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Antiviral mechanisms of candidate chemical medicines and traditional Chinese medicines for SARS-CoV-2 infection

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ABSTRACT

The Coronavirus Disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has rapidly become a global pandemic. Up to now, numerous medicines have been applied or approved for the prevention and control of the virus infection. However, the efficiency of each medicine or combination is completely different or still unknown. In this review, we discuss the types, characteristics, antiviral mechanisms, and shortcomings of recommended candidate medicines for SARS-CoV-2 infection, as well as perspectives of the drugs for the disease treatment, which may provide a theoretical basis for drug screening and application.

1. Introduction

The Coronavirus Disease 2019 (COVID-19, 2019 Novel Coronavirus Pneumonia, 2019-NCP) that outbroke in Wuhan, China at the end of 2109 has rapidly become a global pandemic (Li et al., 2020a). Up to 21 Jun 2020, it was estimated that more than 8,708,008 confirmed cases and 461,715 deaths were detected in more than 210 countries, areas, or territories (https://www.who.int/). The common clinical symptoms of the disease are firstly reported as fever, dry cough, dyspnoea, fatigue, sore throat, headache, mild upper respiratory tract illness, severe viral pneumonia with respiratory failure, and even death (Tian et al., 2020; Wang et al., 2020b; Zhou et al., 2020b). Recent studies have found that in addition to the above symptoms, it seems to have a wide range of clinical features, including asymptomatic, diarrhea, myalgia, discomfort, loss of taste and smell, lymphopenia, cytokines storm, etc. (Guan et al., 2020; Li et al., 2020c; Liu et al., 2020a; Tabata et al., 2020; Ye et al., 2020). Surprisingly, it is estimated that the proportion of asymptomatic patients is 18–50 %, or even as high as 87.9 % in some cases (Ji et al., 2020; Lai et al., 2020; Li and Ren, 2020; Luan et al., 2020; Sutton et al., 2020). These results suggest that the disease has strong infectious and pathogenicity, with alarming morbidity and mortality, which needs extensive attention to prevent and control the disease. Moreover, due to the rapid spread of the diseases and the dramatic increase in the number of patients worldwide, effective antiviral medicine is urgently needed.

The aetiological agent of COVID-19 has been confirmed as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is a newly identified virus belonging to the family *Coronavirus*, genus *Betacoronavirus,* and subgenus *Sarbecovirus* (Adhikari et al., 2020; Jiang and Shi, 2020; Li et al., 2020a; Zhou et al., 2020b). The virus contains a single positive-strand RNA of about 30 kb, which encodes at least eleven proteins, including ORF1ab, spike protein (S), ORF3a, envelope protein (E), membrane protein (M), ORF6, ORF7a, ORF7b, ORF8, nucleocapsid phosphoprotein (N), and ORF10 (Chan et al., 2020; Jiang and Shi, 2020; Li et al., 2020a; Zhou et al., 2020b). Among these viral proteins, S protein can recognize and bind the cellular receptor angiotensin-converting enzyme 2 (ACE2), followed by priming of the S protein by host proteases, especially by the serine protease TMPRSS2, resulting in cleavages at the S1/S2 and the S2′ sites of the S protein (Hoffmann et al., 2020; Zhou et al., 2020b). Therefore, the S protein is considered as the main antigen of the virus. ORF1ab protein can be cleaved into at least 16 predicted nonstructural proteins (nsp), among which nsp3, nsp5, nsp12, and nsp13 encode putative papain-like viral protease (PLVP), 3C-like protease (chymotrypsin-like or 3C-like protease, $3CL^{pro}$), RNA-dependent RNA polymerase (RdRp), and helicase, respectively (Chan et al., 2020). Besides, the viral ORF1ab, ORF10, and ORF3a proteins can attack heme on hemoglobin 1-β chain synergistically, resulting in decomposing iron to form porphyrin, which will

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subsequently lead to less and less hemoglobin carrying oxygen and carbon dioxide, produce extremely strong poisoning and inflammation in lung cells, and interfere with the normal heme anabolism pathway (Liu and Li, 2020). Therefore, S protein and proteins derived from the ORF1ab as well as their cellular receptors, such as ACE2 (Zhou et al., 2020b), AGTR2 (angiotensin II receptor type 2) (Cui et al., 2020), TMPRSS2 (Hoffmann et al., 2020), and CD147 (Basigin or EMMPRIN) (Wang et al., 2020c), are the most favorable cellular targets for the development of antiviral compounds.

Since the disease newly emerges, there is no clinically approved antiviral therapy or vaccines for the disease. Hopefully, the virus has highly relationship with bat coronavirus isolate RaTG13 (GenBank No.: MN996532) base on the full-length genome (Jiang and Shi, 2020; Li et al., 2020a; Zhou et al., 2020b). Thus, many experts and clinicians suggest using anti-coronavirus drugs to prevent and control the disease. Up to now, numerous medicines have been registered or approved for clinical trials for COVID-19 treatment (https://clinicaltrials.gov/ and http://www.chictr.org.cn/). However, the efficiency of each medicine or combination is quite different or still unknown. In this review, we discuss the types, characteristics, antiviral mechanisms, and shortcomings of several recommended candidate medicines for SARS-CoV-2 infection, as well as perspectives of the drugs for the disease treatment. The mechanisms discussed in this article may provide a theoretical basis for drug screening and application.

