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.

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Review

COVID-19 challenges and its therapeutics

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ABSTRACT

COVID-19, an infectious disease, has emerged as one of the leading causes of death worldwide, making it one of the severe public health issues in recent decades. nCoV, the novel SARS coronavirus that causes COVID-19, has brought together scientists in the quest for possible therapeutic and preventive measures. The development of new drugs to manage COVID-19 effectively is a challenging and time-consuming process, thus encouraging extensive investigation of drug repurposing and repositioning candidates. Several medications, including remdesivir, hydroxychloroquine, chloroquine, lopinavir, favipiravir, ribavirin, ritonavir, interferons, azithromycin, capivasertib and bevacizumab, are currently under clinical trials for COVID-19. In addition, several medicinal plants with considerable antiviral activities are potential therapeutic candidates for COVID-19. Statistical data show that the pandemic is yet to slow down, and authorities are placing their hopes on vaccines. Within a short period, four types of vaccines, namely, whole virus, viral vector, protein subunit, and nucleic acid (RNA/DNA), which can confer protection against COVID-19 in different ways, were already in a clinical trial. SARS-CoV-2 variants spread is associated with antibody escape from the virus Spike epitopes, which has grave concerns for viral re-infection and even compromises the effectiveness of the vaccines. Despite these efforts, COVID-19 treatment is still solely based on clinical management through supportive care. We aim to highlight the recent trends in COVID-19, relevant statistics, and clinical findings, as well as potential therapeutics, including in-line treatment methods, preventive measures, and vaccines to combat the prevalence of COVID-19.

1. SARS-CoV, nCoV, and COVID-19

Coronaviruses are a group of viruses that cause various diseases. They cause moderate to serious diseases, such as Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS) [1]. The most common infection caused by coronaviruses are infections of the respiratory and gastrointestinal tract. Coronavirus in the Coronaviridae family, a positive stranded RNA virus, enveloped genetically in four major genes: *gamma coronavirus*, *beta coronavirus*, *alphacoronavirus*, and *delta coronavirus* [2,3]. The former two classes cause infection primarily in mammals, while the latter mainly infect birds [4]. Coronaviruses that infect humans are responsible for several virus outbreaks. These includes alphacoronaviruses (HCoV-229E, and HCoV-NL63) and betacoronaviruses (HCoV-OC43, SARS-CoV, HCoV-HKU1, and MERS-CoV) [4,5].

The SARS epidemic in 2003, accompanied by the MERS in 2012, and the most recent outbreak of the novel coronavirus (nCoV) attract global attention [6–8]. SARS and MERS coronaviruses are particularly pathogenic by nature [9–11]. Both of the viruses are most likely transferred from bats to palm civets [12] or dromedary camels [13,14] and then to humans [9]. The coronavirus genome is approximately 26,000–32,000 bases long and contains a shifting number of open reading frames (ranging from 6 to 11) [6]. The first open reading frame constitute approximately 67% of the genome and codes for 16 non-structural proteins, while the remaining open reading frames code for accessory and structural proteins [9]. The essential structurally-defined proteins are surface spike glycoprotein (S), an envelope protein (E), matrix protein (M), and nucleocapsid protein (N). The surface spike glycoprotein is crucial if receptors are attached to the host cell in defined tropism [2,15]. Various receptor-binding domains in the SARS and MERS virus spike proteins hitch to different receptors of host cells. SARS virus uses angiotensin-converting enzyme 2 (ACE 2) receptor as the principal receptor [16], while for MERS, dipeptidyl peptidase 4 (DPP4) is the major one [17].

A novel coronavirus (nCoV) is a mutant strain not discovered earlier in humans. It is observed that it has a different epidemiological

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Table 1
COVID-19 statistics [127].

Active Cases	
Currently infected patients	190,833,853
Cumulative Deaths reported	4,100,087
Recovered Cases	173,878,834
Active cases in mild condition	12,774,290 (99.4%)
Active cases in serious condition	80,642 (0.6%)
Closed Cases	
Cases which had an outcome	177,978,921
Recovered or Discharged	173,878,834 (98%)
Reported Deaths	4,100,087 (2%)

character from the formerly known SARS-CoV. The nCoV develops well in the upper respiratory tract and is likely to create symptoms to appear somewhat slowly [18]. This property is similar to conventional human coronaviruses, which are a primary reason for common colds in the winter season. In COVID-19 infected individuals, many active viruses are produced during a prodrome period in the upper respiratory tract, responsible for the abruptly spread of infection. Unlike the current COVID-19 spread, SARS-CoV transmission did not occur readily during the prodromal period. Those affected were slightly ill; however, most transmissions in persons with serious illness from the virus SARS-CoV outbreaks were easier to monitor [19]. The novel SARS coronavirus (nCoV) can also replicate in lower respiratory tract cells due to its attachment affinity for these cells, leading to lower respiratory tract lesions [20,21].

2. COVID-19 outbreak

2.1. Statistical report

According to the weekly epidemiological updates of the World Health Organization (WHO) till July 18, 2021, 190,833,853 cases and 4,100,087 deaths have been confirmed, and 3,402,275,866 doses of vaccines have been administered globally. America has the highest number of cases, followed by India, Brazil, and France, as reported by the WHO. In addition, India is experiencing a very alarming situation, with 31,106,065 cases reported as of June 18, 2021. According to statistical data, 59% of the deaths were males, and 41% were females, while 51% of the cases were females and the remaining 49% were males. In both sexes, the 30–39 age group has the highest number of cases, whereas the 65 + age group had the highest death rate. Further statistical details are presented in Table 1.

2.2. Illness severity

Most patients with COVID-19 experience a minor to uncomplicated disease; however, approximately 14% develop a severe illness that requires hospitalization and oxygen treatment, with 5% requiring admission to an intensive care unit [22]. Acute respiratory distress syndrome (ARDS), septic shock, and sepsis are common complications in COVID-19 serious cases, as are various organ failures such as heart injury and acute kidney injury [23]. In addition, COVID-19 severe illness and mortality have been linked to older age and comorbidity such as heart failure, elevated blood pressure, lung disease, or diabetes [24].

3. Mode of transmission

Epidemiologic investigation showed initial association of the seafood market of China Wuhan city is responsible for the beginning of the COVID-19 outbreak [25]. At the outbreak progression, the person-to-person spread is considered the primary mode of transmission. One USA-based study describes the first person-to-person transmission of COVID-19 in people in close contact with each other (about to range of 6 feet) [26]. Like the spread of influenza, when an individual coughs or sneezes, the respiratory droplets may contact the nearby people through the mouth or nose and may be inhaled into the lungs. Generally, symptomatic people are thought to be the most contagious. The life cycle of nCoV in human cells may provide enlightenment for viral transmission, and its potential therapeutic targets is shown in Fig. 1.

