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

Chapter 7

Current therapeutic strategies to combat coronavirus disease 2019

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Chapter outline

7.1 Introduction 137
7.2 Antiviral agents 139
7.2.1 Remdesivir 139
7.2.2 Lopinavir-ritonavir 139
7.2.3 Hydroxychloroquine and chloroquine 139
7.2.4 Interferon-α 140
7.2.5 Favipiravir 140
7.2.6 Oseltamivir (Tamiflu) 140
7.3 Supporting agents 141
7.3.1 Azithromycin 141
7.3.2 Dexamethasone 142
7.3.3 Vitamin C (ascorbic acid) 142
7.3.4 Corticosteroids 143
7.3.5 Sirolimus 143
7.3.6 Tocilizumab 143
7.4 Miscellaneous agents and therapies 144
7.4.1 Angiotensin-converting enzyme 2 receptor 144
7.4.2 Colchicine 144
7.4.3 Niclosamide and ivermectin 144
7.4.4 Convalescent plasma 145
7.4.5 Diacerein 145
7.5 Traditional herbal medicines 146
7.6 Future projections 146
7.7 Conclusion 147
List of abbreviations 147
Acknowledgment 148
References 148

7.1 Introduction

Coronavirus 2019 (COVID-19) is a highly infectious disease that has suddenly spread throughout the world. It is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 has a diverse impact on different countries according to their social standards, alleviation efforts, and health

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support system. SARS-CoV-2 was identified in December 2019 and recognized in early January 2020 in China [1,2]. On February 11, 2020, the International Committee on Taxonomy of Viruses declared SARS-CoV-2 as a new virus.

The name "coronavirus" was derived from their crown-like spikes that exist on their exterior. Coronaviruses are classified into four main subgroups: alpha, beta, gamma, and delta coronaviruses. SARS-CoV-2 belongs to the beta subgrouping. Being a positive-sense single-stranded RNA virus, it has 29,891 bases with 96% genome similarity to that of bat coronavirus and 79.6% sequence identity to SARS-CoV [3]. SARS-CoV-2 encodes the spike S protein-containing receptor-binding domain that binds to the human angiotensin-converting enzyme 2 (ACE2) and enhances membrane coalition and uptake of the virus into individual cells such as the respiratory system by endocytosis [4]. In the human cells, SARS-CoV-2 captures the human cells' protein synthesis mechanism to manufacture its own viral proteins and congregate the proteins resulting in viral replication [5].

Fortunately, a large number of SARS-CoV-2—infected patients are asymptomatic, most probably due to the activation of the good response; this good response activates the innate immune system of the human body by triggering the host antiviral defense mechanisms including natural killer cells and antiviral T cells and induction of interferon (IFN) [6]. Unfortunately, there has been no significant discovery of drugs for the management of this disease. Moreover, patients are provided a medication based on their noticeable or diagnosable symptoms. Therefore, it represents the major hurdle to prefer an effective therapeutic strategy to limit and treat COVID-19 sufferers. Effective vaccines are essential to fight this extremely contagious SARS-CoV-2. At present, researchers are working to develop vaccines and new molecules.

Researchers are attempting to discover a remedy to treat COVID-19. The investigation thus far has shown that Western medicines, natural products, and traditional Chinese medicines including Indian ayurvedic may have possible efficiency against this disease. Some of these drugs have been immediately examined in clinical investigations and exhibited preliminary effectiveness against COVID-19. At present, the treatment of COVID-19 patients is mainly based on symptomatic conditions. Considering acute respiratory distress syndrome (ARDS), followed by secondary infections, antibiotics, antiviral agents, systemic corticosteroids, and anti-inflammatory drugs are frequently incorporated in the treatment schedule. In addition to antiviral agents, other agents such as RNA synthesis inhibitors, convalescent plasma therapy, and herbal medicines are also prescribed for the treatment of COVID-19 patients [7]. However, the efficacy of these therapeutic agents remains to be verified by suitably planned clinical trials.

