REVIEW ARTICLE

A global treatments for coronaviruses including COVID-19

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Abstract

In late December 2019 in Wuhan, China, several patients with viral pneumonia were identified as 2019 novel coronavirus (2019-nCoV). So far, there are no specific treatments for patients with coronavirus disease-19 (COVID-19), and the treatments available today are based on previous experience with similar viruses such as severe acute respiratory syndrome-related coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV), and Influenza virus. In this article, we have tried to reach a therapeutic window of drugs available to patients with COVID-19. Cathepsin L is required for entry of the 2019-nCoV virus into the cell as target teicoplanin inhibits virus replication. Angiotensin-converting-enzyme 2 (ACE2) in soluble form as a recombinant protein can prevent the spread of coronavirus by restricting binding and entry. In patients with COVID-19, hydroxychloroquine decreases the inflammatory response and cytokine storm, but overdose causes toxicity and mortality. Neuraminidase inhibitors such as oseltamivir, peramivir, and zanamivir are invalid for 2019-nCoV and are not recommended for treatment but protease inhibitors such as lopinavir/ritonavir (LPV/r) inhibit the progression of MERS-CoV disease and can be useful for patients of COVID-19 and, in combination with Arbidol, has a direct antiviral effect on early replication of SARS-CoV. Ribavirin reduces hemoglobin concentrations in respiratory patients, and remdesivir improves respiratory symptoms. Use of ribavirin in combination with LPV/r in patients with SARS-CoV reduces acute respiratory distress syndrome and mortality, which has a significant protective effect with the addition of corticosteroids. Favipiravir increases clinical recovery and reduces respiratory problems and has a stronger antiviral effect than LPV/r. currently, appropriate treatment for patients with COVID-19 is an ACE2 inhibitor and a clinical problem reducing agent such as favipiravir in addition to hydroxychloroquine and corticosteroids.

KEYWORDS

antiviral, coronavirus, COVID-19, drug, treatment

1 | HISTORY

Looking at the major pandemics of respiratory viruses, we are mainly exposed to the influenza virus, the pandemics that occurred in 1918, 1957, 1968, and 2009, and various theories predict that the next pandemic of this category of respiratory infections will occur between 2020 and 2050 and be capable of causing a human epidemic (Holmes, 2013). Seasonal influenza is primarily an upper respiratory disease that recurs in different forms each year. The "flu shot" or annual vaccine is the best way to prevent the flu, and all high-risk

healthcare workers are advised to be vaccinated every year. But sometimes more dangerous and even deadly forms occur that are likely to lead to epidemics and pandemics (Andrews, 2006).

In late December 2019 in Wuhan, China, several patients were diagnosed with viral pneumonia, now known as the 2019 novel coronavirus (2019-nCoV). Subsequently, a large number of cases of the disease were found to either reside in Wuhan or travel to the city. The researchers were able to obtain the 2019-nCoV genome sequence by performing bronchoalveolar lavage and culture of patients' lungs and by conducting phylogenetic analyzes of the genome and investigating the evolutionary relationship between 2019-nCoV and other coronaviruses, they found the origin of 2019-nCoV and its evolutionary history. The 2019-nCoV genomic sequence obtained from the patients showed that 98.99% of their gene sequences matched. The genome also has an 88% similarity to the genome of the bat-SL-CoVZC45 and bat-SL-CoVZXC21 bat coronavirus genomes that appeared in Zhoushan, China, but with the severe acute respiratory syndrome-related coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) coronaviruses, 79% and 50% were similar, respectively. Also by homology modeling, a model for the virus receptor was obtained, which, by comparing homology models, concluded that despite differences in some amino acids, the structure of the domains attached to the receptor at 2019-nCoV and SARS-CoV was similar. SARS-CoV spike (S) protein is essential for entry into the host cell. The Spike S1 subunit contains the receptor-binding domain (RBD). The SARS-CoV virus uses the angiotensin-converting-enzyme 2 (ACE2) receptor to bind the host cell, that contains a diversity of respiratory epithelial cells, alveolar macrophages, and monocytes. Considering the relatively high identity of the RBD in 2019-nCoV and SARS-CoV, it is crucial to evaluate the cross-reactivity of anti-SARS-CoV antibodies with 2019-nCoV spike protein, which could have significant implications for rapid development of vaccines and therapeutic antibodies against 2019-nCoV. These structures displayed that SARS-CoV RBD contains a core structure and a receptor-binding motif (RBM), and that the RBM binds to the outer surface of ACE2. The ACE2 is the only known human homolog of the key regulator of blood pressure ACE. SARS-CoV-2 RBD showed significantly higher binding affinity to ACE2 receptor than SARS-CoV RBD and could block the connection and, therefore, binding of SARS-CoV-2 and SARS-CoV RBD to ACE2-expressing cells, so inhibiting their infection to host cells. Therefore, ACE2 also serves as the cellular entry site for the SARS-CoV, a main target for pharmacological intervention and improved new monoclonal antibodies that could attach specifically to 2019-nCoV RBD. SARS-CoV RBD-specific antibodies possibly will cross-react with SARS-CoV-2 RBD protein, and SARS-CoV RBD-induced antisera could neutralize SARS-CoV-2, suggesting the potential to improve SARS-CoV RBD-based vaccines for inhibition of SARS-CoV-2 and SARS-CoV infection (Tai et al., 2020; Wan, Shang, Graham, Baric, & Li, 2020).

