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

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Review

A review of therapeutic agents and Chinese herbal medicines against SARS-COV-2 (COVID-19)

Fangfang Huang[a], Ying Li[b], Elaine Lai-Han Leung[c], Xiaohua Liu[a], Kaifeng Liu[d], Qu Wang[d], Yongqi Lan[d], Xiaoling Li[e], Haibing Yu[f], Liao Cui[g], Hui Luo[h], Lianxiang Luo[h,*]

[a] Graduate School of Guangdong Medical University, Zhanjiang, 524023, China
[b] University of Texas Health Science Center at San Antonio, San Antonio, TX 78229, United States
[c] State Key Laboratory of Quality Research in Chinese Medicine, Macau University of Science and Technology, Macau, SAR, China
[d] The First Clinical College of Guangdong Medical University, Zhanjiang, 524023, China
[e] Animal Experiment Center of Guangdong Medical University, Zhanjiang, 524023, China
[f] Department of Epidemiology and Health Statistics, Public Health School of Guangdong Medical University, Dongguan, Guangdong, China
[g] Guangdong Key Laboratory for Research and Development of Natural Drugs, Guangdong Medical University, Zhanjiang, Guangdong, 524023, China
[h] The Marine Biomedical Research Institute, Guangdong Medical University, Zhanjiang, 524023, China

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ABSTRACT

The epidemic of pneumonia (COVID-19) caused by novel coronavirus (SARS-CoV-2) infection has been listed as a public health emergency of international concern by the World Health Organization (WHO), and its harm degree is defined as a global "pandemic". At present, the efforts of various countries focus on the rapid diagnosis and isolation of patients, as well as to find a treatment that can combat the most serious impact of the disease. The number of reported COVID-19 virus infections is still increasing. Unfortunately, no drugs or vaccines have been approved for the treatment of human coronaviruses, but there is an urgent need for in-depth research on emerging human infectious coronaviruses. Clarification transmission routes and pathogenic mechanisms, and identification of potential drug treatment targets will promote the development of effective prevention and treatment measures. In the absence of confirmed effective treatments, due to public health emergencies, it is essential to study the possible effects of existing approved antivirals drugs or Chinese herbal medicines for SARS-CoV-2. This review summarizes the epidemiological characteristics, pathogenesis, virus structure and targeting strategies of COVID-19. Meanwhile, this review also focus on the re-purposing of clinically approved drugs and Chinese herbal medicines that may be used to treat COVID-19 and provide new ideas for the discovery of small molecular compounds with potential therapeutic effects on novel COVID-19.

In late December 2019, an outbreak of pneumonia of unknown cause began in Wuhan, Hubei Province, China, spreading rapidly around the world [1]. Chinese researchers discovered a previously unknown betacoronavirus through the use of unbiased sequencing in samples from patients with pneumonia [2]. This coronavirus, named SARS-CoV-2, causes a disease called COVID-19 that can be transmitted from person to person [3,4]. COVID-19 may rapidly develop into acute respiratory distress syndrome (ARDS) and in some cases, lead to multiple organ dysfunction or death. In view of alarming levels of spread and severity, COVID-19 was declared a public health emergency of international concern on January 30, 2020 and situated as a pandemic on March 11, 2020 by WHO [5,6]. As of May 3, 2020, there have been more than 3.3 million reported cases and 230,000 deaths in more than 200 countries. Unfortunately, no drugs or vaccines have been approved for combating the virus [7]. Considering the growing threat of COVID-19 pandemic, it is essential to study the efficacy of existing antiviral drugs as well as Chinese herbal medicines against SARS-CoV-2. In this review, we summarized the epidemiological characteristics, pathogenesis, virus structure and targeting strategies of COVID-19, with emphasis on the re-purposing of clinically approved drugs and Chinese herbal medicines that may be used to treat COVID-19 and provide new ideas for the discovery of small molecular compounds with potential therapeutic effects on COVID-19.

1. Genome structure and pathogenesis of SARS-CoV-2

SARS-CoV-2 is a spherical, enveloped, single-stranded positive RNA virus with a diameter of 80 nm–160 nm and a genome size of 29.9 kb

* Corresponding author.
E-mail address: luolianxiang321@163.com (L. Luo).

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[8]. SARS-CoV-2 falls within the subgenus *Sarbecovirus* of the genus Betacoronavirus that shares about 79.6 % identity with genome of SARS-CoV [9,10]. The architecture of virions is composed of nucleic acid and nucleocapsid protein to form the helical nucleocapsid. Lipid envelope which is studded with structural protein including the membrane (M) glycoprotein, the envelope (E) protein, and the spike (S) glycoprotein [11].

Virus infection is initiated by the interaction between S protein and host cell surface receptors. The S protein would be cleaved by the cellular serine proteases TMPRSS2 into S1 and S2 subunits, which are responsible for receptor recognition and membrane fusion [12,13]. The C-terminal domain (CTD) of S1 specifically binds to host cell receptors angiotensin-converting enzyme 2 (ACE2) or CD147, which causes the conformational change of S2. Then two heptad repeats join in S2 forming an anti-parallel six-helix bundle that allows for the mixing of viral and cellular membranes, resulting in release of the viral genome into the cytoplasm subsequently [14,15]. After release, the viral genomic RNA begins to express. The replicase gene encodes two large ORFS, rep1a and rep1b, which express two co-terminal polyproteins, pp1a and pp1ab. They produce 16 unstructured proteins which assemble into the replicase–transcriptase complex (RTC). RTC creates an environment suitable for RNA synthesis and is ultimately responsible for RNA replication and transcription of the sub genome RNAs. After replication and sub genome RNA synthesis, the S, E and M viral structural proteins are translated and inserted into the endoplasmic reticulum (ER), subsequently moved into endoplasmic reticulum-Golgi intermediate compartment (ERGIC) [16]. There, N protein encapsulates viral genome buds into a membrane containing ERGIC to form mature viruses, which are transported to the cell surface in vesicles and released by exocytosis [17].