2. Chemical pharmaceuticals

Repurposed drugs have emerged as attractive sources for the prevention and treatment of the SARS-CoV-2 infection, which could shorten the time and reduce the cost compared to *de novo* drug screen (Baron et al., 2020; Chen et al., 2020c; Liu et al., 2020d; Omar, 2020; Sohini and Narayanaswamy, 2020; Xu et al., 2020a; Zhou et al., 2020c). For example, the antiviral medicines ledipasvir or velpatasvir are particularly attractive candidates to treat COVID-19 with minimal side effects (Chen et al., 2020c). As reported by Chen and colleagues, Epclusa (velpatasvir/sofosbuvir) and Harvoni (ledipasvir/sofosbuvir) could be attractive drugs that can inhibit 3C-like protease of the virus (Chen et al., 2020c). Zhou et al. identified three potential drug combinations (sirolimus plus dactinomycin, mercaptopurine plus melatonin, and toremifene combined with emodin) targeting SARS-CoV-2 by network-based methodologies (Zhou et al., 2020c). Sohini et al. found 20 known candidates, including some synthetic molecules and phytochemicals, which might exhibit antiviral activities by binding to the main protease of SARS-CoV-2 (Sohini and Narayanaswamy, 2020). Among the repurposed drugs (Table 1), remdesivir, chloroquine, hydroxychloroquine, lopinavir/ritonavir, and ribavirin are promising candidates in the development of the antiviral drugs for SARS-CoV-2 infection, which have shown efficacy to inhibit the coronavirus *in vitro* or in animal models (Belhadi et al., 2020; Chen et al., 2020c; Guo et al., 2020; Martinez, 2020; Xu et al., 2020a). Furthermore, according to the 7th edition of the Guideline recommended by the Prevention, Diagnosis, and Treatment of Novel Coronavirus-induced Pneumonia issued by the National Health Commission (NHC) of the People' Republic of China for the treatment of COVID-19, interferon α (IFN-α), lopinavir/ritonavir, ribavirin, chloroquine phosphate, and arbidol are priority recommendation (PRC, 2020). A recent survey showed that the main antiviral drugs are IFN-α (69.5 %), lopinavir/ritonavir (65.0 %), arbidol (60.0 %), and ribavirin (55.7 %) in China (Liu et al., 2020c).

Based on the target of the antiviral medicine, there are mainly two types of antiviral compounds recommended in the treatment of the COVID-19. The first type is targeting host protease or other cellular proteins, such as teicoplanin, arbidol, chloroquine and derivatives, and niclosamide. The second type mainly acts on viral proteins, such as niclosamide, lopinavir/ritonavir, remdesivir, favipiravir, and ribavirin.

2.1. Host protein targeted medicines

Chloroquine (CQ) and its derivatives, especially hydroxychloroquine (HCQ) and chloroquine phosphate, are widely-used antimalarial and autoimmune disease drugs, which can be distributed throughout the whole body after oral administration (Chang and Sun, 2020; Devaux et al., 2020; Gao et al., 2020a; Kearney, 2020; Li and Liu, 2020; multicenter collaboration group of Department of, S., Technology of Guangdong, P., Health Commission of Guangdong Province for chloroquine in the treatment of novel coronavirus, p., 2020; Wang et al., 2020d). In recent years, CQ is proved to be a broad-acting antiviral effective agent against numerous viruses, including Influenza viruses, Human immunodeficiency virus (HIV), Hand-Foot-and-Mouth Disease (HFMD), Kaposi's sarcoma-associated herpesvirus (KSHV), Chikungunya virus (CHIKV), hepatitis B virus (HBV) and other inflammation-related viruses (Devaux et al., 2020; Khan et al., 2010; Tan et al., 2018; Yang et al., 2016). CQ and its derivatives can increase the pH value of endosome, interfere with glycosylation of cellular receptors, inhibit autophagosome-lysosome fusion, interfere signal pathways, disturb the post-translational modification of viral proteins, modulate the immune responses, and reduce inflammatory reactions (Chang and Sun, 2020; Devaux et al., 2020; Kearney, 2020; Khan et al., 2010; Sinha and Balayla, 2020; Wang et al., 2020a; Yang et al., 2016), and thus blocking the early and late stages of the virus infection. Furthermore, CQ and HCQ can prevent the ORF1ab, ORF3a, and ORF10 of SARS-CoV-2 from attacking heme to form porphyrin, and inhibit the viral ORF8 and surface glycoprotein from binding to porphyrin, thus effectively relieving respiratory distress symptoms (Liu and Li, 2020). Because of its immunomodulatory activities, CQ and its derivatives were also used to control cytokine storms in critical patients with SARS-CoV-2 infection in the late stage (Zhou et al., 2020a). Moreover, hydroxychloroquine is safer and more effective than CQ at inhibiting SARS-CoV-2 *in vitro* and *in vivo* (Gautret et al., 2020; Liu et al., 2020b; Yao et al., 2020b; Zhou et al., 2020a). Therefore, it was recommended to use 400 mg of hydroxychloroquine sulfate twice daily for 1 day, followed by 200 mg twice daily for 4 more days for the treatment (Yao et al., 2020b). Furthermore, a combination of hydroxychloroquine sulfate (200 mg, three times per day during ten days) and azithromycin (500 mg on day1 followed by 250 mg per day, the next four days) can significantly reduce the viral load compared with that of the hydroxychloroquine treatment alone (Gautret et al., 2020). Taken together, the CQ and its derivatives can shorten the course of SARS-CoV-2, reduce the inflammatory responses to infection, inhibit the deterioration of pneumonia, improve lung imaging performance, and promote the negative conversion of the virus (Kearney, 2020; Li and Liu, 2020). However, recent reports show that treatment with HCQ is associated with numerous adverse effects in patients with COVID-19, such as frequent QTc prolongation, erythema multiforme, acute generalized exanthematous pustulosis (Bessiere et al., 2020; Delaleu et al., 2020; Mercuro et al., 2020; Monte Serrano et al., 2020; Ren et al., 2020b; Torjesen, 2020). On Jun 16, 2020, the US Food and Drug Administration revoked the emergency use authorization for chloroquine and hydroxychloroquine due to their lack of efficacy and safety concerns (http://www.chinadaily.com.cn/). Therefore, the safety assessment of CQ/HCQ and the combination of HCQ and other medicine should be conducted for patients with COVID-19.

