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Current status of potential therapeutic candidates for the COVID-19 crisis

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ABSTRACT

As of April 15, 2020, the ongoing coronavirus disease 2019 (COVID-2019) pandemic has swept through 213 countries and infected more than 1,870,000 individuals, posing an unprecedented threat to international health and the economy. There is currently no specific treatment available for patients with COVID-19 infection. The lessons learned from past management of respiratory viral infections have provided insights into treating COVID-19. Numerous potential therapies, including supportive intervention, immunomodulatory agents, antiviral therapy, and convalescent plasma transfusion, have been tentatively applied in clinical settings. A number of these therapies have provided substantially curative benefits in treating patients with COVID-19 infection. Furthermore, intensive research and clinical trials are underway to assess the efficacy of existing drugs and identify potential therapeutic targets to develop new drugs for treating COVID-19. Herein, we summarize the current potential therapeutic approaches for diseases related to COVID-19 infection and introduce their mechanisms of action, safety, and effectiveness.

1. Introduction

Coronavirus disease 2019 (COVID-2019), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in Wuhan, China in December 2019 and has spread rapidly across the world due to its high transmissibility and pathogenicity (Munster et al., 2020; Zhu et al., 2020). SARS-CoV-2 is a distinct clade of beta coronaviruses encompassing severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) (Lu et al., 2020). Although most cases of the disease caused by most pathogenic coronaviruses are mild (Su et al., 2016), the SARS-CoV and MERS-CoV outbreaks in 2002 and 2012, respectively, demonstrated their high lethality (Schoeman and Fielding, 2019). SARS-CoV-2 bears an 82% resemblance to the genomic sequence of SARS-CoV (Chan et al., 2020); however, COVID-19 presents a lower case fatality rate and higher infectiousness than SARS, with mortality rates of approximately 3.7% for COVID-19 and 10% for SARS (WHO, 2003; WHO, 2020a). COVID-19 patients often exhibit mild symptoms, such as fever, cough, myalgia, and fatigue and generally have a good prognosis. However, a large proportion of COVID-19 cases have rapidly progressed to severe types, especially among older men with underlying diseases (Chen et al., 2020c; Huang et al., 2020; Liu et al., 2020c; Wang et al., 2020a). Severe cases can include dyspnea (Lin et al., 2020), shock (Wang et al., 2020a), organ dysfunction [acute respiratory distress syndrome (ARDS)] (Guan et al., 2020; Wang et al., 2020a; Xu et al., 2020; Yang et al., 2020; Yao et al., 2020), acute cardiac injury (Han et al., 2020a; Strabelli and Uip, 2020; Wang et al., 2020a; Yao et al., 2020; Zhou et al., 2020a), acute kidney injury (Guan et al., 2020; Li et al., 2020a; Pan et al., 2020; Wang et al., 2020a; Yao et al., 2020), acute liver injury (Xie et al., 2020; Xu et al., 2020; Yao et al., 2020; Zhang et al., 2020a), neurological injury (Mao et al., 2020; Wu et al., 2020), gastrointestinal injury (Yao et al., 2020), immune injury (Chen et al., 2020b; Guan et al., 2020; Qin et al., 2020; Wang et al., 2020b; Xu et al., 2020; Yao et al., 2020; Liu et al., 2020b; Zheng et al., 2020), coagulation impairment (Han et al., 2020b; Tang et al., 2020a), and even death (Huang et al., 2020; Wang et al., 2020a) (Fig. 1). In addition, COVID-19 pandemic has great impact on psychological stress and mental health worldwide (Bao et al., 2020; Kang et al., 2020; Li et al., 2020; Pfefferbaum and North, 2020; Shi et al., 2020a).

At present, the pathogenesis and etiology of COVID-19 remain unclear, and there are no targeted therapies for COVID-19 patients, who are empirically administered symptomatic treatments, with organ support for those who are seriously ill (Wang et al., 2020a). Given the pandemic spread of COVID-19 and the resulting global economic loss, developing alternative agents to contain SARS-CoV-2 is imperative. In this review, we summarize the potential therapeutic candidates under

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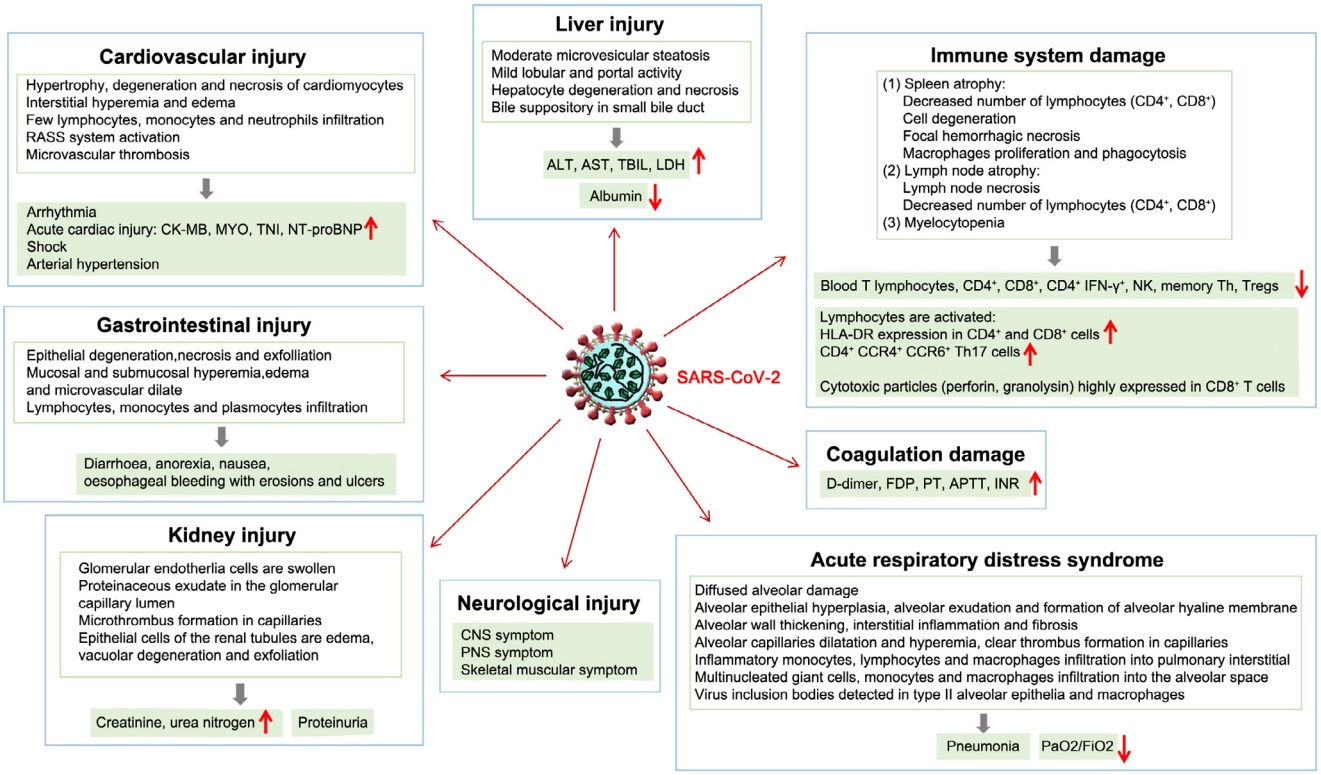