7.2 Antiviral agents

7.2.1 Remdesivir

Remdesivir is a potential antiviral drug for the treatment of COVID-19. Remdesivir has inhibitory effects on pathogenic animal and human coronaviruses, including SARS-CoV-2. It was developed by Gilead Sciences in the year 2017 as a medication for Ebola virus infection [8]. Remdesivir is a prodrug that is biotransformed into its active moiety, GS-441524, which combines into nascent viral RNA chains, resulting in premature termination. Wang and coworkers demonstrated that remdesivir potently prevents SARS-CoV-2 infection at a low range of micromolar concentrations (half maximal effective concentration (EC_{50}), 0.77 μM) [9]. To evaluate the potency and safety of the drug in COVID-19 patients, a randomized, placebo-controlled, double-blind, multicenter, phase III clinical trial began on February 5, 2020, in China. Patients in the experimental group administered an initial dose of 200 mg of remdesivir and a subsequent dose of 100 mg for 9 consecutive days by intravenous route in addition to routine medication. Control group patients received the same dose of placebo treatment. This dose of remdesivir treatment is related to that of a former randomized clinical trial against the Ebola virus [10]. Results demonstrate that approximately 70% of patients had progression in terms of oxygen intake, and mechanical ventilation of many patients has been extubated. This study indeed suggests a promising therapeutic effect of remdesivir.

7.2.2 Lopinavir-ritonavir

Lopinavir is a protease blocker with high efficacy for HIV-1 protease. Lopinavir is administered in combination with ritonavir because lopinavir has limited oral bioavailability and high rate of biotransformation. Ritonavir inhibits lopinavir metabolism by blocking enzymes that play a significant role in metabolism. Moreover, its co-administration enhances lopinavir bioavailability and increases antiviral activity [11]. However, the adverse effects such as diarrhea, nausea, and asthenia were reported in patients receiving a lopinavir-ritonavir—based regimen [12]. A study report from South Korea revealed that lopinavir-ritonavir administration on a single COVID-19 patient remarkably reduced coronavirus titers [13].

7.2.3 Hydroxychloroquine and chloroquine

In the current scenario of COVID-19 infection, chloroquine and hydroxychloroquine represent a significant example of possible repositioning of drugs. Both the drugs have multiple activities. Hydroxychloroquine alkalizes the

phagolysosome and inhibits the low pH-dependent steps of viral replication including fusion and uncoating [14]. Chloroquine acts by inhibiting the invasion of SARS-CoV-2 and blocking of virus−cell fusion by preventing glycosylation of the ACE2 receptor and its subsequent binding with spike protein. Thus, this mechanism revealed that chloroquine therapy could be a potential remedy in the initial stage of the infection. Hydroxychloroquine exerts an antiinflammatory effect on Th17-related cytokines in healthy people and rheumatoid arthritis patients [15]. The US FDA has released emergency authorization regarding the use of chloroquine and hydroxychloroquine for the treatment of COVID-19 patients. Recently, Tang et al. [16] demonstrate that the use of hydroxychloroquine did not cause significant negative conversion rates but had antiinflammatory effects.

7.2.4 Interferon-α

IFN-α is a broad-spectrum antiviral agent administered to cure hepatitis. IFN-α has shown some potentials to prevent SARS-CoV reproduction when tested in vitro. The fifth edition of the National Health Mission guidelines of China recommends antivirals such as IFN-α and lopinavir/ritonavir. The recommended way for the administration of IFN-α is vapor inhaling at a dose of 5 million U with 2 mL of water for injection for elderly patients twice a day. Ribavirin (500 mg) was suggested to be administered via intravenous infusion for adults, 2 to 3 times/day in combination with IFN-α or lopinavir/ritonavir [17].

7.2.5 Favipiravir

Favipiravir is a guanine analog with pyrazine carboxamide structure. Its antiviral activity is limited to the presence of purine nucleosides. Favipiravir exerts antiviral effect by targeting the conservative catalytic region of RNA-dependent RNA polymerase of RNA viruses, hindering the nucleotide inclusion process during viral RNA replication [18]. This antiviral agent has been used in the therapy of infectious conditions such as influenza, Ebola, and norovirus infections caused by RNA viruses [19]. Current in vitro and clinical investigations have established favipiravir as a test agent for COVID-19 therapy. Clinical trials testing favipiravir against COVID-19 have been carried out passionately in numerous countries, especially China and Japan. A randomized control trial (ChiCTR200030254) performed on COVID-19 affected patients and results obtained shows that COVID-19 patients treated with favipiravir have a higher healing rate compared to umifenovir (55.86%). Moreover, significant improvement in the duration of fever and cough relief time was observed [20].

