Chinese Therapeutic Strategy for Fighting COVID-19 and Potential Small-Molecule Inhibitors against Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)

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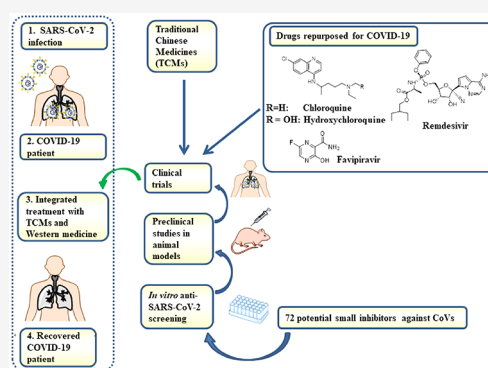
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ABSTRACT: The coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to more than 20 million people infected worldwide with an average mortality rate of 3.6%. This virus poses major challenges to public health, as it not only is highly contagious but also can be transmitted by asymptomatic infected individuals. COVID-19 is clinically difficult to manage due to a lack of specific antiviral drugs or vaccines. In this article, Chinese therapy strategies for treating COVID-19 patients, including current applications of traditional Chinese medicine (TCM), are comprehensively reviewed. Furthermore, 72 small molecules from natural products and TCM with reported antiviral activity against human coronaviruses (CoVs) are identified from published literature, and their potential applications in combating SARS-CoV-2 are discussed. Among these, the clinical efficacies of some accessible drugs such as remdesivir (RDV) and favipiravir (FPV) for COVID-19 are emphatically summarized. We hope this review provides a foundation for managing the worsening pandemic and developing antivirals against SARS-CoV-2.

1. INTRODUCTION

1.1. CoVs and Types. Coronaviruses (CoVs) represent a group of enveloped, positive-sense, single-stranded RNA viruses with a genome size of 27–33 kb. They can cause diseases of the respiratory tract, intestinal tract, liver, and nervous system of many animal species, including humans, with varying degrees of severity.[1] *Coronaviridae* in the order *Nidovirales* is divided into four genera: α-, β-, γ-, and δ-CoVs, of which only α- and β-CoVs can infect humans. There are seven known types of human CoVs. Four human CoVs are known to be prevalent: HCoV-229E, HCoV-OC43, HCoV-HKU1, and HCoV-NL63, which are common and cause mild to moderate respiratory infections, such as the common cold.[1] Two other β-CoVs, severe acute respiratory syndrome CoV (SARS-CoV) and Middle East respiratory syndrome CoV (MERS-CoV), have zoonotic origins and have been linked to fatal illness in past years.[2] SARS-CoV was the causal agent of SARS outbreaks in 2002 and 2003 in China.[3−5] The SARS outbreak was contained in 2004 following a highly effective public health response, with 8454 confirmed cases and 792 deaths.[6] In 2012, Middle East respiratory syndrome (MERS), caused by MERS-CoV, emerged in the Kingdom of Saudi Arabia and subsequently spread to 27 countries.[7] MERS presented as a severe respiratory disease with frequent gastrointestinal and renal complications. As of September 12, 2017, 2080 confirmed cases and 722 deaths have been reported.[7] The seventh human CoV, termed SARS-CoV-2, is a novel β-CoV that first emerged in Wuhan city, Hubei Province, China.

1.2. The COVID-19 Pandemic. In December 2019, pneumonia cases caused by a novel pathogen emerged in Wuhan, a city of 11 million people in Central China. The pathogen was soon identified as the novel CoV SARS-CoV-2, which is closely related to SARS-CoV.[8] Recently, Dorp et al. estimated that the initial timing of human infection with SARS-CoV-2 may have been in early December or even earlier in 2019 by analyzing the emergence of genomic diversity of SARS-CoV-2.[9] However, the native host(s) of SARS-CoV-2 and the place of origin of human SARS-CoV-2 infections remain uncertain, even though Wuhan was the first city in which this disease was detected and managed. As of March 30, 2020, COVID-19 has led to over 80 000 confirmed cases with over 3000 deaths in China. Due to strict quarantines throughout China, new cases have sharply decreased since mid-March, and the outbreak was successfully contained in China. Unfortunately, as of August 14, 2020, this virus has now spread to over 200 other countries and areas worldwide and

A

Table 1. Clinical Classification of COVID-19 Patients and the Corresponding Therapeutic Regimen According to the Seventh Edition of the Guidelines for the Diagnosis and Treatment of COVID-19 Issued by the NHC of China[14,a]

clinical classification	criteria for classification	therapeutic regimen
Mild	Nonspecific clinical symptoms and no manifestation of pneumonia based on medical imaging.	**General treatment:**
Moderate	Fever and respiratory tract symptoms, and manifestation of pneumonia based on medical imaging.	(1) Stay in bed to rest, strengthen supportive treatment, keep a balanced diet and maintain the balance of water and electrolytes.
		(2) Effective oxygen therapies, including nasal catheter oxygen inhalation, oxygen inhalation with a mask or high-flow nasal cannula with a hydrogen and oxygen mixture (H_2/O_2) of 66.6%/33.3%, if possible.
	At least one of the following symptoms in adults:	(3) Antiviral therapies: IFN-α nebulization (5×10^6 units or equivalent per time, add 2 mL of sterile water, aerosol inhalation, BID); lopinavir/ritonavir (200 mg/50 mg per capsule, 2 capsules each time, BID); ribavirin (500 mg by venoclysis per time, BID, combination treatment with IFN-α or lopinavir/ritonavir are recommended); CQ phosphate (500 mg per time, BID), Arbidol (200 mg per time, TID). The above dosages are suitable only for adults, and the course of treatment with above antivirals should be ≤10 days. Monitor side effects such as diarrhea, nausea, vomiting, and liver damage related to lopinavir/ritonavir as well as harmful interactions with other drugs. Simultaneous use of three or more types of antiviral drugs is not recommended, and relevant drug treatments should be stopped if unbearable side effects occur.
	(1) Respiratory distress, respiration rate (RR) > 30/min;	(4) Traditional Chinese medicine (TCM) treatments, shown in Table 2.
Severe	(2) Pulse oxygen saturation (SpO_2) of ≤93% at resting state;	**Treatment of severe and critical cases:**
	(3) Arterial partial pressure of oxygen (PaO_2)/oxygen concentration (FiO_2) of ≤300 mmHg.	(1) Respiratory support: oxygen inhalation, noninvasive ventilation, invasive ventilation; salvage therapies (lung recruitment), and extracorporeal membrane oxygenation (ECMO).
	For high altitude regions (above 1000 m), PaO_2/FiO_2 should be adjusted based on equation of $PaO_2/FiO_2 \times$ (atmospheric pressure (mmHg)/760).	(2) Circulatory support: on the basis of adequate fluid resuscitation, improved microcirculation, and
	Patients with >50% lesions progression within 24–48 h in pulmonary imaging should be treated as severe cases of COVID-19.	(3) Use of vasoactive drugs.
	Meeting any of the following:	(4) Renal replacement therapy for patients with renal failure.
	(1) Respiratory failure occurs and mechanical ventilation is required;	(5) Convalescent-phase plasma therapy.
	(2) Shock;	(6) Blood dialysis.
Critical	(3) Complicated with other organ failure that requires monitoring and treatment in an intensive care unit (ICU).	(7) Immunotherapy: trastuzumab for patients with a high IL-6 level.
		(8) Other therapies, including low dosage of methylprednisolone ($\leq1-2$ mg kg^{-1} day^{-1}) and intestinal microecological regulators.

[a]BID, twice a day; TID, three times a day.

B

Table 2. Frequently Used TCM Prescriptions and Therapeutic Regimens for COVID-19 Patients in China[14,a]

clinical classification	clinical manifestations	proprietary Chinese medicine/TCM prescription	administration and dosage
Medical observation period	Fatigue with fever	**Jinhua Qinggan granule (JHQGG):** *Lonicerae japonicae flos, Gypsum Fibrosum, Herba Ephedrae, Semen Armeniacae Amarum, Radix Scutellariae, Fructus Forsythiae, Fritillariae Thunbergii Bulbus, Rhizoma Anemarrhenae, Fructus Arctii, Herba Artemisiae Annuae, Herba Menthae Haplocalycis, and Radix Glycyrrhizae.*	6 g per packet, 1 bag each time, BID
		Lianhua Qingwen capsule (LHQWC): *Fructus Forsythiae, Lonicerae japonicae flos, roasted Herba Ephedrae, roasted Semen Armeniacae Amarum, Gypsum Fibrosum, Radix Isatidis, Rhizoma Dryopteridis Crassirhizomatis, Herba Houttuyniae, Herba Pogostemonis, Radix et Rhizoma Rhei, Radix et Rhizoma Rhodiolae Crenulatae, L-Menthol, and Radix Glycyrrhizae.*	0.35 g per softgel, 1 softgel each time, TID
		Clinical Treatment Period (Confirmed Cases)	
Basic prescription for mild, moderate, severe, and critical patients		**Lung-cleansing and detoxifying decoction (LCDD) (also named Qingfei Paidu Tang, QFPDT):** *Herba Ephedrae (9 g), roasted Radix Glycyrrhizae (6 g), Semen Armeniacae Amarum (9 g), raw Gypsum Fibrosum (15–30 g, decocted first), Ramulus Cinnamomi (9 g), Rhizoma Alismatis (9 g), Polyporus Umbellatus (9 g), Rhizoma Atractylodis Macrocephalae (9 g), Poria (15 g), Radix Bupleuri (16 g), Radix Scutellariae (6 g), Rhizoma Pinelliae Preparata (9 g), Rhizoma Zingiberis Recens (9 g), Radix Asteris (9 g), Flos Farfarae (9 g), Rhizoma Belamcandae (9 g), Herba Asari (6 g), Rhizoma Dioscoreae (12 g), Fructus Aurantii Immaturus (6 g), Pericarpium Citri Reticulatae (6 g), and Herba Pogostemonis (9 g).*	One dose per day, BID
Moderate	Fever, cough with less sputum or yellow sputum, chest tightness, and shortness of breath	**Prescription 3 (also named Xuanfei Baidu Tang, XFBDT):** *Raw Herba Ephedrae (6 g), Semen Armeniacae Amarum (15 g), raw Gypsum Fibrosum (30 g), raw Semen Coicis (30 g), Rhizoma Atractylodis (10 g), Herba Pogostemonis (15 g), Herba Artemisiae Annuae (12 g), Rhizoma Polygoni Cuspidati (20 g), Herba Verbenae (30 g), dry Rhizoma Phragmitis (30 g), Semen Lepidii (15 g), Exocarpium Citri grandis (15 g), and Radix Glycyrrhizae (10 g).*	One dose per day, BID
Severe	Fever, flushing, cough, less yellow sticky sputum with or without blood, fatigue, wheezing and shortness of breath, and poor appetite	**Prescription 5 (also named Huashi Baidu Tang, HSBDT):** *Raw Herba Ephedrae (6 g), Semen Armeniacae Amarum (9 g), Gypsum Fibrosum (15 g), Radix Glycyrrhizae (3 g), Herba Pogostemonis (10 g, decocted later), Cortex Magnoliae Officinalis (10 g), Rhizoma Atractylodis (15 g), Fructus Tsaoko (10 g), Rhizoma Pinelliae Preparatum (9 g), Poria (15 g), raw Radix et Rhizoma Rhei (5 g), raw Radix Astragali seu Hedysari (10 g), Semen Lepidii (10 g), and Radix Paeoniae Rubra (10 g).*	One dose per day, TID, administered alone or in combination with Xue Bi Jing injection
	Severe fever and polydipsia, anhelation, delirium, blurred vision, hematemesis, epistaxis, and convulsion of the limbs	**Xue Bi Jing Injection:** *Carthami flos, Radix Paeoniae Rubra, Chuanxiong rhizoma, Radix Salviae Miltiorrhizae, and Angelicae sinensis radix.*	100 mL each time by venoclysis after dilution, BID

[a]Notes: (1) TCM should be chosen according to individual conditions and clinical symptoms. Generally, one course of TCM treatment lasts for 3 days; however, the period of TCM treatment for an individual patient highly depends on the patient's conditions and recovery process. (2) TCM could be used alone or in combination with antiviral agents. Using two or more TCM prescription decoctions at the same time is not recommended. However, for severe patients, TCM injection can be used in combination with a TCM decoction. (3) Generally, one dose of TCM prescription is decocted with approximately 10–12 times water (w/w) until 300–500 mL remains; the decoction is taken in the morning, noon, and evening before meals. BID, twice a day; TID, three times a day.

