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European Journal of Pharmacology 883 (2020) 173372

Contents lists available at ScienceDirect

European Journal of Pharmacology

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

Full length article

Advances in the possible treatment of COVID-19: A review.

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ARTICLE INFO

Keywords:
Antivirals
COVID-19
Epidemiology
Therapeutics
Treatments
Vaccines

ABSTRACT

The emergence of the global pandemic caused by novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has put a challenge to identify or derive the therapeutics for its prevention and treatment. Despite the unprecedented advances in the modern medicinal system, currently, there are no proven effective therapies. However, rapid research on SARS-CoV-2 epidemiology help unveiling some new targets for potential drug therapies. Many drugs have been screened, and even their clinical trials are going on at an exceptional pace. Amongst these RNA-dependent RNA polymerase inhibitors (favipiravir and remdesivir) and steroids especially dexamethasone showed promising effects. The biological agents like tocilizumab, interferons, and convalescent plasma prove to be beneficial in viral clearance. Moreover, many immunomodulatory and viral S protein targeting vaccines have their ongoing clinical trials. The establishment of various *in vitro* and *in vivo* models for preclinical studies can additionally help the current research. The volume and the pace of the clinical trials launched to evaluate the safety and efficacy of various agents against coronavirus disease 2019 (COVID-19) reflect the need for high-quality evidence for various therapies to be practiced by clinicians. This study aims to sum up all the current advances in the global medicinal system against the COVID-19.

1. Introduction

Coronaviruses are enveloped, giant, unsegmented positive-sense single-stranded RNA viruses having varying genome sizes between 26 to 32 kb. They can infect humans and also a wide range of wild animals (Cronjé, 2017). To date, four subfamilies, namely alpha, beta, gamma, and delta coronaviruses, out of which alpha and beta have their origin from bats while gamma and delta subspecies originated from birds and pigs. Six coronavirus species have the potential to cause human disease out of which four, namely 229E, OC43, NL63, and HKU1 are prevalent, causing common cold-like symptoms (Hui et al., 2020). The remaining two having zoonotic origin are severe acute respiratory syndrome coronavirus (SARS-CoV), responsible for the severe acute respiratory syndrome outbreaks (SARS) in 2002–2003 in Guangdong, China (Chan et al., 2020; Zhu et al., 2020) and Middle East respiratory syndrome coronavirus (MERS-CoV) the causal agent for severe respiratory disease outbreaks in 2012 in the Middle East (Chowell et al., 2015). Recently a new coronavirus outbreak having origin from Wuhan, China (Hui et al., 2020), had posed a severe threat to public health worldwide (Zhu et al., 2020). To date (July 3, 2020), approximately 10.71 million persons belonging to 215 countries and territories are suffering from the pandemic with a death toll of more than 517,877 (Organization, 2020b). The USA is the most affected country, and it contributes about 25.80% of the total COVID-19 cases, followed by Brazil, Russia, and India (Organization, 2020b). Being a contagious disease, COVID-19 mainly transmits person to person (Ralph et al., 2020), but the origin of the disease was the result of a human-animal interface (Lake, 2020; Wu et al., 2020). SARS-CoV-2 can replicate in both upper as well as lower respiratory tract, and the virus enters the lung epithelial cells via interaction between viral spike (S) protein and angiotensin-converting enzyme II (ACE2) receptor (Dhama et al., 2020). The mean incubation period of the virus is 5–6 days, with a range of 2–14 days (Mission, 2020). Major

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https://doi.org/10.1016/j.ejphar.2020.173372
Received 19 March 2020; Received in revised form 4 July 2020; Accepted 13 July 2020
Available online 17 July 2020

common symptoms at the onset of illness are fever (88.7%), cough (67.8%), fatigue (38.1%), dyspnea (18.7%), and myalgia (14.9%) (Guan et al., 2020). These could be followed by other symptoms with less rate of an occurrence like sputum production, headache, dizziness, abdominal pain, vomiting, diarrhea, and upper respiratory tract symptoms, including sore throat, nasal congestion, and rhinorrhoea. The severity of infection can lead to complications like septic shock (Guan et al., 2020), acute respiratory distress syndrome (ARDS), arrhythmia (Guan et al., 2020), RNAaemia (Wang et al., 2020), acute kidney injury (Guan et al., 2020), acute cardiac injury (Huang et al., 2020) pneumonia (Guan et al., 2020) and secondary infections (Huang et al., 2020). COVID-19 has a current death rate of 1.4% (Olson et al., 2020), lower than the initial estimate of 3.4% (Lai et al., 2020), but the disease has more severity in the older age, with a death rate of 14.8% in the patients having age above 80 years. In contrast, children are the least affected, showing milder or even asymptomatic infection (Columbus et al., 2020). Recent studies had shown that the fatality rate changes with the pre-existing medical conditions where the person with cardiovascular diseases, diabetes, chronic respiratory diseases, and cancer are at higher risk (Liu et al., 2020). COVID-19 being highly contagious transmits and spreads at a very faster rate despite a large number of preventive measures like respiratory hygiene, quarantization, isolation, social distancing, avoidance of public gatherings, etc. (Cetron and Landwirth, 2005; Columbus et al., 2020). Developing some potential therapeutics against COVID-19 infection is the only way to cope with such a pandemic.

2. Methods

We searched Google Scholar, Embase, and Pubmed for drugs and vaccines for COVID-19. Relevant articles from the search results were selected, including 'associated articles' and the cited references therein. We also accessed the World Health Organisation (WHO) situation reports and Centres for Disease Control and Prevention (CDC) reports. The data was compiled from all the retrieved scientific literature, and an attempt was made to review the significant aspects of the COVID-19 pandemic with particular reference to its possible treatments.

3. Results

3.1. Mechanism of SARS-CoV-2 infection

SARS-CoV-2 is a single-stranded RNA virus that uses its surface spike glycoproteins (S proteins) to invade target cells. S proteins bind with high affinity to human angiotensin-converting enzyme 2 receptor (Li, 2016). Viral S protein consists of two regions S1 and S2, S1 is used for the binding to host cell receptor, whereas S2 is used for membrane fusion. After binding with receptors, virus particles enter into cells via receptor-mediated endocytosis involving host cell receptors and endosomes (Gui et al., 2017). Once it comes inside the cell, it synthesizes viral polyproteins that encode for the replicase-transcriptase complex. After that, the virus synthesizes its RNA via RNA dependent RNA polymerase (RdRp). Structural proteins are synthesized, which leads to the assembly and release of viral particles (Chen et al., 2020d; Fehr and Perlman, 2015; Fung and Liu, 2014). S protein binding to the ACE2 receptor in the case of SARS-CoV and likely SARS-CoV-2 has been documented to induce a negative feedback loop, which ultimately results in the downregulation of ACE2 expression. The drop in ACE2 then directs its substrate angiotensin I to increase its related enzyme, angiotensin-converting enzyme (ACE) (Fung and Liu, 2014).

Increased activity of ACE, therefore, results in the elevated levels of angiotensin II and overactivated AT1 receptors (Angiotensin II receptor type 1), which lead to lung injury (Kuba et al., 2005). ACE2 receptors are widely distributed, and SARS-CoV-2 can affect a range of organs showing distinct clinical manifestations (Zou et al., 2020).

3.2. Possible treatments

Currently, COVID-19 positive patients are receiving anti-viral, antibiotic, and steroid therapies (Guan et al., 2020; Huang et al., 2020), however many patients are receiving oxygen therapy, whereas mechanical ventilation is initiated generally in severe cases as compared to nonsevere ones. In a study of 1099 confirmed patients, 41.3% of patients received oxygen therapy, and 6.1% received mechanical ventilation (Guan et al., 2020).

According to the guidelines, Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (7th edition), issued by National Health Commission & State Administration of Traditional Chinese Medicine, several agents are recommended for the treatment of COVID-19 including antivirals such as interferon alfa (IFN-α), lopinavir/ritonavir, arbidol chloroquine phosphate, and ribavirin. In severe cases with extensive lung lesions and with an increased IL-6 level, tocilizumab is suggested (Table 1). For COVID-19 patients with a critical illness, glucocorticoids are recommended for a short period (3–5 days). Besides these, Traditional Chinese Medicines are also recommended in the guidelines for the treatment of various levels of COVID-19 cases (Commision, 2020). In silico studies have demonstrated that anti-SARS-CoV-2 compounds might be present in Chinese herbal remedies used traditionally for the treatment of viral respiratory infection (Zhang et al., 2020), showing the potential of natural compounds against coronavirus. Various potent nutraceuticals might help in the prevention and control of RNA virus infections, including coronavirus by increasing type 1

Table 1
Agents\Drugs recommended in the Guidelines (version 7) by the National Health Commission & State Administration of Traditional Chinese Medicine for treatment of COVID-19.