Bats host a reservoir of various zoonotic viruses, including coronaviruses. Regulatory studies and phylogenetic analyzes have shown that there is a high genetic diversity among SARS-like viruses in bats, allowing for the recombination and evolution of new species. It has been shown that the bat virus with 96% nucleotide sequence similarity to human SARS-CoV can use human ACE2 as a receptor. This represents the same state of entry into the cell as human SARS-CoV. For example, bat SL-CoV-WIV1 can grow on human epithelial cells and Vero E6 cells, which is neutralized by human SARS-CoV convalescent sera (Ge et al., 2013; Yang et al., 2016). The recent crisis was the outbreak of novel *Coronavirus* from emerged Wuhan in central China, referred to as 2019-nCoV, has recently caused a pandemic scale of pneumonia in humans and resulted in a huge threat to the global public and a high number of hospitalizations. The damage to the lungs, which leads to fluid leaking from small blood vessels in the lungs. The fluid collects in the lungs' air sacs or alveoli. This makes it difficult for the lungs to transfer oxygen from the air to the blood. While there's a shortage of information on the type of damage that occurs in the lungs during 2019-nCoV (Tian et al., 2020; Wu, Leung, & Leung, 2020). So far, there are no specific treatments for patients with coronavirus disease-19 (COVID-19), and the treatments available today are based on previous experience with similar viruses such as SARS-CoV, MERS-CoV, influenza virus, and other viral infections. In this article, we have tried to study the different treatments performed on patients with COVID-19 and the advantages and disadvantages of existing drugs and we have tried to reach a therapeutic window of drugs available to patients with COVID-19. Molecular mechanisms and therapeutic targets of drugs that have been used to treat COVID-19 (Figure 1). Also, potential antiviral therapeutics for experimental treatment of COVID-19 shown in Table 1.