C

led to over 20 million people infected and over 750 000 deaths.[10] Currently, there are no vaccines or drugs available.

2. CHINESE THERAPEUTIC STRATEGY AND THE APPLICATION OF TCMS AS TREATMENTS FOR COVID-19

Developing a vaccine for a new pathogen needs at least 18 months, and thus, vaccinations are unlikely to control emergent epidemics. Developing novel drugs against this virus could take a longer time than developing a vaccine. However, since SARS-CoV-2 shares high similarity in gene sequence and pathogenic mechanism with previous human pathogenic CoVs, especially SARS-CoV (82% sequence identity),[11,12] existing therapeutic strategies for combating SARS might be effective for managing COVID-19. In 2002−2003, the SARS outbreak first started in South China and subsequently spread to 31 countries worldwide. Patients in mainland China accounted for over 60% of the total cases. Interestingly, the average death rate in mainland China (approximately 6.5%) was lower than the worldwide average death rate (9.3%). The higher cure rate in China for SARS infections was attributed to combining traditional Chinese medicine (TCM) with Western medicine in China.[13] Since the outbreak of COVID-19 in early January 2020, some therapeutic strategies for SARS, including the application of TCM, have been repurposed for combating COVID-19 in China.

2.1. Chinese Therapeutic Strategy. On January 20, 2020, the National Health Commission (NHC) of China issued the first edition of the Guidelines for the Diagnosis and Treatment of COVID-19. Subsequently, these guidelines have been frequently revised, and the seventh version was released on March 4, 2020. In the seventh edition of the Guidelines for the Diagnosis and Treatment of COVID-19, COVID-19 patients are classified into four groups based on the severity of illness: mild, moderate, severe, and critical, and the therapeutic regimen varies according to this classification (Table 1).[14] Among the recommended antiviral drugs, interferon α (IFN-α) represents one of the broad-spectrum antiviral interferons extensively and clinically used to induce the host innate immune response. Lopinavir−ritonavir, the anti-human immunodeficiency virus (HIV) combination drugs, was shown to be beneficial for MERS-CoV infections,[15] while its effect on COVID-19 is currently being assessed in clinical trials along with umifenovir (also named Arbidol) and ribavirin. Chloroquine (CQ), a widely used antimalarial and immunomodulatory drug, showed *in vitro* activity against SARS-CoV-2 at low micromolar concentrations.[16] These findings led to 15 clinical trials of CQ or hydroxychloroquine (HCQ) in China to test their efficacy and safety for COVID-19 patients. Results from more than 100 patients so far have demonstrated reduced hospital stays and improved the progression of COVID-19 pneumonia after CQ phosphate treatment with no severe adverse reactions.[17] Given these findings, CQ phosphate was included in the seventh edition of the Guidelines for the Diagnosis and Treatment of COVID-19.

It has been thought that deaths induced by SARS-CoV-2 infection are due to vigorous systemic inflammation caused by "cytokine storms", driven by proinflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), and interferon γ (IFN-γ), similar to those induced by SARS-CoV and highly pathogenic influenza A virus (IAV) infections.[18] Tocilizumab, a monoclonal antibody with interleukin 6 (IL-6)-neutralizing activity, has been used to clinically treat rheumatoid arthritis. In a recent initial clinical trial, tocilizumab was used in 21 severe COVID-19 cases. The results showed that all patients had resolution of fever within 24 h, with reported relief of clinical symptoms. All 21 patients were discharged from the hospital within 2 weeks, although two were readmitted to the hospital by the end of follow-up.[19] Glucocorticoids were extensively used to treat SARS patients in 2002−2003 due to their significant suppression of exaggerated systemic inflammation induced by SARS-CoV infections. However, high-dose therapy with glucocorticoids could cause severe side effects to SARS patients, including immunosuppression, delayed virus clearance, and osteoporosis.[20] In the Guidelines for the Diagnosis and Treatment of COVID-19, glucocorticoid methylprednisolone was prudently recommended to treat severe patients at a low dose ($\leq$1−2 mg kg^{-1} day^{-1}).

2.2. Application of TCMs in the Treatment of COVID-19. TCMs have been used for thousands of years to treat pandemic and endemic diseases, and there is evidence of efficacy against SARS-CoV reported in 2002−2003,[21] including marked improvement of symptoms, shortened disease course, reduced side effects caused by conventional therapeutics, and dramatically reduced fatality.[22,23] Taking into account the similarities between SARS-CoV-2 and SARS-CoV in epidemiology and genomics, TCM is expected to have therapeutic value for SARS-CoV-2.[11,12] Since the fourth edition of the Guidelines for the Diagnosis and Treatment of COVID-19, different TCMs have been recommended for the treatment of COVID-19.[14] In the seventh edition of the Guidelines for the Diagnosis and Treatment of COVID-19, 15 commercially available proprietary Chinese medicines (formulas) and 10 TCM decoction prescriptions were recommended for patients in different phases of the disease and stages, including medical observation period, clinical treatment period, and recovery period, as shown in Table 2 and Supplementary Table 1. As of March 23, 2020, 392 clinical trials aimed at evaluating the efficacy and safety of various treatments for COVID-19 patients had been launched in China. Among them, 78 trials (19.9%) utilized TCMs, including 21 (5.3%) examining the effects of the combined treatment of TCM and Western medicine.[24] A total of 92% of COVID-19 patients in China received TCM treatment, with a total effective rate of 90%.[25] Among the recommended TCM formulas and prescriptions, three formulas, including Jinhua Qinggan granule (JHQGG), Lianhua Qingwen capsule (LHQWC), and Xue Bi Jing injection (XBJI), and three prescriptions, including Qingfei Paidu Tang (QFPDT), Xuanfei Baidu Tang (XFBDT), and Huashi Baidu Tang (HSBDT) (shown in Table 2), were widely used in the treatment of COVID-19 patients due to their significant clinical efficacy. JHQGG and LHQWC were recommended to treat mild and moderate COVID-19 patients. A comparative clinical trial showed that among the recruited 80 COVID-19 patients, the average duration of viral nucleic acid detection was 7 ($\pm$4) days in the JHQGG administration group (44 patients) and 10 ($\pm$4) days in the control group (36 patients).[26] In February 2020, Hu and collaborators performed a prospective multicenter open-label randomized controlled trial to determine the safety and efficacy of LHQWC in COVID-19 patients. A total of 284 patients were randomized to receive standard treatment alone or in combination with LHQWC (142 patients in each group) for 14 days. The results

indicated that the symptom (fever, fatigue, and coughing) recovery rate was significantly higher in the combined treatment group than in the control group (91.5% vs 82.4%), and no serious adverse events were reported.[27] QFPDT, consisting of 21 components that included both herbs and mineral drugs, was recommended as a basic prescription for treating mild to severe cases of COVID-19. A clinical survey evaluating the effect of QFPDT showed that among the 1263 recruited COVID-19 patients from 66 hospitals in 10 cities in China, 1214 patients were cured and discharged, and none of the patients with mild and moderate disease progressed to the severe stage. Among these patients, out of the 49 severe patients who were treated with both QFPDT and Western medicine, 42 were cured.[28,29]

Unlike chemical drugs, which generally function on defined targets with clearly understood mechanisms of action, TCM prescriptions consist of multiple herbs with multiple targets. Recently, Yang and colleagues comprehensively analyzed the chemical constituents of QFPDT using liquid chromatography coupled with high-resolution mass spectrometry (HRMS). A total of 129 compounds were identified or tentatively characterized from QFPDT, including 58 flavonoids, 20 glycosides, 13 carboxylic acids, 7 saponins, 6 alkaloids, and 4 terpenes. *In silico* approaches such as network pharmacology and molecular networking revealed multiple constituents, such as glycyrrhizic acid (glycyrrhizin, GL), saikosaponins (SSs), scutellarein, and betulonic acid. Various compounds from different herbs in QFPDT may interfere with the disease process of COVID-19 through multiple signaling pathways, such as Toll-like receptor activation and IFN response induced by viral infection, thereby reducing the secretion of inflammatory cytokines and inhibiting viral replication to protect patients.[25]

TCM was established on a different theoretical system than Western medicine, emphasizing diagnosis and treatment based on the patient's overall condition rather than targeting specific etiologies or pathologies. Therefore, the prescription principle of TCM treatment on COVID-19 includes strengthening body resistance and eliminating pathogenic factors (Table 2). Most of the herbal medicines included in the Guidelines for the Diagnosis and Treatment of COVID-19 fall into three categories: drugs for clearing heat and resolving dampness plus detoxification, drugs for promoting blood circulation, and drugs for enhancing host antiviral immune responses. For example, in the QFPDT prescription, *Gypsum Fibrosum* and *Scutellaria Radix* clear heat, and *Citri reticulatae pericarpium* and *Pogostemonis herba* clear dampness and detoxify; *Ephedrae herba*, *Cinnamomi ramulus* and *Zingiberis rhizome* promote blood circulation; *Glycyrrhizae radix*, *Polyporus*, *Atractylodis macrocephalae rhizoma*, and *Poria* enhance host antiviral immune responses.[30,31] Given that TCM theory has widely appreciated clinical effects, it has been promoted by the Chinese government in its campaign against SARS-CoV-2. The Health Commissions in 26 provinces officially recommended TCM in combination with Western medicine in the treatment of COVID-19.

3. POTENTIAL SMALL-MOLECULE INHIBITORS OF SARS-COV-2

As a supplement to conventional medicine, TCM treatment has played important roles in the campaign of managing the SARS-CoV-2 pandemic in China. However, the effects of TCM are often influenced by multiple factors, including

esoteric TCM theory; inconsistent medicinal material quality, which could be significantly affected by soil and climate conditions, agricultural methods, and the process involved in their final preparation; unclear effective ingredients and mechanism of action. Furthermore, whether TCM is effective in the clinic often relies on the clinician's experience. These variations make it very difficult to develop a standardized TCM regimen for a particular disease.[32,33] In addition, only a few Asian countries have the tradition of using TCM, and most countries in the world do not practice TCM as a complementary medicine. Therefore, potent antiviral agents against SARS-CoV-2 and other pathogenic CoVs are urgently needed. Since the outbreak of SARS in 2002−2003 and MERS in 2012, some research groups have been devoted to the development of antivirals against CoVs and documented a number of effective compounds. As there are limited numbers of CoVs and as these CoVs have relatively similar structures,[11] it is possible that the drugs developed for other CoVs might be useful for managing COVID-19. In particular, SARS-CoV-2 shares 82% sequence identity with SARS-CoV (GenBank code NC_004718.3), and there is greater than 90% sequence identity in several of the essential enzymes of SARS-CoV and SARS-CoV-2,[12] indicating that inhibitors of SARS-CoV might be effective against SARS-CoV-2. Indeed, some commercially available drugs, such as antiparasitic CQ/HCQ and antiviral favipiravir (FPV), with reported activity against SARS-CoV and other CoVs, have shown pronounced inhibition of SARS-CoV-2.[16] However, to date, few reviews have focused on small molecules with reported anti-CoV activity. In this review, we identify 72 reported small molecules with activity against human CoVs and discuss their potential application in combating COVID-19. On the basis of inhibitory mechanisms against CoV replication, these compounds are categorized in Tables 3−7. Table 3 shows the *in vitro* and *in vivo* antiviral activities of compounds (**1−9**) against CoVs, including SARS-CoV-2. Table 4 includes compounds targeting SARS-CoV proteases: 3C-like serine protease ($3CL^{pro}$) inhibitors (**10−31**) and papain-like cysteine protease (PL^{pro}) inhibitors (**32−36**). These compounds have been reported to bind $3CL^{pro}$ or PL^{pro} and suppress their enzymatic activity through competitive, noncompetitive, or mixed mechanisms of action. Table 5 contains compounds (**37−44**) targeting SARS-CoV helicase (Hel). Table 6 includes compounds for other targets of SARS-CoV, including SARS-CoV-2 (**45−50**). Table 7 includes compounds (**51−72**) with undefined inhibiting mechanisms against various CoVs. The chemical structures of the 72 inhibitors are shown in Figures 1 and 4−7.