Agent	Dosage
IFN-α	5 million U, twice a day.
Lopinavir/ Ritonavir	200 mg/50 mg per pill for adults, two pills each time, twice a day, no longer than ten days.
Ribavirin	500 mg intravenous injection for adults, 2–3 times per day, suggested being used jointly with IFN-α or lopinavir/ ritonavir, no longer than ten days.
Chloroquine phosphate	500 mg twice a day for a week for adults over 50 kg of body weight. 500 mg twice a day for the first and second day and 500 mg once a day for days 3–7 for adults with body weight below 50 kg.
Arbidol	200 mg three times per day for adults, no longer than ten days.
Tocilizumab	4–8 mg/kg (initial dose). 400 mg (recommended dose, infusion rate 1.66 ml/min) diluted with 0.9% normal saline to final makeup of 100 ml, not more than 2 infusions.

interferon production via amplifying either the signaling of toll-like receptor 7 (TLR7) or mitochondrial antiviral-signaling proteins (MAVS) (McCarty and DiNicolantonio, 2020).

Apart from the above-mentioned drugs, there are other candidates for the treatment of COVID-19 patients that are currently being investigated and theoretically considered all over the globe (Tables 2 and 3). The efficacy and safety profile of all the candidate drugs in the treatment of COVID-19 needs to be confirmed in further preclinical and clinical trials. Following are some of the widely discussed potential candidates for treating SARS-CoV-2-infected patients;

3.2.1. Antimalarial drugs

3.2.1.1. Chloroquine. Chloroquine is an aminoquinolin that is quinoline substituted by chlorine at position 4 and by a [5-(diethylamino)pentan-2-yl]amino group at position 7 (Thomé et al., 2013). Chloroquine, recently reported as a potential wide-spectrum antiviral drug (Wang et al., 2020b), is majorly used for reducing and combating malaria. It seems to be beneficial in the diagnosis of lupus erythematosus, rheumatoid arthritis, hepatic amoebiasis, and light-sensitive skin eruptions as an anti-inflammatory agent. Also, it has a role as an autophagy inhibitor (Thomé et al., 2013). Chloroquine is effective against SARS-CoV-2 *in vitro* and may have an immunomodulatory effect (Gao et al., 2020; Wang et al., 2020b).

When given orally, chloroquine gets widely distributed throughout the body, including the lungs. In Vero E6 cells, the EC90 value of chloroquine against SARS-CoV-2 was 6.90 μM, which can be clinically attained in the plasma as observed in the case of rheumatoid arthritis patients undergoing 500 mg administration (Kapoor and Kapoor, 2020). Wang et al. indicated that chloroquine blocks SARS-CoV-2 infection with an EC50 value of 1.13 μM and CC50 higher than 100 μM (Wang et al., 2020b). The EC50 values for chloroquine were 23.90 and 5.47 μM, respectively, at 24 h and 48 h against SARS-CoV-2 in another *in vitro* study (Yao et al., 2020). The specific mechanism of action of chloroquine is not known; however, it increases the endosomal pH necessary for virus/cell fusion and also interferes with the glycosylation of SARS-CoV cell surface receptors (Vincent et al., 2005). In addition to its antiviral activity *in vitro*, chloroquine possesses a resistant-modulating role that can therapeutically improve it's *in vivo* antiviral effect (Colson et al., 2020; Cortegiani et al., 2020; Savarino et al., 2006). Data from over 100 COVID-19 patients have shown that chloroquine phosphate is better when compared to control treatment by inhibiting pneumonia exacerbation, enhancing lung imaging tests, encouraging a virus-negative conversation, and reducing the disease course (Gao et al., 2020). Any severe adverse reactions to chloroquine phosphate have not been reported in the treated patients (Gao et al., 2020). Despite the promising effect, cardiovascular toxicity and supply problems in the United States restrict the use of chloroquine (McCreary and Pogue, 2020). Chloroquine's anti-viral and anti-inflammatory properties may contribute to its efficient effectiveness in the treatment of COVID-19 pneumonia patients. However, more studies are required regarding the safety and efficacy of chloroquine.

3.2.1.2. Hydroxychloroquine. To counter chloroquine-resistant malaria, another antimalarial drug that is hydroxychloroquine (a chloroquine analog) was synthesized. Hydroxychloroquine is a 4-aminoquinoline with activities such as immunosuppression, anti-autophagy, and antimalarial (McCreary and Pogue, 2020). Chloroquine and its derivative hydroxychloroquine have large total apparent amounts of delivery, as well as a one-month or longer half-lives of terminal removal that requires nearly a year to clear the body completely. Such long half-lives have made such medicines active anti-malaria prophylactic agents (McCreary and Pogue, 2020).

Additionally, hydroxychloroquine is widely used for autoimmune diseases, including systematic rheumatoid arthritis and lupus erythematosus. Hydroxychloroquine was reported to have an *in vitro* efficacy against SARS-CoV (Biot et al., 2006). The clinical safety profile of hydroxychloroquine is higher than that of chloroquine (long-term use), which allows for a higher regular dose, with fewer questions regarding drug-drug interactions (Marmor et al., 2016). Findings from the *in vitro* study of hydroxychloroquine against SARS-CoV-2 showed potent antiviral activity. It was able to minimize the concentration-dependent replication of the virus. Hydroxychloroquine was reported to have a more substantial effect than chloroquine against SARS-CoV-2 (*in vitro*) with EC50 values 0.72 μM vs. 5.47 μM, respectively at 48 h (Yao et al., 2020). Hydroxychloroquine, like chloroquine, also acts as a weak base that can increase the pH of endosomes preventing virus/cell fusion (Yao et al., 2020). Initial clinical findings from a closed-label non-randomized clinical trial with 36 COVID-19 patients showed substantial viral load suppression in hydroxychloroquine treated patients relative to control patients (Gautret et al., 2020). In most cases, hydroxychloroquine was successful in eliminating nasopharyngeal carriage of SARS-COV-2 in patients infected with COVID-19 in just three to six days. There was a significant difference among hydroxychloroquine treated patients and controls even after the third day of post-inclusion (Gautret et al., 2020). The lower dose-dependent toxicity profile of hydroxychloroquine in humans relative to chloroquine (Marmor et al., 2016), makes it possible to use even at higher doses than the observed 50% effective dose (ED50) (Yao et al., 2020).

Recent data from large randomized controlled trials showed no evidence of benefit for viral clearance, mortality or other outcomes of chloroquine and hydroxychloroquine treatment over standard care in hospitalized patients with COVID-19 (Tang et al., 2020). Moreover, previous reports of reduced viral shedding with the treatment of these two drugs have not been consistently replicated. Also, the current US treatment guidelines do not recommend the use of chloroquine or hydroxychloroquine in hospitalized patients with COVID-19 (FDA Revokes EUA, 2020; Letter revoking EUA, 2020). On the other hand, serious side effects, including methemoglobinemia and cardiac adverse events in COVID-19 patients, the known and potential benefits of these two drugs do not outweigh the known and potential risks for the authorized use. Therefore, based on the collective scientific evidence available, food and drug administration (FDA) revoked emergency use authorization (EUA) for chloroquine and hydroxychloroquine on June 15, 2020 (FDA Revokes EUA, 2020; Letter revoking EUA, 2020). Meanwhile, on June 17, 2020, WHO stopped the hydroxychloroquine arm of the solidarity trial to find an effective COVID-19 treatment (Solidarity clinical trial, 2020).

3.2.2. HIV-1 protease inhibitors

3.2.2.1. Lopinavir/ritonavir. Lopinavir/ritonavir is a human immunodeficiency virus (HIV) drug used in conjunction with other medical products to treat children over 14 days of age and adults diagnosed with HIV-1 (Su et al., 2019). Lopinavir is a highly-specific HIV-1 protease inhibitor. Such inhibitors are derived structurally from a sequence of symmetry-based lead compounds, constructed by considering the target

enzyme's C2 symmetric structure (Abraham, 2007). Ritonavir significantly inhibits the metabolism of lopinavir, ritonavir/lopinavir coadministration in healthy human volunteers increased the region under the plasma concentration-time curve for lopinavir by more than a hundred times (Hurst and Faulds, 2000). Chu et al. described lopinavir/ritonavir's *in vitro* anti-SARS-CoV activity and confirmed in clinical trials also (Chu et al., 2004). In 2003, they tested a series of antivirals against SARS-CoV *in vitro*. They recorded 4 mg/ml of lopinavir and 50 mg/ml of ribavirin inhibited SARS-CoV after incubation of 48 h and the agents when combined act synergistically (Chu et al., 2004). Later de Wilde and colleagues identified the antiviral activity of lopinavir against SARS-CoV and showed an EC50 value of 17.1 ± 1 μM in Vero E6 cells, which is close to the upper limit of previously reported lopinavir's plasma concentrations in patients diagnosed with HIV (de Wilde et al., 2014). Lopinavir and ritonavir can bind to Mpro (main protease), a key coronavirus enzyme which plays a significant role in facilitating viral replication (Liu and Wang, 2020). Lopinavir appears to block the key protease of SARS-CoV, which inhibits the replication of the virus (Ratia et al., 2008).