2 | DRUGS USED TO TREATMENT OF CORONAVIRUSES

2.1 | Antibacterial drugs

2.1.1 | Teicoplanin

A glycopeptide antibiotic commonly used to treat a bacterial infection is active against SARS-CoV and is on the list of drugs that are also used to treat COVID-19 (J. Zhang et al., 2020). This antibiotic is commonly used to treat Gram-positive bacterial infections, especially staphylococcal and streptococcal infections, which are effective against viruses such as Ebola, influenza virus, flavivirus, hepatitis C virus, HIV, and on coronaviruses such as MERS-CoV and SARS-CoV (Lo, Spengler, Erickson, & Spiropoulou, 2019). Teicoplanin acts in the early stages of the virus's life cycle, which is blocked by the low pH cleavage of the viral spike protein by cathepsin L in the late endosomes, thus blocking the release of the viral RNA genome and the virus replication cycle (Cathepsin L requires entry of the 2019-nCoV virus into the cell, the S protein region known as target teicoplanin, which is also present in the 2019-nCoV virus). A study by Junsong Zhang found that cleavage site cathepsin L is conserved between SARS-CoV and 2019-nCoV S protein. The concentration of
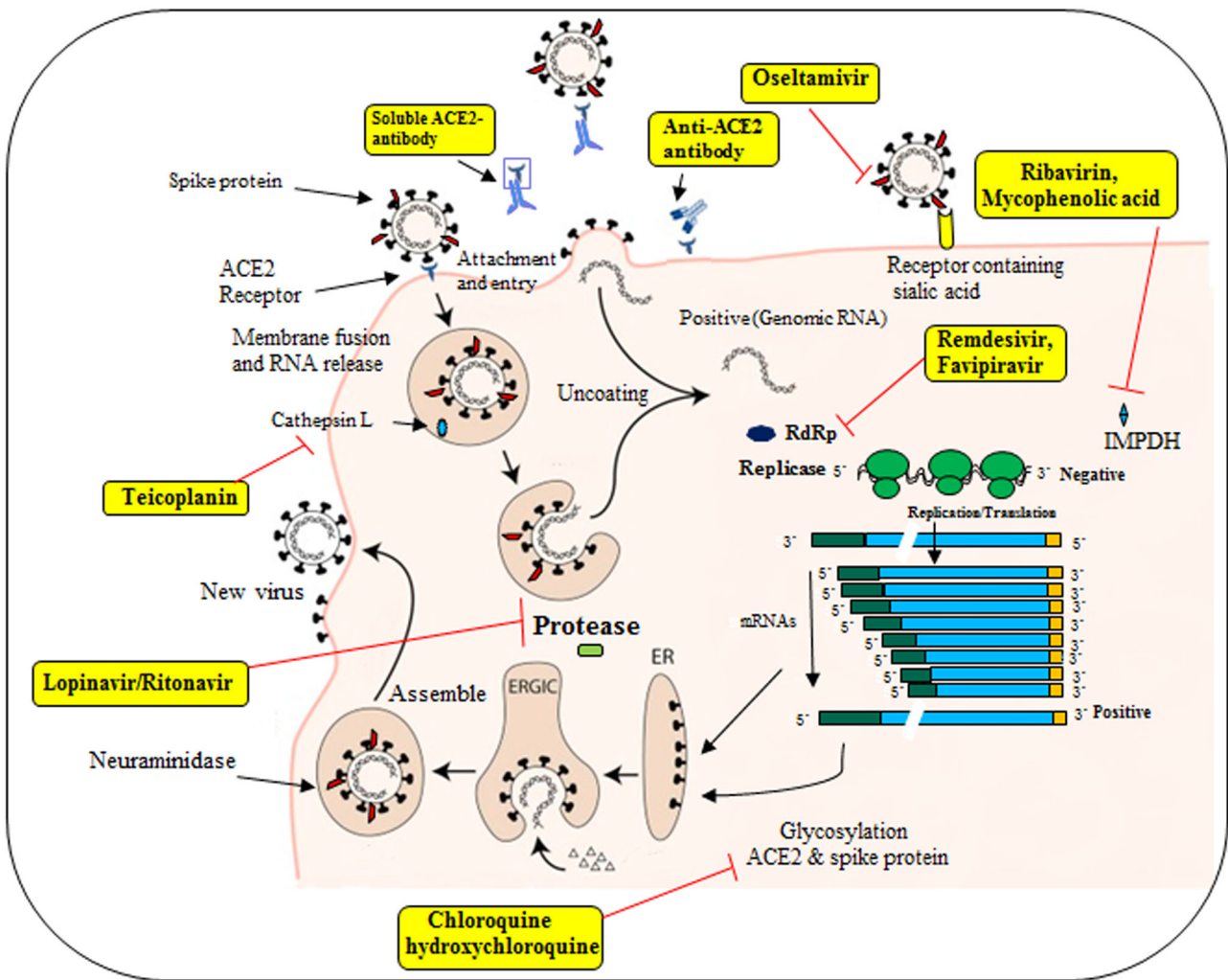
FIGURE 1 Molecular mechanisms and therapeutic targets of drugs that have been used to treat COVID-19. ACE2, angiotensin-converting enzyme 2 receptor; COVID-19, coronavirus disease-19; ER, endoplasmic reticulum; IMPDH, inosine monophosphate dehydrogenase; RdRp, RNA-dependent RNA polymerase

teicoplanin required for IC50 in vitro is 1.66 μM, well below the human blood concentration (8.78 μM for a daily dose of 400 mg; J. Zhang et al., 2020).

2.2 | Antiprotozoal drugs

2.2.1 | Chloroquine/hydroxychloroquine (Plaquenil)

First-line treatments used for prophylaxis of malaria, amebiasis, and autoimmune diseases such as rheumatoid arthritis, systemic sclerosis, and systemic lupus erythematosus inhibit the proliferation of several DNA and RNA-containing viruses, including coronaviruses. There is some evidence that chloroquine is effective in animal models of mice on viruses such as human coronavirus OC43, enterovirus EV-A71, Zika virus, and influenza A H5N1 virus. It is also active in ex vivo conditions on Ebola virus in mice (T. Sheahan et al., 2017; Tan, Yam, Sun, & Chu, 2018; Yan et al., 2013).

