text View - ClinicalTrials.gov, (n.d.).
[81] Z. Kashour, M. Riaz, M.A. Garbati, O. AlDosary, H. Tlayjeh, D. Gerberi, M. H. Murad, M.R. Sohail, T. Kashour, I.M. Tleyjeh, Efficacy of chloroquine or hydroxychloroquine in COVID-19 patients: a systematic review and meta-analysis, J. Antimicrob. Chemother. 76 (2021) 30–42, https://doi.org/10.1093/jac/dkaa403.
[82] Immune Modulators for Treating COVID-19 - ClinicalTrials.gov, (n.d.).
[83] M.T. Dolinger, H. Person, R. Smith, L. Jarchin, N. Pittman, M.C. Dubinsky, J. Lai, Pediatric Crohn disease and multisystem inflammatory syndrome in children (MIS-C) and COVID-19 treated with infliximab, J. Pediatr. Gastroenterol. Nutr. 71 (2020) 153–155, https://doi.org/10.1097/MPG.0000000000002809.
[84] C. Bezzio, G. Manes, F. Bini, L. Pellegrini, S. Saibeni, Infliximab for severe ulcerative colitis and subsequent SARS-CoV-2 pneumonia: a stone for two birds, Gut (2020), https://doi.org/10.1136/gutjnl-2020-321760.
[85] V.C. Marconi, A.V. Ramanan, S. de Bono, C.E. Kartman, V. Krishnan, R. Liao, M. B. Lucia Piruzeli, J.D. Goldman, J. Alatorre-Alexander, R. de Cassia Pellegrini, V. Estrada, M. Som, A. Cardoso, S. Chakladar, B. Crowe, P. Reis, X. Zhang, D. H. Adams, E. Wesley Ely on, R. Liao, M.L.B. Piruzeli, A. Cardoso, S. Chakladar, B. Crowe, X. Zhang, D. Adams, Baricitinib plus standard of care for hospitalized adults with COVID-19, MedRxiv (2021), https://doi.org/10.1101/2021.04.30.21255934.
[86] Baricitinib drug can reduce mortality in patients with moderate to severe COVID-19, (n.d.).
[87] Baricitinib Receives Emergency Use Authorization from the FDA for the Treatment of Hospitalized Patients with COVID-19, (n.d.).
[88] Hydroxychloroquine and Nitazoxanide Combination Therapy for COVID-19 - Full Text View - ClinicalTrials.gov, (n.d.).
[89] J.M. Calderón, H.M. Zerón, S. Padmanabhan, Treatment with hydroxychloroquine vs hydroxychloroquine + nitazoxanide in covid-19 patients with risk factors for poor prognosis: a structured summary of a study protocol for a randomised controlled trial, Trials 21 (2020) 21–23, https://doi.org/10.1186/s13063-020-04448-2.
[90] C. Ferreira, S.D. Viana, F. Reis, Gut microbiota dysbiosis–immune hyperresponse–inflammation triad in coronavirus disease 2019 (Covid-19): Impact of pharmacological and nutraceutical approaches, Microorganisms 8 (2020) 1–29, https://doi.org/10.3390/microorganisms8101514.
[91] A.S. Ojo, S.A. Balogun, O.T. Williams, O.S. Ojo, Pulmonary fibrosis in COVID-19 survivors: predictive factors and risk reduction strategies, Pulm. Med. 2020 (2020), https://doi.org/10.1155/2020/6175964.
[92] Full-dose blood thinners decreased need for life support and improved outcome in hospitalized COVID-19 patients | National Institutes of Health (NIH), (n.d.).
[93] Synairgen announces positive results from trial of SNG001, (n.d.).
[94] E. Davoudi-Monfared, H. Rahmani, H. Khalili, M. Hajiabdolbaghi, M. Salehi, L. Abbasian, H. Kazemzadeh, M.S. Yekaninejad, A randomized clinical trial of the efficacy and safety of interferon β-1a in treatment of severe COVID-19, Antimicrob. Agents Chemother. 64 (2020), https://doi.org/10.1128/AAC.01061-20.
[95] Q. Zhou, V. Chen, C.P. Shannon, X.S. Wei, X. Xiang, X. Wang, Z.H. Wang, S. J. Tebbutt, T.R. Kollmann, E.N. Fish, Interferon-α2b treatment for COVID-19, Front. Immunol. 11 (2020), https://doi.org/10.3389/fimmu.2020.01061.