Arbidol (ARB, also known as umifenovir) is a broad-spectrum antiviral drug that can inhibit numerous DNA and RNA viruses, including influenza virus, Zika virus, West Nile virus and hepatitis C virus (Blaising et al., 2014; Haviernik et al., 2018). It was reported that ARB can interact with both cellular membranes and viral and/or cellular proteins, and thus preventing membrane fusion, blocking trimerization of the spike glycoprotein and virus infection (Blaising et al., 2014; Vankadari, 2020). ARB also has immunostimulating effects, such as stimulating the production of interferon, activating the humoral and cellular immune defense of the body, enhancing the phagocytic activity

Table 1
Possible antiviral mechanisms and characteristics of the candidate medicines recommended in the treatment of the SARS-CoV-2 infection.

Drug	Proposed antiviral spectrum	Possible target of the SARS-CoV-2	Possible mechanism	Proposed usage		Merit	Shortcoming	Ref.
				In vitro	*In vivo*			
Chloroquine and derivatives	Widely-used anti-malarial and autoimmune disease drug, Multiple viruses,	Viral entry and replication	Increasing endosomal pH, interfering with the glycosylation of cellular receptors, immune-modulating, interfere with terminal glycosylation of the cellular receptor ACE2	EC_{50} = 1.13 μM, EC_{90} = 6.90 μM	Oral, pre-exposure of 250−500 mg daily, post-exposure at 8 mg/kg/day for 3 days or 500 mg twice per day for 7−10 days	Broad-spectrum antiviral activity, cheap and safe, easy to take, tolerated, low toxicity, limited contraindications	Gastrointestinal effects including nausea, vomiting, diarrhea, and abdominal discomfort, and cardiotoxic effects including rhythm disorders	(Chang and Sun, 2020; Kearney, 2020; Liu and Li, 2020; multicenter collaboration group of Department of et al., 2020; PRC, 2020; Wang et al., 2020d; Xu et al., 2020a)
Arbidol	Multiple viruses	Cellular membranes and viral and/or cellular proteins	Interacting with both cellular membranes and with viral and/or cellular proteins	10−30 μM	Oral, 200 mg, 3 times/d, 10 days	Well tolerated	Allergic reactions	(Deng et al., 2020; Dong et al., 2020; PRC, 2020; Wang et al., 2020g)
Teicoplanin	Bacteria and viruses, such as staphylococcal, streptococcus, Ebola, IAV, HCV, flavivirus, HIV, MERS-CoV, SARS-CoV, SARS-CoV-2	Host cysteine proteases cathepsin L in the late endosomes	Blocking virus entry by specifically inhibiting the activity of cathepsin L thereby preventing the release of genomic viral RNA and the continuation of the virus replication cycle	IC_{50} = 1.66 μM	Intravenous or oral, 400−1200 mg/day	Broad-spectrum antiviral activity, low and side effects, long half-life in blood plasma, convenient administration, and high safety when used in combination with other antibiotics	Adverse reactions are rare	(Baron et al., 2020; Colson and Raoult, 2016; Ren et al., 2020c; Zhou et al., 2016)
Niclosamide/2-chloro-4-nitroanilide derivatives/O-alkylamino-tethered derivatives	Multiple viruses, tapeworm	Viral 3C-like protease, autophagy	Inhibiting 3CL-pro, increasing autolysosomes, and affecting the autophagic flux	EC_{50} < 0.1 μM	Adults: 2 g on day 1 followed by 1 g daily for 6 days, oral	Broad-spectrum antiviral activity, multifunctional, inexpensive and well-tolerated old drug	Cytotoxicity and limited aqueous solubility, low absorption, and oral bioavailability	(Xu et al., 2020a)
Remdesivir	Multiple viruses, such as Ebola, MERS-CoV, SARS-CoV	RdRp	Obscuring viral RNA polymerase and evading proofreading by viral exonuclease, causing a decrease in viral RNA production, delaying chain cessation of nascent viral RNA	EC_{50} = 0.77 μM, EC_{90} = 1.76 μM, IC_{50} = 0.651 μM, 5 μM	Intravenous, 200 mg on day 1 followed by 100 mg for 9 days	Broad-spectrum antiviral activity, longer half-life (50 d), high renal clearance,	NA	(Al-Tawfiq et al., 2020; Gao et al., 2020b; Ko et al., 2020; Li et al., 2020c; Wang et al., 2020d; Xu et al., 2020a; Zhang and Zhou, 2020)
Lopinavir/Ritonavir	HIV	Viral protease (M^{pro}) and endopeptidase C30 (EP_C30)	Binds to the viral EP_C30 and induces significant conformation changes of the proteases, therefore blocking the multiplication cycle of SARS-CoV-2	NA	Oral, 200 mg/50 mg/ capsule, 2 capsules each time, 2 times/day, no more than 10 days	NA	Diarrhea, nausea, asthenia, hypokalemia, increased serum cholesterol and triglycerides	(Cao et al., 2020a; Lin et al., 2020b; Liu et al., 2020a; Liu and Wang, 2020; Wang et al., 2020d; Xu et al., 2020a)
Favipiravir	Multiple viruses	RdRp or E and ORF7a,	Inhibiting the interaction between the viral E and ORF7a and cellular porphyrin, prevent the virus from entering host cells, and catching free porphyrins.	NA	Oral, 1600 mg/time on the first day, twice a day; 600 mg/time the following days, twice a day, 7−10 days	Broad-spectrum antiviral activity	Teratogenic, raised serum uric acid	(Chen et al., 2020a; Delang et al., 2018; Dong et al., 2020; Liu and Li, 2020)