After SARS-CoV-2 infection, pathogenic T cells are rapidly activated to produce granulocyte macrophage colony stimulating factors, such as GM-CSF and IL-6 [18]. GM-CSF will further activate CD14+/CD16+ inflammatory monocytes to produce a large amount of IL-6 and other inflammatory factors by a positive feedback effect [19,20]. In addition, high levels of neutrophil extracellular traps may also contribute to cytokine release [21]. Ultimately, uncontrolled inflammatory responses may lead to shock and tissue damage in the heart, liver and kidney, as well as respiratory failure or multiple organ failure, causing death in patients with severe COVID-19 [22,23] (Fig. 1).

2. Key targets and their roles in SARS-CoV-2 infection

Therapeutics with high specificity and efficacy is the ultimate goal of pathogenesis study, while target discovery is the foundation. Based on previous studies, spike protein, ACE2, TMPRSS2, 3CLpro, RdRp and PLpro are considered as major targets for antiviral drugs against SARS and other coronavirus infections [24]. Sharing high conservation of the catalytic site and homology with SARS-CoV [9,25], the above six proteins may be potential targets for the treatment of COVID-19. From the view of virus and cell fusion, Arbidol, a broad-spectrum antiviral drug, as a virus-host cell fusion inhibitor, can prevent virus from entering host cells to treat COVID-19 [26]. It has also been shown that SARS-CoV-2 depends on Spike proteins on the surface to entry into host cells by binding to Angiotensin-converting enzyme 2 (ACE2) receptors on the host cell surface [12]. ACE2 is the host cell surface receptor, which is the key to the initial stage of SARS-CoV-2 invasion into the host. Therefore, excess soluble forms of ACE2 or ACE2 inhibitors could be a possible methodology to treat COVID 19. In addition, Transmembrane Protease Serine 2 (TMPRSS2) can activate Spike protein and promote SARS-CoV-2 infection of host cells, which plays an important role in the process of SARS-CoV-2 infection of host cells [12]. The existing TMPRSS2 inhibitor Carmustat mesylate, bromhexine hydrochloride may also be an effective treatment for COVID-19 [12,27]. From the view of virus proteases, 3C-like protease (3CLpro) and Papain-like protease (PLpro) are two viral proteases responsible for cleaving viral peptides into functional units for virus replication and packaging in host cells. It has been shown that SARS-CoV-2 3CLpro inhibitors, baicalin and baicalein exhibit strong antiviral activity in cell-based systems [28]; 6-Mercaptopurine (6 M P) and 6-thioguanine (6 TG) are specific inhibitors of SARS-CoV and MERS-CoV papain, deubiquitinated and isg-depleted cysteine proteases [29,30], they may be reasonable candidates. From view of virus replication, Nsp12, an RNA-dependent RNA polymerase (RdRp), is an important enzyme of the coronavirus replication/transcription complex [31]. Currently, inhibitors targeting RdRp are mainly ribavirin, remdesivir, etc., and these drugs mainly compete with physiological nucleotides for the RdRp active site [32].

3. Therapeutic agents for treatment of COVID-19

Detailed insights into viral structure, pathogenesis and host immune responses described above can boost the identification of COVID-19 therapeutics including novel drugs, new application of United States Food and Drug Administration (FDA) approved drugs, even new drug target discovery. Several small molecule drugs are being tested for their efficacy on COVID-19, some of which have reached clinical trials, while others are still in preclinical phase [33]. We grouped potential drugs into structure, mechanism and evidence based on their reported effects in similar viruses, so their impact on SARS-CoV-2 infection could be prioritized to be evaluated. In this chapter, we will specially focus on the research progress of Chloroquine, Hydroxychloroquine, Remdesivi and Lopinavir/Ritonavir.

3.1. Chloroquine and hydroxychloroquine

Chloroquine and Hydroxychloroquine (CQ/HCQ) have a long-standing history as a broad-spectrum antiviral drug in the prevention and treatment of malaria [34]. CQ/HCQ block viral from entering into cells by inhibiting glycosylation of host receptors, proteolytic processing, and endosomal acidification, as well as regulate immunity through attenuation of cytokine production, inhibition of autophagy and lysosomal activity in host cells [35,36]. CQ can inhibit SARS-CoV-2 infection at a low-micro molar concentration and HCQ is more potent than CQ [37,38]. A multicenter clinical trial involving more than a dozen hospitals in China showed that CQ can improve radiologic findings, enhance viral clearance and reduce disease progression in the treatment of patients with COVID-19, so China has included CQ in the recommendations regarding the prevention and treatment of COVID-19 [37,39,40]. At the same time, another clinical trial showed that HCQ can significantly shorten the clinical recovery time and promote the absorption of pneumonia among patients with COVID-19 [41]. Notably, azithromycin reinforced the effect of CQ/HCQ in COVID-19 patients, but the publishing journal's society subsequently declared that the trial did "not meet the Society's expected Standard" [42,43]. Conversely, the higher CQ dosage should not be recommended for critically ill patients with COVID-19 because of its potential safety hazards, especially when taken concurrently with azithromycin and oseltamivir [44,45]. In summary, although CQ/HCQ have shown anti-SARS-CoV-2 efficacy both *in vivo* and *in vitro* trials as well as relatively well tolerated, some clinical trial designs and outcome data have not been submitted or published to peer review [46]. It is not recommended in the use of CQ/HCQ for COVID-19 outside of the hospital or a clinical trial due to lack of reliable efficacy data and potential toxic effects [47,48].