3.1. Antivirals with *in Vitro* and *in Vivo* Activity against CoVs. Recently, Li et al. summarized a list of approved antiviral drugs with anti-CoV potential, including preclinical compounds under consideration for further study or as starting points for further development of newer agents.[11] The efficacy of the commercially available drugs ribavirin, nitazoxanide, penciclovir, nafamostat, CQ/HCQ, remdesivir (RDV, GS-5734), and favipiravir (FPV, T-705) was evaluated for activity against SARS-CoV-2 *in vitro*. Among all seven tested drugs, CQ/HCQ and RDV potently blocked viral infection at low micromolar concentrations in cell cultures and showed a high selective index (SI) against SARS-CoV-2.[16] The findings of this study, along with other previous important studies on CQ/HCQ, RDV and FPV against CoVs, are discussed in the following section.

Table 3. In Vitro and in Vivo Antiviral Activity of Some Potential Compounds against CoVs, Including SARS-CoV-2

no.	compd	reported mechanism of action	in vitro/in vivo	effect	CoV type	ref
1	Chloroquine (CQ)	Increases endosomal pH; disrupts intracellular trafficking and viral fusion events; and interferes with glycosylation of cellular receptors of CoV.	In vitro	IC$_{50}$: 1.13 μM; CC$_{50}$: >100 μM; SI: >88	SARS-CoV-2	Wang et al. [16]
				IC$_{50}$: 0.33 μM; CC$_{50}$: >20 μM; SI: >60	HCoV-OC43	Shen et al. [1]
				IC$_{50}$: 4.1 μM; CC$_{50}$: >128 μM; SI: >31	SARS-CoV	de Wilde et al. [36]
				IC$_{50}$: 3.3 μM; CC$_{50}$: >50 μM; SI: >15	HCoV-229E	
				IC$_{50}$: 0.30 μM; CC$_{50}$: 419 μM; SI: 1369	HCoV-OC43	Keyaerts et al. [38]
				IC$_{50}$: 8.8 μM; CC$_{50}$: 261 μM; SI: 30	SARS-CoV	Keyaerts et al. [37]
			Mouse model	Intranasal administration of CQ (50 mg/kg BW) resulted in a minor reduction in viral titers in the lung.	SARS-CoV	Barnard et al. [79]
				A 98.6% survival of newborn C57BL/6 mice infected with HCoV-OC43 when mother mice were treated daily with CQ at a dose of 15 mg/kg BW.	HCoV-OC43	Keyaerts et al. [38]
2	Hydroxychloroquine (HCQ)	The same as CQ.	Open-label clinical trial	Shorter median time to negative conversion and the duration of fever.	SARS-CoV-2	Huang et al. [39]
			In vitro	IC$_{50}$: 0.72 μM	SARS-CoV-2	Yao et al. [80]
			Open-label, controlled clinical trial	Significantly associated with viral load reduction/disappearance in COVID-19 patients. Synergetic effects when used in combination with azithromycin.	SARS-CoV-2	Gautret et al. [41]
			Randomized controlled clinical trial	Shorter time to clinical recovery and promoted the absorption of pneumonia.	SARS-CoV-2	Chen et al. [42]
			Open-label, randomized controlled clinical trial	No difference in negative conversion with standard of care alone in mild and moderate patients; higher adverse events such as diarrhea.	SARS-CoV-2	Tang et al. [44]
			Open-label, controlled clinical trial	No improvement in survival for COVID-19 patients who required oxygen.	SARS-CoV-2	Mahévas et al. [45]
3	Remdesivir (RDV)	Inhibits RdRp and blocks viral RNA synthesis; terminates the nonobligate chain.	In vitro	IC$_{50}$: 0.77 μM; CC$_{50}$: 100 μM; SI: >129	SARS-CoV-2	Wang et al. [16]
				IC$_{50}$: 0.15 μM; CC$_{50}$: >10 μM; SI: >66	HCoV-OC43	Brown et al. [51]
				IC$_{50}$: 0.024 μM; CC$_{50}$: >10 μM; SI: >400	HCoV-229E	
				IC$_{50}$: 0.06 μM; CC$_{50}$: >10 μM; SI: >167	SARS-CoV	Agostini et al. [52]
			Mouse model	Ameliorated SARS-CoV-induced weight loss; reduced SARS-CoV-induced lung pathology and viral load in the lungs; and improved clinical signs of disease as well as respiratory function.	SARS-CoV	Sheahan et al. [53]
			Observational, retrospective study	Clinical improvement was observed in 36 of 53 patients (68%) in patients receiving oxygen support.	SARS-CoV-2	Grein et al. [55]
			Double-blind, randomized, controlled clinical trial	RDV was superior to placebo in shortening the time to recovery in patients with lower respiratory tract infection.	SARS-CoV-2	Beigel et al. [56]
			Double-blind, randomized, controlled clinical trial	No significant improvements in clinical or antiviral effects in severe patients.	SARS-CoV-2	Wang et al. [57]
4	Favipiravir (FPV)	Inhibits RdRp and blocks viral RNA synthesis.	In vitro	IC$_{50}$: 61.8 μM; CC$_{50}$: >400 μM; SI: >6.46	SARS-CoV-2	Wang et al. [16]
			Open-label, controlled clinical trial	Significant shorter time to viral clearance and improvement in chest imaging compared with lopinavir/ritonavir, another antiviral drug.	SARS-CoV-2	Cai et al. [62]
			Open-label, randomized, controlled clinical trial	Did not significantly improve the clinical recovery rate on day 7 and did not shorten the latency to relief for pyrexia and cough.	SARS-CoV-2	Chen et al. [64]
5	Ribavirin	Inhibits viral RNA synthesis and mRNA capping.	In vitro	The cytopathic effect of SARS-CoV was inhibited by ribavirin at 50 μg/mL.	SARS-CoV	Chu et al. [66]
				IC$_{50}$: 109.5 μM; CC$_{50}$ >400 μM; SI >3.65	SARS-CoV-2	Wang et al. [16]
6	Lopinavir	Inhibits 3CL^{pro} and blocks the cleavage of viral peptides into functional units.	In vitro	The cytopathic effect of the SARS-CoV was inhibited by lopinavir at 4 μg/mL.	SARS-CoV	Chu et al. [66]
	Lopinavir/ritonavir	A fixed dose of ritonavir was used to increase lopinavir half-life through the inhibition of cytochrome P450.	In vitro	IC$_{50}$: 17.1 μM; CC$_{50}$ >32 μM; SI: >2.0	SARS-CoV	de Wilde et al. [36]
				IC$_{50}$: 6.6 μM; CC$_{50}$ >37.6 μM; SI: 5.7	HCoV-229E	
			Randomized, controlled, open-label clinical trial	No benefits in the time to clinical improvement and/or mortality rate at day 28 for severe COVID-19 patients, compared with standard care group.	SARS-CoV-2	Cao et al. [69]

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Table 3. continued

no.	compd	reported mechanism of action	in vitro/in vivo	effect	CoV type	ref
7	Matrine sodium chloride	Regulates immunity function and inhibits the release of inflammatory factors.	Mouse model	Intraperitoneal injection of matrine sodium chloride significantly improved the pathological damage of lung tissue and reduced lung index.	HCoV-229E	Jing et al.[73]
8	Lycorine	Inhibits replication with an undefined mechanism.	In vitro	IC_{50}: 0.0157 μM; CC: 14.9 μM; SI: 954	HCoV-OC43	Li et al.[76]
				IC_{50}: 0.15 μM; CC: 4.37 μM; SI: 29.1	HCoV-OC43	Shen et al.[1]
				IC_{50}: 0.47 μM; CC: 3.81 μM; SI: 8.11	HCoV-NL63	
			Mouse model	Intraperitoneal injection at 15 mg/kg provided an 83.3% protection for infected mice.	HCoV-OC43	
9	Camostat	Inhibits transmembrane protease serine 2.	In vitro	Blocked cellular entry of the SARS-CoV-2 virus into Caco-2 cells with an EC_{50} of 1 μM.	SARS-CoV-2	Hoffmann et al.[78]
			Mouse model	Protected mice against SARS-CoV lethal infection with a survival rate of 60%.	SARS-CoV	Zhou et al.[77]

3.1.1. CQ, HCQ, RDV, and FPV: Four Potential Drugs against SARS-CoV-2. a. CQ and HCQ. CQ (**1**), a widely used antimalarial and autoimmune inhibitory drug, was reported to be a potential broad-spectrum antiviral drug.[34,35] Recently, Wang et al. evaluated the antiviral effect of CQ against a clinical isolate of SARS-CoV-2 *in vitro* in Vero E6 cells. CQ was able to block viral replication at a low concentration [effective concentration for 50% inhibition (IC_{50}) of 1.13 μM] with acceptable cytotoxicity (50% cytotoxic concentration (CC_{50}) of >100 μM).[16] Previously, Shen et al.,[1] de Wilde et al.,[36] and Keyaerts et al.[37] showed that CQ inhibited the replication of three human CoVs, HCoV-OC43, SARS-CoV, and HCoV-229E, respectively, *in vitro* at submicromolar concentrations. Keyaerts et al. developed an *in vivo* model to test CQ against HCoV-OC43 in newborn C57BL/6 mice. The highest survival rate (98.6%) was found when the mother mice were treated daily with CQ at a dose of 15 mg/kg body weight (BW).[38] These results suggested that CQ might be an effective drug to manage human CoV infections. Since the outbreak of the COVID-19 pandemic in February 2020, CQ and its analog HCQ have drawn intense attention, and a series of clinical trials evaluating the therapeutic effects of CQ and HCQ on SARS-CoV-2 have been conducted in several countries. Huang and collaborators performed a multicenter prospective observational study to evaluate the clinical effects of CQ on SARS-CoV-2, in which a total of 197 patients from 12 hospitals in Guangdong and Hubei Provinces in China were treated with CQ, and 176 patients were included as historical controls. The median time for viral RNA to be undetectable and the duration of fever were shorter in the CQ-treated group than in the control group. The authors suggested that CQ could be a cost-effective therapy without serious adverse events for combating the COVID-19 pandemic.[39]

HCQ sulfate, a derivative of CQ, was first synthesized in 1946 by introducing a hydroxyl group into CQ, and it showed significantly reduced (~40%) toxicity compared to CQ.[40] Gautret et al. conducted the first open-label, nonrandomized controlled clinical trial for a therapeutic evaluation of HCQ in 36 COVID-19 patients in France and suggested that 600 mg/day HCQ significantly reduced viral loads in these patients. They also showed that when HCQ was used in combination with azithromycin, it was more efficacious.[41] However, this report was questionable because six HCQ-treated patients who withdrew from the study were excluded from their data analysis. The beneficial outcomes of HCQ treatment on COVID-19 patients were also confirmed by Chen et al., a medical team in Wuhan, China. They conducted a randomized controlled clinical trial that included 62 patients to test the efficacy of HCQ and showed that HCQ treatment significantly shortened the disease course.[42] However, the effectiveness of HCQ for treating COVID-19 has been the subject of debate.[43] Recently, Tang and other groups reported various contradictory effects of HCQ in COVID-19 patients, which disapproved the use of HCQ.[44−47] Tang and colleagues conducted an open-label, randomized controlled trial to evaluate the efficacy of HCQ in 150 COVID-19 patients within the mild to moderate clinical classifications. The results showed that HCQ did not lead to a significantly higher probability of negative conversion compared to standard care alone in hospitalized patients with persistent mild to moderate COVID-19 symptoms. Adverse events, mainly diarrhea, were significantly higher in patients who received HCQ.[44] Another recent study of HCQ in 181 COVID-19 patients who required