7.2.6 Oseltamivir (Tamiflu)

Oseltamivir (Tamiflu) is an antiviral drug that belongs to the antiviral category called neuraminidase inhibitors. Oseltamivir is prescribed for the treatment of

influenza A and B viral infection. It acts by targeting the neuraminidase, which exists on the surface of the influenza virus, thus inhibiting the spread of the influenza virus in the human body [21]. Currently, FDA approves Tamiflu for the prophylaxis and treatment of influenza A and B viral infection. In addition, it has been recommended in a clinical trial along with other potential drugs for the treatment of COVID-19 infection to lessen the length of disease, complexities, and the rate of mortality in COVID-19 affected patients.

7.3 Supporting agents

In the absence of a vaccine or specific therapeutic agents against SARS-CoV-2, many alternative therapies play a significant role as supportive care for COVID-19 patients. These include azithromycin, ascorbic acid, and corticosteroids, sirolimus, and tocilizumab.

7.3.1 Azithromycin

Azithromycin (a macrolide antibiotic) is generally prescribed to treat pneumonia, sexually transmitted diseases, and infections of the ear, throat, and lungs. It acts by preventing the growth of bacteria by interfering with their protein synthesis. Briefly, azithromycin binds to the 50S subunit of the bacterial ribosome, thus inhibiting the translation of mRNA. Initially, the drug azithromycin was suggested administering along with hydroxychloroquine; preliminary results exhibited a synergistic effect of the combination of hydroxychloroquine and azithromycin. Therefore, azithromycin has received notable recognition of researchers as a potential candidate to treat COVID-19. A literature survey reveals that azithromycin was found effective against Zika and Ebola viruses when tested in vitro. It also prevents severe respiratory tract infections when administrated to patients suffering from viral infection. This finding could be explored further to describe whether a combination is more effective in severe cases. Future studies on co-administration of azithromycin with hydroxychloroquine need to be performed. The combination of both drugs could act as an antiviral remedy against SARS-CoV-2, as well as prevent bacterial infections [22].

Researchers have also suggested the use of nitazoxanide in combination with azithromycin for the treatment of SARS-CoV-2. Nitazoxanide is a broad-spectrum antiparasitic and antiviral drug used for the treatment of various helminthic, protozoal, and viral infections. Nitazoxanide is a prodrug and it transformed rapidly to the active metabolites nitazoxanide and nitazoxanide conjugates on oral administration. Nitazoxanide is also recognized to provoke IFN and IFN-β synthesis. In addition, it has demonstrated in vitro effect against MERS-CoV and other coronaviruses. Furthermore, when nitazoxanide was given as 600 mg twice daily for 5 days, it's confirmed to lessen the continuation of symptoms in influenza patients [23]. This dose regimen was

rationally considered to be used in co-administration with azithromycin in a proposed new COVID-19 protocol intending to test the combined potential to reduce SARS-CoV-2 morbidity and mortality.

7.3.2 Dexamethasone

Dexamethasone, a corticosteroid drug that alleviates inflammation, is prescribed for the treatment of rheumatoid arthritis, allergies, and ARDS. Dexamethasone acts by dampening down the host immune system. Coronavirus infection provokes inflammatory conditions as the immune system attempts to fight against it. Dexamethasone may modulate immune-mediated lung injury and decrease progression to respiratory failure and mortality. Recently, researchers conducted a clinical trial on patients suffering from COVID-19 by administering dexamethasone (6 mg given once daily for up to 10 days). The preliminary results showed that dexamethasone administration significantly reduced 4 weeks mortality of COVID-19 patients, receiving invasive mechanical ventilation or oxygen at randomization. However, not among patients not acquiring respiratory support. Based on the forgoing, dexamethasone represents a safe, effective, and inexpensive therapeutic remedy for COVID-19 patients [24]. Chapter 41 of this book gave full insight into the mechanisms of action of dexamethasone.