3.2. Remdesivir

Remdesivir (GS-5734), a prodrug of GS-441524 developed by the American pharmaceutical company Gilead Sciences, showed promise at the peak of the Ebola virus outbreak due to its low EC_{50} and host polymerase selectivity against the Ebola virus [49,50]. Subsequently, research about it also showed significant anti-SARS-CoV and MERS-CoV activity [51,52]. As a nucleoside analog with exonuclease resistance,

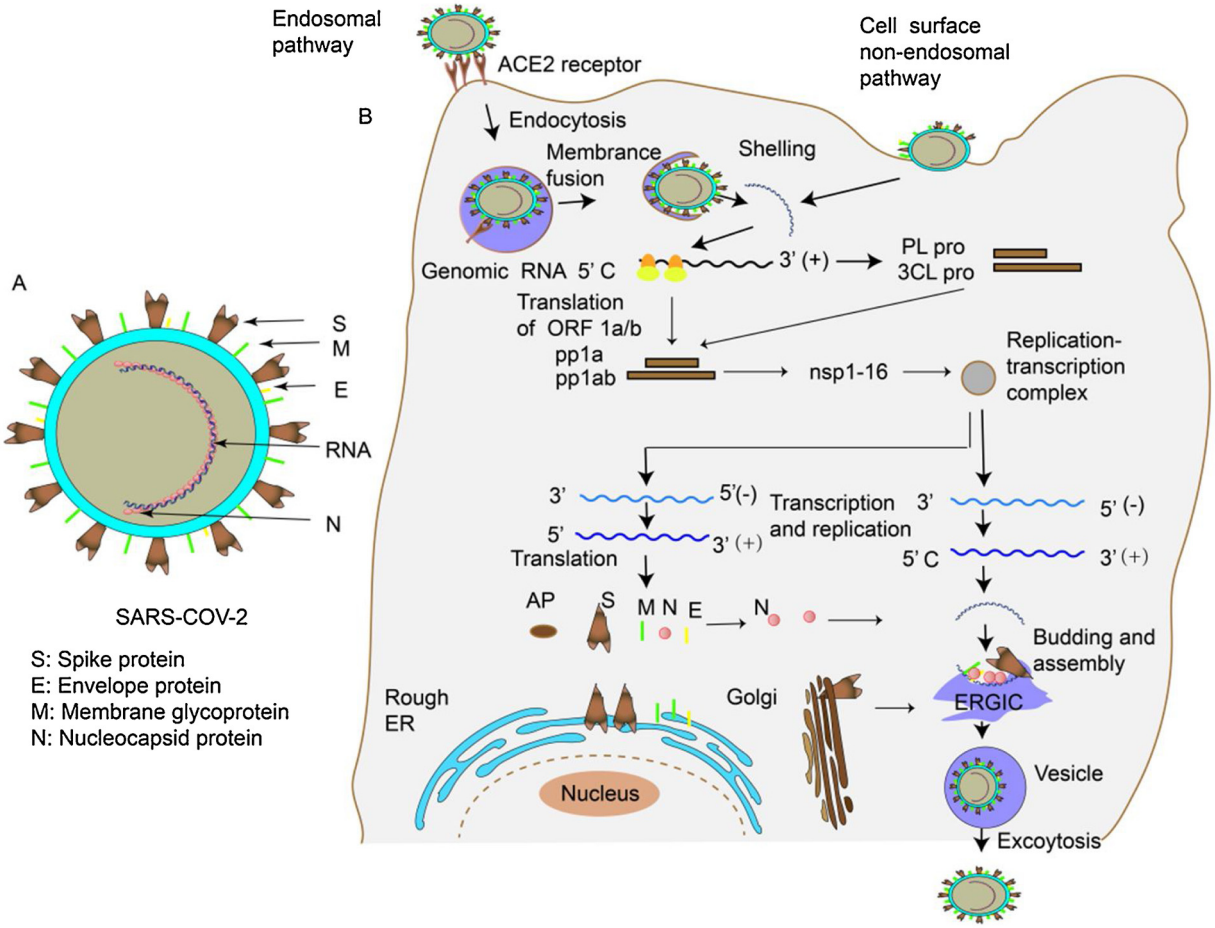


Fig. 1. Life cycle of SARS-CoV-2 in host cells. (A) Structure of SARS-CoV-2. (B) Mechanism of SARS-CoV-2 infection.

remdesivir is metabolized to active nucleoside triphosphates that effectively prevents the elongation of the RNA chain by inhibiting RNA polymerase, but will not be digested with a viral exonuclease (nsp14) with proofreading activity [53]. Compared with ribavirin, penciclovir, nitazoxanide, nafamostat, chloroquine and favipiravir (T-705), remdesivir has the best efficacy and the lowest toxic side effects on anti-SARS-CoV-2 in Vero E6 cells [32]. The United States first reported the clinical case of remdesivir in the treatment of SARS-CoV-2 associated pneumonia [54]. Currently, a number of clinical trials are ongoing, aiming to verify the safety and antiviral activity of remdesivir in the treatment of COVID-19. Clinical findings of the team of Professor Cao Bin of the China-Japan Friendship Hospital suggested that the remdesivir is adequately tolerated but do not provide significant clinical or antiviral effects in severe patients with COVID-19 [55]. However, the results of the global clinical trial are believed that remdesivir can relieve symptoms and reduce mortality, especially for patients in intensive care who require mechanical ventilation [56]. Meanwhile, the clinical trials in Chicago have suggested that early COVID-19 patients benefit more due to the reduction of lung damage [57]. In conclusion, remdesivir is still in the consideration of one of the most promising drugs for treatment COVID-19 currently [58].