(*continued on next page*)

Table 1 (*continued*)

Drug	Proposed antiviral spectrum	Possible target of the SARS-CoV-2	Possible mechanism	Proposed usage		Merit	Shortcoming	Ref.
				In vitro	*In vivo*			
Ribavirin	Multiple viruses	nucleoside analogue	Binding RdRp active site	EC_{50} = 109.5 μM	Intravenous infusion, 500 mg each time, 2–3 times/day in combination with IFN-α or lopinavir/ritonavir, no more than 10 days	Broad-spectrum antiviral activity	Hemolytic anemia, teratogenic, decreased hemoglobin, insomnia, dyspnea, lack of concentration, emotional lability, and irritability, gastrointestinal symptoms, and altered liver function	(Dong et al., 2020; Elfiky, 2020; PRC, 2020; Rios et al., 2020)

Note: IC_{50}, half maximal (50 %) inhibitory concentration; EC_{50}, half maximal (50 %) effective concentration; Ref., reference; NA, Not Available.

of macrophages (Blaising et al., 2014; Haviernik et al., 2018). Moreover, ARB exhibits a prolonged antioxidant capacity by reacting with free radicals in two stages (Proskurnina et al., 2020). Therefore, it was supposed that ARB can inhibit SARS-CoV-2 infection at several stages, which is currently used in several clinical trials for the COVID-19 treatment. Furthermore, it was reported that ARB combined with Lopinavir/Ritonavir (LPV/r) is better than LPV/r alone in the treatment of the COVID-19 (Deng et al., 2020). ARB/IFN-α2b Therapy and ARB/adjuvant therapy are helpful to relieve COVID-19 pneumonia (Chen et al., 2020b; Xu et al., 2020b). However, another group found that arbidol monotherapy has little effect on improving clinical outcomes of mild/moderate patients (Li et al., 2020d). These results demonstrate that a combination of different compounds with ARB targeting different stages of the viral infection might be a promising stream in the antiviral treatment of the COVID-19. Notably, it is not recommended to use three or more antiviral drugs simultaneously (PRC, 2020).

Apart from CQ and ARB recommended by WHO and NHC of China, some compounds also exhibit promising characteristics in the treatment of the COVID-19. The first one is teicoplanin, which is a commonly used glycopeptide antibiotic in the treatment of Gram-positive bacterial infection, especially in *staphylococcal* and *streptococcus* infections (Baron et al., 2020; Ren et al., 2020c). Recently, it was reported that the antibiotic can be used against various viruses such as Ebola, influenza virus, flavivirus, hepatitis C virus, HIV, Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV (Colson and Raoult, 2016; Zhou et al., 2016). Teicoplanin can inhibit entry of the pseudoviruses (HIV-luc/2019-nCoV-S) by specifically blocking the activity of host cysteine proteases cathepsin L in the late endosomes, and thus inhibiting the release of genomic viral RNA and the virus replication cycle (Baron et al., 2020; Ren et al., 2020c). Therefore, the half-maximal (50 %) inhibitory concentration (IC_{50}) of teicoplanin is 1.66 u M on the pseudoviruses, and the recommended usage is 400 − 1200 mg/day intravenously or orally (Baron et al., 2020; Ren et al., 2020c) (Ceccarelli et al., 2020).

Another compound is niclosamide, which is an FDA-approved anthelminthic drug against tapeworm infections for several decades (Xu et al., 2020a). It is a multifunctional drug that can inhibit oxidative phosphorylation and stimulate adenosine triphosphatase activity in the mitochondria, regulate multiple signaling pathways and biological processes, including Wnt/β-catenin, mTORC1, STAT3, NF-κB, Notch, NS2B-NS3 interaction, and pH (Kratky and Vinsova, 2011; Pindiprolu and Pindiprolu, 2020; Xu et al., 2020a). These results suggest that niclosamide has broad-spectrum antiviral activities. Furthermore, the derivatives of niclosamide, such as 2-chloro-4-nitroanilide, O-alkylamino-tethered, or salicylamide derivatives, also exhibit more potent and orally bioavailable for antiviral treatments (Kratky and Vinsova, 2011; Xu et al., 2020a). Moreover, niclosamide may inhibit endocytosis of SARS-CoV-2 by blocking ACE2, and prevent autophagy of SARS-CoV-2 by inhibiting of S-Phase kinase-associated protein 2 (Pindiprolu and Pindiprolu, 2020). However, the antiviral activities of niclosamide and its derivatives in SARS-CoV-2 infection need further research and clinical verification.

2.2. Virus-targeted medicines (direct-acting antiviral drugs)

2.2.1. Viral proteins targeted medicines

The first type of highly recommended medicines direct targeting SARS-CoV-2 in clinical trials is repurposed drugs, which interact with viral proteins, especially viral major proteases.