[96] G. Cavalli, G. De Luca, C. Campochiaro, E. Della-Torre, M. Ripa, D. Canetti, C. Oltolini, B. Castiglioni, C. Tassan Din, N. Boffini, A. Tomelleri, N. Farina, A. Ruggeri, P. Rovere-Querini, G. Di Lucca, S. Martinenghi, R. Scotti, M. Tresoldi, F. Ciceri, G. Landoni, A. Zangrillo, P. Scarpellini, L. Dagna, Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study, Lancet Rheumatol. 2 (2020) e325–e331, https://doi.org/10.1016/S2665-9913(20)30127-2.
[97] G. Dauriat, J. Le Pavec, G. Hayem, T. Huet, H. Beaussier, O. Voisin, S. Jouveshomme, G. Dauriat, I. Lazareth, E. Sacco, J.-M. Naccache, Y. Bézie, S. Laplanche, A. Le Berre, J. Le Pavec, S. Salmeron, J. Emmerich, J.-J. Mourad, G. Chatellier, Anakinra for severe forms of COVID-19: a cohort study, Lancet Rheumatol. 2 (2020) e393–e400, https://doi.org/10.1016/S2665-9913(20)30164-8.
[98] Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19, N. Engl. J. Med. 384 (2021) 1491–1502. https://doi.org/10.1056/nejmoa2100433.
[99] I.O. Rosas, N. Bräu, M. Waters, R.C. Go, B.D. Hunter, S. Bhagani, D. Skiest, M. S. Aziz, N. Cooper, I.S. Douglas, S. Savic, T. Youngstein, L. Del Sorbo, A. Cubillo Gracian, D.J. De La Zerda, A. Ustianowski, M. Bao, S. Dimonaco, E. Graham, B. Matharu, H. Spotswood, L. Tsai, A. Malhotra, Tocilizumab in hospitalized patients with severe Covid-19 pneumonia, N. Engl. J. Med. 384 (2021) 1503–1516, https://doi.org/10.1056/nejmoa2028700.
[100] J. Zhang, X. Rao, Y. Li, Y. Zhu, F. Liu, G. Guo, G. Luo, Z. Meng, D. De Backer, H. Xiang, Z. Peng, Pilot trial of high-dose vitamin C in critically ill COVID-19 patients, Ann. Intensive Care 11 (2021), https://doi.org/10.1186/s13613-020-00792-3.
[101] S. Thomas, D. Patel, B. Bittel, K. Wolski, Q. Wang, A. Kumar, Z.J. Il'Giovine, R. Mehra, C. McWilliams, S.E. Nissen, M.Y. Desai, Effect of high-dose zinc and ascorbic acid supplementation vs usual care on symptom length and reduction among ambulatory patients with SARS-CoV-2 infection: the COVID A to Z randomized clinical trial, JAMA Netw. Open 4 (2021), https://doi.org/10.1001/jamanetworkopen.2021.0369.
[102] I.H. Murai, A.L. Fernandes, L.P. Sales, A.J. Pinto, K.F. Goessler, C.S.C. Duran, C.B. R. Silva, A.S. Franco, M.B. MacEdo, H.H.H. Dalmolin, J. Baggio, G.G.M. Balbi, B. Z. Reis, L. Antonangelo, V.F. Caparbo, B. Gualano, R.M.R. Pereira, Effect of a single high dose of vitamin D3on hospital length of stay in patients with moderate to severe COVID-19: a randomized clinical trial, J. Am. Med. Assoc. 325 (2021) 1053–1060, https://doi.org/10.1001/jama.2020.26848.
[103] S. Abd-Elsalam, S. Soliman, E.S. Esmail, M. Khalaf, E.F. Mostafa, M.A. Medhat, O. A. Ahmed, M.S.A. El Ghafar, M. Alboraie, S.M. Hassany, Do zinc supplements enhance the clinical efficacy of hydroxychloroquine?: a randomized, multicenter trial, Biol. Trace Elem. Res. (2020), https://doi.org/10.1007/s12011-020-02512-1.
[104] S. Ahmed, M.M. Karim, A.G. Ross, M.S. Hossain, J.D. Clemens, M.K. Sumiya, C. S. Phru, M. Rahman, K. Zaman, J. Somani, R. Yasmin, M.A. Hasnat, A. Kabir, A. B. Aziz, W.A. Khan, A five-day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness, Int. J. Infect. Dis. 103 (2021) 214–216, https://doi.org/10.1016/j.ijid.2020.11.191.