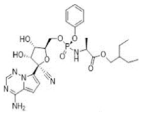
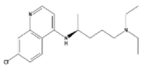
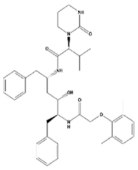
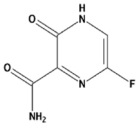
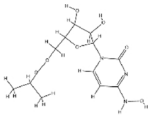
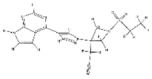
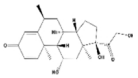
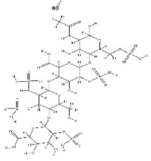
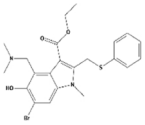
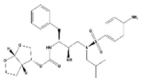
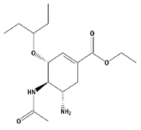
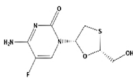
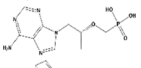
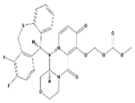
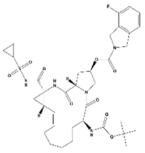
3.3. Lopinavir/Ritonavir

Lopinavir/Ritonavir (LPV/r), also known as Kaletra, is an oral combination agent for treating HIV approved by the FDA, which has shown anti-coronavirus efficacy in studies of SARS and MERS [59–62]. As a new protease inhibitor, LPV/r interrupts viral nucleic acid replication via inhibition of 3CLpro [63]. Xushun Guo's team at Sun Yat-sen University School of Medicine derived a homology modeling to confirm that LPV/r significantly inhibited the function of CEP_C30 to prevent the SARS-CoV-2 reproduction cycle [64]. In addition, two groups in China and Korea have reported LPV/r can improve the clinical symptoms of patients with COVID-19 [65,66]. Besides, LPV/r can achieve better antiviral effects when used with interferon or ninavir than alone [67]. However, the latest evidence suggests that it may cause liver damage and prolong hospital stay in the COVID-19 infected patients [68]. Furthermore, no benefit was observed with LPV/r treatment beyond standard care in hospitalized adult patients with severe COVID-19 [69]. Therefore, whether LPV/r can become an important adjuvant drug in anti-SARS-CoV-2 therapy and improve the clinical outcome of patients remains to be determined (Table 1).

4. Chinese herbal medicines with the potential to inhibit COVID-19

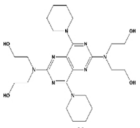
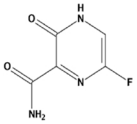
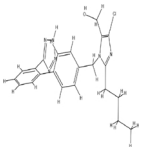
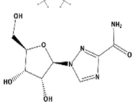
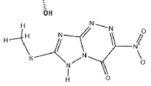
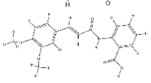
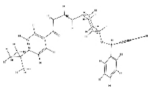
Previously, we summarized small molecules currently used/planned to treat COVID-19, which may be an important short-term strategy for the treatment of COVID-19, but their efficacy and safety in COVID-19 need to be further confirmed by clinical trials. Drug development against COVID-19 appears to be crucial in the context of a rapidly evolving epidemic, however, the conventional development of new drugs is time-consuming with safety concern. Therefore, it seems unrealistic to synthesize new drugs and perform safety and toxicity tests over a short period of time. Antiviral therapy with Chinese herbal medicines have been recorded for a long time in Chinese history, and previous studies have shown that Chinese herbal medicines have great potential for preventing SARS transmission [105]. Given the low

Table 1
Summary of potential therapeutic agents against SARS-CoV-2.

No.	Drug Candidate	Structural Formula	Potential Mechanism of Action on COVID-19	Anti-SARS-CoV-2 Evidence	Reference
1.	Remdesivir/GS-5734		Inhibits RdRp	In Vitro Assay, Clinical Trial	[56,58]
2.	Chloroquine and Hydroxychloroquine		Inhibits endosomal acidification fusion and regulates immunity	In Vitro Assay, Clinical Trial	[48,70]
3.	Lopinavir/Ritonavir(Kaletra)		Inhibits 3CLpro	In Vitro Assay, Clinical Trial	[68,71]
4.	Favipiravir		Inhibits RdRp	In Vitro Assay, Clinical Trial	[72,73]
5.	EIDD-2801		Inhibits RdRp	In Vitro Assay, Clinical Trial	[74,75]
6.	Baricitinib		Inhibits Janus kinase	Clinical Trial	[76]
7.	Methylprednisolone		Inhibits proinflammatory cytokines and anti-fibrotic	Clinical Trial	[77,78]
8.	Heparin		Reverses the hypercoagulability	Clinical report, Clinical Trial	[79,80]
9.	Zinc	Zn	Antiviral and regulates immunity	Clinical report, Clinical Trial	[81,82]
10.	Arbidol/Umifenovir		Inhibits hemagglutinin	In Vitro Assay, Clinical report, Clinical Trial	[83,84]
11.	Darunavir		Inhibits 3CLpro	In Vitro Assay, Clinical Trial	[71,85]
12.	Oseltamivir		Inhibits neuroaminase and sialidase	Clinical Trial	[86,87]
13.	Emtricitabine		Inhibits nucleoside reverse transcriptase	Clinical Trial	[88]
14.	Tenofovir		Inhibits nucleoside reverse transcriptase	Clinical Trial	[88,89]
15.	Baloxavir marboxil		Inhibits Cap-dependent endonuclease	Clinical Trial	[90,91]
16.	Danoprevir		Inhibits NS3/4A protease	Clinical Trial	[92,93]

(*continued on next page*)

Table 1 (*continued*)

No.	Drug Candidate	Structural Formula	Potential Mechanism of Action on COVID-19	Anti-SARS-CoV-2 Evidence	Reference
17.	Dipyridamole		Inhibits phosphodiesterase	Clinical Trial	[94,95]
18.	Fingolimod		Modulates sphingosine 1-phosphate receptor	Clinical Trial	[96]
19.	Losartan		Blocks angiotensin II receptor	Clinical Trial	[97,98]
20.	Azithromycin		Inhibits 50S ribosomal protein	In Vitro Assay, Clinical Trial	[42,99]
21.	Ribavirin		Inhibits viral mRNA and protein synthesis	In Vitro Assay, Clinical Trial	[100,101]
22.	Triazavirin		Inhibits RNA synthesis	Clinical Trial	[102]
23.	Tranilast		Inhibits hematopoietic prostaglandin D synthase	Clinical Trial	[103]
24.	Ebastine		Inhibits H1	In Vitro Assay, Clinical Trial	[104]

toxicity and availability of Chinese herbal medicines, screening active compounds targeting viral or host targets from Chinese herbal medicines may be a potential strategy for treating COVID-19. In this review, we summarized potential Chinese herbal medicines (Table 2) that may treat COVID-19 by targeting proteins such as Spike protein, ACE2, 3CLpro, PLpro and RdRp. We also predicted the binding affinities between these compounds and COVID-19 related targets by molecular docking, with a focus on six compounds: quercetin, andrographolide, glycyrrhizic acid, baicalin, patchouli alcohol, and luteolin. And the binding patterns of these six compounds to the key targets of SARS-CoV-2 are shown in Fig. 2.