Table 4. SARS-CoV inhibitors Targeting 3CL^{pro} and PL^{pro} [a]

	compd	source	IC$_{50}$ (μM)	K_i (μM)	inhibition mode	ref
			Inhibitors Targeting 3CL^{pro}			
10	Betulinic acid	*Betula pubescens*	10	8.2	Competitive	Wen et al.[86]
11	Savinin	*Chamaecyparis obtusa*	25	9.1		
12	Celastrol	*Tripterygium regelii*	10	4.2	Competitive	Ryu et al.[92]
13	Pristimerin		5.5	3.1		
14	Tingenone		9.9	4.0		
15	Iguesterin		2.6	0.8		
16	Hesperetin	*Isatis indigotica*	8.3	NT	-	Lin et al.[93]
17	Dieckol	*Ecklonia cava*	2.7	2.4	Competitive	Park et al.[94]
18	Amentoflavone	*Torreya nucifera*	8.3	13.8	Noncompetitive	Ryu et al.[96]
19	Luteolin		20.2	NT	-	
20	Quercetin		23.8			
20	Quercetin	NM	73	NT	-	Nguyen et al.[97]
21	Epigallocatechin gallate		73			
22	Gallocatechin gallate		47	25	Competitive	
23	Rhoifolin	NM	27.4	NT	-	Jo et al.[98]
24	Herbacetin		33.1			
25	Pectolinarin		37.7			
26	Xanthoangelol E	*Angelica keiskei*	7.1	16.1	Competitive	Park et al.[99]
27	5-Sulfonyl isatin a	Derivative	1.04	NT	-	Liu et al.[100]
28	5-Sulfonyl isatin b		1.18			
29	GC376	Synthesized	4.35	NT	-	Kim et al.[101]
30	Peptide anilide	Synthesized	0.06	0.03	Competitive	Shie et al.[102]
31	Peptidomimetic	Derivative	0.20	NT	-	Kumar et al.[103]
			Inhibitors Targeting Papain-like Protease (PL^{pro})			
32	Hirsutenone	*Alnus japonica*	4.1	10	Noncompetitive	Park et al.[106]
26	Xanthoangelol E	*Angelica keiskei*	1.2	1.2	Noncompetitive	Park et al.[99]
33	Papyriflavonol A	*Broussonetia papyrifera*	3.7	5.9		Park et al.[107]
34	Isobavachalcone	*Psoralea corylifolia*	7.3	4.9	Mixed	Kim et al.[108]
35	Psoralidin		4.2	1.7		
36	Terrestrimine	*Tribulus terrestris*	15.8	10	Mixed	Song et al.[109]

[a]NM, not mentioned; NT, not tested. Competitive inhibition, an inhibitor molecule competes with a substrate by binding at the active site to the protease. Noncompetitive inhibition, an inhibitor binds at an allosteric site to the protease's active site but has an equal or higher affinity than that of the substrate to the protease. Mixed inhibition, an inhibitor molecule binds at an allosteric site to the protease but has a different affinity to substrate-bound protease or free protease.

Table 5. SARS-CoV Inhibitors Targeting Hel

	compd	source	ATPase (μM)	helicase (μM)	ref
37	Bananin	Derivative	2.3	3.0	Tanner et al.[112]
38	Vanillinbananin		0.68	2.7	
39	Iodobananin		0.54	7.0	
40	Eubananin		2.8	5.4	
41	EMMDPD	Synthesized	8.66	41.6	Cho et al.[110]
42	FSPA	Synthesized	2.09	13.2	Lee et al.[113]
43	Myricetin	ChromaDex	2.71		Yu et al.[114]
44	Scutellarein	*Scutellaria baicalensis*	0.86		

Table 6. Inhibitors with Other Targets against SARS-CoV[a]

	compd	reported mechanism of action	IC$_{50}$ (μM)	CC (μM)	SI	CoV type	ref
45	K11777	Targets cathepsin-mediated cell entry and the endosomal proteolysis.	3.2×10^{-4}	NT	NT	SARS-CoV	Zhou et al.[77]
46	SMDC256159		7.0×10^{-5}				
47	SMDC256160		8.0×10^{-5}				
48	Nitazoxanide	Induces the host innate immune response to produce IFNs.	2.12	>35.5	>16.7	SARS-CoV-2	Wang et al.[16]
49	Nafamostat	Inhibits S protein-mediated membrane fusion.	22.5	>100	>4.4		
50	Penciclovir	Inhibits RdRp.	95.9	>400	>4.2		

[a]NT, not tested.

Table 7. Replication Inhibitors with an Undefined Mechanism against CoVs[a]

	compd	source	IC$_{50}$ (μM)	CC (μM)	SI	CoV type	ref
51	Glycyrrhizin (GL)	*Glycyrrhiza glabra*	365	24,000	66	SARS-CoV	Cinatl et al.[118]
52	GL derivatives a		40	3,000	75		Hoever et al.[117]
53	GL derivatives b		35	1,462	41		
54	α-Hederin	Aescin derivative	10	NT	NT		Wu et al.[67]
55	Saikosaponin B2 (SSB$_2$)	*Bupleurum falcatum*	1.7	383	222	HCoV-229E	Cheng et al.[121]
56	Betulonic acid	*Juniperus formosana*	0.63	>100	>180	SARS-CoV	Wen et al.[86]
57	Ferruginol	*Chamaecyparis obtusa*	1.39	80.4	58		
58	8β-Hydroxyabieta-9(11),13-dien-12-one		1.47	>750	>510		
59	7β-Hydroxydeoxycryptojaponol	*Cryptomeria japonica*	1.15	127	111		
60	3β,12-Diacetoxyabieta-6,8,11,13-tetraene	*Juniperus formosana*	1.57	303	193		
61	Mycophenolic acid	*Penicillium* metabolite	1.95	3.55	1.8	HCoV-OC43	Shen et al.[1]
			0.18	3.44	19	HCoV-NL63	
62	Emetine	*Uragoga ipecacuanha*	0.30	2.69	9.0	HCoV-OC43	
			1.43	3.63	2.5	HCoV-NL63	
63	Mycophenolate mofetil	Derivative	1.58	3.43	2.2	HCoV-OC43	
			0.23	3.01	13	HCoV-NL63	
64	Phenazopyridine	Synthesized	1.9	>20	>10	HCoV-OC43	
			2.02	>20	>9.9	HCoV-NL63	
65	Monensin sodium	Derivative	3.81	>20	>5.3	HCoV-OC43	
			1.54	>20	>13	HCoV-NL63	
66	Pyrvinium pamoate	Synthesized	3.21	>20	>6.2	HCoV-OC43	
			3.35	>20	>6.0	HCoV-NL63	
67	Tetrandrine	*Stephania tetrandra*	0.29	14.5	50	HCoV-OC43	Kim et al.[122]
68	Fangchinoline		0.91	12.4	11		
69	Cepharanthine		0.72	10.5	13		
70	Reserpine	*Rauwolfia serpentina*	3.4	25	7.3	SARS-CoV	Wu et al.[67]
71	Aescin	NM	6.0	25	2.5		
72	Valinomycin	NM	0.85	68	80		

[a]NM, not mentioned; NT, not tested.

Figure 1. Compounds with *in vitro* and *in vivo* antiviral activity against CoVs, including SARS-CoV-2.

oxygen also did not support the use of HCQ in patients admitted to the hospital who required oxygen.[45] In addition, Mehra and colleagues recently conducted a multinational registry analysis of the use of HCQ or CQ with or without a macrolide for the treatment of COVID-19, in which 96 032 patients from 671 hospitals on six continents were included. The results showed that HCQ or CQ, used with or without a macrolide, was associated with decreased in-hospital survival, and increased frequency of ventricular arrhythmias.[48] Therefore, the FDA withdrew the emergency approval for HCQ as treatment of COVID-19 based on its ineffectiveness and serious side effects.

b. RDV. RDV (GS-5734, **2**) is a broad-spectrum antiviral nucleotide prodrug with potency against a wide array of RNA viruses, including SARS-CoV and MERS-CoV, in cultured cells and mouse models.[49] It is an adenosine analog that is incorporated into nascent viral RNA chains, leading to premature termination.[50] A recent study conducted by Wang et al. showed that the effective concentration for 90% inhibition (EC_{90}) and effective concentration for 50% inhibition (EC_{50}) values of RDV against SARS-CoV-2 in Vero E6 cells were 1.76 μM and 0.77 μM, respectively. The time-of-addition assay confirmed that RDV affects viral replication postviral entry, supporting its mode of action as a nucleotide analog.[16] Another *in vitro* study reported potent antiviral activity of RDV against HCoV-OC43 and HCoV-229E in Huh7 cells with submicromolar EC_{50} values of 0.15 and 0.024 μM, respectively.[51] Additionally, it potently inhibited SARS-CoV in human airway epithelial (HAE) cells with an IC_{50} of 0.06 μM and SI > 10.[52] Sheahan et al. reported that prophylactic or early therapeutic administration of RDV significantly reduced lung viral loads and improved clinical outcomes in a murine infection model.[53] Holshue and colleagues reported the first patient diagnosed with COVID-19 in Washington, USA, who was compassionately treated with intravenous RDV for the progression of pneumonia on day 7 of hospitalization (illness day 11). Encouragingly, the patient's clinical condition improved since the next day after RDV administration, and no adverse effects were observed.[54] Grein and collaborators reported that in a cohort of hospitalized severe COVID-19 patients who were treated with compassionate use of RDV, clinical improvement was observed in 36 of 53 patients (68%).[55] In another study, a total of 1063 hospitalized COVID-19 patients were included in a double-blind, randomized, placebo-controlled trial to test the efficacy of intravenous RDV against SARS-CoV-2. Preliminary results revealed that RDV therapy resulted in a median recovery time of 11 days compared with 15 days in those who received placebo. This study demonstrated that RDV treatment could shorten the recovery time in hospitalized COVID-19 adult patients with lower respiratory tract infection.[56] However, Wang and collaborators recently reported another study on hospitalized severe COVID-19 adult patients, in which RDV did not yield significant clinical benefits. In this study, 237 patients with severe COVID-19 in 10 hospitals in Wuhan, China, were enrolled and randomly assigned to two groups (158 in the RDV group and 79 in the placebo group) for a treatment course of 10 days. RDV did not significantly shorten time to clinical improvement.[57] Although RDV has been expected to be one of the "powerful weapons" for fighting the current COVID-19 pandemic, its clinical effectiveness remains to be further confirmed.

c. FPV. FPV (T-705, **3**), a guanine analog approved for influenza treatment in Japan in 2014, can effectively inhibit the RNA-dependent RNA polymerase (RdRp) of RNA viruses such as influenza, Ebola, yellow fever, chikungunya, norovirus and enterovirus.[58,59] FPV is converted into an active phosphoribosylated form (FPV-RTP) in cells that is recognized as a substrate by the viral RNA polymerase, thus inhibiting RNA polymerase activity.[60] A recent study conducted by Wang et al. showed that the EC_{50} of FPV against SARS-CoV-2 in Vero E6 cells was 61.88 μM; the CC_{50} value was >400 μM; and the SI was >6.46.[16] FPV was 100% protective against Ebola virus challenge in mice, although the EC_{50} in Vero E6 cells was as high as 67 μM.[61] Since late February 2020, two randomized clinical trials were commenced to evaluate the efficacy of FPV in treating COVID-19 patients in China. Cai et al. conducted an open-label controlled study to evaluate FPV's clinical efficacy for COVID-19. In this study, 35 patients received oral FPV plus IFN-α as an inhaled aerosol, and 45 patients received lopinavir/ritonavir plus IFN-α as an inhaled aerosol. A significantly shorter viral clearance time was observed in the FPV group than in the lopinavir/ritonavir group by day 7. The FPV group also showed significant improvement in chest imaging compared with the lopinavir/ritonavir group, with an improvement rate of 91.4% versus 62.2% at day 4 after treatment. The rate of adverse reactions in the FPV group (11.4%) was significantly smaller compared to the lopinavir/ritonavir group (55.6%).[62]

Chen et al. conducted a prospective, randomized, controlled, open-label multicenter trial involving adult patients with COVID-19. A total of 240 enrolled COVID-19 patients were randomly assigned to receive conventional therapy plus FPV or Arbidol (120 patients in each group), a broad-spectrum antiviral compound that blocks viral fusion,[63] for 10 days. The results showed that FPV led to significantly shorter latencies to relief of pyrexia by 1.70 days and cough by 1.75 days. However, no differences were observed in the rate of auxiliary oxygen therapy or noninvasive mechanical ventilation. The most frequently observed FPV-associated adverse event was elevation of serum uric acid.[64]

FPV currently appears to be relatively safe and effective against COVID-19. Since the two studies reviewed above used other antiviral drugs (lopinavir/ritonavir and Arbidol) as their controls, the exact effectiveness of FPV for COVID-19 remains to be further evaluated with randomized and controlled clinical studies.