Fig. 1. SARS-CoV-2 infection-induced impairment of multiple organ function Impairment of multiple organ function by SARS-CoV-2 infection includes acute respiratory distress syndrome (ARDS), acute cardiac injury, acute kidney injury, acute liver injury, neurological injury, gastrointestinal injury, immune system injury, and coagulation impairment. Abbreviations: ALT, alanine transaminase; APTT, activated partial thromboplastin time; ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; CK-MB, creatine kinase myocardial band; CNS, central nervous system; FDP, fibrinogen degradation products; HLA-DR, human leukocyte antigen DR; INR, international normalized ratio; LDH, lactate dehydrogenase; MYO, myoglobin; NK, natural killer cell; NT-proBNP, N terminal pro-B-type natriuretic peptide; PaO2/FiO2, oxygenation index; PNS, peripheral nervous system; PT, prothrombin time; RAAS, renin-angiotensin-aldosterone system; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TBIL, total bilirubin; Th, helper T cell; TNI, troponin I.

development for COVID-19 based on clinical trials and describe their potential mechanisms of action (Fig. 2 and Fig. 3).

2. Antiviral treatments

2.1. Remdesivir

Remdesivir, a nucleotide prodrug, originally developed to control the Ebola virus (Siegel et al., 2017) and subsequently demonstrating its efficacy in inhibiting coronaviruses such as SARS-CoV and MERS-CoV *in vitro* (Sheahan et al., 2017), presents antiviral activity by interfering with RNA-dependent RNA polymerase, thereby attacking the virus's ability to replicate in the body (Fig. 2) (Agostini et al., 2018). A recent study indicated that remdesivir efficiently protected a human cell line against SARS-CoV-2 infection (Wang et al., 2020c). Treatment with intravenous remdesivir successfully improved the clinical state of the first U.S. COVID-19 patient (Holshue et al., 2020). Remdesivir is now being tested in several clinical trials designed to evaluate its efficacy and safety for the treatment of COVID-19. Notably, Gilead Sciences announced the result of a very recent clinical study on the efficacy of remdesivir on COVID-19 (Grein et al., 2020). In this report, 53 patients infected with severe COVID-19 were tracked, and 34 patients of whom were critically ill, with 30 patients requiring mechanical ventilation and 4 patients relying on extracorporeal membrane oxygenation (ECMO). Over a median follow-up of 18 days, 36 patients (68%) presented with improved oxygen-support class. 20 patients of 34 severely ill patients showed improvement in clinical conditions, with 17 of 30 patients stopped receiving invasive mechanical ventilation and 3 of 4 patients stopped receiving ECMO treatment respectively. The treatment of remdesivir limited the mortality rate of seriously ill patients needing invasive ventilation to 18%, and 5% for those who did not needed. Generally, the efficacy of remdesivir reflected in this study is hopeful. However, the sample size of this study was quite small, and definite effectiveness of remdesivir in the treatment of COVID-19 needs to be further verified (Table 1).

2.2. Lopinavir/ritonavir

Lopinavir/ritonavir (LPV-r) is a co-formulated human immunodeficiency virus (HIV)-specific protease inhibitor that serves as first-line therapy for HIV (Barragan and Podzamczer, 2008). Concomitant use of ritonavir could increase the plasma half-life of lopinavir through cytochrome P450 inhibition in the liver. During the 2003 SARS outbreak, LPV-r was reported to have *in vitro* inhibitory activity against SARS-CoV (Chu et al., 2004a), and combination therapy of LPV-r and ribavirin provided favorable results in treating patients with SARS (Fig. 2) (Chu et al., 2004b). Triple combination therapy with LPV-r, ribavirin, and IFN-α has shown clinical effectiveness for MERS (Kim et al., 2016). Notwithstanding, a recent open-label randomized study with 199 patients in Wuhan showed that LPV-r monotherapy did not produce any therapeutic benefits for COVID-19 patients compared with standard supportive care, which might be caused by the higher throat viral loads in the LPV-r group, concurrent pharmacologic interventions, and late treatment initiation (Table 1) (Cao et al., 2020). The enrolled COVID-19 patients were critically ill, and LPV-r treatment might have been started relatively late. However, in another retrospective cohort study, combination therapy of LPV-r and arbidol was associated with improved pulmonary computed tomography images (Deng et al., 2020).