7.3.3 Vitamin C (ascorbic acid)

Vitamin C, also known as L-ascorbic acid, is a *water-soluble* vitamin that is naturally present in some foods. Humans, unlike most animals, are unable to synthesize vitamin C endogenously, so it is a vital dietary ingredient. Vitamin C exerts antioxidant effect by neutralizing free radicals and assists in preventing cellular damage. Vitamin C is also required in some physiological processes like immune health. Besides, vitamin C possesses antiviral effect, particularly against influenza viruses [25,26]. A literature survey revealed that vitamin C positively transforms the development and maturation of T lymphocytes and natural killer cells involved in the immune response to viral agents. In addition, it inhibits the production of reactive oxygen species and the remodulation of the cytokine network typical of the systemic inflammatory syndrome [27]. In light of these facts, a clinical trial in China to evaluate intravenous doses of vitamin C in severe COVID-19—associated pneumonia affected patients was conducted. The doses ranged between 2 and 10 g per day, administered throughout 8—10-h IV infusion. Results showed that the oxygenation index significantly improved in real time, and finally, all the patients recovered and were discharged [28]. Further emphasis on the roles of vitamins was presented in Chapters 20 and 21 of this book.

7.3.4 Corticosteroids

Corticosteroids are prescribed to treat severe acute respiratory infections of viral etiology because of their antiinflammatory effect. Recently, researchers have reported that methylprednisolone may enhance dysregulated immune response caused by COVID-19—induced sepsis. Furthermore, it also regulates blood pressure [29]. For example, in a retrospective group study, more than 200 COVID-19 patients with ARDS were administered methylprednisolone dose 1—2 mg/kg daily by the intravenous route for 1 week. The results confirmed that methylprednisolone administration is beneficial for ARDS patients with a decrease in mortality rate. However, there are fears that the use of corticosteroids may have harmful effects [30].

7.3.5 Sirolimus

Sirolimus also known as rapamycin is a hydrophobic macrocyclic lactone isolated from *Streptomyces hygroscopicus*. Sirolimus is an immunosuppressant that is used to inhibit organ transplant rejection and to manage lymphangioleiomyomatosis by inhibiting the mammalian target of rapamycin kinase. Earlier researches have validated the mammalian target of rapamycin complex 1 as the key determinant in controlling various viral replications, such as Andes orthohantavirus and coronavirus [31]. In an in vitro analysis, sirolimus has been revealed to affect PI3K/AKT/mTOR pathway, which prevents MERS-CoV activity [32]. In agreement with these facts, the University of Cincinnati has planned a new randomized double-blind, placebo-controlled clinical trial to be conducted till September 2020 to examine the sirolimus therapeutic effect on the improvement of patients admitted to hospital with COVID-19 to advanced respiratory support [33]. Interestingly, a silico study recognized sirolimus as one of the 16 potential therapeutic arsenals for treating COVID-19 patients based on data from other human coronavirus infections applying a network-based drug-repurposing model [30].

7.3.6 Tocilizumab

Tocilizumab is a recombinant humanized monoclonal antibody, which acts against both the soluble and membrane-bound forms of the interleukin-6 (IL-6) receptor. Tocilizumab is recommended mainly to cure rheumatoid arthritis and systemic juvenile idiopathic arthritis, a severe form of arthritis in children. A study promulgated in April 2020 reported that 21 critical COVID-19 patients in China were treated with the compound and showed clinical benefits [34]. Similarly, a retrospective, observational cohort study conducted in Italy on 500 COVID-19 patients suffering from severe COVID-19 pneumonia found reduced risk of invasive mechanical ventilation or mortality in COVID-19 patients with severe pneumonia [35].

7.4 Miscellaneous agents and therapies

7.4.1 Angiotensin-converting enzyme 2 receptor

Recently, a group of researchers demonstrated that the SARS-CoV-2 spike protein binds to the angiotensin I converting enzyme 2 (ACE2). This molecule is a peptidase, which is expressed at the surface of lung epithelial cells and other tissues. It controls the renin-angiotensin-aldosterone system. This receptor is a soft target in the pathogenesis of COVID-19. During early SARS-CoV-2 infection, the ACE2 function is probably impaired either by steric hindrance of the peptidase region of ACE2 followed by the virus attachment or by downregulation of ACE2 mRNA expression and angiotensin I converting enzyme 2 protein. Literature reveals that in hypertensive patients, the prolong administration of angiotensin II type 1 receptor antagonist agents such as losartan, lisinopril, or olmesartan causes cardiac and renal ACE2 overexpression [36]. Continued treatment with these drugs may be essential for attenuating cardiac stress of advancing COVID-19 infection and limit the vasoconstriction and profibrotic effects of angiotensin 2 in alveolar capillaries.