Fomite transmission is discussed in various studies that a person may also likely be infected with the COVID-19 by touching any object or surface that contains the virus, then touching his nose, mouth, or probably eyes. Still, it is not believed to be the primary way of virus transmission [27]. The nCoV has been reported to be stable under experimental conditions on stainless steel and plastic surfaces correlated with copper and cardboard box surfaces. The virus is observed up to 72 h after inoculation of textures with the virus. Nonporous substances such as glass and stainless steel were used to extract active viruses for 28days at 20 °C. In contrast, the recovery of nCoV from porous surfaces was diminished.

A meta-analysis involving 936 neonates of COVID-19 mothers demonstrated vertical propagation but happened in a smaller number of cases. In addition, epidemiological evidence from many cases has shown that nCoV patients have live viruses in feces that indicate potential fecal–oral transmission [28].

Several studies reported the nCoV transmission from asymptomatic infected individuals [29–34]. Next-level serology tests, which are under development, will facilitate understanding asymptomatic infections and epidemiological analysis [35,36].

Viruses constantly mutate upon replication. While most variations are insignificant, some render the virus more infectious or hostile, leading to serious health concerns. In October 2020, the SARS-CoV-2 lineage B.1.617 was discovered in India. It has now become prevalent in several regions within India and the United Kingdom and has spread to many other countries. The lineage is divided into three major subtypes (B1.617.1, B.1.617.2, and B.1.617.3), each with a unique set of spike mutations in the receptor-binding domain, and the N-terminal domain may enhance immune evasion. B.1.617.2, commonly known as variation Delta, is reported to spread more quickly than other variants [37].

4. Sign and symptoms

For COVID-19, the incubation period is estimated to be 14 days after exposure to the virus, typically 4–5 days after exposure [18,38,39].

Pneumonia is the most common and dangerous symptom of COVID-19 infection, which is characterized by fever, coughing, and shortness of breathing [39–42]. Other symptoms include headache, fatigue, sore throat, increased sputum production, rhinorrhea, anorexia, hemoptysis, myalgias, and diarrhea [39,43–46]. On a chest CT scan, pneumonia, respiratory distress syndrome, acute heart injury, and white spots opacities can be seen, both of which can lead to death [47–50]. No specific clinical features for COVID-19 that clearly distinguish it from other respiratory viral infections.

Acute respiratory distress syndrome (ARDS) is a severe complication in patients with chronic disease. Arrhythmia, acute heart injury, and trauma were other complications [42,51,52]. According to the world health organization, the recovery time seems about two weeks for mild infections and 3–6 weeks for severe cases.

5. Prevention

“Prevention is better than cure”, so, it is better to prevent COVID-19 by controlling its drastic spread rather than living with a hope of its precise treatment. However, like other respiratory infections (flu and the common cold), COVID-19 also required critical public health measures to decelerate the spread of the disease. Public health measures comprise everyday preventive actions, which includes [53]:

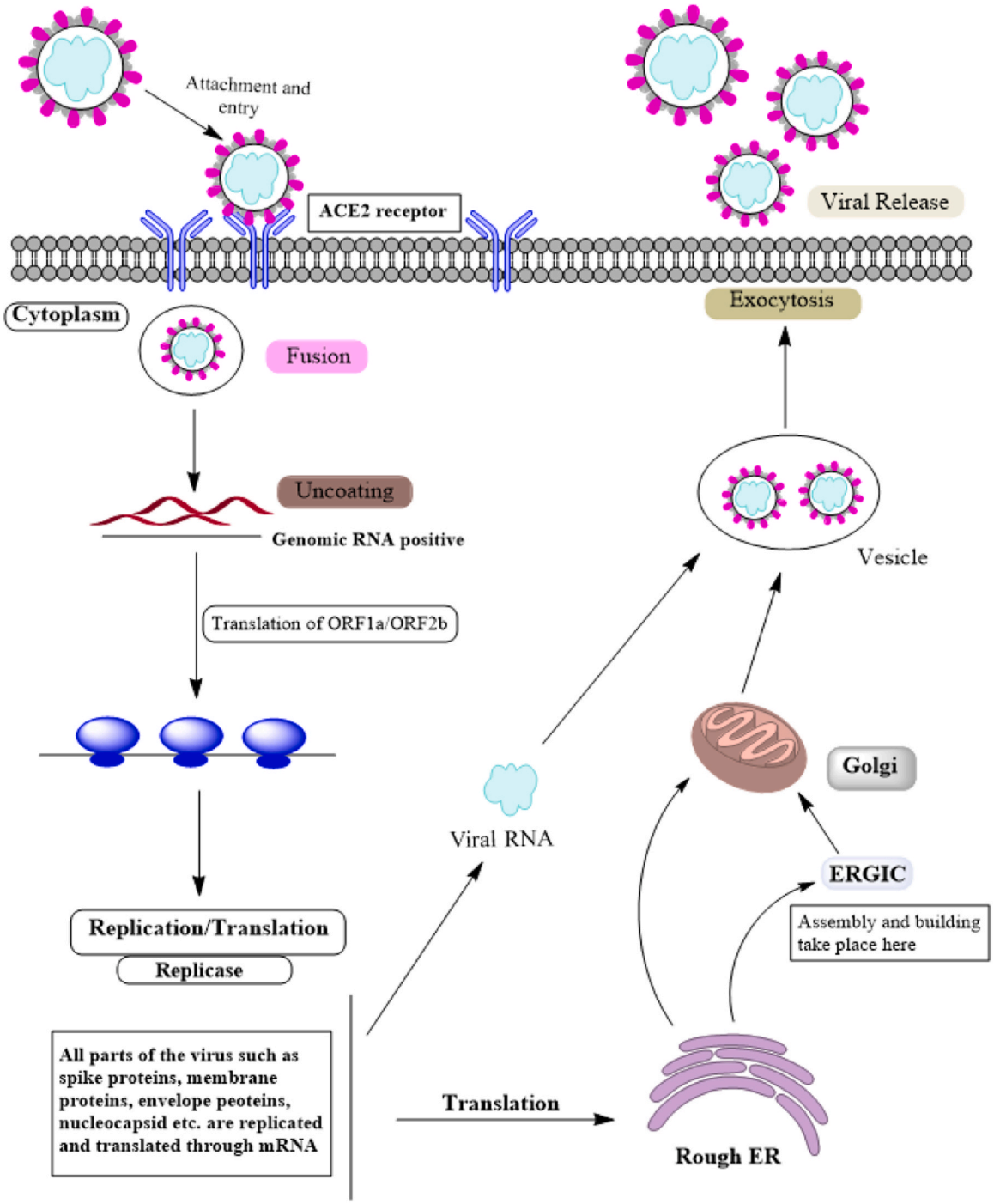

Fig. 1. The nCoV Life Cycle: Stages and Targets The life cycle of nCoV in human cells may provide enlightenment for viral transmission and its potential therapeutic targets. Step-I: The nCoV is distinguished by spikes (S, club-like) on the surface and a distinctive replication scheme. Coronaviruses entry to the cell is based on the viral spike proteins binding to cellular receptors (such as angiotensin-converting enzyme 2 (ACE2)) and its priming by the action of host cell proteases. Step II & III: Once the viral RNA is untied inside the host cell, the translation of polyproteins is initiated. The nCoV genomic RNA encodes non-structural proteins (NSPs), which is crucial in synthesizing viral RNA, and the structural proteins essential for virion assembly. Step IV: To replicate structural protein, RNA replicase–transcriptase complex is required. With the help of endoplasmic reticulum bounds ribosomes, the structural proteins S1, S2, Membrane (M), Envelope (E) are translated and exhibited on its surface for the priming of virion assembly. The nucleocapsids (N) stay in the cytoplasm and are congregate from genomic RNA. Nucleocapsids join the virion precursor, transported to the cell surface from the endoplasmic reticulum through the Golgi Apparatus in small vesicles. Step V**:** By exocytosis, the mature virions are released from the infected cell's surface and set free to infect other host cells.

- ✓ Wear masks in public
- ✓ Stay six feet away from others
- ✓ Get vaccinated when the COVID-19 vaccine available to you
- ✓ Avoid poorly ventilated spaces and crowds
- ✓ Wash hands with water and soap more frequently for at least 20 s
- ✓ Cover coughs and sneezes
- ✓ Clean regularly touched surfaces every day
- ✓ Monitor your health regularly for fever, toxins, breathing difficulty, or other COVID-19 symptoms
- ✓ Staying home when you are sick

✓ Avoiding crowds and unnecessary traveling
✓ Strong immunity is the best approach to combat viruses. Therefore, adopting healthy habits, such as a balanced diet, adequate rest, oral hygiene, regular exercise, and avoiding excessive fatigue and stress, can boost immunity and effectively prevent viral infection [54,55].

6. Treatment

For the optimal functioning of vital organs, existing therapeutic procedures for patient diagnosis and recovery focus primarily on symptomatic treatment and subsequent supportive care [56]. Besides this, some medical centers prescribe antibiotics, antimalarials, and antivirals with limited clinical data. The primary interventions include bed rest, supportive care, adequate calories, water consumption, water balances and homeostasis, psychotherapy, oxygen therapy. Vit C and probiotics can also be used to improve the immune response [57,58]. The very first step is to ensure that the infection is not further transmitted to family members, patients, and healthcare staff by proper insulation. Mild sickness should be treated in the home with appropriate advice on threat signs and strictly follow health practitioner recommendations. Its management incorporates treating cough and fever along with hydration and nutrition monitoring. In confirmed cases, avoid the use of routine antibiotics and antiviral drugs if otherwise recommended by an authorized physician. In hospitals, oxygen is recommended in hypoxic patients via a facial mask, nasal glands, high flux nasal cannula, or non-invasive ventilation. Mechanical or artificial ventilation and extracorporeal membrane oxygen support may be needed if necessary, and renal replacement therapy should also be provided, depending on patient condition. Corticosteroid's role for COVID-19 is not established yet, so the centers for disease control and prevention (CDC) and WHO do not recommend these. Chinese guidelines suggest short-term corticosteroid use in COVID-19 derived ARDS at a low to moderate dose [59,60]. The World Health Organization has released comprehensive guidance on critical care management for COVID-19 [61]. Persons whose residence in the infected region are in danger of being exposed to this virus immediately notify the health care provider. Many pharmaceutical agents are being investigated for SARS CoV-2 antiviral activity. Any of them have been successfully presented for clinical trials based on in vitro evidence. Complete list of international clinical trials can be seen at www.clinicaltrials.gov and on WHO website. It is important to highlight that the efficacy of these investigational agents for COVID-19 is uncertain, due to lack of established data supporting the significance of any of these agents.

6.1. Remdesivir

Remdesivir directly inhibits the RNA-dependent polymerase of nCoV, thus declared the most proficient drug molecule available for COVID-19**.** This drug has also proved efficient SARS-CoV, Ebola virus, and MERS-CoV [62]. Several randomized trials are in progress to test remdesivir efficacy for mild to extreme COVID-19 [63]. Remdesivir, a novel nucleotide analog formulated by Gilead Sciences Inc., is a wide-ranging antiviral treatment proven effective against nCoV in vitro lab tests [64]. It has been discussed by researchers for the Ebola virus in human beings. It has shown positive results in experimental animal studies to treat SARS and MERS [65]. The empathetic use of remdesivir as an investigational new drug was first reported in a case study of the COVID-19 patients in the United States [66]. Remdesivir's clinical impact against COVID-19 is uncertain at this time.

6.2. Chloroquine/hydroxychloroquine

Chloroquine is an antiparasitic drug (antimalarial), prevents viruses from replicating in a pH-dependent manner. Since the COVID-19 outbreak, various in vitro systems have been used to investigate the potential antiviral effects of chloroquine/hydroxychloroquine. *In vitro* studies have revealed the efficacy of chloroquine in suppressing SARS-CoV-2 infection when compared to that of other antiviral drugs, particularly favipiravir, penciclovir, nafamostat, nitazoxanide, and ribavirin [64]. These suggested the significant efficacy of chloroquine and hydroxychloroquine against nCoV. In contrast, hydroxychloroquine is more potent in antiviral action than chloroquine [64,67,68]. In China, Clinical trials evaluating the effectiveness of chloroquine or hydroxychloroquine for COVID-19 are in progress [69]. Studies on the monkey cells (Vero E6) suggested that chloroquine blocks glycosylation of the receptor inhibiting transmission of the virus into these cells and pathogenesis [69]. This application has yielded positive outcomes from nCoV infected human cell lines (Huh-7 cells) under a lab environment [70]. The time-of-addition experimental results revealed that chloroquine might interact with both the entry and post-entry stages of SARS-CoV-2 infection in Vero E6 cells. The authors speculated that chloroquine might be able to synergistically modify the immunological function to increase its antiviral efficacy. The results of the time-of-addition assay suggested that hydroxychloroquine might restrict the entry and post-entry phases of SARS-CoV-2 in the cell and prevent viral genome release. In SARS-CoV-2-infected Vero E6 cells, chloroquine had a greater EC50 than that of hydroxychloroquine [71]. Hydroxychloroquine treatment mainly increased the size and number of endolysosomes, supporting its in vitro anti-SARS-CoV-2 effectiveness [72].