Cao B and colleagues reported that 199 laboratory-confirmed Patients diagnosed with SARS-CoV-2 were randomized; 99 were allocated to the group of lopinavir-ritonavir and hundred patients to the group of standard treatment. In the group of lopinavir-ritonavir and the group of standard care, mortality at twenty-eight days was comparable, and no significant differences in viral clearance were observed. No benefit has been observed beyond standard care with lopinavir-ritonavir treatment in hospitalized adult patients suffering from extreme COVID-19. Potential studies in critically ill patients might help to confirm or exclude the possibility of therapy again (Cao et al., 2020).

3.2.3. Antiviral drugs

3.2.3.1. Remdesivir. Remdesivir is a broad-spectrum antiviral known for containing coronavirus activity *in vitro* (Agostini et al., 2018; Wang et al., 2020b). It is an investigational analog of nucleoside and a monophosphoramidate prodrug of remdesivir-triphosphate (RDV-TP). RDV-TP is an analog of adenosine that acts as an RNA-dependent RNA polymerase (RdRp) inhibitor (Agostini et al., 2018). For incorporation into the nascent viral RNA chain, RDV-TP competes with adenosine-triphosphate. Once incorporated into the viral RNA, it terminates RNA synthesis, thus inhibiting the production of viral RNA. Since RDV-TP does not trigger immediate chain termination, the drug is presumed to evade proofreading by viral exo-ribonuclease activity (Agostini et al., 2018; Ko et al., 2020). Animal studies suggested that remdesivir can significantly reduce the viral load in the lung tissue of MERS-CoV infected mice. It also enhances lung functioning and minimizes pathological disruption of lung tissue (Sheahan et al., 2020).

Wang et al. reported that remdesivir firmly inhibits interference with SARS-CoV-2 at low micromolar (μM) concentrations but has a high selectivity index (Half Maximum Effective Concentration (EC50), 0.77 μM; Half Cytotoxic Concentration (CC50) > 100 μM; IS > 129.87) (Wang et al., 2020b). Holshue et al. documented that remdesivir brought results that were remarkable in the care of a first COVID-19 patient in the United States (Holshue et al., 2020). Various clinical trials have been initiated to determine the drug's safety and efficacy in COVID-19 infected patients.

3.2.3.2. Favipiravir. Favipiravir (T-705; 6-fluoro-3-hydroxy-2-pyrazine carboxamide) is an anti-viral agent that efficiently inhibits RdRp from RNA viruses (Furuta et al., 2005, 2013). It has been explored by chemical modulation of a pyrazine analog, initially screened *in vitro* for anti-influenza activity (Furuta et al., 2017). Following its role against anti-influenza viruses, favipiravir can inhibit the replication of alpha-, flavi-, filo-, arena-, bunya-, noro-, and other RNA viruses. Favipiravir can thus have significant antiviral activity on SARS-CoV-2 also (Delang et al., 2018). Favipiravir is a prodrug that undergoes intracellular phosphorylation and gets converted to its active form, favipiravir-ribofuranosyl-5′-triphosphate (favipiravir-RTP), which interacts with viral RNA polymerase and inhibits viral replication (Furuta et al., 2005, 2017). Because RdRp's catalytic domain is conserved across different types of RNA viruses, this etiology validates a broader range of favipiravir's anti-viral activities. It is proposed that favipiravir may get integrated that into a nascent viral RNA, or it may function by binding to conserved polymerase domains, thereby preventing the incorporation of the nucleotide for replicating and transcribing viral RNA (Furuta et al., 2013, 2017). Yet more work is required to explain the connection between favipiravirs anti-viral activity and suppression of the RdRp activities (Furuta et al., 2017).

National Infectious Diseases Clinical Medical Research Center and the Shenzhen Third People's Hospital obtained remarkable results on February 14, 2020, from a clinical study on favipiravir for the management of COVID-19 (News: szdsyy, 2020). Preliminary findings from a total of eighty patients suggested that the antiviral activity of favipiravir was more efficient than that of lopinavir/ritonavir. No potential side effects in the favipiravir treated groups were found, and it had substantially less detrimental effects than the lopinavir/ritonavir group (Chen et al., 2020a). In a study involving 240 COVID-19 patients, favipiravir was considered as preferred treatment compared to arbidol (Chen et al., 2020a).

3.2.3.3. Arbidol (Umifenovir). Arbidol, a Russian made indole derivative, remains an antiviral drug used to combat influenza infection in china and Russia (Blaising et al., 2014; Wang et al., 2017). Arbidol mainly functions by inhibiting the interaction between the virus and host cells, preventing viral invasion into host cells (Blaising et al., 2014; Kadam and Wilson, 2017). It also exhibits immunomodulatory function by inducing interferon production and macrophages activation (Glushkov et al., 1999).

According to a report, it has been reported that arbidol at a concentration range of 10–30 μM *in vitro* is effective against SARS-COV-2 (Chinanews, 2020). In a clinical study involving 111 patients, it was found that arbidol promotes and strengthens the cycle of viral clearance, enhances focal penetration on radiological images, and decreases demand for the high-flow nasal cannula (HFNC) oxygen therapy in-hospital treatment (Xu et al., 2020a). In a retrospective analysis, arbidol, in combination with lopinavir/ritonavir, showed beneficial effects (Deng et al., 2020). Though, in a randomized clinical study involving 240 COVID-19 patients half of which received arbidol and other half received Favipiravir proved that the clinical retrieval rate of day 7 was 55.86% in the arbidol group and 71.43% in the favipiravir group showing the superiority of favipiravir (Chen et al., 2020a).

3.2.4. Antibiotic

3.2.4.1. Azithromycin. Azithromycin, a member of macrolide antibiotics, is the semisynthetic derivatives of erythromycin. Azithromycin varies from erythromycin by a methyl-substituted nitrogen atom into the lactone ring. It is a bacteriostatic agent, which interrupts protein synthesis by reversibly binding to 50S ribosomal subunits of microorganisms (Matzneller et al., 2013; Moreno et al., 2009). Besides this, the macrolides have anti-inflammatory and immunomodulatory functions beyond its antibacterial function. Macrolides can reduce inflammatory activities and minimize elevated cytokine generation linked with pulmonary viral infections; however, they are unclear regarding their exact influence on viral clearance. Immunomodulatory pathways can include reducing neutrophil chemotaxis (NMPs) to the lungs, minimizing the synthesis of proinflammatory cytokines, inhibiting mucus hypersecretion, decreasing the production of reactive oxygen species, promoting neutrophil apoptosis and disrupting the stimulation of nuclear transcription factors (Kanoh and Rubin, 2010; Zarogoulidis et al., 2012). Azithromycin attenuated acute and chronic respiratory inflammation in a mouse model of viral bronchiolitis, illustrating the anti-inflammatory activity of azithromycin, explaining the rationale of prospective clinical studies, which will examine the efficacy of macrolides on acute viral bronchiolitis and its long-term impact (Beigelman et al., 2010). Azithromycin was also reported to be effective *in vitro* towards Zika and Ebola viruses (Madrid et al., 2015; Retallack et al., 2016), and to suppress severe respiratory tract viral infections (Zhan, 2016).

In a clinical study involving 36 COVID-19 patients, 26 patients received hydroxychloroquine, and ten were taken as control. Six patients among hydroxychloroquine treated groups were given azithromycin to prevent secondary bacterial infections. On the sixth day from the beginning of treatment, all patients undergoing with hydroxychloroquine and azithromycin combination were clinically cured compared to 57.1% of patients treated with hydroxychloroquine alone (Gautret et al., 2020). This indicated that azithromycin added to hydroxychloroquine was substantially effective for virus removal (Gautret et al., 2020).

3.2.5. Anti-inflammatory

3.2.5.1. Baricitinib. The baricitinib is a Janus kinase inhibitor (JAK), an approved drug for rheumatoid arthritis. It can be an effective treatment for SARS-CoV-2 to inhibit viral entry and inflammation (Richardson et al., 2020; Stebbing et al., 2020). Baricitinib, besides being JAK inhibitor, also has more affinity for AP2-associated protein kinase 1 (AAK1) and binds cyclin G-associated kinase (GAK), which are amongst the primary regulators of endocytosis (Lu et al., 2020). Disruption of endocytosis can prevent the virus passage into cells and also the intracellular assembly of viral particles (Sorrell et al., 2016). Drugs that target the members of the numb-associated kinase (NAK) family-including AAK1 and GAK were shown to decrease *in vitro* viral infection (Bekerman et al., 2017; Pu et al., 2018). Janus kinase inhibitor-signal transducer and activator of transcription (JAK-STAT) signaling inhibitors are considered efficient against the effects of high cytokine levels (including interferon α) usually observed in persons with COVID-19 (Huang et al., 2020; Stebbing et al., 2020).