7.4.2 Colchicine

The myocardial impairment appears to be a severe adverse development along with other systemic COVID-19 complications, even without history of preexisting cardiovascular disease. The exploration of drugs already introduced into clinical practice inevitably leads to consideration of the potential of colchicine. Colchicine is an antiinflammatory drug commonly used for gout management. Colchicine exerts its effect by inhibiting the migration of neutrophils to the site of injury or inflammation. Moreover, it prevents the inflammasome complex formation in both neutrophils and monocytes, thus inhibiting IL-1β activation with resulting antiinflammatory effects [37]. Recently, colchicine has been recognized as an inhibitor of NLRP3 inflammasomes and mitigating interleukin activation. There may also be beneficial effects on endothelial function due to colchicine's antifibrotic activities. Currently, four randomized research investigations on COVID-19 patients have been proposed. Some COVID-19 patients with myopathies treated with colchicine were found with low inflammation in the cardiac myocytes [38]. There are several continuing studies investigating colchicine for cytokine storm (NCT04326790, NCT04322682, NCT04322565).

7.4.3 Niclosamide and ivermectin

Niclosamide is an anthelmintic drug used to treat tapeworm infestations. Recently, niclosamide was found to be effective as SARS-CoV virus replication inhibitor at a concentration range of 1.56 uM or higher without hindering the binding of coronavirus onto the cells [39]. This therefore implies

that the probability of niclosamide to inhibit SARS-CoV-2 is considerable. Similarly, ivermectin, a potent anthelmintic drug, has displayed inhibition against SARS-CoV-2 up to 5000-fold at 48 h when tested in vitro. It exerts the inhibition effect on IMP α/β1-mediated nuclear import of viral proteins, which may be the probable cause of its antiviral activity [40]. Future in vivo studies to probe its inhibition effect against SARS-CoV-2 are still required.

7.4.4 Convalescent plasma

Convalescent plasma therapy could be a suitable therapeutic remedy for COVID-19 affected patients. Plasma therapy refers to the transfusion of plasma enriched with antibodies from individuals after a resolution from a distinct pathogen. The key mode of action is through the complexation of the transfused antibodies, following cytotoxicity, phagocytosis, or inactivation of the pathogen [41]. In simple words, plasma therapy can offer short-term, instant immunity for patients. Earlier, plasma therapy was practiced for SARS-CoV and MERS [42]. Recently, a clinical study from China demonstrated that few critically COVID-19 sick patients recovered. After receiving plasma therapy, their fever normalized within 72 h (in four of the five patients), their viral loads became undetectable within 2 weeks, and three of the five patients were in recovery condition at 37 days post-plasma transfusion [43]. Finally, On March 24, 2020, the US FDA approved convalescent plasma therapy for investigational use under the traditional Investigational New Drug Applications regulatory pathway and for COVID-19 affected patients, especially patients with life-threatening conditions such as respiratory failure, septic shock, and multiple organ dysfunction. Apart from this, plasma therapy may pose potential risks including increased risk of a thrombotic event (from 0.04% to 14.9%), scarcity of high-quality research investigation in this domain, and the selection of donors with high neutralizing antibody titers [44].

7.4.5 Diacerein

Diacerein or diacetylrhein is a sustained-acting medicine of the anthraquinone category recommended for osteoarthritis treatment. Diacerein is a prodrug that is metabolized to rhein. Various researches have revealed that diacerein act by inhibiting the multifaceted cytokine and NALP3 inflammasome pathways. Rhein inhibits hepatitis B virus replication and influenza A virus adsorption and replication through regulation of oxidative stress and alterations of the TLR4, Akt, MAPK, and NF-κB signaling pathways. Importantly, rhein abolishes the interaction between the spike protein of coronavirus and ACE2 in a dose-dependent mode, proposing rhein as an effective curative agent for the therapy of COVID-19 patients. In light of these facts, researchers hypothesize that diacerein is a multidimensional drug valuable for COVID-19 treatment.