3.1.2. Other Effective CoV Inhibitors. Another guanine derivative, ribavirin (**4**), approved for treating hepatitis C virus (HCV) and respiratory syncytial virus (RSV) infections clinically, has been evaluated in SARS and MERS patients, but side effects such as anemia can be severe at high doses,[65] and whether it offers sufficient potency against SARS-CoV-2 is uncertain. A fixed dose of the anti-HIV combination therapy, lopinavir/ritonavir, has been proposed for combating COVID-19 as it was effective in treating SARS in various studies.[15,36,66] Lopinavir (**5**) is an HIV-1 protease inhibitor reported to block the SARS-CoV 3CL^{pro}[67] and is usually combined with ritonavir (**6**) to increase the half-life of lopinavir by inhibiting cytochrome P450.[68] On January 18, 2020, a randomized, controlled, open-label trial involving 199 hospitalized severe COVID-19 patients was initiated to evaluate the efficacy of lopinavir/ritonavir treatment in hospitals in Wuhan, China. Disappointingly, no differences were observed between
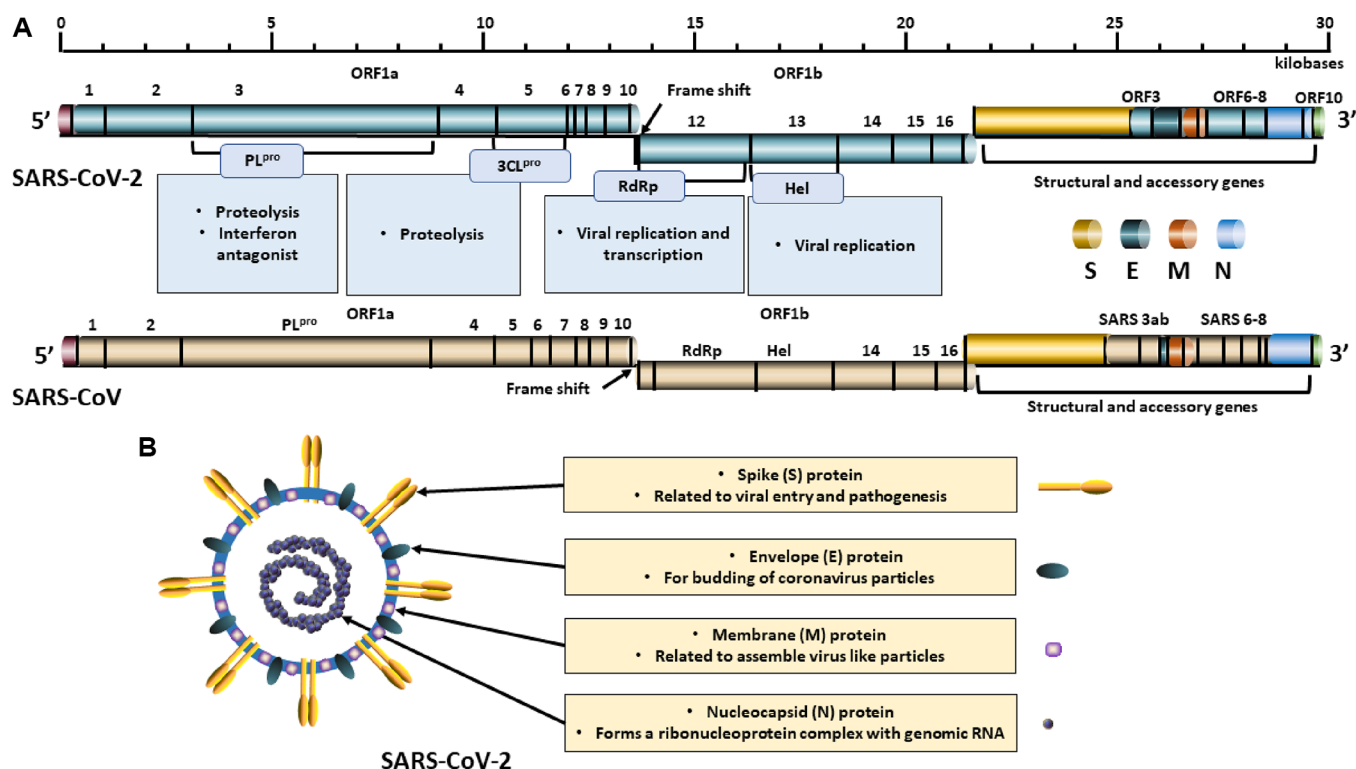
Figure 2. Genome structures of SARS-CoV-2 and SARS-CoV. A typical CoV has a single-stranded positive-sense genome (top panel). Next to the 5′ UTR, two-thirds of the genome consists of partially overlapping ORFs (ORF1a and ORF1b) encoding large NSPs (nsp1 to nsp16). During translation, the ORF1b protein is produced by a 1 bp ribosomal frameshift in the reading frame of ORF1a. The remaining one-third of the genome at the 3′ end encodes structural proteins such as the spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins. Other proteins, such as SARS-CoV-2 ORF3 (NC-045512) and SARS-CoV 3a (NC-004178.3), are shown. The key enzymes, namely, papain-like protease (PL[pro]), 3C-like serine protease (3CL[pro]), RNA-dependent RNA polymerase (RdRp), and helicase (Hel), are shown. The clinical applications of the key pathogenic nonstructural genes or gene products are shown in boxes. (Bottom panel) A schematic representation of the morphology of the SARS-CoV-2 virus. The virus is a large pleomorphic spherical particle with a lipid bilayer composed of the S, M, and E proteins surrounding the helical nucleocapsid-wrapped single-stranded RNA ribonucleoprotein genome.

lopinavir/ritonavir treatment and standard care in clinical improvement or mortality within 28 days.[69]

Alkaloids represent a class of phytocompounds with broad bioactivities, including antiviral activity.[70] Matrine (**7**), an alkaloid extracted from *Sophora flavescens,* shows a wide range of pharmacological effects, including antioxidant, anticancer, and anti-inflammatory effects.[71] Various studies showed that matrine exhibited antiviral activities against coxsackievirus B3 (CVB3) in Vero cells and influenza H3N2 virus in MDCK cells.[72] Recently, Jing et al. evaluated the therapeutic effect of matrine sodium chloride in a mouse pneumonia model infected with HCoV-229E. The results showed that intraperitoneal injection of matrine sodium chloride significantly decreased the pathological damage to the lung tissue and reduced the lung index. The percentage of CD4^{+} and CD8^{+} T cells, the number of B cells in peripheral blood, the production of IL-6, IL-10, TNF-α, IFN-γ, and the viral load in the lung were significantly inhibited compared to those in the controls. Therefore, matrine sodium chloride showed a therapeutic effect on HCoV-229E-infected mice via a mechanism related to the regulation of immune function.[73]

Another alkaloid, lycorine (**8**), isolated from *Amaryllidaceae* plants, has been reported to inhibit poliomyelitis virus, Bunyamwera virus, herpes simplex virus, dengue virus, West Nile virus, and SARS-CoV *in vitro*.[74,75] Lycorine exhibited significant inhibition of SARS-CoV in Vero cell-based cytopathic effect (CPE) inhibition assays, with an EC$_{50}$ of 0.0157 μM, CC$_{50}$ of 14.98 μM, and an SI of 954.[76] The anti-CoV activity of lycorine was recently confirmed by Shen and colleagues.[1] Furthermore, they found that lycorine protected BALB/c mice against lethal HCoV-OC43 infection by suppressing viral replication in the central nervous system. Twenty days after HCoV-OC43 infection, intraperitoneal injection of lycorine at 15 mg/kg provided 83.3% protection in infected mice, similar to the survival rate of the CQ-treated group.[1] These results suggest that lycorine could be a broad-spectrum antiviral agent against CoV infection and might offer promising therapeutic possibilities for combating SARS-CoV-2 infection.

Camostat (**9**) is a serine protease inhibitor used to treat chronic pancreatitis. Zhou et al. reported that camostat was effective in protecting mice from a lethal infection by SARS-CoV, with a survival rate of 60%.[77] Recently, Hoffman et al. indicated that SARS-CoV-2 utilizes the SARS-CoV receptor angiotensin-converting enzyme 2 (ACE2) and the cellular protease transmembrane protease serine 2 (TMPRSS2) to enter lung cells. Camostat was able to inhibit TMPRSS2, effectively inhibiting SARS-CoV-2 entry into mouse lung cells.[78] These findings suggest that camostat may be a valuable therapeutic against COVID-19.

3.2. Potential Plant-Derived Compounds against SARS-CoV-2. Natural products and TCMs are rich sources of antiviral compounds, including terpenoids, alkaloids, flavonoids, and polyphenols.[31,81,82] In the past two decades,
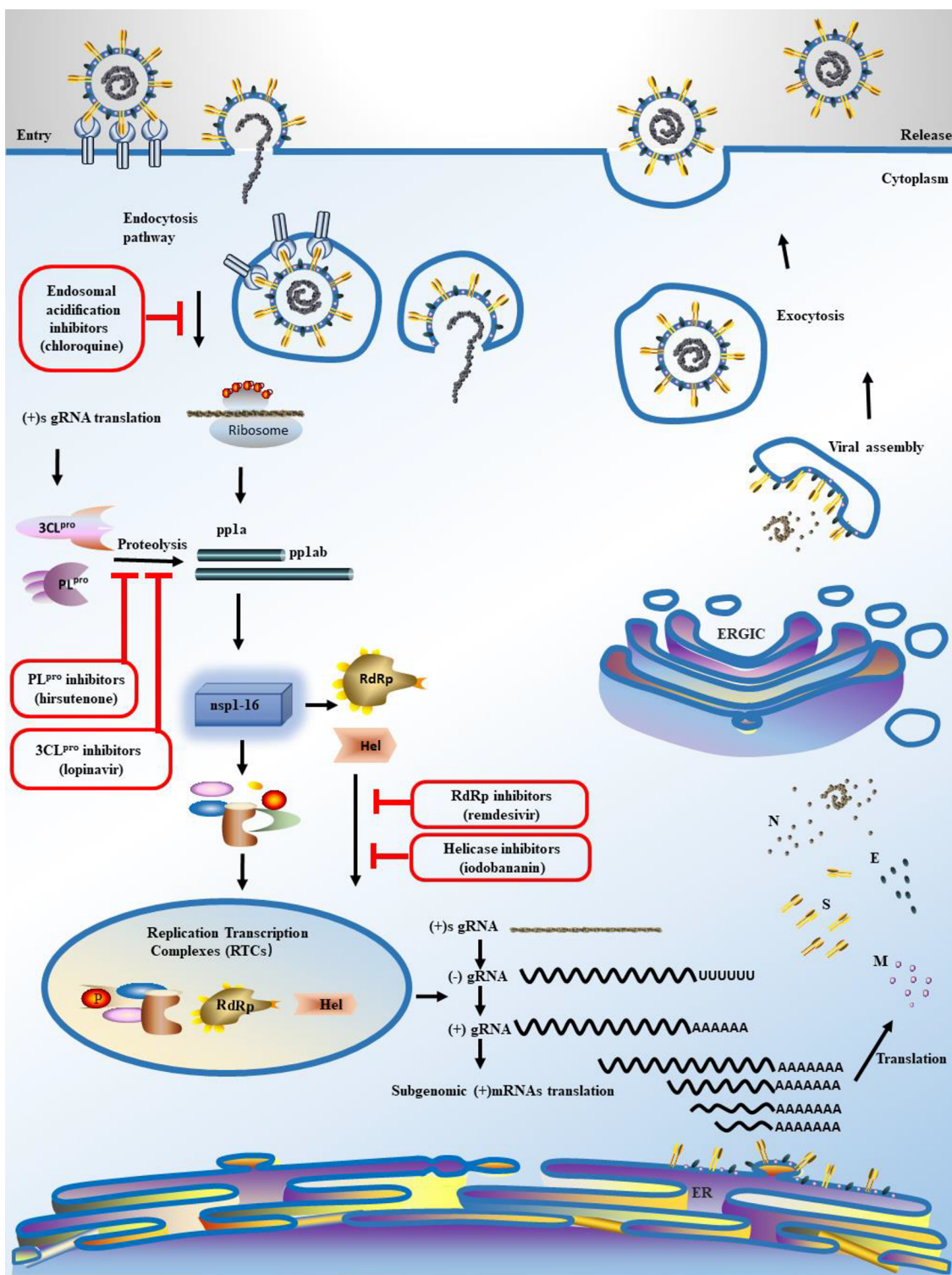
Figure 3. Candidate antiviral agents for SARS-CoV-2 in relation to the viral replication cycle. SARS-CoV-2 enters host cells either through an endosomal pathway or by virus−cell fusion mediated by spike (S) glycoprotein binding to the host cell receptor angiotensin-converting enzyme 2 (ACE2). Viral genomic RNA is unveiled in the cytoplasm, and the single-stranded positive-sense genome is transcribed to produce the viral proteases papain-like protease (PL^{pro}) and 3C-like serine protease (3CL^{pro}), which cleave the two large polyproteins (pp1a and pp1ab) into 16 mature nonstructural proteins (NSPs), including two replicase polyproteins (RNA-dependent RNA polymerase (RdRp) and helicase (Hel)). Mature NSPs and the RdRp and Hel proteins are gathered into replication−transcription complexes (RTCs) for viral replication and transcription. RTCs synthesize negative-strand guide RNA (gRNA) and a set of subgenomic RNAs for viral replication and transcription. The newly produced subgenomic RNAs are translated into viral structural proteins such as the S, membrane (M), and envelope (E) proteins. These proteins are inserted into the membrane of the rough endoplasmic reticulum (ER) and then transported to the ER-Golgi intermediate compartment (ERGIC) to assemble with the N protein-encapsidated RNA to form viral particles. Virions are then released from the cell through exocytosis.

due to ongoing efforts to develop antivirals against SARS-CoV and MERS-CoV infections, multiple small molecules derived from TCMs and natural plants were identified to have significant anti-CoV activity.[1,83] In the next sections, we summarize the natural inhibitors reported to suppress CoV replication. These inhibitors might be developed into effective antiviral treatments against SARS-CoV-2 and emerging novel CoVs.