[105] A. Zeeshan Khan Chachar, K. Ahmad Khan, M. Asif, K. Tanveer, A. Khaqan, R. Basri, Effectiveness of ivermectin in SARS-CoV-2/COVID-19 patients, Int. J. Sci. 9 (2020) 31–35, https://doi.org/10.18483/ijsci.2378.
[106] I.F.N. Hung, K.C. Lung, E.Y.K. Tso, R. Liu, T.W.H. Chung, M.Y. Chu, Y.Y. Ng, J. Lo, J. Chan, A.R. Tam, H.P. Shum, V. Chan, A.K.L. Wu, K.M. Sin, W.S. Leung, W. L. Law, D.C. Lung, S. Sin, P. Yeung, C.C.Y. Yip, R.R. Zhang, A.Y.F. Fung, E.Y. W. Yan, K.H. Leung, J.D. Ip, A.W.H. Chu, W.M. Chan, A.C.K. Ng, R. Lee, K. Fung, A. Yeung, T.C. Wu, J.W.M. Chan, W.W. Yan, W.M. Chan, J.F.W. Chan, A.K.W. Lie, O.T.Y. Tsang, V.C.C. Cheng, T.L. Que, C.S. Lau, K.H. Chan, K.K.W. To, K.Y. Yuen,

Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial, Lancet 395 (2020) 1695–1704, https://doi.org/10.1016/S0140-6736(20)31042-4.
[107] Y. Li, Z. Xie, W. Lin, W. Cai, C. Wen, Y. Guan, X. Mo, J. Wang, Y. Wang, P. Peng, X. Chen, W. Hong, G. Xiao, J. Liu, L. Zhang, F. Hu, F. Li, F. Zhang, X. Deng, L. Li, Efficacy and safety of lopinavir/ritonavir or arbidol in adult patients with mild/moderate COVID-19: an exploratory randomized controlled trial, Med 1 (2020) 105–113.e4, https://doi.org/10.1016/j.medj.2020.04.001.
[108] P.W. Horby, M. Mafham, J.L. Bell, L. Linsell, N. Staplin, J. Emberson, A. Palfreeman, J. Raw, E. Elmahi, B. Prudon, C. Green, S. Carley, D. Chadwick, M. Davies, M.P. Wise, J.K. Baillie, L.C. Chappell, S.N. Faust, T. Jaki, K. Jefferey, W.S. Lim, A. Montgomery, K. Rowan, E. Juszczak, R. Haynes, M.J. Landray, Lopinavir–ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial, Lancet 396 (2020) 1345–1352, https://doi.org/10.1016/S0140-6736(20)32013-4.
[109] C. Schoergenhofer, B. Jilma, T. Stimpfl, M. Karolyi, A. Zoufaly, Pharmacokinetics of lopinavir and ritonavir in patients hospitalized with Coronavirus Disease 2019 (COVID-19, Ann. Intern. Med. 173 (2020) 670–672, https://doi.org/10.7326/M20-1550.
[110] A.S. Clem, Fundamentals of vaccine immunology, in: J. Glob. Infect. Dis., Wolters Kluwer – Medknow Publications, 2011, pp. 73–78, https://doi.org/10.4103/0974-777X.77299.
[111] A.S. Monto, Vaccines and antiviral drugs in pandemic preparedness, Emerg. Infect. Dis. 12 (2006) 55–60, https://doi.org/10.3201/eid1201.051068.
[112] WHO lists two additional COVID-19 vaccines for emergency use and COVAX roll-out, (n.d.).
[113] COVAXIN - India's First Indigenous Covid-19 Vaccine | Bharat Biotech, (n.d.).
[114] comirnaty, (n.d.).
[115] COVID-19 Vaccines Advice, (n.d.).
[116] WHO | SARS-CoV-2 Variants, WHO. (2021).
[117] Accelerating a safe and effective COVID-19 vaccine, (2020).
[118] E. Callaway, The race for coronavirus vaccines: a graphical guide, Nature 580 (2020) 576–577, https://doi.org/10.1038/d41586-020-01221-y.
[119] WHO Guidelines on viral inactivation and removal procedures intended to assure the viral safety of human blood plasma products, (n.d.).
[120] CoronaVac COVID-19 Vaccine — Precision Vaccinations, (n.d.).
[121] F. Amanat, F. Krammer, SARS-CoV-2 vaccines: status report, Immunity 52 (2020) 583–589, https://doi.org/10.1016/j.immuni.2020.03.007.