Lopinavir/Ritonavir (also named as Kaletra or Lopimune, LPV/r) is a fixed-dose combination that is currently used to treat HIV infection. Lopinavir is an inhibitor of HIV protease, which prevents cleavage of the viral Gag-Pol polyprotein and results in the production of immature, non-infectious viral particles (Cao et al., 2020a; Lin et al., 2020b; Liu et al., 2020a; Liu and Wang, 2020; Wang et al., 2020a,2020b; Xu et al., 2020a). Ritonavir works as an inhibitor of cytochrome P450 (CYP450)

enzymes, an inhibitor of P glycoprotein, and a glucuronidase inducer, which can inhibit the CYP3A (CYP_{450}, family 3, subfamily A)-mediated metabolism of lopinavir, thereby increasing the plasma levels of lopinavir (Cao et al., 2020a; Sevrioukova and Poulos, 2014). Belhadi et al. reported that LPV/r was associated with the highest total number (2606) in the clinical trials for the COVID-19 treatment (Belhadi et al., 2020), suggesting the combination is promising in the antiviral therapy of the disease. An evaluation based on molecular modeling showed that both ritonavir and lopinavir can suitably bind to the endopeptidase C30 (EP_C30) of SARS-CoV-2 and induce significant conformation changes of CEP_C30, with a stronger efficacy induced by ritonavir (Lin et al., 2020b). However, some groups showed that there was no significant difference between LPV/r group and the standard care group, and LPV/r might results in more adverse events compared with that of the control group (Cao et al., 2020a; Li et al., 2020d). Therefore, the effectiveness and safety of these drugs need further evaluation.

Additionally, many repurposing drugs targeting viral main proteins were recently evaluated using computer-aided protocols, such as molecular docking (Chen et al., 2020c; Liu et al., 2020d; Omar, 2020; Sohini and Narayanaswamy, 2020). As reported by Omar, the binding energy of aliskiren, dipyridamole, mopidamol and rosuvastatin to COVID-19 main protease ($3CL^{pro}$) is relatively high (Omar, 2020). Atazanavir has a potential to bind to the viral RdRp (Kd 21.83 nM), helicase (Kd 25.92 nM), 3′-to-5′ exonuclease (Kd 82.36 nM), 2′-O-ribose methyltransferase (Kd of 390.67 nM), and endoRNAse (Kd 50.32 nM) (Beck et al., 2020), suggesting the drug can be used for COVID-19 treatment by inhibiting simultaneous all the subunits of the SARS-CoV-2 replication complex. Dai and colleagues synthesized two compounds (11a and 11b) targeting SARS-CoV-2 M^{pro} and found that these compounds showed good pharmacokinetic properties *in vivo* with low toxicity (Dai et al., 2020). However, whether these drugs or compounds have antiviral effects against SARS-CoV-2 infection still needs clinical evaluation.

2.2.2. Nucleoside analogues

The second type of highly recommended drugs targeting the virus is nucleoside analogs, which can disturb or halt the replication of the virus genome.

Remdesivir (GS-5734, RDV) is an adenosine analog originally designed for clinical trials against Ebola virus infections (Amirian and Levy, 2020; Martinez, 2020). As reported, remdesivir exhibit antiviral activity against multiple viruses, including Marburg virus, Nipah virus, Hendra virus, measles and mumps, respiratory syncytial virus, as well as human and zoonotic coronaviruses, such as HCoV-NL63, HCoVOC43, HCoV-229ESARS-CoV and MERS-CoV *in vitro* and in non-human primate models (Ko et al., 2020; Martinez, 2020), suggesting it has broad-spectrum antiviral activities. It was reported that remdesivir has obvious clinical benefits in *rhesus macaques* at the early stage of SARS-CoV-2 infection, supporting the early treatment of remdesivir in patients with COVID-19 to prevent the progression of severe pneumonia (Williamson et al., 2020). The active form of remdesivir in peripheral blood mononuclear cells (PBMCs) can obscure viral RdRp and evade proofreading by viral exonuclease, resulting in a decrease in viral RNA production (Al-Tawfiq et al., 2020; Gao et al., 2020b; Ko et al., 2020; Zhang and Zhou, 2020). Further studies showed that the active form of remdesivir, CHEMBL2016761 and GS-441,524, can bind to the viral RdRp binding pocket and replace natural counterpart ATP, causing insertion of remdesivir as well as three additional nucleotides in the extended viral strand (Cao et al., 2020b; Chang et al., 2020; Gordon et al., 2020; Wang et al., 2020d), and thus resulting in a disturbing viral genome. The relative binding free energy of remdesivir to the RdRp is -8.28 ± 0.65 kcal/mol, which is significantly stronger than that of the natural substrate ATP (Zhang and Zhou, 2020). However, in the past few months, remdesivir has been the most controversial drug in the treatment of COVID-19 due to its potential risks on kidney and liver functions (Adamsick et al., 2020; Davies et al., 2020). Moreover, Remdesivir can only reduce the hospitalization time of patients and has little effect on reducing the mortality rate. Several randomized controlled trials are currently ongoing worldwide to assess the safety and efficacy of this medicine in the treatment of COVID-19.

Favipiravir is a modified pyrazine analog, which acts as a prodrug and undergoes ribosylation and phosphorylation in cells by host enzymes to become active ribofuranosyl triphosphate derivative favipiravir-RTP (Delang et al., 2018; Du and Chen, 2020; Furuta et al., 2017). Favipiravir-RTP can bind to and inhibit the viral RdRp activity, and thus prevent viral transcription and replication (Chen et al., 2020a; Delang et al., 2018; Furuta et al., 2017). Further studies showed that favipiravir-RTP incorporates into a nascent RNA strand, leading to a termination of RNA strand elongation and viral proliferation (Furuta et al., 2017). Favipiravir-RTP also acts as a competitor of purine nucleoside binding to the RdRp (Furuta et al., 2017). These results indicate the compound is a promising antiviral drug targeting a broad range of RNA viruses. Recently, it was reported that favipiravir can inhibit the binding of the E and ORF7a proteins of SARS-CoV-2 to porphyrin, prevent the virus from entering host cells and capture free porphyrin (Liu and Li, 2020). Results from a clinical trial showed favipiravir has a higher clinical recovery rate and a more effectively reduced incidence of fever, cough than ARB for COVID-19 (Chen et al., 2020a). Although favipiravir may cause side effects, such as raised serum uric acid, this effect will soon disappear after drug withdrawal (Chen et al., 2020a). It is worth noting that favipiravir has a teratogenic effect, and therefore cannot be used for pregnant women (Delang et al., 2018; Furuta et al., 2017).