SARS-CoV has a single-stranded RNA genome approximately 30 kb long containing 5′-methylated caps and 3′-polyadenylated tails. The partially overlapping 5′-terminal open reading frame 1a/b (ORF1a/ORF1b) within the 5′ two-thirds of the genome encodes the large replicase polyproteins 1a (pp1a) and pp1ab. The polyproteins are cleaved by two virus-encoded proteinases: PL[pro] and 3CL[pro] to produce 16 nonstructural proteins (NSPs), as shown in Figure 2. Among the 16 NSPs, RdRp and Hel are involved in the transcription and replication of the virus genome. The 3′ one-third of the CoV genome encodes structural proteins essential for virus binding to cell-surface receptors and virion assembly.[65,84,85] 3CL[pro], PL[pro], RdRp, and Hel/RNA nucleoside triphosphatase (NTPase) play pivotal roles in SARS-CoV replication and are therefore ideal drug targets.[86] Some small molecules from the terpenoid, lignoid, polyphenol, and flavonoid classes were identified as effective SARS-CoV inhibitors by targeting viral proteinases.[87,88]

In a recent study, it was demonstrated that SARS-CoV-2 and SARS-CoV share a remarkable 96% sequence identity in their 3CL[pro] and RdRp and 83% sequence identity in their PL[pro].[11,12] Therefore, existing SARS-CoV inhibitors may be effective against SARS-CoV-2.[89,90] Figure 3 represents the candidate antiviral agents for SARS-CoV-2.

3.2.1. SARS-CoV 3CL[pro] Inhibitors. SARS-CoV encodes a chymotrypsin-like protease (3CL[pro]), which is also called the main protease because it plays a pivotal role in processing viral polyproteins and controlling replicase complex activity.[91] Research on drugging SARS-CoV has focused on developing small molecules such as 3CL[pro] inhibitors. Here, we discuss various 3CL[pro] inhibitors from different classes, such as terpenoids, lignoids, phlorotannins, and flavonoids.

Twenty-two compounds were evaluated for activity against SARS-CoV 3CL[pro]. The terpenoid betulinic acid (**10**) and the lignanoid savinin (**11**) inhibited 3CL[pro] activity with IC$_{50}$ values of 10 and 25 μM, respectively.[86] Quinone-methide triterpenes (**12−15**) isolated from *Tripterygium regelii* exhibited potent inhibitory activities of 3CL[pro] with IC$_{50}$ values ranging from 2.6 to 10 μM.[92] Seven flavonoids from *Isatis indigotica* roots were evaluated for their anti-SARS-CoV 3CL[pro] activities. Among them, the flavonoid hesperetin (**16**, IC$_{50}$ = 8.3 μM) showed the highest inhibitory activity of 3CL[pro] in a dose-dependent manner.[93]

Marine algae are rich sources of structurally diverse bioactive compounds that have great potential as pharmaceutical and biomedical agents. Park et al. reported that nine phlorotannins isolated from the edible brown algae *Ecklonia cava* possessed SARS-CoV 3CL[pro] inhibitory activities in a dose-dependent and competitive manner. Among the nine compounds, dieckol (**17**), with a structure of two eckol groups linked to diphenyl ether, exhibited the most potent SARS-CoV 3CL[pro] inhibitory activity with an IC$_{50}$ value of 2.7 μM.[94]

Flavonoids are one class of the most abundant natural products with extensive physiological activities, including antioxidation, anti-inflammation, and antiviral effects.[95] Ryu
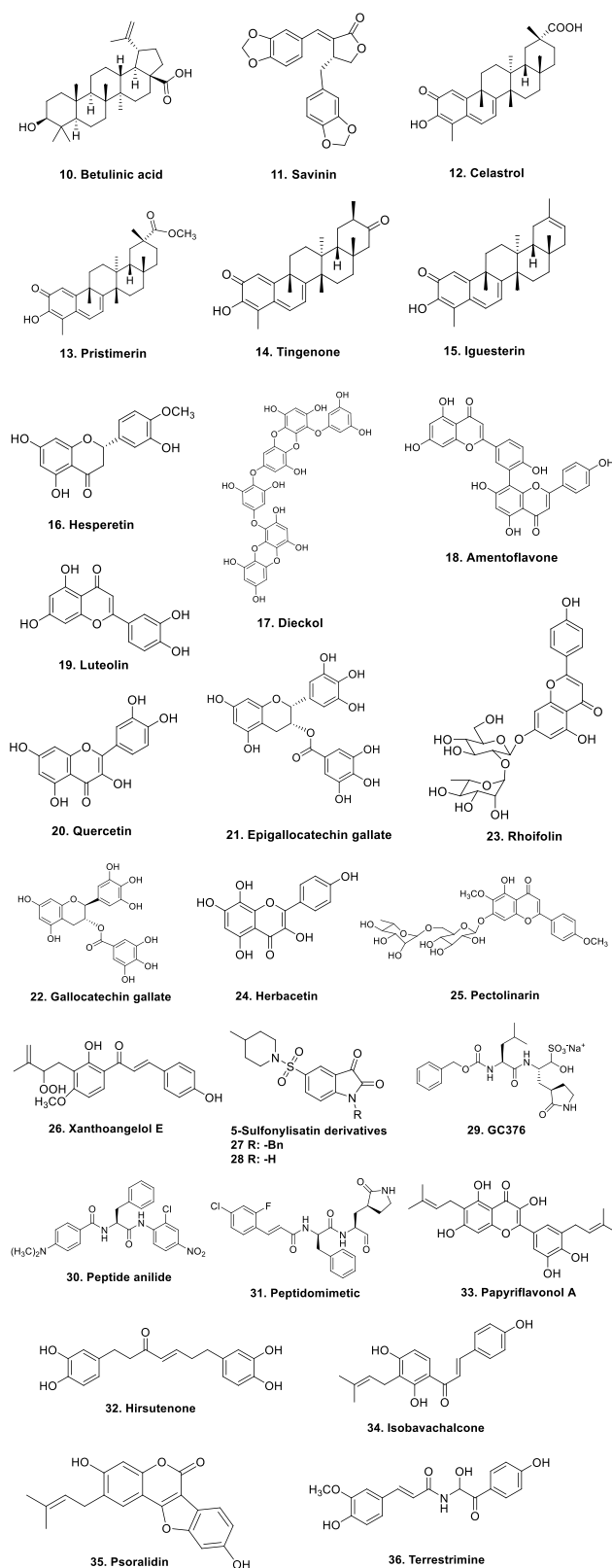

Figure 4. SARS-CoV inhibitors targeting 3CL protease (3CL[pro]) and papain-like protease (PL[pro]).

et al. found that biflavone amentoflavone (**18**) isolated from *Torreya nucifera* possessed stronger SARS-CoV 3CL[pro] inhibitory activity (IC$_{50}$ = 8.3 μM) than two authentic flavonoids, luteolin (**19**) and quercetin (**20**, IC$_{50}$ = 20.2 and
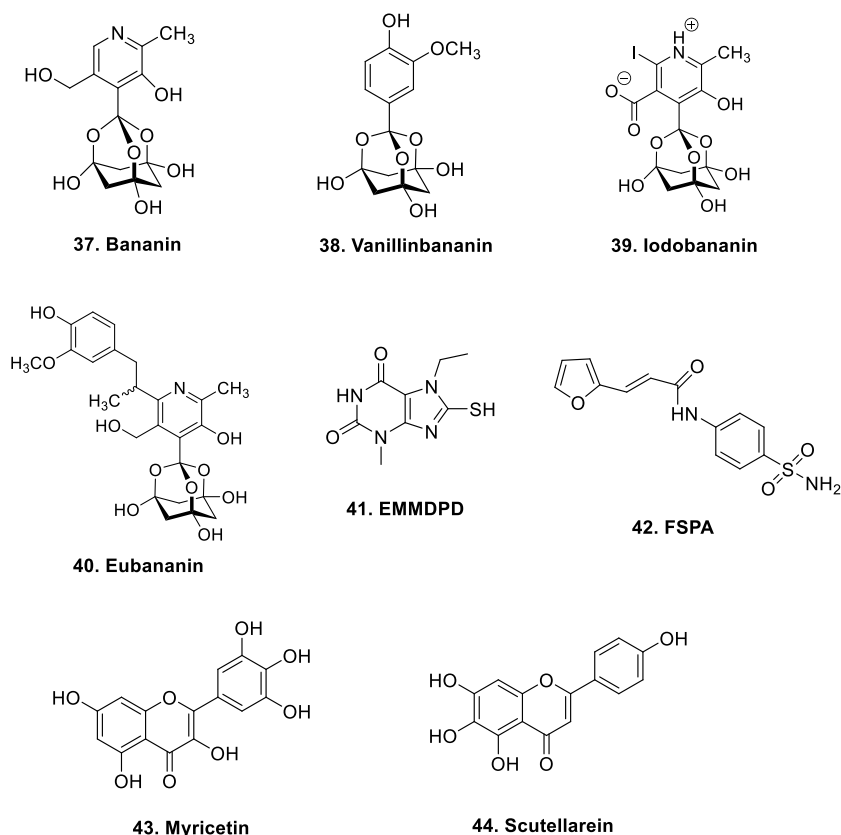
37. Bananin   **38. Vanillinbananin**   **39. Iodobananin**

40. Eubananin   **41. EMMDPD**   **42. FSPA**

43. Myricetin   **44. Scutellarein**

Figure 5. SARS-CoV inhibitors targeting Hel.

45. K11777   **46. SMDC256159**   **47. SMDC256160**
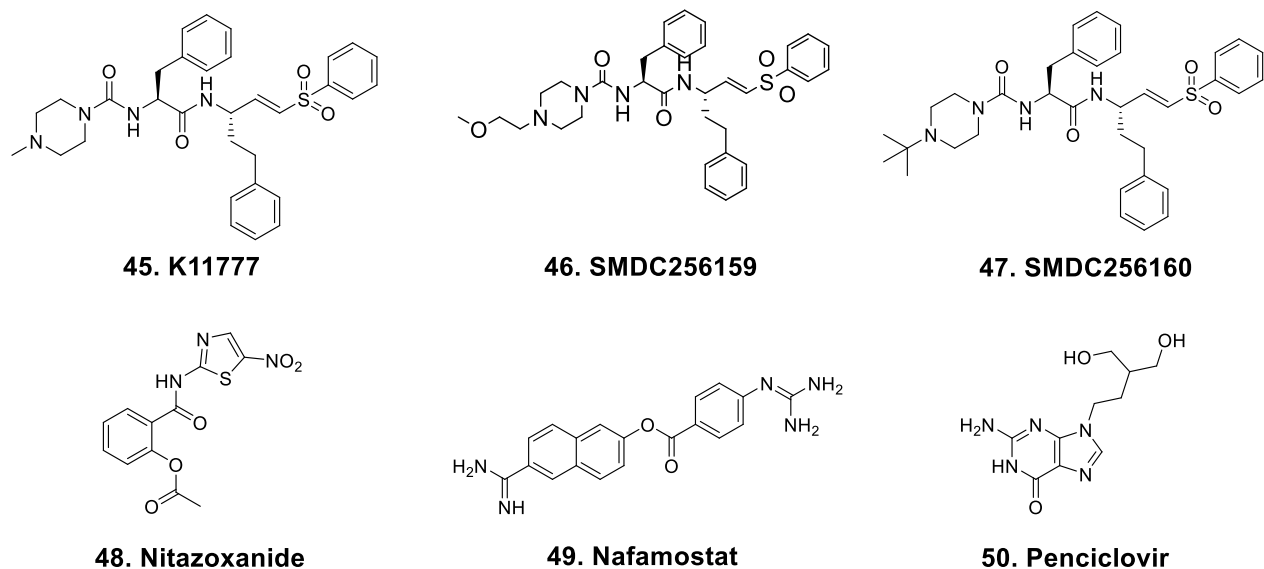
48. Nitazoxanide   **49. Nafamostat**   **50. Penciclovir**

Figure 6. Inhibitors with other targets against SARS-CoV.