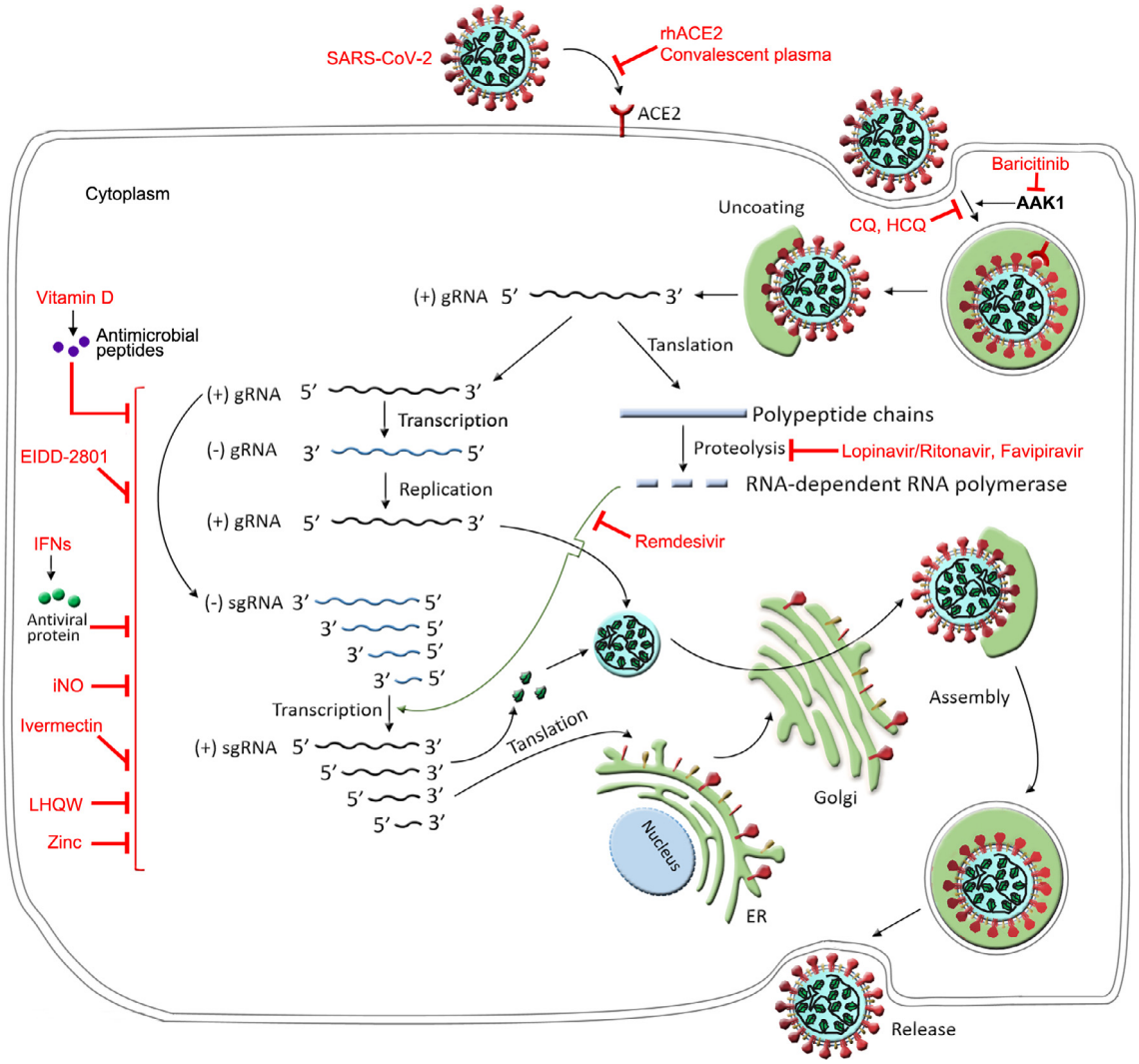

Fig. 2. The hypothetical replication cycle of SARS-CoV-2 and the possible targets of anti-COVID-19 drugs. SARS-CoV-2 binds to the ACE2 receptor on the surface of cells using the Spike protein, which subsequently triggers endocytosis. On releasing the viral nucleocapsid to the cytoplasm, encapsidated positive-strand genomic RNA [(+)gRNA] serves as a template to translate polypeptide chains, which are cleaved to non-structural proteins including RNA-dependent RNA polymerase. The single negative strand RNA [(-)gRNA] synthesized from (+)gRNA template is employed to replicate more copies of viral RNAs. Subgenomic RNAs (sgRNAs) are synthesized by discontinuous transcription from the (+)gRNA template and then encode viral structural and accessary proteins, which are subsequently assembled with newly synthesized viral RNA to form new virions. The nascent virions are then transported in secretory vesicles to the plasma membrane and released by exocytosis. RhACE2, convalescent plasma and JAK inhibitor baricitinib could dampen the binding of the Spike protein on the surface of the SARS-CoV-2 to ACE2 expressed on the cell surface. Lopinavir/ritonavir and favipiravir inhibit the proteolysis of polypeptide chains. Remdesivir inhibits RNA-dependent RNA polymerase. EIDD-2801 could inhibit SARS-CoV-2 replication. NO and Zinc might inhibit SARS-CoV-2 replication. Vitamin D might induce antimicrobial peptides to reduce SARS-CoV-2 replication. Ivermectin could effectively block SARS-CoV-2 growth. Baricitinib could interrupt the passage of SARS-CoV-2 entering cells through inhibition of AAK1-mediated endocytosis. CQ and HCQ inhibit virus/cell fusion process. LHQW and IFNs could block the process of virus replication (RNAs transcription, protein translation, and post-translational modification). Abbreviations: AAK1, adaptor-associated kinase 1; CQ, chloroquine; ER, endoplasmic reticulum; HCQ, hydroxychloroquine sulfate; IFNs, interferons; iNO, inhaled nitric oxide; JAK, janus kinase; LHQW, Lianhua Qingwen; rhACE2, recombinant human angiotensin-converting enzyme 2; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Collectively, the combination therapy of LPV-r and other antiviral agents in early stages of COVID-19 infection might hold promise for treating COVID-19.