Various animal models for SARS-CoV-2 infection have been developed by researchers using non-human primates to examine the therapeutic effects of hydroxychloroquine. Chen et al. observed that there is no significant anti-SARS-CoV-2 impact of hydroxychloroquine either before therapy or early after infection (before the viral load peak) or late after infection (after the viral load peak) [73]. Clinical studies in hospitals have indicated that chloroquine and hydroxychloroquine prevent pneumonia exacerbation, encouraging negative viral conversion and shortening the illness course without apparent side effects [74]. Clinical trials in China have indicated that patients treated with chloroquine recover with normal pulmonary function, reduced fever, and decreased coughs faster than those treated with other antiviral medications [75]. Perhaps most importantly, a clinical trial conducted in critically ill patients with COVID-19 showed that hydroxychloroquine might substantially lower the risk of mortality in these patients without causing any severe side effects [76].

Meanwhile, there are various possible reasons for the lack of efficacy of chloroquine/hydroxychloroquine for the treatment of patients with COVID-19. According to a recent study by Hadjadj et al., patients with severe COVID-19 have decreased IFN-I activity, increased T cell apoptosis, and an increased inflammatory response, while the regulatory effect of chloroquine/hydroxychloroquine on the immune response is not sufficiently effective to constrain the over-activation of the innate immune system [77]. A study suggested that the *ORF3a* gene of SARS-CoV-2 may prevent the fusion of autophagosomes and lysosomes, allowing SARS-CoV-2 to survive. This further complicates the function of autophagy and lysosomes in the SARS-CoV-2 life cycle [78]. It has been reported that the recommended chloroquine/hydroxychloroquine drug regimen for COVID-19 is considerably higher than that for malaria. Anxiety, insomnia, gastrointestinal complications, and cardiomyopathy have all been documented as side effects in clinical trials. Furthermore, the cardiotoxicity induced by chloroquine/hydroxychloroquine seems to be particularly relevant to the infection [73].

6.3. Azithromycin

Azithromycin has received considerable attention owing to its additional immunomodulatory effects on host defense reactions against chronic inflammations [79,80]. It has the ability to modify immune responses and provide a long-term clinical benefit in various conditions like chronic obstructive pulmonary disease, non-eosinophilic asthma, cystic fibrosis, and non-fibrous cystic bronchiectasis [79]. Azithromycin increases the expression of IFN-β, PRR, and IFNλ genes and gene

expression of PRR-stimulated genes [81]. It also raises the pH of the intracellular organelles of primary bronchial epithelial cells, such as trans-Golgi networks, which affects the overall virus activity of the cells. Increasing the pH of these organelles can adversely affect SARS-CoV and enzyme glycosylation [82]. Azithromycin inhibits the spike protein synthesis and slows down the viral entry in the cells, making it more difficult for the virus to spread [82]. *In vitro* testing revealed that a combination of HCQ and azithromycin has a synergistic effect on nCoV at concentrations comparable to those found in human beings [83]. Aside from studies demonstrating the effectiveness of HCQ in combination with azithromycin, several studies have revealed severe side effects, limiting the use of this therapy in COVID-19 treatments [84–86].

6.4. Combinational therapy of hydroxychloroquine with azithromycin

Combination treatment with existing medications is an effective strategy for improving the clinical therapeutic efficacy of drugs. Combination therapy of chloroquine with azithromycin has previously been prescribed in patients with SARS-CoV-2 infection [87]. According to a clinical study in France, the combination of hydroxychloroquine with azithromycin exhibits greater effectiveness than a single-drug regimen in terms of the viral clearance rate. In contrast, most studies have revealed that the combination of hydroxychloroquine with azithromycin does not result in positive clinical outcomes, similar to that in patients with SARS-CoV-2 infection [88]. A retrospective multicenter cohort analysis of data from patients with SARS-CoV-2 infection at New York hospitals revealed no statistically significant difference in the in-hospital mortality rates among the various treatment groups [89]. A retrospective study of the ventilation risk in patients with COVID-19 in the United States revealed no significant differences associated with hydroxychloroquine and azithromycin treatment compared to the control group [90]. Clinical studies have consistently demonstrated that combining hydroxychloroquine with azithromycin has potential adverse effects in patients with COVID-19. In conclusion, most of the existing clinical trials of this combination therapy have not yielded encouraging results for future use in patients with COVID-19, primarily because of its treatment inefficiency and substantially adverse effects on the cardiovascular system [73].

6.5. Capivasertib

Capivasertib is a potent pan-AKT-kinase drug that inhibits AKT1, ACT2, and AKT3. This is an improvement strategy for anti-tumor medicines. Capivasertib is employed as an oral small-molecule AKT inhibitor in clinical trials for drug-resistant breast cancer [91]. The luciferase assay was conducted to explore the role of capivasertib on SARS-CoV-2 S protein pseudo-type virus and VSV-dG in Vero cells. The analyses showed that capivasertib has a concentration-dependent inhibitory effect on SARS-CoV-2 intracellular luciferase activity.

Moreover, capivasertib therapy had little impact on Vero cell growth and survival, suggesting that capivasertib is safe based on in vitro studies. Luciferase activity may represent variations in the viral infection rate from the two phases of viral entry and viral genomic replication or expression. Sun et al. indicated that capivasertib, an AKT-target drug used in non-cytotoxic doses, may limit SARS-CoV-2 entry into cells and has a high potential for clinical trials of anti-SARS-CoV-2 agents [92].

6.6. Lopinavir-ritonavir

In vitro, the combination of these two HIV protease inhibitors exhibits better activity against SARS-CoV [93], along with its in vivo proven efficacy against MERS-CoV [94]. The pharmacological use of this combination for COVID-19 treatment has been reported in case studies [95–97]. China's current COVID-19 treatment guidelines involve 50–200 mg intake for 10 days [98]. Ritonavir-boosted lopinavir (LPV) therapy does not seem to be the preferred treatment for salvage therapy in patients with extreme COVID-19. It may be beneficial to reduce nCoV loads early on to prevent radical secondary immune burst. Ritonavir boosted lopinavir efficacy (by enhancing pharmacokinetic/pharmacodynamics) in patients infected with nCoV. To minimize long-term virus transmission and its associated risk, the duration of the treatment must be provided for at least 14 days.