Chloroquine has recently been shown to be an inhibitor of SARS-CoV-2 in vitro and the hydroxylated form has been suggested as a potential treatment for patients with SARS-CoV-2 infection. Importantly, the overdose of this drug is toxic and can cause death (Devaux, Rolain, Colson, & Raoult, 2020; Weniger & World Health Organization, 1979). M. Wang et al. (2020) reported that the EC50 of Chloroquine against COVID-19 tested on VERO E6 was 1.13 μM and the EC90 was 6.90 μM. Chloroquine inhibits SARS-CoV entry, which exerts its inhibitory effect by altering glycosylation of the ACE2 receptor and spike protein. In patients with COVID-19, hydroxychloroquine has been shown to decrease inflammatory responses and decrease cytokine storm in vitro. Chloroquine also interferes with proteolytic processing of M protein and modifies virion assembly and budding. Also, chloroquine indirectly act against COVID-19 by reducing the production of proinflammatory cytokines and by activating anti-SARS-CoV-2 CD8$^+$ T-cells (Devaux et al., 2020). It has also been used in the treatment of intracellular bacterium *Coxiella burnetii* both in vitro and in vivo and has resulted

TABLE 1 Potential antiviral therapeutics for experimental treatment of COVID-19

Drug	Activity	Effectiveness	The drug's mechanism of action in COVID-19
Kaletra (lopinavir/ ritonavir)	Used to treat HIV infection	400 mg/100 mg twice daily	Protease inhibitor
Chloroquine	Inhibit quinone reductase 2 that used to treat malaria infection	200 mg, three times per day during 10 days	Block virus infection by increasing endosomal pH required for virus/cell fusion, interfering with the glycosylation of cellular receptors of SARS-CoV
Remdesivir (GS-5734)	An adenosine nucleotide analog inhibitor of RdRp	10 mg/kg for 12 days	A novel nucleotide analogs against single-stranded RNA viruses such as coronaviruses
IFN- alpha	Used to treat HBV infection	5 million U bid inhalation 5 million U or equivalent dose each time, two times/day	A broad-spectrum antiviral drug
Umifenovir (Arbidol)	Used to treat influenza virus infection	200 mg each time, three times/day	Inhibit viral entry into target cells and stimulate the immune response
Oseltamivir (Tamiflu)	Used to treat influenza virus infection	75 mg every 12 hr	Neuraminidase inhibitors
Ribavirin	Used to treat RSV infection, hepatitis C, and some viral hemorrhagic fevers	500 mg each time, 2–3 times/day in combination with IFN-α or lopinavir/ritonavir	A synthetic guanosine nucleoside that interferes with the synthesis of viral mRNA
Teicoplanin	A glycopeptide antibiotic that used to treat Gram-positive bacterial infection	To inhibit 50% of viruses (IC50) in vitro was 1.66 μM	Inhibiting the low pH cleavage of the viral spike protein and the continuation of virus replication cycle
Favipiravir (FPV)	Used to treat many RNA viruses infections	600 mg twice daily	Inhibition of viral RdRp

Abbreviations: COVID-19, coronavirus disease-19; HBV, hepatitis B virus; IFN-α interferon-α; mRNA, messenger RNA; RdRp, RNA-dependent RNA polymerase; RSV, respiratory syncytial virus; SARS-CoV, severe acute respiratory syndrome-related coronavirus.

in its elimination (Savarino, Di Trani, Donatelli, Cauda, & Cassone, 2006; M. Wang et al., 2020).

2.3 | Antiviral drugs

2.3.1 | Remdesivir (GS-5734)

An adenosine nucleotide analog introduced by Gilead Sciences in 2017 to treat Ebola virus infection and shown to have antiviral activity against Marburg virus, parainfluenza type 3 virus, Nipah virus, Hendra virus, and measles, mumps, and Pneumoviridae (such as a respiratory syncytial virus [RSV]) in vitro. It is a prodrug monophosphoramidate with widespread antiviral activity against coronaviruses, such as SARS-CoV and MERS-CoV, and has promising antiviral activity against SARS-CoV-2. Remdesivir is a metabolically active form (GS-441524) that affects viral RNA polymerase and prevents the spread of the virus and reduces the production of viral RNA. It has a similar structure to tenofovir alafenamide, a nucleotide analog of adenosine 5-monophosphate with antiviral activity against hepatitis B virus and HIV (Lo et al., 2017; Pedersen et al., 2019; T. Sheahan et al., 2017; Warren et al., 2016).

Pharmacological studies have been conducted on remdesivir and clinical trials for the treatment of Ebola virus with remdesivir are ongoing. One study showed that remdesivir and interferon-beta

(IFN-β) had a better effect on the MERS-CoV mouse model than lopinavir, ritonavir, and IFN-β (Mulangu et al., 2019; Sheahan et al., 2020). Previous studies have shown that nucleotide analogs generally have less effect on coronaviruses, due to the presence of a proofreading exonuclease in the virus. However, remdesivir has a positive effect on SARS-CoV, MERS-CoV, and bat-CoV strains. In tissue cultures, remdesivir is effective in the EC_{50} range of 0.069 μM for SARS-CoV and 0.074 μM for MERS-CoV. It is effective at SARS-CoV-2 at 0.77 μM in Vero E6 cells (EC_{90} was 1.76 μM). It is also active in the submicromolar EC_{50} against several different coronaviruses, including human endemic coronaviruses OC43 (HCoV-OC43) and 229E (HCoV-229), therefore, remdesivir has extensive antiviral activity against coronaviruses (Brown et al., 2019; M. Wang et al., 2020). In a SARS-CoV-infected mouse, remdesivir administration significantly reduced the rate of viral load in the lungs, and the virus titer decreased more than two-fold on Day 4 or 5 postinfection, indicating that remdesivir improved respiratory symptoms in the laboratory model (T. Sheahan et al., 2017).