2.3. Favipiravir

Favipiravir, also known as Avigan® and originally developed and approved for the influenza virus infection epidemic in Japan, has a broad spectrum of antiviral activity (Furuta et al., 2013). Once it enters cells, favipiravir undergoes phosphorylation to convert into its active phosphorylated form (favipinavir-RTP), which potently inhibits viral RNA polymerase, thereby interfering with viral genome replication (Fig. 2) (Furuta et al., 2005). Favipiravir demonstrated efficacy in inhibiting a wide range of viruses, including resistant influenza viruses and other RNA viruses, such as arenaviruses, bunyaviruses, and filoviruses (Delang et al., 2018). Previous studies have showed that favipiravir is efficacious against Ebola virus in rodent models (Oestereich et al., 2014; Smither et al., 2014), while its effectiveness in humans is unproven (Sissoko et al., 2016). Favipiravir appears to be effective in COVID-19. Two clinical trials involving a total of 340 patients were conducted in Wuhan and Shenzhen. At a press conference in March 17, 2020, Xinmin Zhang, an official of China's Science and Technology Ministry, stated that favipiravir appeared to be effective in COVID-19 (Hackett, 2020). Preliminary clinical data from 80 patients in the Third People's Hospital of Shenzhen suggested that favipiravir exerted antiviral effects more potently than LPV-r, with no overt adverse reactions

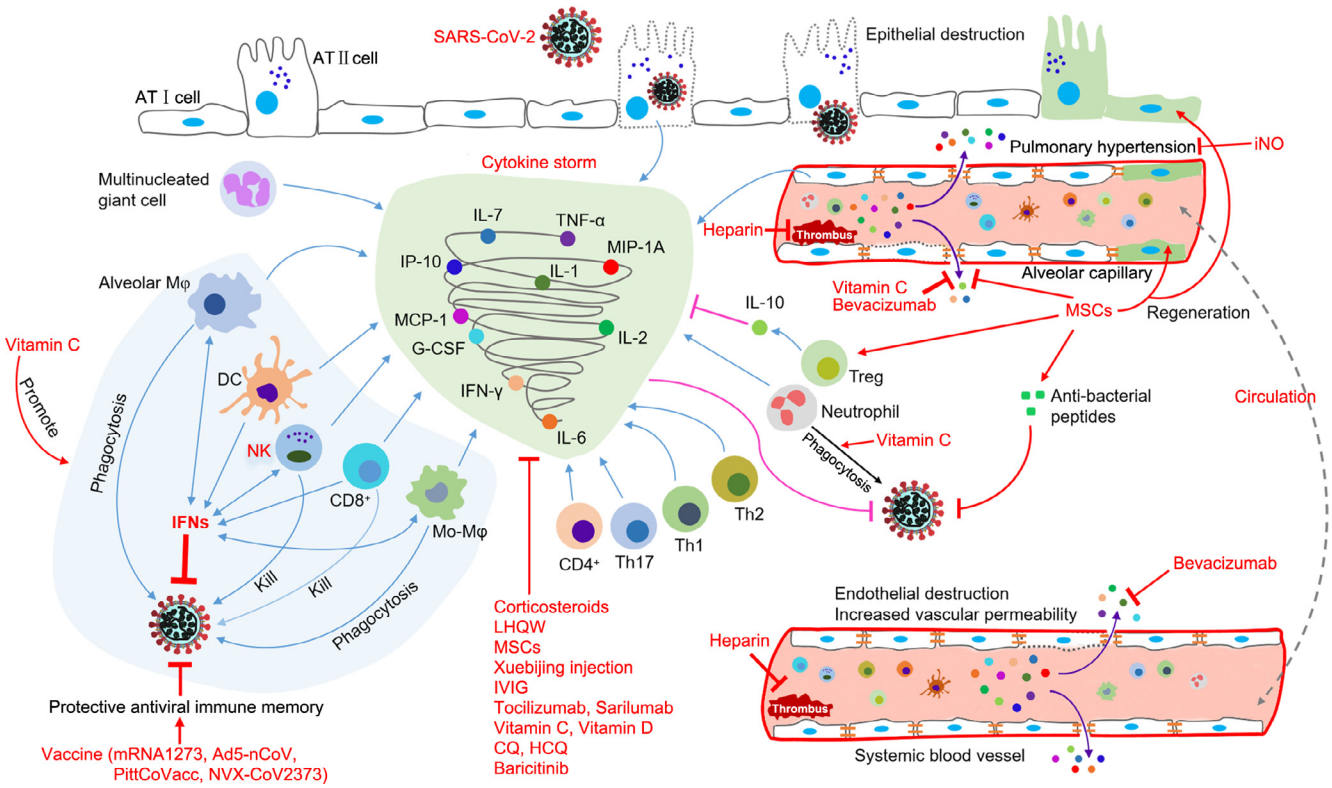

Fig. 3. The hypothetical mechanisms of SARS-CoV-2 infection-induced cytokine storm and antiviral immunity and the possible therapeutic targets of patients with COVID-19 infection. "*Cytokine storms*" might start with inflammatory cytokine secretion into lung tissue and pulmonary blood vessels from virus-infected alveolar epithelial cells, pulmonary vascular endothelial cells, alveolar macrophages, multinucleated giant cells, and other infiltrated immune cells, which mainly serve to limit the replication and spreading of the virus and to induce downstream immune responses via the blood circulation. Following the recruitment and activation by primary cytokines, systemic immune cells (neutrophils, DCs, Mo-Mφ, NK cells, $CD4^+$ T cells, $CD8^+$ T cells, Th1 cells, Th2 cells, and Th17 cells, etc.) further secrete inflammatory cytokines and promote the cascade of inflammatory processes to eliminate virus and virus-infected cells. Vitamin C might inhibit SARS-CoV-2 and alleviate the illness by decreasing inflammatory cytokines, stimulating IFN production, supporting lymphocyte proliferation, boosting the phagocytic capability of neutrophils, monocytes, and macrophages, protecting lung barrier function and reducing lung vascular injury, increasing IFN secretion from alveolar Mφ, Mo-Mφ, DCs, NK cells, and $CD8^+$ T cells. IFNs could enhance NK cell cytotoxicity, enhance expression of major histocompatibility complex I proteins, and promote the production of IFNs and the proliferation of NK cells and Mφ. Bevacizumab could reduce vascular permeability. Vaccines (mRNA1273, Ad5-nCoV, PittCoVacc, and NVX-CoV2373) could induce protective antiviral immune memory, while MSCs could decrease pro-inflammatory cytokines, promote regeneration, secrete multiple paracrine factors and anti-inflammatory cytokines, and enlarge the proportion of Treg cells. iNO could alleviate pulmonary hypertension through its selective pulmonary vasodilation. Corticosteroids, LHQW, Xuebijing, IVIG, tocilizumab, sarilumab, baricitinib, vitamin D, CQ, and HCQ could also reduce inflammation. Heparin blocks the thrombus formation. Abbreviations: AT I, type I alveolar epithelial cell; AT II, type II alveolar epithelial cell; CQ, chloroquine; DC, dendritic cell; G-CSF, granulocyte-colony stimulating factor; HCQ, hydroxychloroquine sulfate; IFN-γ, interferon gamma; IL, interleukin; iNO, inhaled nitric oxide; IP-10, interferon-inducible protein-10; IVIG, intravenous gamma globulin; LHQW, Lianhua Qingwen; MCP-1, monocyte chemotactic protein 1; MIP-1A, macrophage inflammatory protein-1a; Mo-Mφ, monocyte-macrophage; MSCs, mesenchymal stem cells; NK, natural killer cell; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; Th, helper T cell; TNF-α, tumor necrosis factor alpha; Treg, regulatory T cell.