Ribavirin is a well-known nucleoside analogue that can inhibit a broad-spectrum of viruses. Results of molecular docking show that ribavirin can bind to SARS-CoV-2 RdRp with a binding energy of −7.8 kcal/mol, forming 13 hydrogen bonds between the RdRp and ribavirin, resulting in the termination of virus replication (Elfiky, 2020). However, ribavirin monotherapy is ineffective for SARS-CoV-2, but it can cause drug-related side effects including gastrointestinal symptoms, anemia, and liver function changes (Li et al., 2020b; Rios et al., 2020). Due to the combination of ribavirin and IFN is effective in treating MERS, combinations of ribavirin and IFN, and ribavirin and LPV/r are still recommended by the latest edition of the Guideline issued by the NHC, PRC (Du et al., 2020; PRC, 2020). Hung et al. (2020) evaluated a combination of IFN β-1b, LPV/r, and ribavirin for treating patients with COVID-19, and found that triple antiviral therapy using this combination is safe for mild to moderate COVID-19 patients and is superior to LPV/r alone in relieving symptoms, shortening virus shedding and hospitalization time (Hung et al., 2020). These results suggest that a combination of different drugs is feasible in the treatment of COVID-19.

Moreover, other nucleoside analogues, such as IDX-184, Sofosbuvir, and β-D-N4-hydroxycytidine (NHC, EIDD-1931) appear to be promising inhibitors against SARS-CoV-2 (Elfiky, 2020; Sheahan et al., 2020). IDX-184 and Sofosbuvir can bind to the virus RdRp with binding energies of −9.0 and −7.5 kcal/mol, and the numbers of hydrogen bonds are 11 and 7, respectively (Elfiky, 2020). EIDD-1931 produces lethal mutations in the viral genome by increasing the frequency of viral RNA mutations, thus exhibiting a broad-spectrum antiviral activity against SARS-CoV 2, MERS-CoV, SARS-CoV, and Bat-CoVs (Sheahan et al., 2020).

3. Traditional Chinese medicines

Traditional Chinese medicines (TCM) are widely used in China and some Chinese communities outside China, with characteristics of low cost, good curative effect, short duration of treatment, and multiple targets. Numerous facts prove that it is feasible to treat human and animal diseases with TCM, which can effectively relieve symptoms, reduce the development from mild to moderate or severe, improve the cure rate, reduce mortality rate, and promote the recovery of patient by

means of “multi-component, multi-target, multi-pathway” (Cantwell, 2010; Huang et al., 2020; Luo et al., 2020; Tong et al., 2020; Yuan et al., 2016).

During the last months, TCMs are widely used in clinical treatments against SARS-CoV-2 infection in China. As a result, TCMs play important roles and have become a highlight of the prevention and control of the COVID-19 (Ang et al., 2020; Ren et al., 2020a; Xu and Zhang, 2020). It was reported that more than 74,187 (91.5 %) of the confirmed cases of the COVID-19 patients in China were treated with TCMs, 61,449 (90.6 %) of which were used in Hubei Province. Clinical observation shows that the total effective rate of TCMs has reached more than 90 % (http://paper.people.com.cn/rmrb, 2020 − 03-24) (PRC, 2020), indicating the TCMs is effective in the treatment of the COVID-19.

Generally, different therapeutic logic of TCM is used based on the patient's physical condition and different symptoms, as well as the living environmental conditions. During the last six months, numerous prescriptions against COVID-19 were recommended by NHC based on the different symptoms and different patients (Huang et al., 2020; Liu et al., 2020c; Tong et al., 2020). For details dosage, please refer to the latest edition of the guideline issued by the NHC of China (Jin et al., 2020; PRC, 2020; Xu and Zhang, 2020). Among these TCMs, the "three drugs, three recipes" with obvious therapeutic effects, such as Jinhua Qinggan Granules, Lianhua Qingwen Capsules, Xuebijing Injection, Qingfei Paidu Decoction, Huashi Baidu Recipe, and Xuanfei Baidu Recipe, have been screened out and highly recommended to treat SARS-CoV-2 infection (http://paper.people.com.cn/rmrb) (Table 2) (PRC, 2020). For details, please read the review articles by Tong et al. (Tong et al., 2020) and Huang et al. (Huang et al., 2020).

3.1. For medical observation

For medical observation of COVID-19, several prescriptions can be used clinically, including Huoxiang Zhengqi capsules (pills, liquid, or oral solution), Jinhua Qinggan granules/capsules, Lianhua Qingwen capsules/granules, Shufeng Jiedu capsules/granules, Fangfeng Tongsheng pills/granules, and Yupingfeng San (Jin et al., 2020; Liu et al., 2020e; PRC, 2020; Xu and Zhang, 2020).

Huoxiang Zhengqi capsules (pills, liquid, or oral solution, HXZQ) consists of 10 Chinese herbs, with 778–2347 chemical ingredients (Jiang et al., 2020). Among these ingredients, more than 13 ingredients, including protocatechuic acid, chlorogenic acid, caffeic acid, liquiritin, hesperidin, apigetrin, rosmarinic acid, oxypeucedanin hydrate, byakangelicin, apigenin, glycyrrhizin, nobiletin, and 6-gingerol, are recognized as critical chemical marker compounds (Kim et al., 2014). HXZQ is widely used to dissipate cold and eliminate dampness targeting on the clinical features of fatigue and gastrointestinal discomfort (Jin et al., 2020; PRC, 2020). Moreover, this prescription is also used in the treatment of clinical symptoms as hypodynamia accompanied by gastrointestinal upset, as well as the exterior syndrome of cold-dampness (Jin et al., 2020; PRC, 2020). It was reported that HXZQ can regulate the immune response of $CD4^+$ and $CD8^+$ cells and suppress the levels of TNF-α in the intestine (He et al., 2006; Tong et al., 2020). Results of molecular docking showed that PTGS2, HSP90AB1, CAMSAP2, mPGES-1, LTA4H, NOS2 are possible targets of HXZQ in COVID-19 (Huang et al., 2020; Tong et al., 2020). Therefore, HXZQ has anti-inflammatory and immunomodulatory effects in COVID-19 by inhibiting inflammatory factors and regulating immune response (Huang et al., 2020; Tong et al., 2020).