[122] Severe acute respiratory syndrome coronavirus 2 isolate Wuhan-Hu-1, complete genome, GenBank: MN908947.3. (2020).
[123] B. Chen, E.K. Tian, B. He, L. Tian, R. Han, S. Wang, Q. Xiang, S. Zhang, T. El Arnaout, W. Cheng, Overview of lethal human coronaviruses, Signal Transduct. Target. Ther. 5 (2020) 89, https://doi.org/10.1038/s41392-020-0190-2.
[124] P. Kesharwani, S. Banerjee, U. Gupta, M.C.I. Mohd Amin, S. Padhye, F.H. Sarkar, A.K. Iyer, PAMAM dendrimers as promising nanocarriers for RNAi therapeutics, 18 (2015) 565–572. https://doi.org/10.1016/j.mattod.2015.06.003.
[125] M.W. Amjad, P. Kesharwani, M.C.I. Mohd Amin, A.K. Iyer, Recent advances in the design, development, and targeting mechanisms of polymeric micelles for delivery of siRNA in cancer therapy, Prog. Polym. Sci. 64 (2017) 154–181, https://doi.org/10.1016/j.progpolymsci.2016.09.008.
[126] M.W. Amjad, M.C.I.M. Amin, H. Katas, A.M. Butt, P. Kesharwani, A.K. Iyer, In vivo antitumor activity of folate-conjugated cholic acid-polyethylenimine micelles for the codelivery of doxorubicin and siRNA to colorectal adenocarcinomas, Mol. Pharm. 12 (2015) 4247–4258, https://doi.org/10.1021/acs.molpharmaceut.5b00827.
[127] R.K. Tekade, M. Tekade, P. Kesharwani, A. D'Emanuele, RNAi-combined nano-chemotherapeutics to tackle resistant tumors, Drug Discov. Today (2016), https://doi.org/10.1016/j.drudis.2016.06.029.
[128] A. Jain, A. Jain, P. Parajuli, V. Mishra, G. Ghoshal, B. Singh, U.S. Shivhare, O. P. Katare, P. Kesharwani, Recent advances in galactose-engineered nanocarriers for the site-specific delivery of siRNA and anticancer drugs, Drug Discov. Today (2017), https://doi.org/10.1016/j.drudis.2017.11.003.
[129] V. Mishra, P. Kesharwani, N.K. Jain, siRNA nanotherapeutics: a Trojan horse approach against HIV, Drug Discov. Today 19 (2014) 1913–1920, https://doi.org/10.1016/j.drudis.2014.09.019.
[130] P.V. Thanikachalam, S. Ramamurthy, Z.W. Wong, B.J. Koo, J.Y. Wong, M. F. Abdullah, Y.H. Chin, C.H. Chia, J.Y. Tan, W.T. Neo, B. Sen Tan, W.F. Khan, P. Kesharwani, Current attempts to implement microRNA-based diagnostics and therapy in cardiovascular and metabolic disease: a promising future, Drug Discov. Today 23 (2018) 460–480, https://doi.org/10.1016/j.drudis.2017.10.020.
[131] R. Chadar, Afsana, P. Kesharwani, Nanotechnology-based siRNA delivery strategies for treatment of triple negative breast cancer, Int. J. Pharm. 605 (2021), 120835, https://doi.org/10.1016/J.IJPHARM.2021.120835.
[132] D. Singh, P. Kesharwani, N.A. Alhakamy, H.R. Siddique, Accentuating CircRNA-miRNA-transcription factors axis: a conundrum in cancer research, Front. Pharmacol. 12 (2022) 3904, https://doi.org/10.3389/FPHAR.2021.784801/BIBTEX.
[133] P. Kesharwani, V. Gajbhiye, N.K. Jain, A review of nanocarriers for the delivery of small interfering RNA, Biomaterials 33 (2012) 7138–7150.
[134] ChAdOx1-S[recombinant] (COVID-19 Vaccine AstraZeneca) - Food and Drug Administration of the Philippines, (n.d.).