(Third People's, 2020). The other clinical trial in Wuhan showed that, based on conventional therapy, favipiravir demonstrated higher efficacy than arbidol in terms of the 7-day recovery rate and duration of symptom attenuation in patients with moderate COVID-19 infection (Chen et al., 2020a). Taken together, the clinical results of favipiravir are favorable (Table 1); however, further study of favipiravir monotherapy using a large sample size is needed.

2.4. EIDD-2801

Researchers from Emory University, the University of North Carolina, and Vanderbilt University Medical Center tested a new drug, EIDD-2801, for its *in vitro* efficacy against SARS-CoV-2, and its laboratory results are encouraging (Sheahan et al., 2020). Based on EIDD-1931, an orally bioavailable ribonucleotide analog, EIDD-2801 is designed to optimize oral bioavailability and improve drug uptake in humans and non-human primates (Fig. 2). EIDD-1931 has a variety of antiviral activities against numerous causal agents of deleterious viral infectious diseases, including influenza, chikungunya, Ebola, Venezuelan equine encephalitis, and coronavirus-associated diseases (Agostini et al., 2019; Painter et al., 2019; Reynard et al., 2015; Toots et al., 2019). As a ribonucleotide analog, EIDD-1931 shares similar mechanisms of action with remdesivir and exerts antiviral effects by mimicking a ribonucleotide, thereby mistakenly being incorporated into viral RNA, leading to lethal mutagenesis during virion RNA synthesis and inhibiting the RNA-dependent RNA polymerase encoded by the virus during viral replication (Fig. 2) (Painter et al., 2019; Sheahan et al., 2020). The study suggested that EIDD-1931 robustly blocked the replication of SARS-CoV, MERS-CoV, and the newly emerging SARS-CoV-2 in cell assays. EIDD-2801 demonstrated its prophylactic and therapeutic effects in murine models of SARS and MERS, showing diminished viral lung titers, attenuated weight loss, ameliorated lung damage, and improved pulmonary function, which are dependent on the administered dosage and the treatment initiation time. Compared with remdesivir, EIDD-2801 appears to be favorable. EIDD-2801 has a more convenient oral administration, while remdesivir must rely on intravenous administration by a trained specialist. More importantly, EIDD-2801 showed active antiviral activity against

Table 1
Potential therapeutic drugs for COVID-19.

Intervention	Type	Status and mechanisms	Recommendations
Remdesivir	Antiviral	Remdesivir interferes with virus RNA polymerases to inhibit virus replication, and was used for Ebola virus outbreak	Being tested in clinical trials
Lopinavir/Ritonavir	Antiviral	Lopinavir/ritonavir are approved protease inhibitors for HIV	Inconsistent results in completed clinical trials
Favipiravir	Antiviral	Favipiravir inhibits viral RNA polymerase, thus interfering with viral replication	Proven efficacy in completed clinical trials
EIDD-2801	Antiviral	EIDD-2801 is incorporated during RNA synthesis and then drives mutagenesis, thus inhibiting viral replication	Prepared for clinical trials
Convalescent plasma	Antiviral	Convalescent plasma from cured patients provides protective antibody against SARS-CoV-2	Proven efficacy
rhACE2	ACE2 blocker	rhACE2 completely binds to virus S-protein, thus protects host lungs from virus attack	Being tested in clinical trials
Chloroquine Hydroxychloroquine	Antimalaria	Endosomal acidification fusion inhibitor anti-inflammatory activity	Proven efficacy in completed clinical trials (clinical data partly not shown)
Tocilizumab	mAb	Humanized mAb targeting IL-6	Being tested in clinical trials
Sarilumab	mAb	Humanized mAb targeting IL-6	Being tested in clinical trials
Bevacizumab	mAb	Humanized mAb targeting VEGF	Being tested in clinical trials
Baricitinib	JAK inhibitor	Baricitinib attenuates proinflammatory response by inhibiting JAK and blocks virus entering into host cells through inhibiting AAK1	Being tested in clinical trials
MSCs	Cell therapy	MSCs have regenerative and immunomodulatory properties and protect lungs against ARDS	Proven efficacy in completed clinical trials
iNO	Vasodilator	iNO possesses capability of potent and selective pulmonary vasodilation and antimicrobial activity	Being tested in clinical trials
LHQW	TCM	LHQW is used for prevention and treatment for infuenza, and has previously been used for SARS outbreak	Being tested in clinical trials
Xuebijing injection	TCM	Xuebijing serving as endotoxin antagonist, anti-inflammatory agent and anti-coagulant is used for sepsis	Being tested in clinical trials
IFNs	Immunoenhancer	IFNs inhibit viral RNA transcription, protein translation and post translational modifification, thus suppress virus replication	Being tested in clinical trials
IVIG	Immunoenhancer	IVIG provides passive immunity and anti-inflammatory effects	Being tested in clinical trials
NK cell therapy	Immunoenhancer	NK cells can elicit rapid and robust protective effects in defense against viral infections through direct cytotoxicity and immunomodulatory capability	Being tested in clinical trials
Corticosteroids	Corticosteroids	Corticosteroids dampen proinflammatory cytokines and possess antifibrotic property	Still in controversy
Heparin	Anticoagulants	Heparin can reverse the hypercoagulability in severe cases of COVID-19	Proven efficacy in severe types of COVID-19
Vitamin C	Nutritional supportive care	Vitamin C boosts immunity by stimulating IFN production, supplying lymphocyte proliferation and enhancing neutrophil phagocytic capability	Being tested in clinical trials
Vitamin D	Nutritional supportive care	Vitamin D induces secretion of antimicrobial peptides and has immunomodulatory property	Being tested in clinical trials
Zinc	Nutritional supportive care	Zinc is necessary for the immune system and has anti-viral activities	Being tested in clinical trials
Ibuprofen	NSAIDs	Ibuprofen has been widely used to treat fever or pain	Still in controversy
mRNA-1273	Vaccine	mRNA-1273 contains mRNA that can encode S protein of SARS-CoV-2	Being tested in clinical trials
Ad5-nCoV	Vaccine	Ad5-nCoV uses replication-defective adenovirus type 5 as vector to load some gene fragments of SARS-CoV-2 on it to express SARS-CoV-2 S protein	Being tested in clinical trials
PittCoVacc	Vaccine	PittCoVacc utilizes microneedle array to deliver pieces of S-protein of SARS-CoV-2 into body	Prepared for phase I clinical trials
NVX-CoV2373	Vaccine	NVX-CoV2373 is a stable, prefusion protein developed through the advanced nanoparticle technology	Prepared for phase I clinical trials