At recommended doses used to treat patients with rheumatoid arthritis, it is predicted that free plasma concentrations of baricitinib are sufficient to inhibit AAK1, and potentially GAK (Stebbing et al., 2020). The high specificity of baricitinib to NAKs, its anti-inflammatory properties, and its ability to minimize associated chronic interferonopathy inflammation along with its beneficial pharmacokinetic properties seem to make it a suitable candidate for the future SARS-CoV-2 treatment (Stebbing et al., 2020). The ability for combination therapy with baricitinib is significant despite its low binding of plasma proteins and limited interaction with cytochrome p450 (CYP) enzymes and drug transporters. Also, baricitinib may be paired with the direct-acting antivirals (lopinavir or ritonavir and remdesivir) already used in the COVID-19 outbreak. Baricitinib combinations of these direct-acting antivirals will decrease viral infectivity, viral replication, and an abnormal inflammatory response from the host (Stebbing et al., 2020).

3.2.6. Steroids

3.2.6.1. Corticosteroids. Due to the high amount of cytokines produced by SARS-CoV (He et al., 2006; Wong et al., 2004), MERS-CoV (Falzarano et al., 2013; Faure et al., 2014), and SARS-CoV-2 (Huang et al., 2020), corticosteroids are commonly used to treat patients with severe infection. However, studies involving corticosteroid-treated SARS and MERS patients show disrupted infection clearance and no effect on mortality (Arabi et al., 2018; Stockman et al., 2006). It is prescribed that glucocorticoids are being used for a limited time (3–5 days), with a dosage not more than the equivalent of methylprednisolone 1–2 mg/kg/day for COVID-19 patients with severe illness, as a higher dose can prolong the coronavirus elimination due to immunomodulatory effects (Commision, 2020). Therefore, corticosteroids should not be administered routinely. Ongoing clinical studies involving corticosteroid therapy in severely ill COVID-19 patients will help to understand the therapy's efficacy and safety.

Recently, preliminary results of the RECOVERY trial involving dexamethasone (6 mg given once daily for ten days) showed reduced mortality in patients receiving respiratory support (Horby et al., 2020; Ledford, 2020). Dexamethasone reduced the mortality by one-third in patients receiving invasive mechanical ventilation and by one-fifth in patients receiving oxygen support without invasive mechanical ventilation. Whereas, no effect of the drug was noticed in patients in mild condition not requiring oxygen support (Horby et al., 2020; Ledford, 2020). WHO also authorized the use of dexamethasone in severe to critical conditions only (WHO, 2020).

3.2.7. Biological agents

3.2.7.1. Tocilizumab. Tocilizumab is a recombinant monoclonal immunoglobulin G1 (IgG1) antibody against the human interleukin 6 (IL-6) receptor. Membrane-bound IL-6 receptors (sIL-6R and mIL-6R) and soluble are two forms of the receptor to which tocilizumab binds specifically and inhibits downstream signal transduction (Yokota et al., 2005). Tocilizumab is used for the treatment of cytokine release syndrome (CRS) (Le et al., 2018), rheumatoid arthritis (Navarro et al., 2014), and systemic juvenile idiopathic arthritis (Yokota et al., 2005). Besides, it has been reported to play a particular role in Castleman's disease (Nishimoto et al., 2005). It has been shown that a cytokine storm occurred in the pathogenesis of SARS-CoV, involving the significant

release of pro-inflammatory cytokines like IL-6 (Li et al., 2013). Expression of IL-8, IL-1ß, and IL-6 was markedly high in case of Middle East respiratory syndrome, caused by another coronavirus (MERS-CoV). However, MERS-CoV has also reported a delayed induction of proinflammatory cytokine (Lau et al., 2013). Similar in patients with SARS and MERS, COVID-19 patients also show higher plasma levels of cytokines, including IL-6, growth factors and proteins that indicated a cytokine storm and related to the severity of the disease and its prognosis (Chen et al., 2020c; Huang et al., 2020). IL-6 is one of the critical cytokines responsible for an inflammatory storm that lead to impaired diffusion of oxygen in the lungs (Zhou et al., 2020b). Therefore, interfering with IL-6 may also be a possible treatment for severe and critical COVID-19 infections. A study involving 21 patients treated with tocilizumab in China demonstrated rapid improvement in fever, oxygen intake, lung lesion opacity, levels of C-reactive protein, and lymphocyte concentration in peripheral blood. Out of 21, 19 (90.5%) were discharged on an average of 13.5 days after the treatment which shows a promising effect of tocilizumab, however, more studies are required regarding its efficacy and safety (Xu et al., 2020).

3.2.7.2. Convalescent plasma. It is evident from the literature that convalescent plasma from recovered patients can be administered to patients as a medication (Cheng et al., 2005; Mair-Jenkins et al., 2015). In 2003, a case study was done at Taiwan hospital, during the SARS outbreak, convalescent plasma (500 ml) free of residual SARS-CoV confirmed by RT-PCR was collected from three SARS patients and transfused into the three infected healthcare workers. Viral load decreased rapidly one day after transfusion, and all the patients survived (Yeh et al., 2005). In 2014, the WHO also proposed using convalescent plasma obtained from recovered Ebola patients during outbreaks as an effective treatment (Organization, 2014).

Two separate meta-analyses done by Mair-Jenkins et al. (identified severe influenza and 32 studies of SARS coronavirus infection) and Luke TC et al. (identified eight reviews during 1918–1925 involving 1703 patients with influenza pneumonia) showed a reduction in mortality in patients receiving convalescent plasma compared with control (Luke et al., 2006; Mair-Jenkins et al., 2015). One possible explanation for the treatment is that viremia may be suppressed by the antibodies present in the plasma obtained from the recovered patient (Chen et al., 2020b). In a recent case study at the infectious disease department, Shenzhen Third People's Hospital in Shenzhen, China involved five critically ill patients with COVID-19 and ARDS (acute respiratory distress syndrome) who received transfusion with convalescent plasma from 5 recovered COVID-19 patients between 10 and 22 days after admission (Shen et al., 2020). The administration of convalescent plasma results in an improvement in the patient's clinical condition, including the normalization of body temperature, decrease in SOFA score, and viral load (became negative within 12 days after the transfusion). Also, increased PAO2/FIO2 (ratio of the partial pressure of arterial oxygen to the percentage of inspired oxygen.) was observed within 12 days (Shen et al., 2020). Therefore, this technique can be beneficial for the treatment of COVID19 infection; however, further studies must be done to check the efficacy and safety of convalescent plasma transfusion in patients infected with SARS-CoV-2 (Chen et al., 2020b).

3.2.7.3. Stem cell therapy. Mesenchymal stem cells (MSCs) have been broadly used in cell therapies based on various preclinical and clinical studies regarding their safety and efficacy (Kamen et al., 2018; Wilson et al., 2015). MSCs have immunomodulatory effects and are capable of differentiation (Galipeau and Sensébé, 2018). MSC's immunomodulatory effects are due to its ability to communicate directly with immune cells or to the paracrine secretion of several forms of cytokines (Bernardo and Fibbe, 2013). The cytokines are triggered further by the stimulation of toll-like receptors in MSCs on stimulation by pathogen-associated molecules like LPS or double-stranded RNA from the virus (Li et al., 2012; Waterman et al., 2010). After MSC infusions in many diseased conditions, the resulting improvement was attributed mostly to their immunomodulatory effects (Prockop, 2017; Prockop and Oh, 2012). A study where seven COVID-19 patients were administered with human MSCs (10^6 cells per kilogram of weight, intravenously) resulted in improved functional outcomes and fast recovery (Leng et al., 2020). The symptoms of all the patients and pulmonary functions improved in 2 days significantly after transplantation, and also no adverse effects were seen for 14 days. Increases in peripheral lymphocytes, reductions in C-reactive protein, and overactivated cytokine-secreting immune cells (CXCR3+CD8 + T cells, CXCR3+CD4 + T cells, and CXCR3 + natural killer (NK) cells) disappeared within 3–6 days of treatment. Besides that, there was a decline in TNF-α level, whereas IL-10 and a group of CD11c + $CD14^+$ CD11bmid regulatory dendritic cell (DC) population increased (Leng et al., 2020).