Lianhua Qingwen capsules/granules, Shufeng Jiedu capsules/granules, Fangfeng Tongsheng pills/granules, Jinhua Qinggan granules/capsules, and Yupingfeng San are commonly used to against influenza virus infection (Jin et al., 2020; PRC, 2020; Xu and Zhang, 2020). For example, Lianhua Qingwen capsules/granules (LHQW) composed of 13 herbs, with 733–3084 chemical ingredients (Jiang et al., 2020), has broad-spectrum activities against influenza viruses (IAV) (Ding et al.,

Table 2
Possible antiviral mechanisms and characteristics of some traditional Chinese medicines recommended by NHC for the treatment of the SARS-CoV-2 infection.

Drug	Applicable clinical symptoms	Possible targeting patients	Possible mechanism	Proposed usage		Merit	Shortcoming	Ref.
				In vitro	*In vivo*			
Lianhua Qingwen Capsule/ Granule	Fever, cough, and fatigue, chest tightness, dyspnea, and loss of appetite	Medical observation	Blocking the early stages of infection, suppressing virus-induced NF-kB activation and alleviating virus-induced gene expression of IL-6, IL-8, TNF-a, IP-10, and MCP-1. Impairing the nuclear export of the viral RNP. Decreasing the level of inflammatory cytokines in the early stages of infection.	IC_{50} = 411.2 μg/mL, 600 μg/mL	Oral, four capsules each time, three times a day.	Easy to take	NA	(Ding et al., 2017; Government; Li et al., 2020c; PRC, 2020; Ye et al., 2020)
Shufeng Jiedu Capsule/ Granule	Fatigue, fever, sore throat, headache, nasal congestion rhinorrhea, cough	Medical observation	Enhancing autophagy and decreasing apoptosis, regulating signaling pathway, modulated anti-inflammatory, and immunomodulation activity	NA	Oral, four capsules each time, three times a day.	Easy to take	Occasionally nausea	(Government; Ji et al., 2020; Li et al., 2017; Mei et al., 2020; PRC, 2020; Tao et al., 2017; Wang et al., 2020g)
Xuebijing Injection	Systemic inflammatory response syndrome induced by infection and multiple organ dysfunction syndromes	Severe and critical patients	Immunoregulatory, anti-endotoxin, anti-inflammatory, clearing heat, detoxicating and blood-quickening	NA	Intravenous injection, 100 mL/ time, twice a day.	NA	Occasionally itchy skin	(Gao et al., 2013; Government; Jin et al., 2020; PRC, 2020).

Note: Ref., reference; NA, Not Available.

2017) as well as other respiratory diseases, such as chronic rhinosinusitis (Lin et al., 2020a), chronic obstructive pulmonary disease (Dong et al., 2014), etc. LHQW can block the early stage of virus infection, impair the nuclear export of the viral RNP, and modulate immune responses during virus infection (Ding et al., 2017). LHQW also can inhibit the replication of SARS -CoV-2, affect virus morphology, improve human immunity, and decrease inflammatory response or even cytokine storm (Hu et al., 2020; Li et al., 2020c; Tong et al., 2020; Ye et al., 2020). Meanwhile, three components of LHQW, Rutin, Forsythoside E, and Hyperoside, can bind the protease of SARS-CoV-2, with the binding energy of −9.1, −9.0 and −8.7 kcal/mol, respectively, forming hydrogen bonds and hydrophobic interactions between the active components and the viral protease (Ye et al., 2020). Moreover, chemical components of LHQW may also target cellular JAK-STAT, EGFR, ACE2, MAPK, PI3K-AKT, and NF-κB, etc (Huang et al., 2020; Tong et al., 2020). These results demonstrate that LHQW seems an effective TCM against SARS-CoV-2 infection.

Shufeng Jiedu Capsule/Granule (SFJD), consisting of eight medicinal herbs, is a widely used TCM for its antiviral, antibacterial, antitumor, and anti-inflammatory activities (Mei et al., 2020). It was reported that SFJD may protect lung injury and neuronal loss by enhancing autophagy and reducing apoptosis in rats with allergic rhinitis (Mei et al., 2020). It improves upper respiratory tract infection induced by *Pseudomonas aeruginosa* through various targets, especially ERK phosphorylation (Li et al., 2017). SFJD effectively regulates anti-inflammatory and immunoregulatory activities during acute lung injury through AKT1 regulation (Tao et al., 2017). Besides, SFJD combined with oseltamivir treatment significantly reduced IAV-induced airway inflammation and pulmonary virus titer (Ji et al., 2020). These results suggest SFJD may prevent and cure diseases, especially infectious diseases, by regulating various signal pathways.

3.2. For mild infection

For mild infection of SARS-CoV-2, Qingfei Paidu Decoction (QFPD), Sangju yin, and Yinqiao san were suggested to use in clinical (Jin et al., 2020; PRC, 2020; Xu and Zhang, 2020). Additionally, QFPD, Huashi Baidu Recipe, and Xuanfei Baidu Recipe are three new prescriptions specifically designed for the COVID-19, which exhibit active and effective roles in the prevention and treatment of the disease.