Recently, in a nonhuman primate model (rhesus macaque), the therapeutic effect of remdesivir on MERS-CoV infection was investigated, with remdesivir being injected 3 hr before virus inoculation. The results showed that remdesivir prevents lung damage from the virus. However, the same results were observed when remdesivir was injected into the laboratory model 12 hr after virus inoculation. Human trials have shown that remdesivir is safe in the human body

so the effect of this compound against new coronaviruses can be investigated (Brown et al., 2019; de Wit et al., 2020).

2.3.2 | Lopinavir/ritonavir (LPV/r)

Lopinavir is an antiretroviral protease inhibitor used in combination with ritonavir to treat patients with AIDS and HIV infection. Lopinavir is a potent and highly specific inhibitor of HIV-1 protease. Ritonavir inhibits the metabolism of lopinavir, therefore coadministration of lopinavir and ritonavir in healthy volunteers increases the area under the lopinavir plasma concentration-time curve> 100-fold (Hurst & Faulds, 2000). In a study by Cao et al. (2020), the effect of lopinavir plus ritonavir on adult patients with COVID-19 in China showed that concomitant use of these drugs had no advantage over standard care and would be approved or rejected in future trials. The reason for choosing this drug together was its therapeutic experience at SARS-CoV in 2003, which became the drug of choice (Cao et al., 2020).

Jin Yong Kim in Korea also achieved similar results with Cao et al. (2020) in combination with lopinavir/ritonavir (LPV/r) and no decrease in viral titers was observed in patients with COVID-19 but was effective in improving clinical symptoms such as fever and cough. Jin Yong Kim suggested that it may be effective to get a better effect of the drug in the early stages of the disease, but more research is needed within a few days of the disease to determine if better results can be obtained (Lim et al., 2020). But in a study by Jun Zhang at Xixi hospital in Hangzhou, China. A 2020 study showed that 400 mg daily lopinavir with IFN-α2b atomization inhalation, 5 million U twice daily, as well as the use of lopinavir alone could be useful for patients with COVID-19 and increased eosinophils have been suggested as an indicator of improvement in patients, But after starting treatment with this drug, complications such as digestive adverse effect and hypokalemia should be considered by physicians (Liu et al., 2020).

Jinyu Xia's study also showed that the combined effect of Arbidol with LPV/r was greater than that of LPV/r (16 patients received oral Arbidol with LPV/r and 17 patients received LPV/r alone). Arbidol has been shown to have a direct antiviral effect on the initial in vitro replication of SARS-CoV (Deng et al., 2020; Khamitov et al., 2008). Arbidol (Umifenovir) is a broad-spectrum antivirus that works on both enveloped and nonenveloped viruses. It is active on viruses such as influenza A and B and is also known to inhibit hepatitis C. This drug can prevent the fusion of the virus with the target membrane and block the entry of the virus into the target cell (Boriskin, Leneva, Pecheur, & Polyak, 2008).

2.3.3 | Oseltamivir and other NAIs

Oseltamivir is a neuraminidase inhibitor (NAIs) used to treat influenza A and B infections and reduces the mortality of patients, especially those admitted to the intensive care unit (ICU). Oseltamivir and zanamivir are first-line medications for the treatment and

prophylaxis of influenza. Oseltamivir reduces the proliferation of influenza viruses in a dose-dependent manner and prevents epithelial barrier dysfunction and cytotoxicity for up to 4 days. It is an ethyl ester prodrug that is hydrolyzed by hepatic esterases to its active form, oseltamivir carboxylate and has a longer half-life than oseltamivir. The effectiveness of oseltamivir in reducing the mortality of patients with H5N1 influenza virus was related to when the drug was used before the onset of respiratory failure (75 mg oral dose twice daily; Adisasmito et al., 2010; C.-B. Wang et al., 2015). Thus, patients in critical condition who took the drug showed no benefit in improving the disease. The duration of drug use is 5 days, but in people with influenza and acute respiratory distress syndrome (ARDS), pneumonia or immune deficiency, the drug duration can be increased to 10 days (Uyeki et al., 2019).