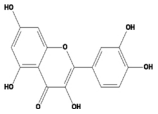
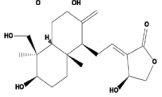
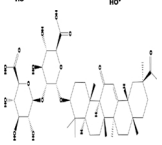
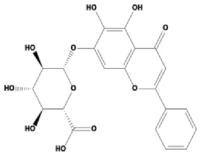
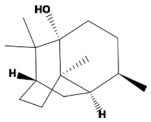
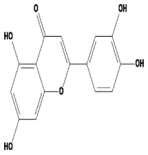
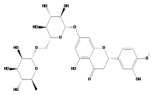
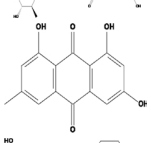
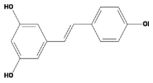
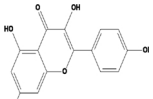
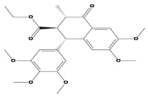
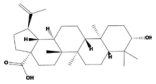
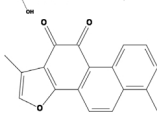
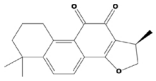
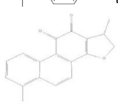
4.1. Quercetin

Quercetin, a flavonoid compound, is widespread in fruit and vegetables. As a dietary source compound, quercetin exerts diverse biological activities including anti-inflammatory, anti-oxidant, anti-viral, anti-allergic, anti-cancer, mood-improving as well as vasoprotective [106–108]. Studies have found that quercetin exhibits antiviral properties against a variety of viruses, including Influenza A Virus (IAV) [108], Hepatitis C Virus (HCV) [109], Enterovirus 71 (EV71) [110], and SARS-CoV, etc [111,112]. It has been confirmed that quercetin showed a good inhibitory effect on SARS-CoV 3CLpro expressed in Pichia pastoris, with an inhibition rate of 82 % [111]. In addition, enzyme inhibition assays *in vitro* also showed that quercetin had inhibitory activity against SARS-CoV 3CLpro [112]. Since the 3CLpro sequence of SARS-CoV-2 is highly similar to that of SARS-CoV [10,25], we speculated that quercetin may also exhibit antiviral effects on SARS-CoV-2. However, it has not been documented whether quercetin inhibits SARS-CoV-2, so we docked quercetin to 3CLpro as well as other key targets, and the docking results showed that quercetin bound well to each target, with a binding energy of -5.6 kcal/mol to 3CLpro. Surprisingly, we found that quercetin bounds better to Spike protein, ACE2, RdRp and PLpro indicating good potential against SARS-CoV-2. In addition, it has a wide range of sources with relatively low cost, so it is worth testing its efficacy against SARS-CoV-2 infection.

4.2. Andrographolide

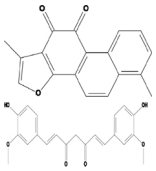
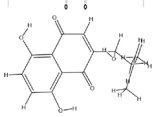
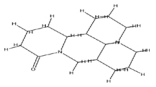
Andrographolide, the main active component isolated from the extract of the herb *andrographis paniculata*, has a wide range of biological activities including immunity regulation, anti-virus, anti-bacteria, anti-parasite, anti-tumor, and anti-hyperglycemia [113,114]. Previous studies have shown that andrographolide has a broad spectrum of antiviral properties, which inhibits various virus infections including influenza A virus (IAV) [115], human immunodeficiency virus (HIV) [116], Chikungunya virus (CHIKV) [117], dengue virus (DENV) [118,119], and Enterovirus D68 (EV-D68) [120]. Atchara Paemanee et al. suggested that andrographolide may exert broad-spectrum antiviral activity by interfering a variety of cellular pathways (including autophagy, unfolded protein response (UPR) pathway and oxidative stress, etc.). They further found the anti-dengue virus activity by acting on GRP78, a key regulator of unfolded protein response [119]. In addition, andrographolide exerts antiviral activity against H1N1 by inhibiting the activation of RLRs signaling pathways and thereby improving H1N1 virus-induced cell death [121]. To test the anti-viral activity against SARS-CoV-2, we docked andrographolide with key targets, and the results also showed that andrographolide bound well to the key targets including Spike protein, ACE2, 3CLpro, RdRp and PLpro, which indicated that andrographolide has potential efficacy against SARS-CoV-

Table 2
Summary of potential Chinese herbal medicines against SARS-CoV-2.