[135] P.M. Folegatti, K.J. Ewer, P.K. Aley, B. Angus, S. Becker, S. Belij-Rammerstorfer, D. Bellamy, S. Bibi, M. Bittaye, E.A. Clutterbuck, C. Dold, S.N. Faust, A. Finn, A. L. Flaxman, B. Hallis, P. Heath, D. Jenkin, R. Lazarus, R. Makinson, A. M. Minassian, K.M. Pollock, M. Ramasamy, H. Robinson, M. Snape, R. Tarrant, M. Voysey, C. Green, A.D. Douglas, A.V.S. Hill, T. Lambe, S.C. Gilbert, A. J. Pollard, J. Aboagye, K. Adams, A. Ali, E. Allen, J.L. Allison, R. Anslow, E. H. Arbe-Barnes, G. Babbage, K. Baillie, M. Baker, N. Baker, P. Baker, I. Baleanu, J. Ballaminut, E. Barnes, J. Barrett, L. Bates, A. Batten, K. Beadon, R. Beckley, E. Berrie, L. Berry, A. Beveridge, K.R. Bewley, E.M. Bijker, T. Bingham, L. Blackwell, C.L. Blundell, E. Bolam, E. Boland, N. Borthwick, T. Bower, A. Boyd, T. Brenner, P.D. Bright, C. Brown-O'Sullivan, E. Brunt, J. Burbage, S. Burge, K. R. Buttigieg, N. Byard, I. Cabera Puig, A. Calvert, S. Camara, M. Cao, F. Cappuccini, M. Carr, M.W. Carroll, V. Carter, K. Cathie, R.J. Challis, S. Charlton, I. Chelysheva, J.S. Cho, P. Cicconi, L. Cifuentes, H. Clark, E. Clark, T. Cole, R. Colin-Jones, C.P. Conlon, A. Cook, N.S. Coombes, R. Cooper, C. A. Cosgrove, K. Coy, W.E.M. Crocker, C.J. Cunningham, B.E. Damratoski, L. Dando, M.S. Datoo, H. Davies, H. De Graaf, T. Demissie, C. Di Maso, I. Dietrich, T. Dong, F.R. Donnellan, N. Douglas, C. Downing, J. Drake, R. Drake-Brockman, R.E. Drury, S.J. Dunachie, N.J. Edwards, F.D.L. Edwards, C.J. Edwards, S.C. Elias, M.J. Elmore, K.R.W. Emary, M.R. English, S. Fagerbrink, S. Felle, S. Feng, S. Field, C. Fixmer, C. Fletcher, K.J. Ford, J. Fowler, P. Fox, E. Francis, J. Frater, J. Furze, M. Fuskova, E. Galiza, D. Gbesemete, C. Gilbride, K. Godwin, G. Gorini, L. Goulston, C. Grabau, L. Gracie, Z. Gray, L.B. Guthrie, M. Hackett, S. Halwe, E. Hamilton, J. Hamlyn, B. Hanumunthadu, I. Harding, S.A. Harris, A. Harris, D. Harrison, C. Harrison, T.C. Hart, L. Haskell, S. Hawkins, I. Head, J.A. Henry, J. Hill, S.H.C. Hodgson, M.M. Hou, E. Howe, N. Howell, C. Hutlin, S. Ikram, C. Isitt, P. Iveson, S. Jackson, F. Jackson, S.W. James, M. Jenkins, E. Jones, K. Jones, C.E. Jones, B. Jones, R. Kailath, K. Karampatsas, J. Keen, S. Kelly, D. Kelly, D. Kerr, S. Kerridge, L. Khan, U. Khan, A. Killen, J. Kinch, T.B. King, L. King, J. King, L. Kingham-Page, P. Klenerman, F. Knapper, J.C. Knight, D. Knott, S. Koleva, A. Kupke, C.W. Larkworthy, J.P.J. Larwood, A. Laskey, A. M. Lawrie, A. Lee, K.Y. Ngan Lee, E.A. Lees, H. Legge, A. Lelliott, N.M. Lemm, A. M. Lias, A. Linder, S. Lipworth, X. Liu, S. Liu, R. Lopez Ramon, M. Lwin, F. Mabesa, M. Madhavan, G. Mallett, K. Mansatta, I. Marcal, S. Marinou, E. Marlow, J.L. Marshall, J. Martin, J. McEwan, L. McInroy, G. Meddaugh, A. J. Mentzer, N. Mirtorabi, M. Moore, E. Moran, E. Morey, V. Morgan, S.J. Morris, H. Morrison, G. Morshead, R. Morter, Y.F. Mujadidi, J. Muller, T. Munera-Huertas, C. Munro, A. Munro, S. Murphy, V.J. Munster, P. Mweu, A. Noé, F. L. Nugent, E. Nuthall, K. O'Brien, D. O'Connor, B. Oguti, J.L. Oliver, C. Oliveira, P.J. O'Reilly, M. Osborn, P. Osborne, C. Owen, D. Owens, N. Owino, M. Pacurar, K. Parker, H. Parracho, M. Patrick-Smith, V. Payne, J. Pearce, Y. Peng, M. P. Peralta