Abbreviation: ARDS, acute respiratory distress syndrome; COVID-2019, corona virus disease 2019; HIV, human immunodeficiency virus; IFNs, interferons; IL-6, interleukin 6; iNO, inhaled nitric oxide; IVIG, intravenous gammaglobulin; LHQW, Lianhua Qingwen; mAb, monoclonal antibody; MSCs, mesenchymal stem cells; NK, natural killer cell; NSAIDs, non-steroidal anti-inflammatory drugs; rhACE2, recombinant human angiotensin-converting enzyme 2; SARS, severe acute respiratory syndrome; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TCM, traditional Chinese medicine; VEGF, vascular endothelial growth factor.

remdesivir-resistant viruses, according to the data presented by the study. Of significant importance, EIDD-1931 appeared to be effective not just for SARS-CoV, MERS-CoV, and SARS-CoV-2, but also other coronavirus species, indicating its potential efficacy for emerging coronaviruses in the future. The U.S. Food and Drug Administration (FDA) has approved an Investigational New Drug application for EIDD-2801, and clinical studies in humans are expected to start as soon as possible (Table 1) (BioSpace, 2020).

3. Convalescent plasma

Convalescent plasma collected from donors who have survived an infectious disease by producing protective antibodies is considered to provide a great degree of protection for recipients affected by the emerging virus (Dodd, 2012). Convalescent plasma has been successfully employed to treat numerous infectious diseases, including the 2003 SARS-CoV-1 epidemic, 2009–2010 H1N1 influenza virus pandemic, and 2012 MERS-CoV epidemic (Dodd, 2012; Hung et al., 2011; Mair-Jenkins et al., 2015), for which modern medicine has no specifically effective treatment. In the absence of specific antiviral agents and vaccines for COVID-19, clinical trials have been conducted aimed at investigating the efficacy of convalescent plasma in treating COVID-19. A very recently published study by Chinese researchers confirmed the efficacy of convalescent plasma in controlling SARS-CoV-2 (Table 1) (Roback and Guarner, 2020). The report suggested that COVID-19 patients showed signs of improvement approximately 1 week after

convalescent plasma transfusion. Another clinical study involved 10 critically ill patients infected with COVID-19 from 3 different hospitals in Wuhan suggested high-titer convalescent plasma transfusion can effectively neutralize SARS-CoV-2, leading to impeded inflammatory responses and improved symptom conditions without severe adverse events. All 10 patients receiving convalescent plasma transfusion showed improvement of clinical outcomes or were cured and discharged from hospital (Duan et al., 2020). Given the clinical effectiveness of convalescent plasma, the FDA has granted clinical permission for applying convalescent plasma to the treatment of critically ill COVID-19 patients (FDA, 2020).