Table 2
Potential Immunomodulatory agents used in COVID-19 infections.

Immunomodulatory agents	Mode of action	References
	Specific immunomodulators	
Anti-cytokines Anakinra	IL-1 receptor antagonist (Anti-cytokine)	[128]
Tocilizumab (Actemra®)	IL-6 receptor antagonist (Anti-cytokine)	[129]
Sarilumab (Kefzara®)	IL-6 receptor antagonist (Anti-cytokine)	[130]
Janus Kinase Inhibitors Ruxolitinib (Jakafi®)	JAK1/JAK2 inhibitor (Anti-cytokine)	[100]
Baricitinib (Olumiant®)	JAK1/JAK2 inhibitor (Anti-cytokine)	[131]
Antitumor Necrosis Factor-α Adalimumab	anti-TNFα(Anti-cytokine)	[132]
Granulocyte–Macrophage Colony-Stimulating Factor Sargramostim (Leukine®)	Recombinant humanized GM-CSF	[133]
Gimsilumab (investigational molecule)	Anti-GM-CSF	[100]
Convalescing plasma	Short-term passive immunity is provided by neutralizing antibodies	[134]
	Non-specific immunomodulators	
Human Immunoglobulin Intravenous immunoglobulin	Antibodies derived from combined plasma have short term passive immunity	[135]
Corticosteroids Dexamethasone	Deliver anti-inflammatory and antifibrotic results to inhibit cytokine reaction	[136]
Methylprednisolone	Deliver anti-inflammatory and antifibrotic results to inhibit cytokine reaction	[137]
Interferon Interferon-β-1b	Antiviral and immunomodulator	[138]
Interferon-α-2b	Antiviral and immunomodulator	[139]
	Miscellaneous	
Statins	Anti-inflammatory as well as immunomodulatory effects	[140]
Renin-Angiotensin-Aldosterone System Inhibitors ACEi/ARB	Anti-inflammatory and immunomodulatory effects	[141]
Macrolides Azithromycin	Anti-inflammatory as well as immunomodulatory effects	[142]
Antimalarial Hydroxychloroquine	Immunomodulatory and anti-inflammatory effects	[143]
Chloroquine	Anti-inflammatory and immunomodulatory effects	[144]
Colchicine	Anti-inflammatory and immunomodulatory effects	[145]

Note:
ACEi (angiotensin-converting enzyme inhibitors), IVIG (intravenous immunoglobulin), JAK (Janus kinase), GM-CSF (granulocyte macrophage colony stimulating factor), ARB (angiotensin II receptor blockers), TNF (tumour necrosis factor), IL (interleukin), IV (intravenous).

6.7. Umifenovir

Umifenovir is also an antiviral medication that has been approved for influenza cure and prevention. However, it has been clinically tested and not authorized by the FDA until now. It is an inhibitor of membrane fusion and is recommended for an oral 10-day dose of 200 mg TDS [98].

Table 3
Medicinal plants, a possible contender for anti-COVID-19 drugs.

Botanical specie	Active Phytochemical	Mechanism	Virus assessed	Reference
Allium sativum (Liliaceae or Amaryllidaceae)	Essential oils	Inhibition of virus proliferation	Influenza Virus	[146, 147]
Mentha piperita Linn. (Lamiaceae or Labiatae)	Essential oils (Menthol)	Relaxation of breathing, Virucidal effect by incrementing virion density	IBV	[148]
Zingiber Officinalis (Zingiberaceae)	Gingerol	ACE inhibition, Block virus entry into the host cell, Immunostimulant effect	Avian influenza virus H9N2	[147, 149]
Glycyrrhiza Glabra (Fabaceae)	Glycyrrhizin	Induction of nitrous-oxide synthase which further inhibit viral replication	nCoV	[150]
Houttuynia cordata (Saururaceae)	Quercetin	Virucidal action prevents ATPase of multi-drug resistance protein	MHV and DENV-2	[151]
Isatis indigotica (Brassicaceae)	Hesperetin and Sinigrin	Prevent viral cleavage	SARS-CoV 3CLpro	[147]
Hyoscyamus niger (Solanaceae)	Alkaloids	Bronchodilator, Ca2 + channels inhibitors	nCoV	[152]
Punica granatum (Lythraceae)	Ellagitannin as well as Punicalagins	ACE inhibitors	nCoV	[153]
Clerodendrum Inerme (Lamiaceae)	Phenolic compounds	Deactivation of virus	nCoV	[119]
Verbascum thapsus (Scrophulariaceae)	Phenolic compounds	Antiviral activity	influenza viruses	[154]
Coriandrum sativum (Apiaceae)	Linalool	Inhibition of ACE-2 block the virus entry to the host cell, Immunostimulant effect	nCoV	[155]
Strobilanthes callosa Nees (Acanthaceae)	Phytosterols	inhibits RNA genome formation	HCoV-NL63	[156]
Reseda luteola (Resedaceae)	Luteolin	Inhibit entry of SARS-CoV, have great affinity for S2 protein thus interfere virus-cell fusion process	nCoV	[157]
Vitex negundo (Lamiaceae)	linalool as well as Viridiflorol	HIV inhibitors, reverse transcriptase activity of HIV	HIV-1	[158]
Syzygium cumini (Myrtaceae)	Kaemferol Ellagic acid and Isoquercetin,	Inhibit viral protease activity	Avian Influenza virus	[152]
Peganum harmala **Linn** (Zygophyllaceae)	Harmine	Inhibit viral replication	Influenza-A virus	[159]
Scutellaria baicalensis *and* ***Scutellaria lateriflora*** *(*Lamiaceae)	Flavone (baicalein)	block dengue virus penetration into the host cell as well as post-entry viral proliferation.	Dengue virus	[124]

6.8. Corticosteroids

In hospitalized patients with pulmonary viral infections, like those caused by MERS-CoV and SARS-CoV, corticosteroids are commonly used to alleviate lung inflammation and reduce the chance of pulmonary injury. However, corticosteroids also suppress immune responses, which can obstruct viral clearance because it was noticed in certain MERS-CoV patients—considering that in these patients, the utilization of corticosteroids is already controversial, with ongoing clinical trials addressing the problem [99].