23.8 μM, respectively). Structure−activity relationship analysis suggested that flavonoids against 3CL^{pro} appeared to be associated with an apigenin moiety at the C-3′ position.[96] In another study, quercetin (**20**), epigallocatechin gallate (**21**), and gallocatechin gallate (**22**) displayed significant inhibition of 3CL^{pro} with IC$_{50}$ values of 73, 73, and 47 μM, respectively. Gallocatechin gallate was found to be a competitive inhibitor of 3CL^{pro}.[97] Recently, by use of a flavonoid library, several

flavonoids with a wide range of inhibitory activities against 3CL^{pro} were detected. Rhoifolin (**23**), herbacetin (**24**), and pectolinarin (**25**) showed the highest inhibitory activity against SARS-CoV 3CL^{pro}. The enzyme kinetics assay and docking simulation results suggested that the active flavonoids have a wide range of binding affinities to SARS-CoV 3CL^{pro} due to their hydrophobic aromatic rings and hydrophilic hydroxyl groups. The presence of carbohydrate groups appeared to be
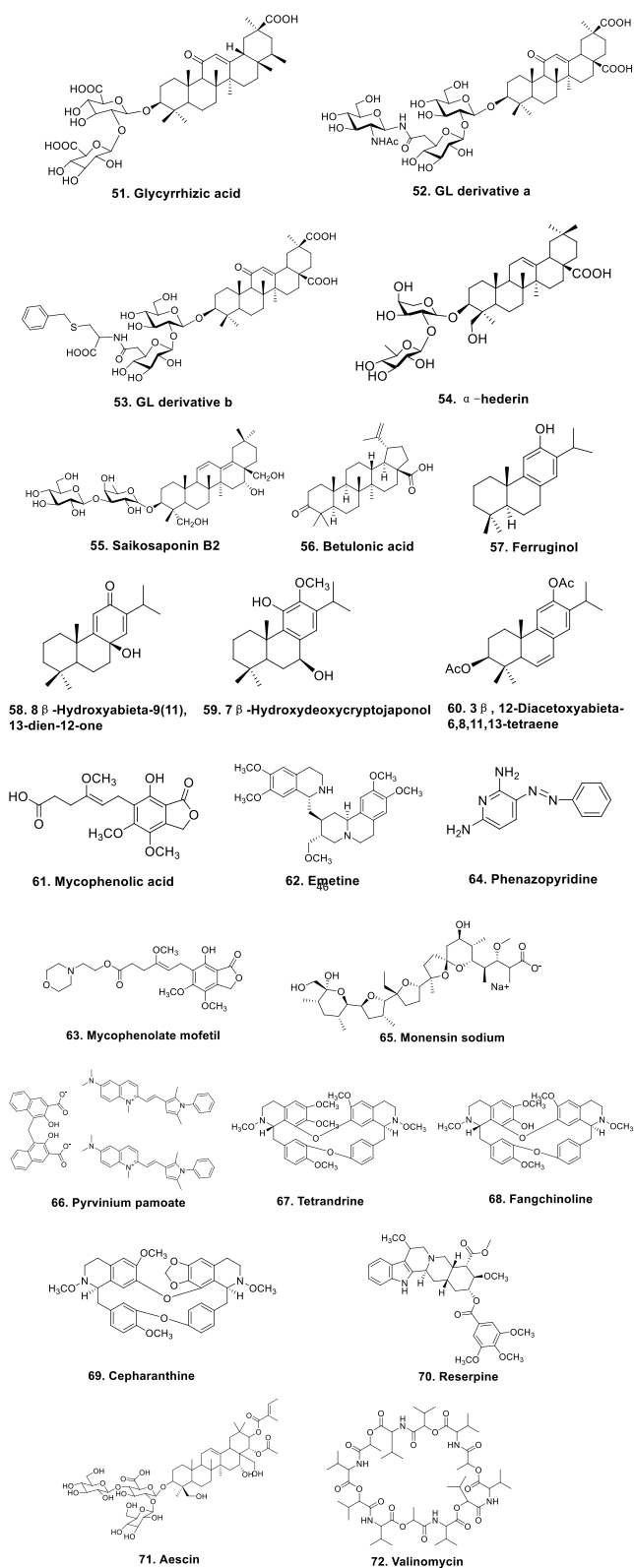
Figure 7. Replication inhibitors with an undefined mechanism against various CoVs.

important for the binding affinity of the chromen-4-one moiety.[98] Therefore, direct inhibition of the 3CL[pro] protein may be the mechanism of action of flavonoids.

Park et al. reported that nine alkylated chalcones isolated from *Angelica keiskei* exhibited different inhibitory activities

against SARS-CoV 3CL[pro] and PL[pro] based on a cell-free assay. Of the nine chalcones, xanthoangelol E (**26**), containing a perhydroxyl group, showed the most potent 3CL[pro] and PL[pro] inhibitory activity (IC$_{50}$ = 7.1 and 1.2 μM, respectively). Protein inhibitor analysis showed that chalcones exhibited competitive inhibition of SARS-CoV 3CL[pro], while noncompetitive inhibition was evident with SARS-CoV PL[pro].[99]

A series of isatin derivatives were designed as possible SARS-CoV 3CL[pro] inhibitors and evaluated by protease assay. Compounds **27** and **28** displayed significant inhibition of 3CL[pro] with IC$_{50}$ values of 1.04 and 1.18 μM, respectively.[100] Additionally, the peptidyl bisulfite adduct GC376 (**29**) was found to be a potent inhibitor with an IC$_{50}$ of 4.35 μM.[101]

For developing anti-SARS agents, Shie et al. prepared a diversified library of peptide anilides and evaluated their inhibition activities against SARS-CoV 3CL[pro]. Among the 32 tested compounds, the peptide anilide JMF1507 (**30**) showed the most potent inhibition, with an IC$_{50}$ value of 0.06 μM and a K_i value of 0.03 μM.[102] Another highly potent compound that is a peptidomimetic inhibitor (**31**) was reported to have a SARS-CoV 3CL[pro] inhibitory activity of 0.20 μM.[103]

3.2.2. SARS-CoV PL[pro] Inhibitors. Recent studies directed at PL[pro] suggested potential roles beyond viral peptide cleavage, including deISGylation, deubiquitination, and involvement in evasion of the innate immune response.[104,105] Compared to the existing SARS-CoV 3CL[pro] inhibitors, fewer natural compounds have been reported for PL[pro] inhibition. Since 2012, Park et al. have made ongoing efforts to develop CoV PL[pro] inhibitors. They isolated nine diarylheptanoids from *Alnus japonica* and found that hirsutenone (**32**) exhibited an IC$_{50}$ value of 4.1 μM with noncompetitive inhibition. Further structure−activity relationship analysis suggested that the α,β-unsaturated carbonyl groups linked to a catechol moiety in the structure of hirsutenone were the key requirement for PL[pro] inhibition.[106] In a later study, they found a polyphenol, papyriflavonol A (**33**), derived from *Broussonetia papyrifera*, with a promising inhibitory effect on PL[pro] (IC$_{50}$, 3.7 μM).[107] Kim et al. found that the ethanol extract of *Psoralea corylifolia* seeds showed strong activity against SARS-CoV PL[pro] (IC$_{50}$ = 15 μg/mL). Furthermore, they demonstrated that six flavonoids isolated from the ethanol extract displayed PL[pro] inhibition in a dose-dependent manner with IC$_{50}$ values ranging from 4.2 to 38.4 μM, in which the compounds isobavachalcone (**34**) and psoralidin (**35**) were the most promising, inhibiting PL[pro] with IC$_{50}$ values of 7.3 and 4.2 μM, respectively. Interestingly, the inhibition kinetics analysis by Lineweaver−Burk plots showed that isobavachalcone and psoralidin are mixed-type inhibitors, as the two compounds exhibited affinities for both the substrate-bound and free enzymes.[108] Similarly, the cinnamic amide terrestrimine (**36**), isolated from *Tribulus terrestris* fruits, was also found to be a mixed-type inhibitor with an IC$_{50}$ value of 15.8 μM.[109]

3.2.3. SARS-CoV Hel Inhibitors. The SARS-CoV NTPase/ Hel, another NSP (nsp13), is also an attractive target, as it is indispensable for viral replication.[110] Hel has been reported to possess the ability to translocate along with nucleic acids by hydrolyzing ATP.[111] Important progress has been made in the identification of novel CoV Hel inhibitors in natural compounds and their derivatives. Tanner et al. reported that four adamantane-derived bananins, including bananin (**37**), vanillinbananin (**38**), iodobananin (**39**), and eubananin (**40**), exhibited potent inhibition against both ATPase and Hel activity with IC$_{50}$ values in the ranges of 0.54−2.8 μM and

2.7−7.0 μM, respectively. In a cell culture system of SARS-CoV, bananin (**37**) showed significant antiviral activity with an EC_{50} of less than 10 μM and a CC_{50} of 390 μM.[112] Another compound, 7-ethyl-8-mercapto-3-methyl-3,7-dihydro-1*H*-purine-2,6-dione (EMMDPD, **41**), was identified as a SARS-CoV Hel inhibitor and was able to suppress ATP hydrolysis.[110] Similarly, (*E*)-3-(furan-2-yl)-*N*-(4-sulfamoylphenyl)acrylamide (FSPA, **42**) was also found to inhibit ATP hydrolysis and Hel activities and did not show significant cytotoxicity at 40 μM.[113] Two natural compounds, myricetin (**43**) and scutellarein (**44**), were reported as strong inhibitors of the ATPase activity of SARS-CoV Hel (IC_{50} = 2.71 and 0.86 μM, respectively).[114]

3.2.4. Inhibitors of Other Targets against SARS-CoV. Zhou et al. synthesized a series of vinyl sulfone analogs and evaluated their antiviral activity against SARS-CoV. Among all tested analogs, K11777 (**45**), SMDC256159 (**46**), and SMDC256160 (**47**) showed the most potent antiviral activities in 293T-ACE2 cells, with IC_{50} values of 3.2×10^{-4}, 7.0×10^{-5}, and 8.0×10^{-5} μM, respectively. Structurally, the potent antiviral activity of vinyl sulfones is associated with the presence of a basic piperazine ring at the P3 position, which is consistent with accumulation in endosomal (acidic) compartments where the target cysteine proteases required for viral entry are located.[77] Thus, vinyl sulfones are promising antiviral lead compounds for further optimization as potential CoV inhibitors.