The chest computed tomography (CT) scan on the 9th day after MSC transplantation revealed that ground-glass opacity and inflammation of pneumonia were significantly decreased. MSCs' gene expression profile shows that they were negative with ACE2 and type-2 transmembrane serine protease (TMPRSS2), suggesting that MSCs are free of SARS-CoV-2 infection. The intravenous transplantation of MSCs was, therefore, not only effective but also safe for the treatment of patients with COVID-19 pneumonia, especially patients under critically severe conditions (Leng et al., 2020). However, additional studies are required in a more number of patients to validate this therapeutic intervention further.

3.2.7.4. Interferons. Interferons (IFNs) consist of a group of secreted a-helical cytokines triggered by stimulation of toll-like receptors in response to different cell surface biomolecules. Interferon-alfa (IFN-α) is a broad-spectrum antiviral, widely used to combat hepatitis. It is documented to impair *in vitro* SARS-CoV reproduction (Stockman et al., 2006). Interferon-beta (IFN-ß) is a naturally occurring protein that orchestrates antiviral responses of the body (Stockman et al., 2006). IFN-α and -ß both have shown anti-SARS-CoV activity *in vitro* (Hensley et al., 2004; Ströher et al., 2004). IFN-ß has also displayed potent activity against MERS-CoV *in vitro* with an IC50 of 1.37 U/ml (Hart et al., 2014). Antiviral effect of IFN type I (IFN-α and IFN-ß) against SARS-CoV were stated in twelve *in vitro* studies (Stockman et al., 2006). It is also apparent from previous reports that IFN-ß was superior to IFN-α against SARS-CoV (Scagnolari et al., 2004). Effective synergistic results for leukocytic IFN-α with ribavirin (Chen et al., 2004), IFN-ß with ribavirin (Morgenstern et al., 2005), and IFN-ß with IFN-α have also been reported against SARS-CoV (Sainz et al., 2004; Scagnolari et al., 2004). In an *in vitro* study, following recombinant type-I IFN-α treatment, SARS-CoV-2 revealed a significant decrease in viral replication (Lokugamage et al., 2020). Besides several other agents, IFN-α is also recommended for the treatment of COVID-19 in the guidelines issued by the National Health Commission & State Administration of Traditional Chinese Medicine (Commision, 2020). Further preclinical/clinical studies are required to depict the efficacy and the safety of interferons for the COVID-19 treatment.

Table 2
Widely discussed potential agents for the treatment of SARS-CoV-2 infection.

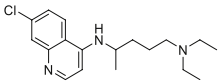
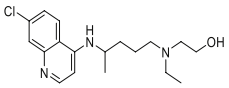
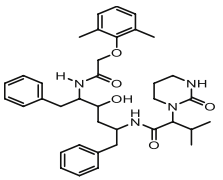
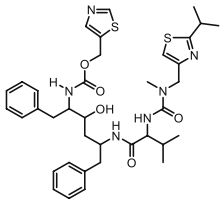
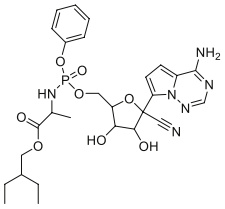
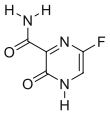
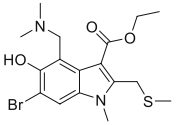
Agent	Chemical Formula	Chemical Structure	Comments	Clinical status	References
Chloroquine (Antimalarial)	$C_{18}H_{26}ClN_3$		Chloroquine has shown *in vitro* efficacy against SARS-CoV-2 with an EC50 (half-maximum effective concentration) value of 5.47 μM at 48 h. Data from over 100 COVID-19 patients have demonstrated that chloroquine phosphate is superior to control treatment.	NCT04307693, NCT04320277, NCT04323527, NCT04306497, NCT04325893, NCT04323592, NCT04315948 ChiCTR2000030031, ChiCTR2000029741, ChiCTR2000029740, ChiCTR2000029868, ChiCTR2000029939, ChiCTR2000029935, ChiCTR2000029899, ChiCTR2000029898, ChiCTR2000029988, ChiCTR2000029542.	(Gao et al., 2020; Yao et al., 2020)
Hydroxychloroquine (Antimalarial)	$C_{18}H_{26}ClN_3O$		Hydroxychloroquine was found to have a strong anti-SARS-CoV-2 effect (*in vitro*) with an EC50 value of 0.72 μM at 48 h. Clinical findings involving 36 COVID-19 patients have shown considerable viral load suppression in patients treated with hydroxychloroquine as compared to control patients.	NCT04308668, NCT04325893, NCT04328467, NCT04329923, NCT04321278, NCT04307693, NCT04320277, NCT04315948, NCT04326725, ChiCTR2000029740, ChiCTR2000029868, ChiCTR2000029899, ChiCTR2000029898.	(Gautret et al., 2020; Yao et al., 2020)
Lopinavir/Ritonavir (HIV-1 protease Inhibitor)	$C_{37}H_{48}N_4O_5$/ $C_{37}H_{48}N_6O_5S_2$	 	de Wilde et al. recognized the lopinavir's antiviral activity against SARS-CoV and showed an EC50, 17.1 ± 1 μM in Vero E6 cells. In a study involving 199 COVID-19 patients (99 assigned to a lopinavir/ritonavir group and 100 patients to the standard treatment. Group) reported that no benefit with lopinavir/ritonavir treatment beyond standard care was observed in hospitalized adult patients with severe COVID-19.	NCT04255017, NCT04315948, NCT04330690, NCT04252885, NCT04261907, NCT04276688, NCT04307693, ChiCTR2000029539, ChiCTR2000029387, ChiCTR2000030218, ChiCTR2000029741.	(Cao et al., 2020; de Wilde et al., 2014)
Remdesivir (Antiviral)	$C_{27}H_{35}N_6O_8P$		Wang et al. demonstrated that remdesivir inhibits SARS-CoV-2 infection in Vero E6 cells (EC50 = 0.77 μM). Holshue et al. reported that remdesivir treatment leads to remarkable results in the care of a first COVID-19 patient in the United States.	NCT04252664, NCT04257656, NCT04280705, NCT04292730, NCT04292899, NCT04315948, NCT04335123,	(Holshue et al., 2020; D. Wang et al., 2020; M. Wang et al., 2020)
Favipiravir (Antiviral)	$C_5H_4FN_3O_2$		Preliminary findings from a total of 80 patients suggested that the antiviral activity of favipiravir was more efficient than that of lopinavir/ritonavir. In a study involving 240 COVID-19 patients, favipiravir was considered as preferred treatment as compared to arbidol.	NCT04336904, NCT04310228, ChiCTR2000030113.	Chen et al. (2020)
Arbidol (Umifenovir) (Antiviral)	$C_{22}H_{25}BrN_2O_3S$		According to a report, arbidol at a concentration range of 10–30 μM *in vitro* is effective against SARS-COV-2. In a clinical study involving 111 COVID-19 patients-infected pneumonia, it was found that arbidol could accelerate and enhance the process of viral clearance whereas, in another study, arbidol in combination with Lopinavir/ritonavir showed beneficial effects.	NCT04252885, NCT04254874, NCT04255017, NCT04260594, ChiCTR2000029573.	(Chen et al., 2020; Deng et al., 2020)

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Table 2 (*continued*)