QFPD has more than 300 active ingredients and can act on more than 790 targets. QFPD might inhibit the invasion and replication of SARS-CoV-2 by directly targeting the viral 3C protein and host ACE2 (Huang et al., 2020). Recent studies showed that QFPD can improve several pathways in patients with COVID-19, such as response to oxygen levels, response to oxidative stress, and blood circulation (Wang et al., 2020e). Moreover, QFPD also can inhibit arachidonic acid metabolic pathway, and thereby regulating inflammatory cytokines (Ren et al., 2020c), suggesting this decoction has a positive effect on COVID-19 treatment. However, the exact biological mechanisms and side effects of these prescriptions need to be further evaluated.

Moreover, Xuanfei Baidu Recipe (XFBD) consists of 13 herbs, which acts on lung meridian by balancing immunity, eliminating inflammation, regulating hepatic and biliary metabolism, and recovering energy metabolism balance (Wang et al., 2020f).

3.3. For severe and critical infection

For severe and critical infection of SARS-CoV-2, Xuebijing Injection, Maxing Shigan tang, and Baihe Gujin tang can be used in clinically (Jin et al., 2020; PRC, 2020; Xu and Zhang, 2020). Xuebijing Injection derived from 5 herbs is suitable for systemic inflammatory response syndrome induced by infection and multiple organ dysfunction syndromes (Government, 2020; Jin et al., 2020; PRC, 2020; Tong et al., 2020). It was reported that the injection has the potential immunoregulatory ability, antibacterial, anti-endotoxin effects (Gao et al., 2013), as well as an anti-inflammatory effect by inhibiting the release of serum pro-inflammatory cytokines (Shen et al., 2013). Therefore, for severe and critical patients of the COVID-19, Xuebijing Injection is recommended for clearing heat, detoxicating, and blood-quickening (Jin et al., 2020; PRC, 2020).

4. Others

Interferon and glucocorticoid are also used in the treatment of the COVID-19. Interferons are well-known agents with broad-spectrum antiviral activities. Recent studies have shown that SARS-CoV-2 is sensitive to type I interferon pretreatment *in vitro* (Lokugamage et al., 2020). During the SARS-CoV-2 infection, phosphorylation of signal transducers and activators of transcription 1 (STAT1) and levels of IFN stimulated gene (ISG) proteins were significantly induced in the IFN-pretreated cells compared with that of the control cells and the cells infected with SARS-CoV but without IFN pretreatment (Lokugamage et al., 2020). Therefore, as recommended by NHC, China, IFN-α is used by atomization inhalation, with 5 million U or equivalent dose each time, 2 times/day for no more than 10 days (Dong et al., 2020; PRC, 2020). Besides, IFN combined with other antiviral compounds is also suggested for the treatment of the COVID-19, such as LPV/r combined with IFN-β, ribavirin plus IFN (Jin et al., 2020; PRC, 2020).

Additionally, glucocorticoids can exhibit anti-inflammatory activity by inhibiting gene transcription or immune response. It was reported that corticosteroid dexamethasone may reduce the mortality of severe COVID-19 patients by about one-third via limiting pro-inflammatory cytokines (Ledford, 2020; Theoharides and Conti, 2020). However, glucocorticoid-induced side effects are complex and frequent, such as inhibiting the protective function of T cells and B cells, blocking the clearance function of macrophages, etc. (Schacke et al., 2002; Theoharides and Conti, 2020). Therefore, glucocorticoid is suggested for a short period with 1 − 2 mg/kg/d for 3–5 days (Du et al., 2020; Jin et al., 2020; PRC, 2020). Notably, the side effects caused by interferon and glucocorticoid cannot be ignored. Therefore, only appropriate use of interferon and glucocorticoids are recommended, which can significantly improve the clinical symptoms of patients with SARS-CoV-2, reduce disease progression, and accelerate the absorption of lung lesions (Du et al., 2020; Jin et al., 2020; Li et al., 2020b; PRC, 2020).

5. Conclusion and perspective

In conclusion, SARS-CoV-2 is a highly infectious and pathogenic virus. It can be transmitted through contact and air, and may also be transmitted via mother-to-fetus and fecal-oral transmission routes. Although a variety of candidate medicines have been applied in clinical trials, the efficacy of these drugs still needs further research, especially in double-blinded, randomized, placebo-controlled trials.

It is worth noting that SARS-CoV-2 is an RNA virus that is easy to mutate, and some variations in the population were reported in recent studies, which may substantially affect its pathogenicity (Cao et al., 2020b; Wang et al., 2020a; Yao et al., 2020a; Zhao et al., 2020). Drugs against the viral proteins may be ineffective as viral genes continue to mutate, while drugs targeting cellular proteins may have better application prospects. Therefore, it is still one of the most important tasks to screen efficient and safe drugs according to the conserved sequences of the virus or the characteristics of host proteins. Besides, since candidate drugs and therapies are still being screened or in clinical trials, the combination of traditional Chinese medicine and other antiviral drugs as the first choice for the treatment of the disease can achieve better therapeutic effects. For critical patients, reasonable use of drugs should be combined with the actual situation of patients. Moreover, the adverse effects of each drug or therapy need further evaluation and follow-up.

CRediT authorship contribution statement

Chang Li: Writing - original draft, Funding acquisition. **Lin Wang:** Supervision, Funding acquisition, Writing - review & editing. **Linzhu Ren:** Conceptualization, Writing - original draft, Supervision, Funding acquisition, Writing - review & editing.

Declaration of Competing Interest

The author declares no conflict of interest. All authors have approved the final version of the manuscript.

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Appendix A. Supplementary data

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