Nitazoxanide (**48**) is a commercially available antiprotozoal agent with potential antiviral activity against a number of viruses, including animal and human CoVs. Wang et al. recently reported that nitazoxanide inhibited SARS-CoV-2 with an EC_{50} of 2.12 μM. Nafamostat (**49**), a highly efficacious inhibitor of MERS-CoV as it prevents membrane fusion, inhibited SARS-CoV-2 with an EC_{50} of 22.5 μM. However, the nucleoside analog penciclovir (**50**) was required for viral inhibition, yielding an EC_{50} of 95.96 μM. Further *in vivo* studies of the two drugs against SARS-CoV-2 infection are recommended.[16]

3.2.5. Inhibitors with Undefined Replication Inhibiting Mechanisms against CoVs. Terpenoids display a wide range of biological activities against various diseases, such as influenza, malaria, cancer, and inflammation.[115] One of the important bioactive compounds from licorice root (*Glycyrrhiza radix*) is the triterpene glycoside GL **51**.[116] It has been reported to have broad-spectrum antiviral activity[117] and is currently used to treat patients infected with HCV and upper respiratory tract infections.[117] Cinatl et al. examined the antiviral effects of GL on clinical isolates of SARS-CoV (strains FFM-1 and FFM-2) in Vero cells. GL was effective when given both during and after the virus adsorption period with an EC_{50} value of 365 μM and little cytotoxicity (CC_{50} = 24 000 μM).[118]

The antiviral activities of 15 GL derivatives against SARS-CoV replication in Vero cells were evaluated by Hoever and colleagues. Among the 15 derivatives tested, seven inhibited SARS-CoV replication at concentrations lower than GL. Addition of *N*-acetylglucosamine into the GL glycoside chain increased anti-SARS-CoV activity approximately 9 times compared to GL. Compound **52** inhibited SARS-CoV replication (EC_{50} = 40 μM with a CC_{50} of >3000 μM), resulting in an SI of >75. It is proposed that addition of the *N*-acetylglucosamine residue into the carbohydrate part of the GL molecule increases its hydrophilic properties, which might be important for the interaction of GL with viral proteins, especially the highly glycosylated S protein on the virus envelope. The S protein is important for viral entry into the cell by binding to cellular receptors.[119] It is speculated that viral entry was inhibited by *N*-acetylglucosamine binding to the carbohydrates of the S proteins.[117] In addition, the anti-SARS-CoV activity of several GL glycopeptides has been studied. For example, the glycopeptide containing L-Cys (SBn, **53**) exhibited the strongest activity with an EC_{50} of 35 μM and a CC_{50} of 1462 μM, which was 10-fold increased antiviral activity compared to GL (EC_{50}, 365 μM).[117] One derivative of aescin, α-hederin (**54**), showed strong anti-SARS-CoV activity at concentrations of <100 μM.[67] In addition, previous studies demonstrated that modification of GL may lead to novel anti-SARS-CoV drugs with increased activity.

SSs, including SSa, SSb, SSc, and SSd, are active triterpenoids isolated from *Bupleurum* species.[120] These compounds are effective against viruses such as HIV, influenza virus, and herpes simplex virus.[121] Cheng et al. evaluated the antiviral activity of four types of SSs against HCoV-229E in Vero cells and found that saikosaponin B_2 (SSB_2, **55**) exhibited the strongest anti-HCoV-229E activity with an IC_{50} value of 1.7 μM. Time-of-addition studies showed that SSb (**55**) interferes with viral replication early during the viral replication cycle, likely due to absorption and penetration of the virus.[121] In addition, triterpenoid betulonic acid (**56**) was found to be a potent inhibitor for SARS-CoV replication with an EC_{50} value of 0.63 μM and CC_{50} of >100 μM in an *in vitro* study reported by Wen and colleagues. Meanwhile, they found that diterpenoids (**57**−**60**) were also potent SARS-CoV inhibitors with EC_{50} values ranging from 1.15 to 1.57 μM. These findings provide a new direction for the development of anti-SARS-CoV agents.[86]

Shen et al. screened a 2000-compound library of approved drugs and pharmacologically active compounds and identified seven compounds (lycorine (**8**), mycophenolic acid (**61**), emetine (**62**), mycophenolate mofetil (**63**), phenazopyridine (**64**), monensin sodium (**65**), and pyrvinium pamoate (**66**)) as broad-spectrum inhibitors for four CoVs (HCoV-OC43, HCoV-NL63, MERS-CoV, and MHV-A59) with EC_{50} values ranging from 0.12 to 4.12 μM *in vitro*.[1] In addition, three bisbenzylisoquinoline alkaloids, including tetrandrine (**67**), fangchinoline (**68**), and cepharanthine (**69**) isolated from *Stephania tetrandra*, have shown anti-HCoV-OC43 activity in MRC-5 human lung cell cultures. The IC_{50} values of tetrandrine, fangchinoline, and cepharanthine were 0.29, 0.91, and 0.72 μM, respectively, indicating that compound **67** was more effective against HCoV-OC43 than the other two alkaloids. Tetrandrine appeared to inhibit viral replication during the early infection stage, likely related to interaction with the viral S and N proteins.[122]

A SARS-CoV and Vero E6 cell-based assay was developed to screen existing drugs to identify effective anti-SARS agents. The potent inhibitors found were reserpine (**70**), a well-known antihypertensive drug derived from several members of the genus *Rauwolfia*, andaescin (**71**), a cerebrovascular drug widely used in Europe, and valinomycin (**72**), a peptide insecticide targeting potassium ion transporter. The IC_{50}, based on ELISA, and SI for reserpine, aescin, and valinomycin were 3.4 μM (SI = 7.3), 6.0 μM (SI = 2.5), and 0.85 μM (SI = 80), respectively, against SARS-CoV.[67]

In Table 7, compounds **54**−**72** showed significant antiviral activity against CoV replication *in vitro* with $IC_{50} \leq 10$ μM. Although GL and its derivatives (**51**−**53**) exhibited less inhibitory activity with IC_{50} values ranging from 35 to 365 μM,

their cytotoxicity was much lower with CC_{50} values ranging from 1462 to 24 000 μM. The detailed mechanism(s) of action of these compounds needs to be investigated further to better target SARS-CoV-2.

4. OUTLOOK AND FUTURE PERSPECTIVES

The present pandemic caused by SARS-CoV-2 is spreading globally and has posed major challenges to public health due to a lack of a specific vaccine and antiviral drugs. Complementary and alternative treatments are urgently needed for the management of COVID-19 patients. In China, TCM has been used for thousands of years in the treatment of pandemic and endemic diseases. Since the outbreak of COVID-19 in early January 2020, integrated treatments of TCMs with conventional medicines have been extensively used to treat COVID-19 patients in China and have achieved positive effects. However, the major challenges in the use of TCM are inconsistencies in the origins of the herbs used and incomplete understandings of the active compounds in these preparations and their mechanisms of action.

While randomized, double-blind and placebo-controlled studies are the most effective methods to assess therapeutic efficacy; most studies evaluating the efficacy of TCMs in the treatment of SARS-CoV infections were found to be poorly designed. Hopefully, current and future clinical studies to evaluate the efficacy of TCMs in the treatment of COVID-19 will be conducted using stricter protocols and allocation concealment. Furthermore, standardized manufacturing, quality control and monitoring should be established to ensure consistency. Although the identification of all components in a TCM formula is almost impossible, the identification of harmful components and the main active components is indispensable for understanding the underlying mechanism of TCMs and avoiding potentially harmful TCMs in the treatment of COVID-19. Some TCM herbs are reported to contain mutagens and nephrotoxins,[123] while the toxicology of most TCM herbs remains to be fully understood.[124] In addition, some components in TCMs might interact with Western medicines and lead to additive, synergistic, or antagonistic effects.[125] Thus, the safety of TCMs used against COVID-19 should be carefully evaluated.

Since the COVID-19 outbreak in early January 2020, global ongoing efforts to identify effective drugs against COVID-19 have been undertaken, including clinical trials to evaluate the effectiveness of some commercially available drugs. CQ and its analog HCQ have received the highest attention; however, the FDA has withdrawn the emergency approval for HCQ as a treatment of COVID-19 based on its ineffectiveness and serious side effects. RDV and FPV might be relatively effective drugs for COVID-19 at present, but the exact effectiveness of the two drugs remains to be further evaluated with randomized and controlled clinical studies. Therefore, effective therapeutics against COVID-19 are still urgently needed. Various stages of the SARS-CoV-2 viral life cycle could be targeted by small molecule antiviral inhibitors. Four viral NSPs, including protease 3CL^pro, PL^pro, RdRp, and Hel play pivotal roles in SARS-CoV replication and are therefore ideal targets. The drug-repurposing effort summarized in this report focuses primarily on small-molecule inhibitors known to be effective against CoVs, including SARS-CoV and MERS-CoV, with a wide variety of chemical structure categories. However, among the 72 identified small-molecule inhibitors summarized in Tables 3–7, only a few potential inhibitors have progressed

beyond the identification of having an effect *in vivo*, and most of the agents with *in vitro* anti-CoV activity remain to be evaluated for their *in vivo* antiviral activity.

Suitable animal models are critical for testing anti-CoV drugs. Some non-human primates were found permissive to SARS-CoV, but none consistently reproduced severe human disease.[126] Small animals, including mice strains such as BALB/c, knockout mice with immune deficiencies, ferrets, and golden Syrian hamsters can be productively infected with SARS-CoV, but few develop clinical symptoms.[126] Recently, Sun et al. successfully developed a mouse model expressing human ACE2 via inoculation with a replication-deficient adenovirus (Ad5-hACE2). These mice showed weight loss, severe pulmonary pathology, and high viral load in the lungs post-SARS-CoV-2 infection but no mortality.[127] Therefore, the limited availability of animal models remains an obstacle[65]

Due to the acute nature of COVID-19 and the importance of immunopathology, combination therapies aimed at the virus and host are likely to yield the best clinical outcomes. Fatal SARS-CoV-2 cases are closely related to cytokine storms in patient lungs, similar to SARS-CoV and highly pathogenic IAV infections.[128,129] Thus, the application of anti-inflammatory drugs for COVID-19 patients, especially for severe cases, is almost equally as important as antivirals. In fact, glucocorticoids such as methylprednisolone have been approved to treat some severe COVID-19 patients in combination with antiviral agents in China. Recently, researchers at the University of Oxford found that a low-to-moderate dose (6 mg/day for 10 days) of dexamethasone reduced deaths in hospitalized COVID-19 patients who were on ventilators by one-third or receiving oxygen support by one-fifth, but the steroid did not benefit hospitalized COVID-19 patients who did not require respiratory support.[130] However, the use of glucocorticoids might cause side effects for patients, including immunosuppression, delayed virus clearance time, and osteoporosis.[20] In this regard, nonsteroidal anti-inflammatory drugs (NSAIDs) that are not associated with these side effects might be a preferred option for treating COVID-19 patients in combination with antiviral agents. Further studies are urgently needed to identify potent anti-inflammatory drugs for COVID-19 patients from a large number of NSAIDs. In addition, treatment (especially antiviral therapy) should be started as early as possible to prevent extensive lung damage.

The COVID-19 pandemic represents the greatest challenge to global public health in the past century. However, the speed and number of basic and clinical studies aimed at identifying and developing potential vaccines and drugs bring hope that effective countermeasures against SARS-CoV-2 will be made available in the coming months.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jmedchem.0c00626.

Tables of TCM prescriptions and therapeutic regimens and Latin names of herbs for treatment (PDF)

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■ ABBREVIATIONS USED

3CL^{pro}, 3C-like serine protease; ACE2, angiotensin-converting enzyme 2; BALB/c, albino, laboratory-bred strain of the house mouse; CC$_{50}$, 50% cytotoxic concentration; CoV, coronavirus; COVID-19, coronavirus disease 2019; CPE, cytopathogenic effect; CVB3, coxsackievirus B3; GL, glycyrrhizic acid (glycyrrhizin); HAE, human airway epithelial; HCoV-229E, human coronavirus 229E; GFP, green fluorescent protein; HCoV-HKU1, human coronavirus HKU1; HCoV-NL63, human coronavirus NL63; HCoV-OC43, human coronavirus OC43; HSBDT, Huashi Baidu Tang; IC$_{50}$, the half maximal inhibitory concentration; IFN-β, interferon β; JHQGG, Jinhua Qinggan granule; LHWQC, Lianhua Qingwen capsule; MERS-CoV, Middle East respiratory syndrome coronavirus; NHC, National Health Commission; NSP, nonstructural protein; NTPase/Hel, RNA nucleoside triphosphatasehelicase; PL^{pro}, papain-like cysteine protease; QFPDT, Qingfei Paidu Tang; RdRp, RNA-dependent RNA polymerase; NTPase, RNA nucleoside triphosphatase; SARS-CoV, severe acute respiratory syndrome coronavirus; SI, selective index; TCM, traditional Chinese medicine; TMPRSS2, transmembrane protease, serine 2; XFBDT, Xuanfei Baidu Tang.

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