Of recent concern about the use of oseltamivir was the emergence of resistance in 23% of patients with H1N1, which was associated with high mortality. Recently, the drug baloxavir has been used to treat resistant strains and has been recognized as an effective drug especially for patients admitted to the ICU (Behillil et al., 2019; Ison et al., 2018). Zanamivir solution is also a class of neuraminidase inhibitors that are used for patients who are ventilated and show drug resistance to oseltamivir. Peramivir is also used intravenously as an antiviral drug. It is especially useful for patients who do not respond to oseltamivir or zanamivir. Oseltamivir is a clinical trial for Phase 3 for 2019-nCoV in the treatment of COVID-19 patients with an HIV protease inhibitor (ASC09F) as a 3CLpro inhibitor and is in use alone in Phase 4 2019-nCoV (Li & De Clercq, 2020). Oseltamivir has been used orally for the treatment of 2019-nCoV and suspected cases in Chinese hospitals, but there is no conclusive evidence that it can be effective in treating COVID-19 patients. According to the latest research, neuraminidase inhibitors such as oseltamivir, peramivir, and zanamivir are invalid for nCoV-2019 and are not recommended for the treatment of patients (Li & De Clercq, 2020).

2.3.4 | Ribavirin

Ribavirin is a guanosine nucleoside analog and antiviral compound used to treat various viral infections, such as RSV, hepatitis C virus, bunyavirus, herpesvirus, adenovirus, poxvirus, and some viral hemorrhagic fevers. Ribavirin was first used in 1980 to treat the RSV in children. The antiviral activity of ribavirin is by intracellular guanosine depletion through inhibition of the inosine monophosphate dehydrogenase enzyme, which disrupts guanosine synthesis, it also has an indirect effect on virus replication by increasing *IFN* gene expression and modulating immune responses. Ribavirin is an inhibitor of RNA synthesis by viral RdRp as well as an inhibitor of mRNA capping (Graci & Cameron, 2006; Martinez, 2020). In animal studies of coronaviruses, ribavirin, although weakly inhibitory, can reduce the release of macrophage proinflammatory cytokines in mice and alter the Th-2 response to Th-1 response and act as an immunomodulator (Ning et al., 1998). In most cases, ribavirin is combined with IFN, and although the results of ribavirin and IFNα-2b

in a MERS-CoV rhesus macaque model were promising, with the results of the trial and the effect of ribavirin and IFN (either α2a or β1) on MERS-CoV infected patients it was different, however, ribavirin lowers hemoglobin concentrations in respiratory patients and therefore reduces its potential as an antiviral against SARS-CoV-2 (Arabi et al., 2017; Falzarano et al., 2013). IFNα-2b and ribavirin, when used for MERS-CoV treatment, showed that they were 8-fold and 16-fold reduced in their single-dose regimen, respectively and they further stimulate cytokine release and immune responses, reducing viral replication, modulating host response, and improving clinical outcomes. Studies using ribavirin plus lopinavir/ritonavir on patients with SARS have reduced ARDS and mortality. There was also a significant decrease in ARDS and mortality in patients with SARS-CoV who received corticosteroids with ribavirin, lopinavir/ritonavir (Chu et al., 2004; Zheng & Wang, 2016).

2.3.5 | Favipiravir (T-705 or avigan)

Favipiravir (FPV) a guanosine analog and an oral anti-influenza drug that targets RNA-dependent RNA polymerase (RdRP), which converts to active phosphoribosylated form in cells and acts as an RNA polymerase inhibitor. Also, favipiravir is a broad-spectrum drug that blocks the replication of flavivirus, poliovirus, rhinovirus, filovirus, and arenaviruses. The effective dose of favipiravir used is Day 1: 1,600 mg twice daily, Days 2–5: 600 mg twice daily but its effective dose for treatment of COVID-19, and 600 mg tid with 1,600 mg first loading dosage for no more than 14 days. However, favipiravir is contraindicated in pregnant women due to teratogenicity and embryotoxicity in animals and cannot be used in this group of patients (Delang, Abdelnabi, & Neyts, 2018; Shiraki & Daikoku, 2020).

A study by Fang et al. (2020) found that favipiravir could play an important role in protecting mice from the fatal infection of wild-type and oseltamivir-resistant-influenza B viruses. Favipiravir has also been used in combination with zanamivir to successfully clear the type B influenza virus in immunocompromised children (Lumby et al., 2020). In a randomized clinical trial, Chen et al. (2020) showed that in patients with moderate COVID-19 who were untreated with antiviral drugs, favipiravir increased clinical recovery over 7 days and reduced fever, cough, and respiratory problems, it was therefore used as an effective drug in these patients. Another study by Jianjun Gao on 80 patients with COVID-19 at the Hospital of Shenzhen, China, showed that favipiravir had a stronger antiviral effect than the lopinavir/ritonavir drug combination and reported no adverse effects (Furuta, Komeno, & Nakamura, 2017).