The multitarget mode of action involved the control of hyperinflammatory ailments by multifaceted cytokine inhibition, antiplatelet aggregation activity, and significant effects on viral infection and replication [45].

7.5 Traditional herbal medicines

Based on ancient records and data of SARS and H1NI influenza prevention, Chinese herbal medicine could be an effective alternative for the prevention of COVID-19. Currently, China and South Korea have recognized traditional medicinal treatment guidelines for COVID-19. The significant epidemiologic and biological affinity between SARS-CoV-2 and SARS-CoV paved way for the use of some herbal remedies to treat SARS-CoV-2 patients in China and Korea [46]. The most common herbal medicinal products used in China against COVID-19 are *Astragalus membranaceus*, *Glycyrrhiza uralensis*, *Saposhnikovia divaricata*, *Rhizoma Atractylodis Macrocephalae*, *Lonicerae Japonicae Flos*, *Fructus Forsythiae*, *Atractylodis rhizoma*, *Radix platycodonis*, *Agastache rugosa*, and *Cyrtomium fortunei* J. Sm.

Withania somnifera, commonly known as Ashwagandha, is a highly valued herb of the traditional Indian systems of medicines. *W. somnifera* possess antiviral effect against herpes simplex virus including antiinfluenza characteristics. Recently, Indian researchers validated antiviral potential of *W. somnifera* ingredients against COVID-19 by in silico method. Literature reveals that natural phytochemical withanone, isolated from *W. somnifera*, has distinct effects on viral RBD and host ACE2 receptor complex. Briefly, a molecular docking study was employed to screen numerous phytoconstituents including withanone against the ACE2−RBD complex. The result showed that withanone docked very well in the binding interface of AEC2−RBD complex; subsequently, interruption of electrostatic interactions between the RBD and ACE2 could block or weaken COVID-19 entry and its subsequent infectivity. Thus this suggests that *W. somnifera* could become a choice of herb for the treatment of COVID-19 [47].

Furthermore, a group of Indian researchers conducted in silico studies of the phytoconstituents of some Indian medicinal plants as possible COVID-19 inhibitors (Table 7.1). Results found while comparing their binding affinity with the binding affinity of hydroxychloroquine show that *Aloe vera* and giloy extracts had some prospects against COVID-19 [48].

7.6 Future projections

This chapter highlights the status of currently available therapeutic drugs to treat SARS-CoV-2. Until there is no clinical landmark achieved for this fatal disease, extensive clinical trials and research need to be performed to make a consensus about the validated therapeutic effect of these drugs. In addition, comprehensive clinical measures need to be conducted to test the efficacy of alternative medicine and the possible side effects of these drugs.

TABLE 7.1 Indian medicinal herbs and active constituent as inhibitors of COVID-19 protease.

S/No.	Medicinal plants	Active constituents
1.	Giloy	Berberine, sitosterol
2.	Ashwagandha	Withanolide, withaferin A
3.	Ginger	Gingerol, shogaol
4.	Tulsi	Ursolic acid, apigenin
5.	*Aloe vera*	Aloenin, aloesin
6.	Turmeric	Curcumin
7.	Neem	Nimbin
8.	Red onion	Quercetin
9.	Cannabis	Cannabidiol
10.	Black pepper	Piperine

7.7 Conclusion

COVID-19 has emerged as the biggest global public health emergency. Expectantly, researchers are working to develop vaccines and specific medicine to target SARS-CoV-2. This chapter suggests the therapeutic importance of currently available drugs, including traditional herbal medicines that are being used for a long time to treat viral infection and replication, inflammatory conditions, fever, and respiratory complexities. Coincidently, these ailments are associated with COVID-19 and these drugs have the potential to ameliorate.

List of abbreviations

ACE2 Angiotensin-converting enzyme 2
ARDS Acute respiratory distress syndrome
AT1R Angiotensin II type 1 receptor
COVID-19 Coronavirus disease 2019
FDA Food and Drug Administration
HIV Human immunodeficiency virus
IFN Interferon
IL Interleukin
IV Intravenous
MERS-CoV Middle East respiratory syndrome coronavirus
NIH National Health Commission
RBD Receptor-binding domain

RNA Ribonucleic acid
SARS-CoV-2 Severe acute respiratory syndrome coronavirus 2
TNF Tumor necrosis factor

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