4. Spike Protein-Angiotensin-Converting enzyme 2 blockers

4.1. Angiotensin-converting enzyme 2 (ACE2)

ACE2 serves as a negative regulator of the renin angiotensin system (RAS) and is widely distributed among lung tissue and many extrapulmonary tissues, including brain, heart, liver, kidney, endothelium, and intestine (Fig. 2) (Crackower et al., 2002; Ding et al., 2004; Hamming et al., 2004). Of them, alveolar epithelial type II cells possess an abundance of ACE2 receptors (Zhao et al., 2020). Unfortunately, ACE2 is also a functional receptor of SARS-CoV (Li et al., 2003) and SARS-CoV-2 (Zhou et al., 2020b). The spike (S) protein of SARS-CoV and SARS-CoV-2 binds to the host ACE2 receptor and then enters target cells (Fig. 2). Critically, SARS-CoV-2 shows higher affinity for ACE2 than SARS-CoV (Wrapp et al., 2020). Moreover, the S protein of SARS-CoV-2 contains a site that can be recognized and activated by a host enzyme called furin, which is highly expressed in the lungs (Coutard et al., 2020). These findings might provide strong evidence for the high pathogenicity of SARS-CoV-2. Due to the pivotal role of widely distributed ACE2 in the entry and replication of viruses, blocking S protein binding to ACE2 might offer some protection against SARS-CoV-2 infection (Fig. 1). A study using a murine model of SARS showed that SARS-CoV S protein binding to ACE2 led to RAS downregulation and consequently contributed to severe lung injury (Imai et al., 2005). Therefore, recombinant human ACE2 (rhACE2) might protect host lungs against infection through an enhanced ACE2 level to neutralize the S protein on the SARS-CoV-2 surface. Clinical evidence has demonstrated the safety of rhACE2 application (Haschke et al., 2013; Khan et al., 2017). A recent *in vitro* study demonstrated that the fusion protein of rhACE2 with an Fc fragment shows high affinity binding to the receptor-binding domain of SARS-CoV-2 and potently neutralizes SARS-CoV-2 (Lei et al., 2020). Additionally, the findings from a newly online published report in *Cell* were strongly supportive of potential efficacy of rhACE2 for SARS-CoV-2 infection (Monteil et al., 2020). The study showed that clinical-grade human recombinant soluble ACE2 (hrsACE2) displayed potently inhibitory activity against SARS-CoV-2 in cell cultures and in engineered replicas of human blood vessels and kidneys in a dose-dependent manner. The researchers found that before infecting cells, SARS-CoV-2 co-incubated with hrsACE2, rather than mouse recombinant soluble ACE2, demonstrated dropped activity to infect cells. In the organoid level, administration of hrsACE2 significantly blocked SARS-CoV-2 infection in both engineered human blood vessels and kidneys without observed toxicity. However, note that this study focused on the early stages of SARS-CoV-2 infection, it is still unclear whether hrsACE2 can play a role in the later infection process. Taken together, it is likely that rhACE2 has potentially curative effectiveness in COVID-19. A clinical trial is underway to investigate the efficacy of rhACE2 in the treatment of COVID-19 (NCT04287686) (Table 1).

ACE inhibitors (ACEIs)/angiotensin receptor blockers (ARBs) are widely used for treating cardiovascular diseases. Studies have shown that ACEIs/ARBs can upregulate ACE2 expression (Ferrario et al., 2005; Ishiyama et al., 2004; Karram et al., 2005), which might correlate with the susceptibility to SARS-CoV-2. However, evidence has shown that RAS activation and decreased ACE2 expression contribute to the pathological process of lung injury after SARS-CoV infection (Kuba et al., 2005). Serum angiotensin II levels are markedly elevated and exhibit a linear positive correlation to viral load and lung injury in COVID-19 (Liu et al., 2020d). Consequently, the effects of ACEIs/ARBs on lung-specific ACE2 expression in COVID-19 remain unknown. ACEIs/ARBs might have a dual role in COVID-19. On the one hand, the elevated ACE2 level might increase susceptibility to SARS-CoV-2, while on the other, ACE2 activation and RAS deregulation might ameliorate the acute lung injury, heart injury, and renal damage induced by SARS-CoV-2 (Guo et al., 2020). However, there has been no definite evidence on whether taking ACEIs/ARBs is beneficial or harmful for COVID-19 infected patients.

5. Chloroquine and hydroxychloroquine

Chloroquine (CQ), a drug widely used in treating malarial and autoimmune diseases, also confers considerable broad-spectrum antiviral effects even against SARS-CoV (Table 1) (Keyaerts et al., 2004b; Savarino et al., 2006; Yan et al., 2013). A recent study demonstrated that CQ has anti-SARS-CoV-2 activity *in vitro* (Fig. 3) (Wang et al., 2020c). A subsequent letter in *Bioscience* confirmed that CQ is efficacious in treating COVID-19 pneumonia in numerous related clinical trials (Gao et al., 2020). CQ therapy resulted in improved pulmonary lesions, shortened disease course, and good outcomes (Table 1) (Gao et al., 2020). Given the efficiency displayed by CQ in clinical practice, CQ has been included in the Guidelines for the Diagnosis and Treatment of COVID-19 (7th edition) issued by the National Commission of the People's Republic of China (NHPFC, 2020).

Hydroxychloroquine sulfate (HCQ) shares a similar chemical structure and mechanisms of action with CQ but with lower ocular toxicity (Lim et al., 2009) and has proven efficacious in containing SARS-CoV-2 *in vitro* (Liu et al., 2020a). CQ and HCQ exert antiviral function through various mechanisms. CQ has been shown to interfere with the glycosylation process of ACE2 in host cells, thereby inhibiting the efficiency of the binding of S protein with ACE2, in turn disrupting the virus/cell fusion process (Fig. 3) (Savarino et al., 2006). CQ can increase the pH of acidic cellular organelles required for virus entry into host cells (Savarino et al., 2003). In addition to its direct antiviral activity, CQ and HCQ can attenuate major "*cytokine storms*" (an overreaction of the immune system causing inflammatory "*storms*") by decreasing cytokine production (interleukin [IL]-1, IL-6, and tumor necrosis factor [TNF], etc.) (Fig. 3) (van den Borne et al., 1997). Notably, high cytokine concentrations have been observed in seriously ill COVID-19 patients (Huang et al., 2020), indicating that over-reactive immune responses exacerbate COVID-19. Therefore, the immune-modulating activity of HCQ might partially account for its efficient control of SARS-CoV-2 infection. CQ and HCQ are therefore promising drugs of choice for large-scale use due to their low cost, wide availability and potential efficacy for treating COVID-19. CQ and HCQ need to be administered with caution when treating COVID-19 infection to prevent toxicity.

A recent open-label study in France showed that HCQ treatment was significantly associated with viral load reduction/disappearance in COVID-19 patients and that its effect was reinforced by azithromycin (Gautret et al., 2020). Although this study is an open-label study using small sample size, the combination of HCQ and azithromycin could be promising candidate for COVID-19 patients. In contrast, a multinational, network cohort and self-controlled case series study demonstrated that short-term HCQ treatment is safe (Lane et al., 2020). However, combination of HCQ and azithromycin may induce an increased risk of 30 day cardiovascular mortality, chest pain/angina, and heart failure (Lane et al., 2020). Therefore, we must pay the attention for the combination therapy in the management of COVID-19 patients.