2.4 | Immunosuppressant drugs

2.4.1 | Corticosteroids

Corticosteroids, such as methylprednisolone, have been proposed as adjunctive therapy, albeit with concerns about their use for novel coronavirus patients. Corticosteroids are widely used to treat severe community-acquired pneumonia to prevent lung damage because they have suppressive effects of severe and systemic inflammation. But numerous studies show evidence of the ineffectiveness of corticosteroid treatment on viral pneumonia such as SARS-CoV, MERS-CoV, and H1N1 virus. Long-term administration of high doses of corticosteroids in the early stages of treatment also has negative effects (Arabi et al., 2018; Jiang et al., 2019). Low or physiological doses of corticosteroids do not reduce the mortality caused by septic shock following primary pulmonary infection; but it can also have benefits, such as an earlier reversal of shock, a shorter time for the patient to exit the ICU and mechanical ventilation (Rhodes et al., 2017). Corticosteroid therapy for severe patients with ARDS can reduce pulmonary fibrosis and prevent the progression of serious pathological conditions; Also, the use of low doses can lead to a severe reduction in H1N1 mortality All of these results suggest that the appropriate use of low-dose corticosteroids may lead to recovery and treatment for patients with 2019-nCoV infection; however, this treatment should be performed following the guidelines recommended for patients with novel coronavirus pneumonia (NCP) who have specific clinical symptoms, such as ARDS or septic shock Systematic corticosteroids treatment in the first 3–5 days could increase oxygen saturation and arterial oxygen tension/inspiratory oxygen fraction, however, corticosteroids do not affect the recovery and survival of NCP patients with ARDS and shock. There are no specific and consistent clinical guidelines for the therapeutic use of corticosteroids in patients in intensive care units. Generally, corticosteroids should be avoided unless the patient has symptoms such as moderate or severe ARDS, sepsis, or septic shock until used following recommended WHO clinical guidelines. Corticosteroids are also not recommended for mild or early ARDS, because early corticosteroids can delay the clearance of the virus and increase the risk of death (Zhou et al., 2020).

2.4.2 | Mycophenolic acid (MPA)

A cellular inosine monophosphate dehydrogenase inhibitor and an immunomodulator that has antiviral effects on a range of viruses, including influenza A, reovirus, flavivirus, and coxsackie B3 virus, it is also used as an inhibitor of nucleotide synthesis in lymphocytes and an immunosuppressant in transplantation and treatment of autoimmune diseases (Diamond, Zachariah, & Harris, 2002; Padalko et al., 2003). It has also been shown to inhibit hepatitis B and hepatitis C virus replication in combination with IFN-α and cyclosporine A. Mycophenolic acid (MPA) in use with cyclosporine, it is also a potent inhibitor of MERS-CoV but has a less inhibitory effect on SARS-CoV. In studies of coronaviruses in the mouse model, it did not affect SARS-CoV, but at standard concentrations at oral doses, it was able to inhibit MERS-CoV (Chan et al., 2013; Henry et al., 2006; Markland, McQuaid, Jain, & Kwong, 2000).

MPA acts as a synergism with IFN-β1b and thiopurine analogs but it has less protective effect than the combined effect of

lopinavir/ritonavir with IFN-β1b. The use of this compound in bedside coronaviruses was that with the IFN-β1b used in Saudi Arabia to treat MERS-CoV all patients using this drug combination could survive but patients had lower acute physiology and chronic health (Allison & Eugui, 1993). MPA also had a significant inhibitory effect on the proliferation of HCoV-OC43 and HCoV-NL63 at EC50 concentrations of 1.95 μM and 0.19 μM, respectively (Shen et al., 2019). Lin et al. (2018) also showed that MPA along with disulfiram and 6-thioguanine was synergistically inhibitors of the MERS-CoV papain-like protease (MERS-CoV PL^pro).