6.9. Immunomodulatory agents

Immunomodulatory agents can activate, inhibit, or modulate various immune system components, such as the immune system, innate and adaptive. Immunostimulants, such as those mentioned in Table 2, are often recommended to improve the immune response to infectious diseases. Rate and extent of inflammation are directly linked to mortality and severity of COVID-19 patients, so interacting cytokine signaling via immunomodulatory techniques reduces overall hyper inflammation in such patients [100].

6.10. Convalescent plasma

As part of convalescent plasma therapy, plasma from recovered patients is utilized to treat patients with infections. Convalescent plasma therapy has been used to treat SARS [101,102], MERS [103], Ebola [104], Machupo virus [105], and Junin virus [106], although mixed therapeutic outcomes have been observed. Convalescent plasma is used as an adjunct to antiviral therapy. The protective effect of convalescent plasma might persist for several weeks to months. After proper assessment of a donor, pheresis equipment can collect 200–600 mL of plasma.

Convalescent plasma therapy is a promising treatment option for COVID-19 [107]. A case series from China recently demonstrated better outcomes following COVID-19 convalescent plasma transfusion. The US Food and Drug Administration (FDA) recently approved the use of convalescent plasma as an emergency treatment for individuals with serious or life-threatening illnesses, such as COVID-19 [108]. Although convalescent plasma shows promising results in many cases, there remains insufficient evidence to support its use in the treatment of COVID-19.

According to several studies, convalescent plasma transfusion is safe and has a proven role in lowering the viral load and enhancing survival in critically ill patients. Convalescent plasma has therapeutic relevance, including alleviating clinical symptoms, although the decrease in mortality of critically ill patients is not statistically significant [109]. Only two adverse events were noted in a randomized trial [110], including 52 patients receiving convalescent plasma therapy. In addition, a study found that transfusion of convalescent plasma was safe in hospitalized patients with COVID-19 [111]. These two reports confirmed the safety of convalescent plasma transfusion. The viral load and quantitative reverse-transcription polymerase chain reaction (qRT-PCR) assays were used to assess the effectiveness of the treatment. After the transfusion, we found that the viral load had decreased and become negative after a few days (e.g., 3 days, 12 days, or 28 days) [112]. The mechanism of antibodies and peak time of viremia contribute to the first week following the infection being the optimal time to treat patients with plasma. According to a clinical study by Hegerova et al., [113] no patients died if they were treated with plasma within 7 days of admission, while the mortality rate in patients who received convalescent plasma transfusion after 7 days of hospitalization was 10%, compared to 30% in patients who did not receive plasma. This shows that the therapeutic effect of convalescent plasma transfusion is time-dependent, which is compatible with the viral illness mechanism. One study showed that a 37-year-old man with immunodeficiency and severe SARS-CoV-2 infection improved quickly after receiving convalescent plasma [114].

Furthermore, there are no standardization or evidence-based reasons for donor selection, convalescent plasma quality control, or recipient transfusion indications due to a lack of understanding of the exact mechanism of convalescent plasma and precise therapeutics.

6.11. Herbal medicines

Herbal medicines are used extensively to cure and prevent numerous

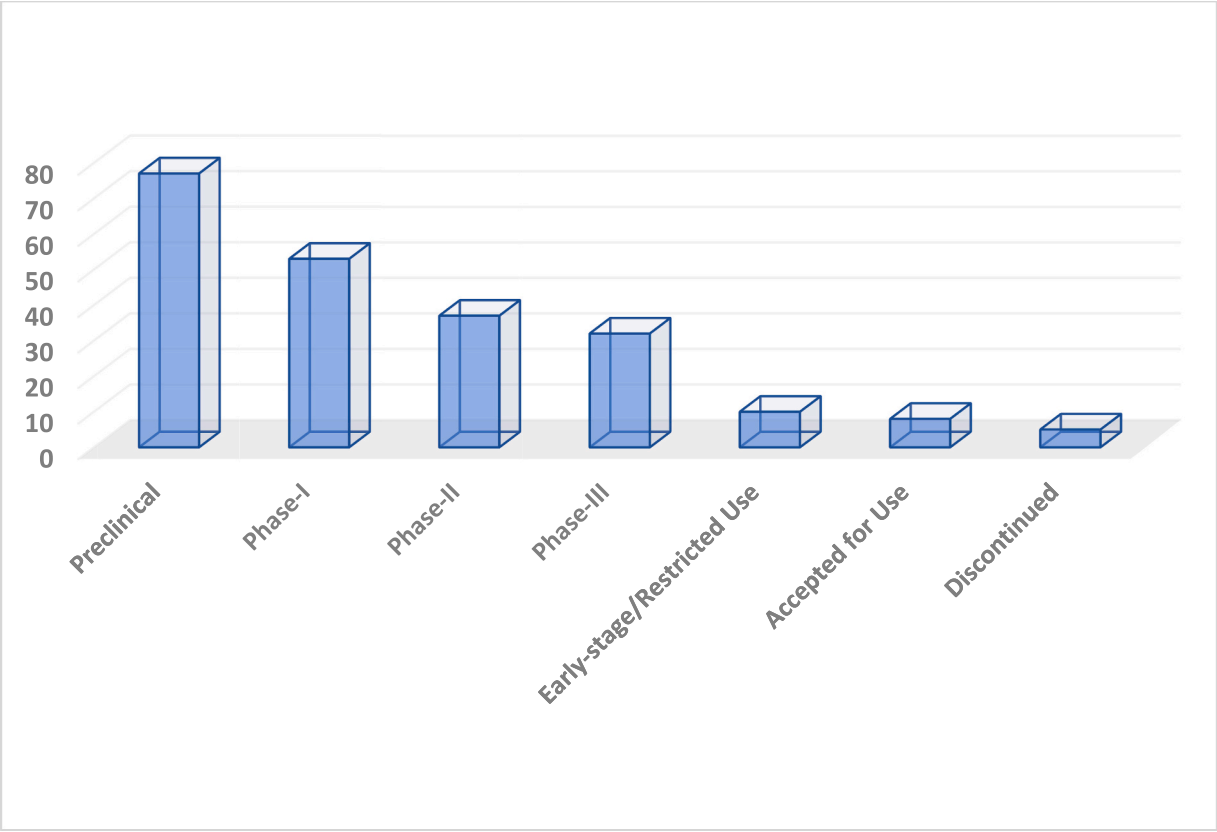

Fig. 2. Vaccines clinical trials status The graph represents the number of vaccines in various stages of the vaccine development process. The conventional pattern is observed having a bigger number of vaccines in preclinical trials than clinical trials (Phase-I to Phase-III) stages and the approved ones. To date, limited vaccines have granted emergency approval from WHO for use in the general population.