No.	Potential Natural Compounds	Structural Formula	Effect or Mechanism of Antiviral	Molecular Docking (Binding Energy) (kcal/mol)					Reference
				ACE2	3CLpro	Spike	PLpro	RdRp	
1.	Quercetin		Inhibits 3CLpro and interacts with viral HA protein to inhibit virus entry into the cell	−7.3	−5.6	−6.5	−7.3	−7.2	[108,111,112]
2.	Andrographolide		Inhibits 3CLpro and virus-induced activation of RLRs signaling pathway	−6.8	−5.7	−6.1	−6.5	−6.2	[121,122]
3.	Glycyrrhizin		Inhibits replication, adsorption and penetration of the virus	−7.0	−6.9	−6.5	−7.3	−7.2	[125]
4.	Baicalin		Inhibits 3CLpro and HIV-1 Env protein mediated fusion with cells expressing CD4/CXCR4 or CD4/CCR5.	−7.9	−6.4	−6.5	−8.5	−6.9	[28,142]
5.	Patchouli alcohol		Inhibits activation of PI3K/Akt and ERK/MAPK signaling pathways to block viral infection and replication	−5.6	−5.1	−5.1	−4.9	−6.0	[136]
6.	Luteolin		Inhibits 3CLpro and the expression of the coat protein I complex and interferes with viral replication at an early stage of infection	−7.1	−6.4	−6.7	−7.5	−7.0	[112,139]
7.	Hesperidin		Inhibits 3CLpro	−8.8	−7.0	−6.5	−8.0	−6.9	[143,144]
8.	Emodin		Blocks the SARS-CoV spike protein and ACE2 interaction and inhibits 3a protein to reduces virus release;	−7.2	−5.6	−6.4	−7.5	−6.8	[145,146]
9.	Resveratrol		Inhibits RNA and nucleocapsid expression	−6.1	−5.3	−6.1	−7.2	−6.7	[147]
10.	Kaempferol		Inhibits 3a channel protein	−6.9	−5.4	−6.4	−7.1	−6.3	[148]
11.	Lignan		Inhibits virus replication and 3CLpro	−5.8	−4.3	−5.3	−6.7	−4.4	[149]
12.	Betulinic acid		Inhibits virus replication and 3CLpro	−6.8	−5.8	−7.1	−8.3	−6.3	[149]
13.	Tanshinone		Inhibits 3CLpro and PLpro	−7.8	−6.4	−7.3	−8.6	−7.3	[150]
14.	Cryptotanshinone		Inhibits 3CLpro and PLpro	−7.8	−6.2	−7.2	−9.0	−7.5	[150]
15.	Dihydrotanshinone I		Inhibits 3CLpro and PLpro	−6.6	−8.5	−6.2	−6.6	−9.3	[150]
16.	Tanshinone IIA		Inhibits 3CLpro and PLpro	−7.8	−6.4	−7.3	−8.6	−7.0	[150]

(*continued on next page*)

Table 2 (*continued*)

No.	Potential Natural Compounds	Structural Formula	Effect or Mechanism of Antiviral	Molecular Docking (Binding Energy) (kcal/mol)					Reference
				ACE2	3CLpro	Spike	PLpro	RdRp	
17.	Curcumin		Inhibits virus replication and 3CLpro	−6.4	−5.1	−5.5	−7.7	−7.6	[149]
18.	Shikonin		Inhibits 3CLpro	−5.7	−5.2	−6.1	−8.1	−5.9	[151]
19.	Matrine		Improves abnormal laboratory parameters and clinical symptoms in patients, and significantly shortens the time to nucleic acid conversion	−6.9	−5.7	−5.7	−7.0	−6.3	[152]

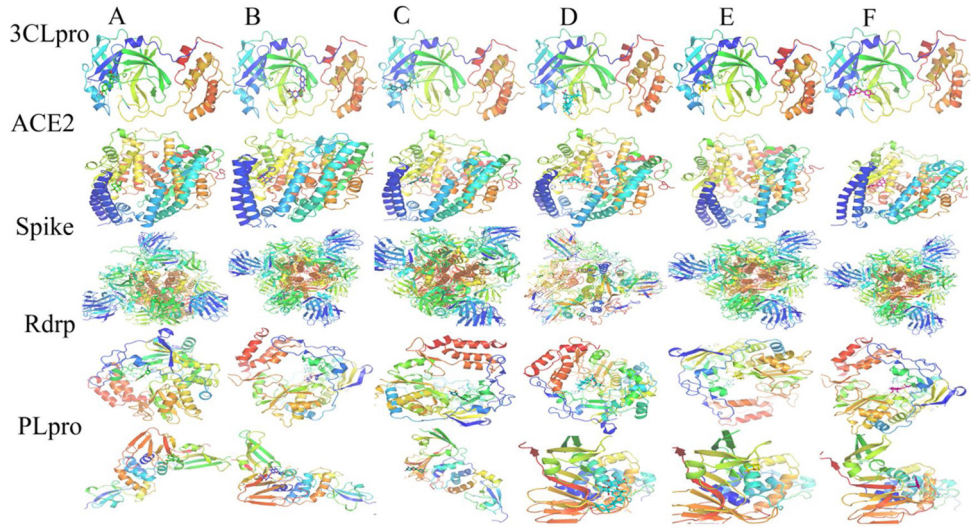


Fig. 2. The optimized binding patterns of ligands with key targets of SARS-CoV-2 by molecular docking, including (A) Andrographolide, (B) Baicalin, (C) Quercetin, (D) Glycyrrhizic acid, (E) Patchouli alcohol and (F) Luteolin.

2. Moreover, Enmozhi, S. K. et al. proved andrographolide as a potential inhibitor of SARS-CoV-2 3CLpro through in silico studies [122]. Overall, as a plant-derived compound, andrographolide is widely distributed with low cytotoxicity, but its potent antiviral activity against a variety of viruses calls for further investigation.

4.3. Glycyrrhizic acid

Glycyrrhizic acid is a plant product isolated from the traditional Chinese medicine *licorice* (Chinese name: Gan Cao). Glycyrrhiza uralensis contains active ingredients such as thymol and carvacrol, which have significant antiviral and bactericidal effects [123]. A large number of studies have shown that *licorice* and its chemical components have protective effect on lung inflammation and damage, and it is a promising herbal medicine for treating SARS [124]. Cinatl J et al. compared the effects of conventional antiviral drugs ribavirin, 6-azouridine, pyrazofurin, mycophenolic acid, and glycyrrhizic acid on SARS-CoV, and the experimental results showed that glycyrrhizic acid had a better viral inhibitory effect than the other four drugs in inhibiting the viral adsorption and penetration [125]. Hoever G et al. also showed that glycyrrhizic acid has a good anti-SARS-CoV effect, while SARS-CoV-2 and SARS-CoV belong to different subclasses of coronaviruses with similar structures [126]. In addition, glycyrrhizic acid can promote IFN-γ production by T cells [127]. Recent studies have shown that SARS-CoV-2 and SARS-CoV have the same receptor ACE2, and glycyrrhizic acid can bind to this receptor, suggesting that glycyrrhizic acid may have therapeutic effects on SARS-CoV-2 [128]. To discuss whether glycyrrhizic acid has an anti-SARS-CoV-2 effect, we performed molecular docking of glycyrrhizic acid with the binding energy of glycyrrhizic acid and ACE2 -7.0 kcal/mol (As the shown in Table 2). At the same time, the binding energy of glycyrrhizic acid with other targets: 3CLpro, PLpro, RdRp and Spike is -6.9 kcal/mol, -7.3 kcal/mol, -7.2 kcal/mol, -6.5 kcal/mol, respectively. It can be seen that glycyrrhizic acid also has strong binding affinity to other targets. Given the antiviral effect of glycyrrhizic acid on SARS-CoV, and its potential interaction with ACE2, we speculated that glycyrrhizic acid may have potential to treat SARS-CoV-2. Moreover, glycyrrhizic acid plays an important role in inhibiting immune hyperactivation and cytokine storm factor development [129], therefore, we believe it is worth testing its efficacy against SARS-CoV-2 infection.