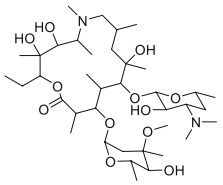
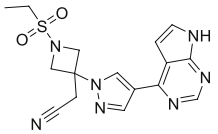
Agent	Chemical Formula	Chemical Structure	Comments	Clinical status	References
Azithromycin (Antibiotic)	$C_{38}H_{72}N_2O_{12}$		In a clinical study involving 36 COVID-19 patients (on the sixth day from the start of treatment), all the patients treated with hydroxychloroquine and azithromycin combination were virologically cured as compared to 57.1% patients treated with hydroxychloroquine alone.	NCT02735707, NCT04321278,	Gautret et al. (2020)
Baricitinib (Anti-inflammatory)	$C_{16}H_{17}N_7O_2S$		Baricitinib can be a potential treatment for SARS-CoV-2 to inhibit viral entry and inflammation due to its affinity for AP2-associated protein kinase 1 (AAK1) and cyclin G-associated kinase (GAK).	NCT04320277.	(Richardson et al., 2020; Stebbing et al., 2020)
Tocilizumab (Immunosuppressive)	$C_{6428}H_{9976}N_{1720}O_{2018}S_{42}$		Tocilizumab is a recombinant monoclonal antibody against the human interleukin 6 (IL-6) receptor. A study involving 21 patients treated with tocilizumab in China demonstrated rapid improvement, and about 90.5% (19) were discharged on average of 13.5 days after the treatment.	NCT04306705, NCT04310228, NCT04317092, NCT04324047, ChiCTR2000029765.	Xu et al. (2020)
Convalescent plasma			A case study, five critically ill COVID-19 and ARDS (acute respiratory distress syndrome) patients received convalescent plasma from 5 COVID-19 recovered patients showed remarkable improvement in the clinical status of patients within 12days after the transfusion.	NCT04292340, ChiCTR2000029850, ChiCTR2000030039, ChiCTR2000030046, ChiCTR2000030627.	Shen et al. (2020)
Stem cell therapy			In a case study, seven COVID-19 patients were administered with human Mesenchymal stem cells (MSCs) (10^6 cells per kilogram of weight) intravenously. The symptoms in all the patients and pulmonary functions improved in 2 days significantly after transplantation, and also no adverse effects were observed for 14 days.	NCT04252118, NCT04269525, NCT04288102, NCT04313322, NCT04331613, ChiCTR2000029580.	Leng et al. (2020)
Interferons			In an *in vitro* study, pre-treatment of recombinant type I IFN-α showed a significant reduction in SARS-CoV-2 viral replication. IFN- α has also been recommended for the treatment of COVID-19 in Chinese guidelines.	NCT04276688, NCT04315948, NCT04320238, ChiCTR2000029387, ChiCTR2000029638, ChiCTR2000030480, ChiCTR2000030082, ChiCTR2000030535.	(Commision, 2020; Lokugamage et al., 2020)
Corticosteroids			Due to the high amount of cytokines in COVID-19 patients, corticosteroids are frequently used to treat patients with severe illness. For COVID-19 patients with severe illness, glucocorticoids can be used for a short period (3–5 days), and a higher dose should be avoided as it will delay the coronavirus clearance due to immunosuppressive effects. However, preliminary results of the RECOVERY Trial involving dexamethasone (6 mg given once daily for ten days) showed reduced mortality in patients receiving respiratory support.	NCT04273321, NCT04244591, NCT04323592, NCT04381936, NCT04325061, NCT04347980, NCT04395105, NCT04344730, NCT04327401, NCT04445506, NCT04402840.	(Commision, 2020; Huang et al., 2020; Horby et al., 2020)

Table 3
Agents that are currently being investigated or hypothetically considered for the treatment of SARS-CoV-2-infection.

Agent	Chemical Formula	Comments	Clinical status	References
Ribavirin (Antiviral)	($C_8H_{12}N_4O_5$)	It is a guanosine analog used to treat the hepatitis C virus, respiratory syncytial virus (RSV), and some viral hemorrhagic fevers. *In vitro* activity of ribavirin against SARS-CoV-2 (EC50 = 109.5 μM) was found to be less potent than remdesivir (EC50 = 0.77 μM) and chloroquine (EC50 = 1.13 μM).	ChiCTR2000029387, NCT04276688, NCT04293887, NCT04306497.	(D. Wang et al., 2020; M. Wang et al., 2020; Zumla et al., 2016)
Oseltamivir (Antiviral)	($C_{16}H_{28}N_2O_4$)	Neuraminidase inhibitor used to treat influenza A and B. It blocks the release of viral particles from host cells, reducing the spread in the respiratory tract. Oseltamivir was already being used during the COVID-19 epidemic in China, and currently, it is in clinical trials.	NCT04255017, NCT04261270, NCT02735707.	Uyeki (2018)
Nitazoxanide (Antiviral)	($C_{12}H_9N_3O_5S$)	It is used to treat helminthic, protozoal, and viral infection-caused diarrhea. It inhibited SARS-CoV-2 *in vitro* with an EC50 of 2.12 μM in Vero E6 cells.		(Guo, 2020; D. Wang et al., 2020; M. Wang et al., 2020)
Darunavir {Antiretroviral and cobicistat (CYP3A inhibitor)}	($C_{27}H_{37}N_3O_7S$) ($C_{40}H_{53}N_7O_5S_2$)	Darunavir is an HIV protease inhibitor, whereas cobicistat boosts darunavir by inhibition of cytochrome P450 (CYP3A). In China, during February 2020, researchers announced that darunavir inhibited SARS-CoV-2 infection *in vitro* and at a concentration of 300 μM inhibited viral replication *in vitro*.	NCT04252274, NCT04304053, ChiCTR2000029541,	(Mathias et al., 2010; Santos et al., 2019)
Azvudine (Antiviral)	($C_9H_{11}FN_6O_4$)	It is a nucleoside reverse transcriptase inhibitor with activity on the HIV virus, hepatitis B virus, and hepatitis C virus. The clinical trials for Azvudine's efficacy against COVID-19 are going on in China.	ChiCTR2000030487, ChiCTR2000030424, ChiCTR2000029853.	Wang et al. (2014)
Baloxavir marboxil (Antiviral)	($C_{27}H_{23}F_2N_3O_7S$)	Baloxavir marboxil (Xofluza) acidic endonuclease inhibitor used to treat Influenza A and B flu. The clinical trials for Xofluza's efficacy against COVID-19 are going on in China.	ChiCTR2000029544, ChiCTR2000029548.	O'Hanlon and Shaw (2019)
Nelfinavir (Antiretroviral drug)	($C_{32}H_{45}N_3O_4S$)	Based on homology modeling and molecular docking studies, nelfinavir is suggested to be a potential drug for SARS-CoV-2.		Xu et al. (2020)
Ivermectin (Anti-parasitic)	($C_{48}H_{74}O_{14}$) 22,23-dihydro-avermectin B_{1a} ($C_{47}H_{72}O_{14}$) 22,23-dihydro-avermectin B_{1b}	Ivermectin has shown to have antiviral activity against a broad range of viruses. Its antiviral activity is due to its ability to target the host importin (IMP) α/β1 nuclear transport proteins responsible for nuclear entry of cargoes such as integrase and NS5. A study by Caly et al. has demonstrated that ivermectin was able to inhibit SARS-CoV-2 *in vitro* with a single addition to Vero-hSLAM cells 2 h after infection with SARS-CoV-2. By 48h, there was a ~5000-fold decrease in viral RNA ivermectin treated samples as compared to control.		(Caly et al., 2020; Yang et al., 2020)
Xiyanping (TCM)		Xiyanping is a Traditional Chinese Medicine (TCM) preparation with andrographolide as its main component and has antibacterial and antiviral properties. Xiyanping injection (100 mg, twice a day) is suggested for treating severe and critical COVID-19 patients in guidelines (7th edition) issued by the National Health Commission & State Administration of Traditional Chinese Medicine.	ChiCTR2000030117, ChiCTR2000030218.	(Commision, 2020; Tang, 2016)
ASC09 (HIV protease inhibitor)	($C_{38}H_{53}N_5O_7S_2$)	ASC-09 (TMC-310911) is a protease inhibitor (PI) that is which has demonstrated marked activity against a variety of HIV-1 strains. It is currently in clinical trials in combination with other drugs as a potential treatment for COVID-19.	ChiCTR2000029603, NCT04261270.	Stellbrink et al. (2014)
Camostat mesylate	($C_{20}H_{22}N_4O_5$) (CH_3SO_3H)	It is a transmembrane protease serine 2 (TMPRSS2) inhibitor approved in Japan to treat multiple conditions, including pancreatitis. In a study camostat mesylate was able to block SARS-CoV-2 infection of lung cells. It is currently in a clinical trial for the treatment of COVID-19.	NCT04321096.	Hoffmann et al. (2020)
Vitamin C	($C_6H_8O_6$)	Vitamin C, also known as ascorbic acid, has antioxidant properties and acts as a cofactor for various enzymes. It is an electron donor, and electrons from ascorbate account for its physiological properties. However, there are no preclinical data of its activity against SARS-CoV-2. It has entered into clinical trials for the treatment of COVID-19.	NCT04264533, ChiCTR2000029768.	Padayatty and Levine (2016)
Anakinra (Immunosuppressive)	($C_{759}H_{1186}N_{208}O_{232}S_{10}$)	It is an interleukin-1 receptor antagonist used to treat rheumatoid arthritis. Phase III clinical trial of anakinra in sepsis demonstrated reduced mortality in patients with hyper inflammation, without adverse	NCT02735707, NCT04324021.	(Mehta et al., 2020; Shakoory et al., 2016)

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Table 3 (*continued*)

Agent	Chemical Formula	Comments	Clinical status	References
		effects. It is hypothesized that immunosuppression could improve the survival of COVID-19 patients.		
Losartan (Anti-hypertension)	($C_{22}H_{23}ClN_6O$)	Losartan is commonly used to treat high blood pressure and kidney disorders. It has been suggested that angiotensin II receptor 1 (ATR1) blockers like losartan can be used against SARS-CoV-2, which may reduce severity and mortality due to its infection. It is currently in clinical trials for the treatment of COVID-19.	NCT04335123, NCT04330300.	Gurwitz (2020)
Emapalumab (Monoclonal antibody)	($C_{6430}H_{9898}N_{1718}O_{2038}S_{46}$)	It is an anti-interferon-gamma antibody used for the treatment of hemophagocytic lympho-histiocytosis (HLH). It has entered into a clinical trial along with anakinra for the treatment of COVID-19.	NCT04324021.	Association (2018)
Bevacizumab (Monoclonal antibody)	($C_{6638}H_{10160}N_{1720}O_{2108}S_{44}$)	Bevacizumab is a humanized anti-vascular endothelial growth factor (VEGF) monoclonal antibody. It has entered into clinical trials for the treatment of COVID-19.	NCT04275414, NCT04305106.	Wang et al. (2004)

Table 4
Vaccines against SARS-CoV-2 undergoing clinical trials as of May 27, 2020 (https://clinicaltrials.gov; https://chictr.org.cn).