diseases and complications, including viral respiratory infections. Several traditionally used plant extracts have now been discovered to have promising antiviral properties. They can improve patients' health, but in COVID-19, there is still no confirmed proof of their efficacy. *Allium sativum*, *Mentha piperita*, *Lianhua qing wen*, and *Zingiber officinale* (ginger), *Syzygium aromatic* (Clove), *Cassia fistula, Lagenaria breviflorus, Phyllanthus amarus, and Citrullus colocynthis* are among the plants with proven efficacy against respiratory viral infections [115]. Glycyrrhiza glabra has traditionally is being used to combat cough and sore throat and to enhance digestion. *Diammonium glycyrrhizinate* has the anti-inflammatory properties of COVID-19 for regulating liver problems. Extracts from *Torreya nucifera*, *Artemisia annua*, *lindera aggregata*, *Houttuynia cordata*, *Lycoris radiata*, *Isatis indigotica* demonstrated efficacy against SARS. Baicalein, a flavone derived from the roots of *Scutellaria baicalensis* and *Scutellaria lateriflora*, has been shown to block dengue virus penetration into the host cell and post-entry viral proliferation [116]. *Pelargonium sidoides* and *Taraxacum officinale* (Dandelion) roots possess anti-influenza properties due to virus penetration and inhibited enzyme activity [117]. Herbal medicines that have the potential to stop viruses from replicating are often chosen as viable alternatives for combating viral outbreaks. As a result, *G. glabra* (licorice) and *A. sativum* (garlic) may be used as COVID-19 remedy alternatives. *Clerodendrum inerme,* a possible nCoV remedy plant, inhibits viral ribosome inactivation and protein translation [118]. *Strobilanthes Cusia* also prevents the development of RNA genomes, which makes it a good candidate for human coronaviruses [119].

Numerous medicinal plants with antiviral properties, such as *Eugenia jambolana* (*Syzygium cumini*), *Hyoscyamus niger* (Henbane), *Justicia adhatoda, Allium sativum* (Garlic), *Peganum harmala* Linn, and *Verbascum thapsus*, have mitigated disease infections caused by influenza viruses [120]. The bronchodilator Henbane also has a Ca2 + channel inhibitory property [121] as a result, it effectively stops virus spread downstream. Angiotensin converting enzyme (ACE) has been the subject of several clinical studies, intending to prevent virus entry. Certain species of plants, such as *Coriandrum sativum* and *Punica granatum* have shown important results in this regard [122]. An annual herbaceous plant called *Andrographis paniculate* has potent antiviral properties [123]. MPs with the ability to target HIV reverse transcriptase function, such as *Ocimum sanctum* (Basel), *Solanum nigrum*, and *Vitex negundo*, may be used to explore COVID-19 drug candidates [124]. Many HIV proteins and molecules are involved in SARS-CoV pathogenesis and are likely to be involved in nCoV pathogenesis [125].

During pandemics, timeliness is a fundamental prerequisite for any drug development; thus, natural products could serve as suitable and effective options because their safety is instantly evaluated for combating patients. Therefore, we build a list of MPs summarized in Table 3 with their active molecule known for possessing antiviral activities. These could be suitable choices for combating the situations from the COVID-19 pandemic.

There are so many pharmacological interventions of interest, but with no or limited clinical data. Such studies need to be evaluated in more extensive randomized trials to establish their efficacy and safety before presenting them to the world community.

7. COVID-19 vaccines

Manufacturers and public labs worldwide were in a close race to discover vaccines for COVID-19 and now compete for approval in the open world market to combat nCoV. This type of vaccine is developed and manufactured faster than conventional vaccines. Generally, if we talk about the use of vaccines against any disease, it means an effort of researchers for years because it needs a lot of time and resources to reach

Table 4
Vaccines approved for full use or in limited use.

Vaccine	Manufacturer	Trial Phase	Approval	Doses
Comirnaty or BNT162b2	Pfizer (USA) and BioNTech (Germany)	Phase 3	Approved for emergency use in E.U, U.S, and other countries	2 doses
mRNA-1273	Moderna (USA) and NIH	Phase 3	Approved in Switzerland. Emergency use in E.U, U.S, and other countries	2 doses
Sputnik V (also known as Gam-Covid-Vac)	Gamaleya Research Institute, (Russia's Ministry of Health)	Phase 3	Approved for emergency use in Russia and other countries	2 doses
AZD1222 (also known as Covishield in India)	Oxford University and the British-Swedish company, AstraZeneca	Phase 3	Approved in Brazil and emergency use in E.U, U.K, and other countries	2 doses
Convidecia (also known as Ad5-nCoV)	CanSino Biologics, (China)	Phase 3	Approved in China. Approved for emergency use in other countries	1 dose
Ad26. COV	Beth Israel Lahey Health and Johnson & Johnson in collaboration	Phase 3	Emergency use in E.U, U.S, and other countries	1 dose
EpiVacCorona	(Vector Institute) Russian biological research center	Phase 3	Approved in Turkmenistan and early use in Russia	2 doses
ZF2001	Anhui Zhifei Longcom and the Institute of Medical Biology at the Chinese Academy of Medical Sciences	Phase 3	Approved for emergency use in China and Uzbekistan	3 doses
BBIBP-CorV	Beijing Institute of Biological Products and Sinopharm	Phase 3	Approved in China, UAE, Bahrain, and emergency use in other countries	2 doses
CoronaVac (formerly PiCoVacc)	Sinovac Biotech	Phase 3	Approved in China, and emergency use in other countries	2 doses
Wuhan vaccine	Wuhan Institute of Biological Product and Sinopharm	Phase 3	Approved by WHO in China and limited use in U.A.E.	2 doses
Covaxin (also known as BBV152 A, B, C)	Indian Council of Medical Research and the National Institute of Virology	Phase 3	Approved for emergency use in India, Brazil, Mexico, and other countries	2 doses
CoviVac	Russian Academy of Sciences	Phase 3	Early use in Russia	No information
QazVac	Research Institute for Biological Safety Problems (Kazakhstan)	Phase 3	Authorized in April for the public in Kazakhstan	2 doses
Abdala	Center for Genetic Engineering and Biotechnology (Cuba)	Phase 3	Emergency use in Cuba	3 doses
	Finlay Vaccine Institute, Cuba	Phase 3	Emergency use in Iran	2 doses
Soberana 2 or Pasteur (in Iran)				
Shenzhen Kangtai vaccine	Shenzhen Kangtai Biological Products	Phase 3	Emergency use in China	No information
COVIran Barekat	Shafa Pharmed Pars	Phase 3	Emergency use in Iran	No information

Table 5
List of abandoned Vaccines.