4.4. Baicalin

Baicalin, a component of *Scutellaria baicalensis Georgi* (Chinese name: Huang Qin), has a wide range of therapeutic effects, including sensitization and anti-apoptosis [130,131]. Chen et al. have

demonstrated the antiviral activity of baicalin against SARS coronavirus, with an EC_{50} value of 12.5 μg/mL at 48 h, and the activity tended to decrease with incubation time beyond 48 h [132]. Due to the similarities between SARS-CoV-2 and SARS-CoV, it can be speculated that baicalin may also have an antiviral effect on SARS-CoV-2. In addition, Deng et al. used UV spectrophotometry to determine angiotensin-converting enzyme inhibitory activity and found that baicalin could inhibit ACE *in vitro*, with an IC_{50} value of 2.24 mM [133]. Hansen Chen et al. used molecular docking technology to find that baicalin may have a strong binding effect with ACE2, and the possible binding sites are ASN-149, ARG-273, HIS-505 [128]. Haixia Su et al. showed that baicalin, as a non-covalent inhibitor of SARS-CoV-2 3CLpro, has high ligand binding efficiency and specific binding to proteases by ITC map, native electrospray ionization mass spectrometry (ESI-MS) and its chemical structure [28]. At the same time, we used molecular docking to study the docking of baicalin to other key targets of SARS-CoV-2, in which the binding energy of baicalin to the target PLpro was -8.5 kcal/mol. The results of docking showed that baicalin bounds strongly to other targets of SARS-CoV-2 (Table 2). Therefore, it can be reasonably speculated that baicalin is one of the potential drugs for COVID-19 treatment. In view of the low toxic effect of baicalin, its effect against SARS-CoV-2 warrants further study.

4.5. Patchouli alcohol

Patchouli alcohol (PA), a tricyclic sesquiterpene compound extracted from the traditional Chinese medicine *patchouli*, has a wide range of pharmacological and biological effects including antiviral, immunomodulatory, anti-inflammatory, antioxidative, and antitumor [134]. PA has been found to have anti-influenza A (IAV) effect *in vitro*, while H1N1 virus is the most sensitive to PA [135]. In addition, Yunjia Yu et al. found that intracellular PI3K/Akt and ERK/MAPK signaling pathways may be involved in the anti-IAV effect of PA and PA significantly inhibits the *in vitro* proliferation of different IAV, suggesting that PA may block IAV infection by directly killing viral particles and interfering with some early stages after viral adsorption [136]. Another study showed that PA also has an effect against influenza virus (IFV) *in vivo* and enhances protection against IFV infection in mice by enhancing host immune responses and attenuating systemic and pulmonary inflammatory responses [137]. To investigate the anti-SARS-CoV-2 activity of PA, we investigated the possibility of PA binding to SARS-CoV-2 related targets using molecular docking (Table 2). The docking results showed that the binding effect of PA and Rdrp was satisfactory, which provided some support for the antiviral effect of PA. The above study results showed that patchouli alcohol had antiviral effect and also modulated the levels of inflammatory cytokines, suggesting that PA may be a novel and effective antiviral and anti-inflammatory drug for COVID-19.

4.6. Luteolin

Luteolin, a natural flavonoid extracted from Chinese herbal medicine, displays multiple biological activities, including anti-inflammatory, anti-cancer, antioxidant, antiviral, and heart protective [138]. It was reported that luteolin can interfere with the virus in early virus life cycle, to a certain extent, block the absorption and internalization of influenza virus, thereby inhibited the replication of IAV [139]. The above experiments suggested that luteolin is a potential antiviral drug that inhibits viral replication by regulating host proteins. In addition, Minhua Peng et al. confirmed luteolin inhibited the dengue virus NS2B/NS3 protease activity by analyzing the nucleotide sequence of the luteolin-resistant escape mutant [140]. It also has been documented luteolin has an anti-Epstein-Barr virus (EBV) effect, and in immunoblot analysis, 20 μg/mL of luteolin showed a significant inhibitory effect on EBV lytic cycle [141]. Another study showed that luteolin extracted from *Torreya Nucifera* is an effective SARS-CoV 3CLpro inhibitor [112]. To interrogate the anti-SARS-CoV-2 effect of luteolin, we performed molecular docking of luteolin to key targets of SARS-CoV-2. The docking results showed that luteolin bound well to the key target of SARS-CoV-2. Among them, the binding energy of luteolin to ACE2 was -7.1 kcal/mol (Table 2). Taken together, luteolin has a good antiviral effect, which suggests that luteolin may be a potential drug for the treatment of COVID-19.