Name	Type of Vaccine	Developer	Comments	Clinical Trials
Ad5nCoV	Recombinant adenovirus type 5 vector (Non-replicating)	CanSino Biological Inc. and Beijing Institute of Biotechnology.	Engineered genetically to express SARS-CoV-2 spike (S) protein with replication-defective adenovirus type 5 as a vector.	Phase I NCT04313127, Phase II NCT04341389, Phase I ChiCTR2000030906.
mRNA 1273	novel lipid nanoparticle (LNP)- encapsulated mRNA	Moderna/ National Institute of Allergy and Infectious Diseases (NIAID).	The mRNA-1273 vaccine contains an mRNA that encodes for prefusion stabilized SARS-CoV-2 spike protein.	Phase I NCT04283461, Phase II NCT04405076.
INO- 4800	DNA plasmid	Inovio Pharmaceuticals.	Plasmid encoding S protein is transported into cells by electroporation using a device known as CELLECTRA.	Phase I NCT04336410.
aAPCs	Lentiviral vector-based artificial antigen-presenting cells (aAPC)	Shenzhen Geno-Immune Medical Institute.	aAPCs vaccine is a lentiviral-based vector system made to express viral proteins and immune-modulatory genes to modify aAPC and to activate T cells.	Phase I NCT04299724.
Lentiviral Minigene Vaccine (LV-SMENP) DC	Lentiviral vector-based dendritic cells	Shenzhen Geno-Immune Medical Institute.	It is made by modification of dendritic cells with a lentivirus vector made to express SARS-CoV-2 minigene SMENP and immune-modulatory genes.	Phase I NCT04276896.
Bacille Calmette-Guérin (BCG)	Live attenuated strain of *Mycobacterium bovis*	Albert Calmette and Camille Guérin.	BCG vaccine is used against tuberculosis. In various *in vitro* and *in vivo* studies, it has been shown to protect against other respiratory tract infections and reported noteworthy decreases in morbidity and mortality. The hypothesis behind the trial is that BCG vaccination induces partial protection against the susceptibility to SARS-CoV-2 infection.	Phase III NCT04327206, Phase III NCT04328441, Phase III NCT04379336, Phase IV NCT04348370.
AZD1222(ChAdOx1 nCoV-19)	Adenovirus vector-based vaccines	University of Oxford/Astra Zeneca.	Adenovirus (attenuated) expressing the SARS-CoV-2 spike protein.	Phase I\II NCT04324606.
NVX-CoV2373	SARS-COV-2 rS nanoparticle vaccine with or without matrix-M adjuvant	Novavax.	NVX-CoV2373 is a stable prefusion protein prepared using nanoparticle technology, whereas matrix-M adjuvant is used to increase the immune response.	Phase I/II NCT04368988.
BNT162a1 BNT162b1 BNT162b2 BNT162c2	RNA vaccines	BioNTech and Pfizer Inc.	Two of the vaccine candidates include a modified nucleoside mRNA (modRNA); one candidate uses self-amplifying mRNA (saRNA), whereas the other one contains uridine containing mRNA (uRNA). Each mRNA setup is joined with a lipid nanoparticle (LNP) formulation, and the receptor-binding domain (RBD) of the vaccines contain the piece of the spike, which is essential for eliciting antibodies that can inactivate the virus.	Phase I/II NCT04368728, Phase I/II NCT04380701.
V-SARS	Plasma	Immunitor LLC.	A heat-inactivated vaccine prepared from the plasma of donors infected with COVID-19.	Phase I/II NCT04380532.
CoronaVac	Inactivated vaccine	Sinovac Biotech Co. Ltd.	Inactive type of viral vaccines is made by proliferating viruses in cell culture, followed by inactivation through chemical means. Vaccination of inactivated vaccines permits the body to produce an immune response against introduced viral antigens without having an actual threat of being infected since the virus is inactive.	Phase I/II NCT04352608.
Inactivated vaccine	Inactivated	Beijing Institute of Biological Products Co., LTD.	Inactive type of viral vaccines is synthesized by proliferating viruses in cell culture, followed by inactivation through chemical means. Vaccination of inactivated vaccines permits the body to produce an immune response against introduced viral antigens without having an actual threat of being infected since the virus is inactive.	Phase I/II ChiCTR2000032459.

3.2.8. Vaccines

Vaccines are harmless preparation of pathogens, which provides immunity against infectious disease. It stimulates the immune response in the body and produces memory B cells and T cells in large numbers. Therefore, whenever the body gets exposed to a similar pathogen in the future, it recognizes and destroys them (Mak et al., 2013). Currently, there are no approved COVID-19 vaccines available. However, as per the DRAFT landscape of COVID-19 candidate vaccines-WHO (May 27, 2020), about 115 candidate vaccines are in preclinical evaluation (DRAFT, 2020), whereas the most advanced ones have their ongoing clinical trials (United States clinical trials, 2020; China clinical trials, 2020) (Table 4).

3.3. In vitro COVID-19 models

To understand the mechanism of viral pathogenesis, antiviral drug action, and to treat viruses safely in the laboratory, we need cell lines in which SARS-CoV-2 can replicate successfully. Evaluation of antiviral activities of various compounds in different cell lines infected with SARS-CoV-2 can facilitate the treatment strategies (Kaye et al., 2006). Recent studies performed against SARS-CoV-2 have shown that the cell lines such as Vero (derived from the kidney of an African green monkey), Vero E6 (clone of Vero 76 cell line) and Huh7 (Human hepatocytes cell line) have shown susceptibility to SARS-CoV-2 infection (Wang et al., 2020b). The clinically isolated strain of the SARS-CoV-2 virus, C-Tan-nCoV Wuhan strain 01, was propagated in Vero cells and the anti-SARS-CoV-2 activity of chloroquine and hydroxychloroquine were also investigated using SARS-CoV-2 infected Vero cells (Yao et al., 2020). Wang and colleagues have also demonstrated chloroquine and remdesivir's *in vitro* activity against SARS-CoV-2 in Vero E6 cells. These two compounds potently blocked SARS-CoV-2 infection in Vero E6 cells (Wang et al., 2020b). In addition to this, favipiravir, penciclovir, nafamostat, and nitazoxanide were also found to be inhibitive against SARS-CoV-2 infection in Vero E6 cells (McCreary and Pogue, 2020; Wang et al., 2020b).

A study from China reported that scientists successfully isolated SARS-CoV-2 from infected patients in Huh7 and Vero cell lines (Malik et al., 2020). Also, in a study TMPRSS2-expressing Vero E6 cell lines were found to be highly susceptible to SARS-CoV-2 (Matsuyama et al., 2020). Therefore, it is evident from these studies that Vero, Vero E6, and Huh7 are permissive to SARS-CoV-2 replication. However, several other cell lines from different origin like Monkey (FRhK-4 cells, MA-104 cells, COS cells, and BGM) (Kaye et al., 2006; Morgenstern et al., 2005), Human (HEK- 293, HepG2, HPEK, PMBCs, and Caco2) (Kaye et al., 2006; Morgenstern et al., 2005; Ng et al., 2004), and Pig (PS, POEK, and Pk-15) (Peiris and Porterfield, 1979) have shown to be permissive to SARS-CoV and MERS-CoV replication, which suggests that these cell lines can also be susceptible to SARS-CoV-2 infection.