Producer name (Country)	Phase completed	Vaccine type	Status	Reason
Imperial college London and Morningside Ventures	Phase 1/2	RNA Vaccine	Abandoned on 27th January 2021	Not produced the required response
Merck and Institut Pasteur	Phase-1	Viral vectors vaccine	Abandoned on 25th January 2021	Side effects
Merck partnered with IAVI	Phase-1	Viral vectors vaccine	Abandoned on 25th January 2021	Did not produced antibodies
University of Queensland (Australia)	Phase-1	No information	Abandoned on 10th December 2021	Side infection
Maryland-based Altimmune	Phase-1	No information	Abandone on June 29, 2021	Produce lower level of antibodies

a vaccine to the clinic. However, researchers broke all the records this time by developing a safe and effective COVID-19 vaccine in less than a year. Medical experts around the world work intensely to produce new vaccinations against the infectious COVID-19. Scientists around the globe make history by putting four types of vaccines in clinical trials: whole virus, viral vector, protein subunit, and nucleic acid (RNA/DNA), that claim to secure peoples by producing immunity in a somewhat different way. It is reported that eight vaccines are approved for full use for the first time while the other six vaccines got approval for limited use against COVID-19, and all this happen in less than a year. As of June 2021, there are over 170 official vaccine projects. At least 77 vaccine candidates are in animal studies (Preclinical studies), while almost 97 vaccine candidates are in human trials, out of which 32 are in final trials, and some are put for use in the general population (as shown in Fig. 2). Millions of people worldwide are already vaccinated against the COVID-19 by using these vaccines [126]. The first to win WHO backing from a non-Western nation is one of mainly two Chinese Coronavirus Vaccines, which have collaboratively been given to millions of people in China and outside. It is also the first time that the WHO has approved a Chinese vaccine for urgent situation use for all infections. Tables 4, 5, and 6 present the pharmaceutical companies that have competitively developed vaccines for COVID-19. The WHO already granted Covid 19 vaccines formulated by Pfizer-BioNTech, AstraZeneca, Johnson & Johnson, and, last week, Moderna emergency permission.

There are dozens of distinct SARS-CoV-2 variants that circulate throughout the world. Those with the most potentially problematic alterations are referred to as "variants of concern" and are closely monitored by health experts. These include the Indian or Delta variant (B.1.617.2), Kent, United Kingdom or Alpha variant (B.1.1.7), Brazilian or Gamma variant (B.1.351), and South African or Beta variant (P.1). All of these have swiftly spread to an increasing number of countries worldwide. Monoclonal antibodies against the N-terminal domain and receptor-binding domain, including bamlanivimab, cannot neutralize

Table 6
Vaccines now undergoing Phase III clinical trials.

Vaccine	Manufacturer	Clinical Trial	Approval	Doses
CVnCoV,	CureVac (Germany)	Phase 3	NA	2 doses
ZyCoV-D	Zydus Cadila (India	Phase 3	NA	3 doses
ARCoV	Academy of Military Medical Sciences, Suzhou Abogen Biosciences and Walvax Biotechnology	Phase 3	NA	No information
AG0302-COVID19	AnGes in partnership with Osaka University and Takara Bio (Japan)	Phase 2/3, combined phases	NA	2 doses
GRAd-COV2	ReiThera and Lazzaro Spallanzani National Institute for Infectious Diseases (Italy)	Phase 2/3, combined phases	NA	No information
NVX-CoV2373	Maryland-based Novavax (USA)	Phase 3	NA	2 doses
Soberana 2	Finlay Vaccine Institute (Cuba)	Phase 3	NA	No information
CoVLP	Canada-based Medicago and GSK, UK	Phase 3	NA	2 doses
Corbevax	Baylor College of Medicine	Phase 3	NA	No information
QazCovid	Research Institute for Biological Safety Problems	Phase 3	NA	No information
BRACE	Murdoch Children Research Institute (Australia)	Phase 3	NA	No information
VLA 2001	French vaccine maker Valneva along with Dynavax.	Phase 3	NA	No information
COVIran	Shafa Pharmed Pars, an Iranian pharmaceutical company	Phase 3	NA	No information

NA: Not approved

the Delta variant because they are diminished on binding to the spike. A study suggested that sera from convalescent patients collected up to 12 months after COVID-19 symptom onset are four times less effective against the Delta variant than against the Alpha variant (B.1.1.7). Sera from individuals who had only received one dose of the Pfizer or AstraZeneca vaccination minimally suppressed the Delta variant [107]. This indicates that variant spread is associated with antibody escape from the virus spike epitopes and serious concerns regarding re-infection and the efficacy of all types of vaccines.

8. Conclusion

Since the nCoV outbreak, scientists worldwide have been exploring suitable therapeutics for COVID-19. They are working to identify short-term preventive alternatives and long-term vaccines to combat the COVID-19 threat. Despite significant improvements and favorable outcomes from vaccine candidate trials, numerous challenges remain, including the logistical challenges of mass production and delivery of millions or billions of doses to the global population, which would almost certainly be the most considerable constraint. In addition, due to the limitations of vaccines and the time-consuming process of developing new drugs, FDA-approved molecules with established efficacy for viruses and various inflammatory conditions are considered more attractive in COVID-19 therapy. Nevertheless, successful clinical trials are necessary to provide adequate evidence to ensure the safety and effectiveness of these drugs against COVID-19. SARS-CoV-2 variants spread are associated with antibody escape from the virus Spike epitopes, seriously concern re-infection and compromise the effectiveness of all types of the vaccines. Besides COVID-19 therapeutics, it is essential to establish an early diagnostic approach. Consistent research efforts and a thorough understanding of COVID-19 pathophysiology are expected to facilitate effective solutions. Despite the threats posed by the rapidly spreading viral outbreak, the world has seen impressive scientific coordination and collaboration that will undoubtedly act as a roadmap for future pandemic solutions.

CRediT authorship contribution statement

Sabi-Ur-Rehman: Data curation, Writing – original draft, Visualization. **Shaheed Ur Rehman:** Conceptualization, Methodology, Writing – original draft. **Hye Hyun Yoo:** Supervision, Conceptualization, Writing – review & editing.

Conflict of interest statement

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

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