The results of molecular docking are shown in Table 2. From the target point of view, the binding effect of ACE2 and PLpro with these natural compounds was more prominent; while from the natural compounds, the lowest binding energy was -9.0 kcal/mol for Cryptotanshinone and PLpro, while the highest was -4.3 kcal/mol for Lignan and 3CLpro, that is to say, the range of binding energy was from -9.0 kcal/mol to -4.3 kcal/mol, which indicated that the natural compounds had a good binding effect with the target. Our aim of docking was to select natural compounds with high potential efficacy against SARS-CoV-2, but it should be pointed out that these compounds cannot be considered to treat COVID-19 only by such a screen which is aimed to provide priority to focus. Furthermore, the 3D structure of the targets we used were based on the reported gene sequences. If the virus mutates during transmission, new screening is recommended. In conclusion, our review summarizes more than a dozen of natural compounds classified as antiviral/pneumonic protectors, which may directly inhibit SARS-CoV-2. However, their actual effect in the treatment of COVID-19 needs to be verified by further studies.

5. Comparison and combination therapy of clinically approved drugs and Chinese herbal medicines

Developing new application of FDA approved drugs is the most effective strategy for sudden new diseases and will rapidly alleviate the current epidemic situation [153]. Compared with new drugs, existing antiviral drugs have the advantages of safety, pharmacokinetic characteristics, clear clinical adverse reactions. And by further verifying the effectiveness of drugs that have completed at least clinical phase I can save preclinical and partial clinical study time and shorten the time cost of drug research and development. However, because existing antiviral drugs are not designed for SARS-CoV-2, they may not be ideal in antiviral efficacy and require larger doses, which may bring more serious side effects.

From the occurrence of the epidemic to date, traditional Chinese medicines also played an extremely important role. Guided by the theory of traditional Chinese medicine, exerting the advantages of overall regulation of traditional Chinese medicine is an important method for the clinical treatment of COVID-19. At present, Qingfei Paidu Decoction is recommended for the treatment of clinically confirmed cases according to Guideline for the Diagnosis and Treatment of Novel Coronavirus (SARS-CoV-2) Pneumonia (On Trials, the Seventh Edition) in China [39]. A study including 98 patients with COVID-19 showed that Qingfei Paidu Decoction has a good clinical effect for the treatment of COVID-19, it can significantly improve the abnormal laboratory test indicators and clinical symptoms of patients, reduce the adverse reactions of patients, and effectively improve the therapeutic effect [154]. In addition, Lianhua Qingwen was also demonstrated to significantly inhibit SARS-COV-2 replication in Vero E6 cells at the mRNA level as well as markedly reduce the production of pro-inflammatory cytokines, suggesting that Lianhua Qingwen may have a potential inhibitory effect on the cytokine storm induced by SARS-COV-2 [155]. At present, symptomatic and supportive therapy is still the key to clinical treatment. Therefore, traditional Chinese medicines have both antiviral and symptom-relieving effects may lead to better therapeutic effects.

At present, western medicine treatment is mainly based on the principles of symptomatic treatment, prevention of complications, treatment of underlying diseases, and prevention of infection [39], while traditional Chinese medicines play an important role in relieving

the symptoms of patients and delaying or reducing the development of mild diseases into severe diseases [156], and may also play a role in reducing the side effects of western medicine, especially in the recovery of pulmonary function [157]. Both Chinese herbal medicine and approved western medicine have their own advantages in the treatment of COVID-19. In the course of COVID-19's treatment, the combination of Chinese herbal medicine and approved western medicine has shown obvious effect, which is of great value in alleviating the early clinical symptoms of patients and reducing the incidence of patients from mild to severe then to intensive care [158]. The combination of nefenavir and sinomenine significantly reduced the amount of virus accumulation and shortened the time of virus clearance compared with single use of nefenavir and sinomenine [159]. In short, the combination of Chinese herbal medicine and approved western medicine is worth thinking about in the future treatment of COVID-19.

6. Conclusions and future prospects

COVID-19 poses a great threat to global health and safety. It is an urgent task for us to control the spread of the epidemic and reduce the mortality rate as soon as possible. But so far, the specific mechanism of the virus is still unclear, and no specific drug has been developed for the virus. At present, it is important to control the source of infection, cut off the route of transmission, and make use of existing drugs and means to actively control the progress of the disease. Efforts should also be made to develop specific drugs, promote vaccine research and development, reduce disease morbidity and mortality, and better protect the lives of the people.

At present, the potential therapeutic agents used in COVID-19 come from previous experience in treating SARS, MERS or other new influenza viruses. As broad-spectrum antiviral drugs have long been approved on the market to treat different viral infections, their metabolic characteristics, dosage, potential efficacy and side effects are clear. Repurposing of clinically approved drugs may be an important short-term strategy for the treatment of novel coronavirus. But the disadvantage is that these treatments are too "broad-spectrum" to specifically treat COVID-19. In addition, its side effects can not be underestimated. A number of clinical trials are under way to evaluate the effectiveness of other treatment options. Active symptomatic support is still the key to treatment. Although stem cells, monoclonal antibodies, polypeptides, interferon or plasma from recovered patients have been shown to be effective in treating COVID-19 patients, their safeties are still being evaluated and the efficacy remains to be further confirmed.

Except the some undergoing small molecules, this paper also focuses on the most promising compounds in traditional Chinese medicine in recent years, which can be used as effective antiviral drugs for the treatment of diseases caused by SARS-CoV-2 based on *in vitro* and *in vivo* studies. In addition, computer molecular docking shows that these monomers have good binding ability to COVID-19 virus and host targets. The low toxicity and availability of active compounds of traditional Chinese medicine should be used as potential drug candidates for COVID-19 treatment.

This review also has limitations. The large and rapidly published literature on COVID-19's treatment means that the findings and recommendations are constantly evolving as new evidence arises. It is not uncommon that drugs that proved effective at an early stage based on small-scale clinical trials later turned out to be ineffective. We look forward to the cooperation of all scientists around the world to develop effective drugs to treat current and future potential SARS-CoV-2 infections to control the further spread of the epidemic.

Disclosures

All authors have read and approved the final submission.

Declaration of Competing Interest

There is no conflict of interest associated with this article.

Acknowledgments

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