Alvarez, J. Perring, K. Pfafferott, D. Pipini, E. Plested, H. Pluess-Hall, K. Pollock, I. Poulton, L. Presland, S. Provstgaard-Morys, D. Pulido, K. Radia, F. Ramos Lopez, J. Rand, H. Ratcliffe, T. Rawlinson, S. Rhead, A. Riddell, A. J. Ritchie, H. Roberts, J. Robson, S. Roche, C. Rohde, C.S. Rollier, R. Romani, I. Rudiansyah, S. Saich, S. Sajjad, S. Salvador, L. Sanchez Riera, H. Sanders, K. Sanders, S. Sapaun, C. Sayce, E. Schofield, G. Screaton, B. Selby, C. Semple, H. R. Sharpe, I. Shaik, A. Shea, H. Shelton, S. Silk, L. Silva-Reyes, D.T. Skelly, H. Smee, C.C. Smith, D.J. Smith, R. Song, A.J. Spencer, E. Stafford, A. Steele, E. Stefanova, L. Stockdale, A. Szigeti, A. Tahiri-Alaoui, M. Tait, H. Talbot, R. Tanner, I.J. Taylor, V. Taylor, R. Te Water Naude, N. Thakur, Y. Themistocleous, A. Themistocleous, M. Thomas, T.M. Thomas, A. Thompson, S. Thomson-Hill, J. Tomlins, S. Tonks, J. Towner, N. Tran, J.A. Tree, A. Truby, K. Turkentine, C. Turner, N. Turner, S. Turner, T. Tuthill, M. Ulaszewska, R. Varughese, N. Van Doremalen, K. Veighey, M.K. Verheul, I. Vichos, E. Vitale, L. Walker, M.E.E. Watson, B. Welham, J. Wheat, C. White, R. White, A.T. Worth, D. Wright, S. Wright, X.L. Yao, Y. Yau, Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial, Lancet 396 (2020) 467–478, https://doi.org/10.1016/S0140-6736(20)31604-4.
[136] Ad5-EBOV: CanSinoBIO, (n.d.).
[137] An Open Study of the Safety, Tolerability and Immunogenicity of the Drug "Gam-COVID-Vac" Vaccine Against COVID-19 - ClinicalTrials.gov, 2020. (n.d.).
[138] Interim recommendations for the use of the Janssen Ad26.COV2.S (COVID-19) vaccine, (n.d.).
[139] N. Lurie, M. Saville, R. Hatchett, J. Halton, Developing Covid-19 vaccines at pandemic speed, N. Engl. J. Med. 382 (2020) 1969–1973, https://doi.org/10.1056/NEJMp2005630.
[140] M.W. Amjad, P. Kesharwani, M.C.I. Mohd Amin, A.K. Iyer, Recent advances in the design, development, and targeting mechanisms of polymeric micelles for delivery of siRNA in cancer therapy, Prog. Polym. Sci. 64 (2017), https://doi.org/10.1016/j.progpolymsci.2016.09.008.
[141] A.M. Butt, M.C.I.M. Amin, H. Katas, N.A. Abdul Murad, R. Jamal, P. Kesharwani, Doxorubicin and siRNA codelivery via chitosan-coated pH-responsive mixed micellar polyplexes for enhanced cancer therapy in multidrug-resistant tumors, Mol. Pharm. 13 (2016), https://doi.org/10.1021/acs.molpharmaceut.6b00776.
[142] M.W. Amjad, M.C.I.M. Amin, H. Katas, A.M. Butt, P. Kesharwani, A.K. Iyer, *In Vivo* antitumor activity of folate-conjugated cholic acid-polyethylenimine micelles for the codelivery of doxorubicin and siRNA to colorectal adenocarcinomas, Mol. Pharm. 12 (2015) 4247–4258, https://doi.org/10.1021/acs.molpharmaceut.5b00827.
[143] V. Mishra, P. Kesharwani, N.K. Jain, siRNA nanotherapeutics: a Trojan horse approach against HIV, Drug Discov. Today 19 (2014) 1913–1920, https://doi.org/10.1016/j.drudis.2014.09.019.