3.4. Animal models for COVID-19

Transgenic mice that express human ACE2 are likely to be crucial COVID-19 animal models (Bao et al., 2020). Bao et al. reported the development of the clinical disease by transgenic hACE2 mice after infection with SARS-CoV-2, including interstitial pneumonia and weight loss (Bao et al., 2020). In another study, it has been shown that viral spike protein binding to ACE2 receptors in mice downregulates ACE2 expression, which is linked with extreme lung failure. Therefore ACE2 Knockout mice, which were used in ARDS and SARS studies, Can also be of interest to COVID-19 related ARDS studies (Imai et al., 2005; Kuba et al., 2005). There is also the possibility of TMPRSS2 Knockout and STAT 1 Knockout mice as COVID-19 disease models. Since TMPRSS2 assists in the entry of SARS-CoV-2 into the cells, its inhibition may constitute a mechanism for treatment/prophylaxis of COVID-19. So TMPRSS2 knockout mice can aid in researching COVID-19 pathogenesis (Graham et al., 2012). STAT 1 Knockout mice support SARS-CoV replication in the lungs and the establishment of progressive lung disease. Such mice can also be beneficial to study the pathogenesis and antiviral treatments of COVID-19 disease (Frieman et al., 2010; Hogan et al., 2004; Zhou et al., 2020a). In standard mouse strains, the inbred mice were widely used in SARS-CoV studies, young inbred mice like C57BL/6, BALB/c, and 129S6 support viral replication of SARS-CoV and might be useful for the vaccine and antiviral research of COVID-19. They can also help study immune responses to the infection (Subbarao and Roberts, 2006). A new study documented a ferret model of infection and transmission of SARS-CoV-2, which sums up aspects of the human disease where ferrets infected with SARS-CoV-2 display elevated body temperature (Kim et al., 2020). It was observed that SARS-CoV could also infect hamsters, Cynomolgus macaques, rhesus macaques and African green monkeys (McAuliffe et al., 2004; Roberts et al., 2005; Rowe et al., 2004). Therefore it is pertinent to mention here that these animals might also be permissive to SARS-CoV-2 infection and replication.

4. Discussion

Coronaviruss, known for causing SARS and MERS epidemics, lead to another pandemic (COVID-19) having origin from Wuhan, China (Chan et al., 2020). Like other coronaviruses, SARS-CoV-2 is also having an animal origin and is thought to be a result of the human-animal interface (Lake, 2020; Zhu et al., 2020). Currently, 215 countries and territories are affected by about 10.71 million infected individuals and an approximate death toll of 0.51 million (Organization, 2020b). Despite various preventive measures practiced all over the globe, the situation continues to worsen (Columbus et al., 2020). The need for the day is to develop some therapeutics that may help to control and containing the pandemic. Research on viral epidemiology, the efficacy of various agents against the virus, and launching clinical trials on hospitalized patients are being carried at a rapid pace. Although no proven effective drug therapy is available to date, every day, some new aspects of viral epidemiology get unveiled, thereby unveiling the possible drug targets (Columbus et al., 2020).

Many possible therapies have been pre-clinically and clinically tested against the disease, and many more are in process; however, only a few were found to be effective. Chloroquine and hydroxychloroquine both show a similar mode of action by acting as a weak base that can increase the pH of endosomes preventing virus/cell fusion (Yao et al., 2020). Both were found to be active *in vitro* and also successfully eliminated nasopharyngeal carriage of SARS-COV-2 in patients infected with COVID-19. However, recent data from large randomized controlled trials showed no evidence of benefit for viral clearance, mortality or other outcomes of chloroquine and hydroxychloroquine treatment over standard care in hospitalized patients with COVID-19 (Tang et al., 2020). Lopinavir, a highly-specific HIV-1 protease inhibitor, appears to block the critical protease (Mpro) of SARS-CoV, which inhibits the replication of the virus (Ratia et al., 2008). It was found that 4 mg/ml of lopinavir and 50 mg/ml of ribavirin inhibited SARS-CoV after incubation of 48 h and the agents when combined act synergistically (Chu et al., 2004). However, no benefit has been observed beyond standard care with lopinavir-ritonavir treatment in hospitalized adult patients suffering from extreme COVID-19 (Cao et al., 2020).

RNA-dependent RNA polymerase inhibitors inhibit viral replication by binding to conserved polymerase domains, thereby preventing the incorporation of the nucleotide for replicating and transcribing viral RNA (Furuta et al., 2013, 2017). Remdesivir and favipiravir both were found effective against COVID-19. Remdesivir brought results that were remarkable in the care of a first COVID-19 patient in the United States (Holshue et al., 2020), whereas, in a study involving 240 COVID-19 patients, favipiravir was considered as preferred treatment compared to arbidol (Chen et al., 2020a). Arbidol, an antiviral, mainly functions by inhibiting the interaction between the virus and host cells, preventing viral invasion into host cells (Blaising et al., 2014; Kadam and Wilson, 2017). It also exhibits immunomodulatory function by inducing

interferon production and macrophages activation (Glushkov et al., 1999). In a clinical study involving 111 patients, it was found that arbidol promotes and strengthens the cycle of viral clearance, enhances focal penetration on radiological images, and decreases demand for HFNC oxygen therapy in-hospital treatment (Xu et al., 2020a). Azithromycin, an antibiotic, due to its immunomodulatory and anti-inflammatory properties, was reported to be effective *in vitro* towards Zika and Ebola viruses (Madrid et al., 2015; Retallack et al., 2016). It is also known to suppress severe viral infections of the respiratory tract (Zhan, 2016). In a clinical study, it was found that azithromycin added to hydroxychloroquine was substantially effective for SARS-CoV-2 removal (Gautret et al., 2020). Due to the high amount of cytokines produced by SARS-CoV (He et al., 2006; Wong et al., 2004), MERS-CoV (Falzarano et al., 2013; Faure et al., 2014), and SARS-CoV-2 (Huang et al., 2020), corticosteroids are commonly used to treat patients with severe infection. Dexamethasone reduced the mortality by one-third in patients receiving invasive mechanical ventilation and by one-fifth in patients receiving oxygen support without invasive mechanical ventilation. Whereas, no effect of the drug was noticed in patients in mild condition not requiring oxygen support (Horby et al., 2020; Ledford, 2020). WHO also authorized the use of dexamethasone in severe to critical conditions only (WHO media briefing, 2020). However, it is supposed that a higher dose of corticosteroids can prolong the coronavirus elimination due to immunomodulatory effects (Commision, 2020); therefore, corticosteroids should not be administered routinely.

Biological agents like tocilizumab, a recombinant monoclonal immunoglobulin G1 (IgG1) antibody against human interleukin 6 (IL-6) receptor, may also be a possible treatment for severe and critical COVID-19 infections. A study involving 21 patients treated with tocilizumab in China demonstrated rapid improvement. Out of 21, 19 (90.5%) were discharged on an average of 13.5 days after the treatment, which shows a promising effect of tocilizumab (Xu et al., 2020). Convalescent plasma from recovered patients can be administered to patients as a medication (Cheng et al., 2005; Mair-Jenkins et al., 2015). In a recent case study, five critically ill patients with COVID-19 and ARDS (acute respiratory distress syndrome) received transfusion with convalescent plasma from 5 recovered COVID-19 patients between 10 and 22 days after admission (Shen et al., 2020). The administration of convalescent plasma results in an improvement in the patient's clinical condition. Mesenchymal stem cells have immunomodulatory effects due to their ability to communicate directly with immune cells or to the paracrine secretion of several forms of cytokines (Bernardo and Fibbe, 2013). A study where seven COVID-19 patients were administered with human MSCs (10^6 cells per kilogram of weight, intravenously) resulted in improved functional outcomes and fast recovery (Leng et al., 2020). Antiviral effect of IFN type I (IFN-α and IFN-ß) against SARS-CoV were stated in twelve *in vitro* studies (Stockman et al., 2006). In an *in vitro* study, following recombinant type-I IFN-α treatment, SARS-CoV-2 revealed a significant decrease in viral replication (Lokugamage et al., 2020). Besides several other agents, IFN-α is also recommended for the treatment of COVID-19 in the guidelines issued by the National Health Commission & State Administration of Traditional Chinese Medicine (Commision, 2020). As per the DRAFT landscape of COVID-19 candidate vaccines-WHO (May 27, 2020), about 115 candidate immunomodulatory and viral S protein targeting vaccines are under preclinical and clinical evaluation. The establishment of various *in vitro* and *in vivo* models for preclinical studies can additionally help the current research.

4.1. Conclusion

The current pandemic of COVID-19 had generated a global health crisis. Rapid research is being carried on regarding the efficacy of various drugs and vaccines and exploring various new aspects of the disease to be the possible drug target sites. No proven effective therapies have been developed to date.

Ethical approval

Studies with human participants or animal experimentation are not presented in the present study; therefore, no approval was required.

Author statement

Pankaj Chibber: Investigation, Methodology, Writing - Original Draft, Conceptualization. **Irfan Ahmed:** Writing - Original Draft. **Syed Assim Haq:** Writing - Original Draft. **Nusrit Iqbal Andrabi:** Writing - Original Draft. **Gurdarshan Singh:** Validation, Supervision.

Role of funding source

There was no need for funding for designing and framing the article.

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

We authors are very thankful to Mr. Chetan Kumar (Natural Product Chemistry Division, CSIR-IIIM, Jammu) for helping in drawing the chemical structures of the primary drugs against COVID-19.

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