2.5 | Angiotensin-converting enzyme 2 gene-based peptides

Angiotensin-converting enzyme 2 gene (ACE2) is a metalloproteinase with 805 amino acids which is an important receptor for entry of SARS-CoV into the host cell. Domain S1 in the SARS-CoV spike protein binds the virus to the ACE2 cell receptor present in the host cells. Therefore understanding the association between SARS-CoV, SARS-CoV-2, and ACE2 can be an effective therapeutic approach (Lin et al., 2018). ACE2 is a homolog of carboxy peptidase that is best known for cleaving different peptides in the renin-angiotensin system (RAS) and other substrates, such as apelin (Batlle, Wysocki, & Satchell, 2020). This enzyme is mostly present in organs such as the kidneys, gastrointestinal tract, and relatively low level in the lungs and its expression has been reported in Type 2 pneumocytes (Hamming et al., 2004). The extracellular domain of ACE2 acts as the SARS-CoV and SARS-CoV-2 spike protein receptor. The new coronavirus also uses membrane-bound ACE2 as the receptor. ACE2 neutralizes SARS-CoV-2 in vitro by combining with the Fc protein of immunoglobulin (Lei et al., 2020). In addition, SARS-CoV-2 binds to ACE2 with a higher affinity than SARS-CoV. In this context, the preparation of a soluble and recombinant form of ACE2 protein in humans could be useful as a novel biological treatment to counter or limit the progression of infection caused by coronaviruses that use ACE2 as a receptor (Wrapp et al., 2020). Thus, if ACE2 is presented as a suitable recombinant protein in its soluble form, it may be a new factor to counteract the spread of coronavirus by limiting the binding of coronavirus to the cell membrane or entry of the virus as well as its proliferation in infected individuals (Batlle et al., 2020). Viral replication in the presence of ACE2 the most efficient approach for extensive vaccine production. In addition, recently recognized early spike protein priming by transmembrane protease serine 2 is an important factor for entry/viral spread of 2019-nCoV through interaction with the ACE2 receptor. Moreover, soluble ACE2 may competitively bind with 2019-nCoV and survive cellular ACE2 activity which negatively normalizes the RAS to protect the lung from damage through weakening viral entry into cells also a viral expansion to protect the lung from injury. ACE2, fused to an immunoglobulin Fc domain, providing a neutralizing antibody help to avoid any viral escape, while also recruit the immune system to shape lasting immune respaces (Kruse, 2020; Smith, 2008; H. Zhang et al., 2020).

3 | CONCLUSION

2019-nCoV outbreak from Wuhan, China offered a respiratory viral pandemic that currently there are no effective therapies for this infection. Despite a crucial need to find options to help these patients and prevent potential death. For this reason, vaccine research should be pursued intensely, until the infection can be controlled with a protective vaccine to prevent 2019-nCoV infection. Despite the different treatments used by different countries to treat COVID-19, it is clear that the use of these drugs alone will not produce the desired results, and some drugs will cause side effects in certain groups of people. For example, excessive use of chloroquine is toxic and can even be fatal, or the use of favipiravir in pregnant women is not recommended, as it is associated with teratogenicity and embryotoxicity in animals or corticosteroids that are immunosuppressive and are not recommended for mild or early ARDS, because early use of corticosteroids can delay the clearance of the virus and increase the risk of death, long-term administration of high doses of corticosteroids in the early stages of treatment has negative effects. Generally, corticosteroids should be avoided unless the patient has symptoms such as moderate or severe ARDS, sepsis or septic shock. MPA also has no effective inhibitory effect on SARS-CoV, so they are not recommended for treatment. Lopinavir is associated with side effects such as digestive adverse effects and hypokalemia that should be considered by physicians. The use of neuraminidase inhibitors is also invalid due to resistance to nCoV-2019 and is not recommended for the treatment of patients.

However, the use of hydroxychloroquine as prophylaxis is appropriate because it blocks the entry of the virus and prevents virus replication, and remdesivir has extensive antiviral activity against coronaviruses. Therefore, the appropriate recommendation for the treatment of patients with COVID-19 is a combination of existing drugs. IFNα-2b together with ribavirin, when used for the treatment of MERS-CoV, showed that their effective dose was decreased compared to the single-dose regimen and better-stimulated cytokine release and inflammatory responses, and decreased viral replication, modulated host response, and improved clinical outcomes. Ribavirin plus lopinavir/ritonavir in patients with SARS-CoV reduces ARDS and mortality, and in patients with SARS-CoV who receive corticosteroids with ribavirin, lopinavir/ritonavir, their ARDS and mortality significantly decreased. Lopinavir also has a stronger antiviral effect than the LPV/r, and the combination of arbidol and LPV/r is more effective than LPV/r. In addition to these drugs, if ACE2 is presented in its soluble form as a suitable recombinant protein, it may be a new factor in counteracting the spread of coronavirus as well as its proliferation in infected individuals. Another possible treatment option could be the use of serums that are obtained from the blood of patients infected with the new coronavirus during their recovery and also targeting the cellular components involved in the host's inflammatory response to the virus is also a good way of targeting viral damage by targeting a cellular protein.

CONFLICT OF INTERESTS

All the authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

M. E. investigated and supervised the findings of this study, wrote the article, supervised the project, and contributed to the interpretation of the results. B. Y. designed the study, helped supervise the project, and conceived the original idea. S. V. developed the theoretical framework. H. G. processed the experimental data. A. V. processed the experimental data. M. K. designed the model and the computational framework and analyzed the data. All the authors discussed the results and commented on the manuscript, provided critical feedback, and helped to shape the research, analysis, and manuscript as well as contributed to the final version of the manuscript.

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