[144] N. Pardi, M.J. Hogan, F.W. Porter, D. Weissman, mRNA vaccines-a new era in vaccinology, Nat. Rev. Drug Discov. 17 (2018) 261–279, https://doi.org/10.1038/nrd.2017.243.
[145] L.A. Jackson, E.J. Anderson, N.G. Rouphael, P.C. Roberts, M. Makhene, R. N. Coler, M.P. McCullough, J.D. Chappell, M.R. Denison, L.J. Stevens, A. J. Pruijssers, A. McDermott, B. Flach, N.A. Doria-Rose, K.S. Corbett, K.

M. Morabito, S. O'Dell, S.D. Schmidt, P.A. Swanson, M. Padilla, J.R. Mascola, K. M. Neuzil, H. Bennett, W. Sun, E. Peters, M. Makowski, J. Albert, K. Cross, W. Buchanan, R. Pikaart-Tautges, J.E. Ledgerwood, B.S. Graham, J.H. Beigel, An mRNA vaccine against SARS-CoV-2 — Preliminary report, N. Engl. J. Med. 383 (2020) 1920–1931, https://doi.org/10.1056/nejmoa2022483.
[146] H. Ledford, Moderna COVID vaccine becomes second to get US authorization, Nature (2020), https://doi.org/10.1038/d41586-020-03593-7.
[147] Interim recommendations for use of the Pfizer–BioNTech COVID-19 vaccine, BNT162b2, under Emergency Use Listing, (n.d.).
[148] DNA Medicines Pipeline | INOVIO Pharmaceuticals, (n.d.).
[149] DNA Medicines Technology | INOVIO Pharmaceuticals, (n.d.).
[150] Recombinant DNA, Britannica. (2020).
[151] R.M. Bill, Recombinant protein subunit vaccine synthesis in microbes: a role for yeast? J. Pharm. Pharmacol. 67 (2015) 319–328, https://doi.org/10.1111/jphp.12353.
[152] A. Jain, G. Sharma, G. Ghoshal, P. Kesharwani, B. Singh, U.S. Shivhare, O. P. Katare, Lycopene loaded whey protein isolate nanoparticles: an innovative endeavor for enhanced bioavailability of lycopene and anti-cancer activity, Int. J. Pharm. 546 (2018) 97–105, https://doi.org/10.1016/J.IJPHARM.2018.04.061.
[153] A. Jain, K. Jain, P. Kesharwani, N.K. Jain, Low density lipoproteins mediated nanoplatforms for cancer targeting, J. Nanopart. Res. 15 (2013), https://doi.org/10.1007/s11051-013-1888-7.
[154] A. Tiwari, P. Kesharwani, V. Gajbhiye, N.K. Jain, Synthesis and characterization of dendro-PLGA nanoconjugate for protein stabilization, Colloids Surf. B Biointerfaces 134 (2015), https://doi.org/10.1016/j.colsurfb.2015.06.064.
[155] F. Zeeshan, M. Tabbassum, P. Kesharwani, Investigation on secondary structure alterations of protein drugs as an indicator of their biological activity upon thermal exposure, Protein J. 38 (2019) 551–564, https://doi.org/10.1007/s10930-019-09837-4.
[156] S.G. Reed, M.T. Orr, C.B. Fox, Key roles of adjuvants in modern vaccines, Nat. Med. 19 (2013) 1597–1608, https://doi.org/10.1038/nm.3409.
[157] D.J. Marciani, Vaccine adjuvants: Role and mechanisms of action in vaccine immunogenicity, Drug Discov. Today 8 (2003) 934–943, https://doi.org/10.1016/S1359-6446(03)02864-2.
[158] Novavax to Present COVID-19 Vaccine Candidate Progress at 2nd ISV COVID-19 Vaccines Virtual Congress | Novavax Inc. - IR Site, (n.d.).
[159] Clover Biopharmaceuticals Initiates Phase 1 Clinical Trial for COVID-19 Vaccine Candidate | Business Wire, (n.d.).
[160] China's Zhifei Finishes Covid-19 Vaccine's Phase II Clinical Trial in Three Months in Race to the Market, (n.d.).
[161] B. Gorain, S.K. Bhattamishra, H. Choudhury, U. Nandi, M. Pandey, Overexpressed receptors and proteins in lung cancer, Nanotechnol.-Based Target. Drug Deliv. Syst. Lung Cancer (2019) 39–75, https://doi.org/10.1016/B978-0-12-815720-6.00003-4.
[162] A. Singh, S.K. Maharana, R. Shukla, P. Kesharwani, Nanotherapeutics approaches for targeting alpha synuclien protein in the management of Parkinson disease, Process Biochem 110 (2021) 181–194, https://doi.org/10.1016/J.PROCBIO.2021.08.008.
[163] A. Roldão, M.C.M. Mellado, L.R. Castilho, M.J.T. Carrondo, P.M. Alves, Virus-like particles in vaccine development, Expert Rev. Vaccin. 9 (2010) 1149–1176, https://doi.org/10.1586/erv.10.115.
[164] COVID-19 vaccine development program, Medicago. (2020).
[165] R. Lu, X. Zhao, J. Li, P. Niu, B. Yang, H. Wu, W. Wang, H. Song, B. Huang, N. Zhu, Y. Bi, X. Ma, F. Zhan, L. Wang, T. Hu, H. Zhou, Z. Hu, W. Zhou, L. Zhao, J. Chen, Y. Meng, J. Wang, Y. Lin, J. Yuan, Z. Xie, J. Ma, W.J. Liu, D. Wang, W. Xu, E. C. Holmes, G.F. Gao, G. Wu, W. Chen, W. Shi, W. Tan, Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding, Lancet 395 (2020) 565–574, https://doi.org/10.1016/S0140-6736(20)30251-8.
[166] W. Tai, L. He, X. Zhang, J. Pu, D. Voronin, S. Jiang, Y. Zhou, L. Du, Characterization of the receptor-binding domain (RBD) of 2019 novel coronavirus: implication for development of RBD protein as a viral attachment inhibitor and vaccine, Cell. Mol. Immunol. 17 (2020) 613–620, https://doi.org/10.1038/s41423-020-0400-4.
[167] C. Yi, X. Sun, J. Ye, L. Ding, M. Liu, Z. Yang, X. Lu, Y. Zhang, L. Ma, W. Gu, A. Qu, J. Xu, Z. Shi, Z. Ling, B. Sun, Key residues of the receptor binding motif in the spike protein of SARS-CoV-2 that interact with ACE2 and neutralizing antibodies, Cell. Mol. Immunol. 17 (2020) 621–630, https://doi.org/10.1038/s41423-020-0458-z.
[168] A. Casadevall, L.A. Pirofski, The convalescent sera option for containing COVID-19, J. Clin. Invest 130 (2020) 1545–1548, https://doi.org/10.1172/JCI138003.
[169] A. Maxmen, How blood from coronavirus survivors might save lives, Nature 580 (2020) 16–17, https://doi.org/10.1038/d41586-020-00895-8.
[170] Y. Cheng, R. Wong, Y.O.Y. Soo, W.S. Wong, C.K. Lee, M.H.L. Ng, P. Chan, K. C. Wong, C.B. Leung, G. Cheng, Use of convalescent plasma therapy in SARS patients in Hong Kong, Eur. J. Clin. Microbiol. Infect. Dis. 24 (2005) 44–46, https://doi.org/10.1007/s10096-004-1271-9.
[171] C. Sheridan, Convalescent serum lines up as first-choice treatment for coronavirus, Nat. Biotechnol. 38 (2020) 655–658, https://doi.org/10.1038/d41587-020-00011-1.
[172] A.A. Nguyen, S.B. Habiballah, C.D. Platt, R.S. Geha, J.S. Chou, D.R. McDonald, Immunoglobulins in the treatment of COVID-19 infection: proceed with caution!, Clin. Immunol. 216 (2020), 108459, https://doi.org/10.1016/j.clim.2020.108459.
[173] K. Dhama, S. Khan, R. Tiwari, S. Sircar, S. Bhat, Y.S. Malik, K.P. Singh, W. Chaicumpa, D.K. Bonilla-Aldana, A.J. Rodriguez-Morales, Coronavirus disease 2019–COVID-19, Clin. Microbiol. Rev. 33 (2020) 1–48, https://doi.org/10.1128/CMR.00028-20.
[174] Draft landscape of COVID-19 candidate vaccines, (n.d.).
[175] Vaccines – COVID19 Vaccine Tracker, (n.d.).
[176] WHO validates Sinovac COVID-19 vaccine for emergency use and issues interim policy recommendations, (n.d.).
[177] S. Mallapaty, China's COVID vaccines are going global — but questions remain, Nature 593 (2021) 178–179, https://doi.org/10.1038/d41586-021-01146-0.