6. Human monoclonal antibody

6.1. Tocilizumab and sarilumab

Tocilizumab (TCZ) and sarilumab are monoclonal antibodies against IL-6 receptors and have been employed to treat rheumatoid arthritis (Nishimoto et al., 2000; Raimondo et al., 2017). TCZ and sarilumab efficiently inhibit IL-6 through both membrane-bound and soluble IL-6R (Fig. 3) (Raimondo et al., 2017; Sakkas, 2016). TCZ has been approved by the FDA for treating cytokine release syndrome marked by excessive cytokine production and consequently rapid multiorgan damage (lungs, kidney, and heart) (Shimabukuro-Vornhagen et al., 2018). COVID-19 disease severity depends on the increase in pro-inflammatory factors [IL-6, IL-1, IL-2, IL-7, IL-10, granulocyte-colony stimulating factor, interferon-γ-inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein-1 alpha, and TNF-α] (Huang et al., 2020; Ruan et al., 2020; Zhou et al., 2020a), suggesting that cytokine storms are involved in the development of COVID-19. One of the key cytokines involved in the immune system perturbation is IL-6 (Mehta et al., 2020). As IL-6 receptor antagonists, TCZ and sarilumab have therefore been hypothesized to exert suppressive effects on exuberant and dysfunctional systematic inflammation in patients infected with SARS-CoV-2 and further improve patients' condition. Three clinical trials (ChiCTR2000030196, ChiCTR2000030442, and ChiCTR2000029765) for TCZ have been approved for COVID-19, and the National Health and Family Planning Commission of China has approved the treatment with TCZ in patients with elevated IL-6 level. (Table 1) (NHPFC, 2020). Encouraging results have been seen in Italy where three seriously ill patients administered TCZ showed the signs of improvement (Italian ANSA News Agency, 2020). According to the announcement from Regeneron Pharmaceuticals and Sanofi on March 16, 2020, a phase II/III clinical trial in the U.S. for sarilumab has been conducted to assess its therapeutic effects in patients with severe COVID-19 infection (Table 1) (Regeneron, 2020).

6.2. Bevacizumab

Bevacizumab is a monoclonal anti-vascular endothelial growth factor (VEGF) antibody that competes with VEGF receptors on the surface of endothelial cells for VEGF binding, thereby inhibiting the effects caused by binding VEGF to its receptors, such as endothelial cell proliferation and neovascularization (Fig. 3) (Ferrara et al., 2004). VEGF produced by various inflammatory and epithelial cells is a potent vascular permeability inducer (Dvorak et al., 1995). Previous reports have shown that plasma VEGF levels markedly increase in patients with ARDS (Thickett et al., 2001). Given the causal link between ARDS and increased vascular permeability and pulmonary edema (Fanelli and Ranieri, 2015). Bevacizumab might be a potential anti-ARDS therapeutic approach. ARDS is a common complication in severe cases of COVID-19 (Fig. 1). Bevacizumab is therefore likely to be a promising therapy against COVID-19 (Table 1).

7. Janus Kinase inhibitor

7.1. Baricitinib

Baricitinib, a highly selective janus kinase (JAK) inhibitor, has been approved for treating rheumatoid arthritis (Al-Salama and Scott, 2018). JAK-dependent pathways are responsible for producing a variety of cytokines involved in the pathogenesis of the progression process of COVID-19 characterized by elevated levels of inflammatory factors (e.g., IL-6, IL-7, and IL-2) (O'Shea and Plenge, 2012). Baricitinib also serves as an inhibitor of adaptor-associated kinase 1 (AAK1, a member of the numb-associated kinase family), which plays a central role in regulating endocytosis through which the virus invades host cells (Fig. 3) (Richardson et al., 2020). Therefore, baricitinib might exert beneficial effects on COVID-19 pneumonia, not only by impeding overexuberant immune responses by hijacking cytokine signaling pathways but also preventing SARS-CoV-2 from entering host cells. However, blockage of JAK-dependent pathways by baricitinib can also inhibit production of interferons (IFNs) (O'Shea and Plenge, 2012), which might have antiviral activity against SARS-CoV-2 (Fig. 3) (Ströher et al., 2004). Baricitinib treatment is therefore a double-edged sword (Table 1), and choosing the appropriate time to administer baricitinib is vitally important. For severely ill patients with abnormal biomarkers, cautious baricitinib treatment might yield clinically beneficial effects.

8. Mesenchymal stem cells

Mesenchymal stem cells (MSCs) are multipotent cells isolated from diverse mesenchymal tissues (e.g., bone marrow, umbilical cord, adipose tissue) (Lv et al., 2014). By virtue of their low immunogenicity (Chamberlain et al., 2007), proven safety (Zheng et al., 2014), and reparative and immunomodulatory properties (Galipeau and Sensébé, 2018; Mei et al., 2010), MSCs are attractive therapeutic candidates for treating a wide range of diseases [e.g., graft-versus-host disease (Le Blanc et al., 2008), sepsis, and ARDS] (Fig. 3) (Asmussen et al., 2014; Krasnodembskaya et al., 2012). A large body of preclinical data has demonstrated the efficacy of MSCs in treating ARDS, manifested in reduced pulmonary edema, decreased plasma concentrations of pro-inflammatory cytokines, and reduced mortality rates (Chimenti et al., 2012; Devaney et al., 2015; Xu et al., 2007). Although not fully understood, the mechanisms by which MSCs exert protective effects include their direct regenerative ability and secretion of multiple paracrine factors including antibacterial peptides and anti-inflammatory cytokines such as IL-10 (Gupta et al., 2012; Gupta et al., 2007). Another attractive property of MSCs is immune response modulation (Aggarwal and Pittenger, 2005). MSCs have been shown to enlarge the proportion of regulatory T cells and decrease pro-inflammatory factors such as IL-6 and TNF-α (Fig. 3) (Gupta et al., 2012; Li et al., 2012; Prevosto et al., 2007). MSCs showed positive efficacy in a recent study of COVID-19 patients. Treatment with allogenic MSC transplantation at Beijing YouAn Hospital showed significantly improved functional outcomes without obvious adverse effects in 7 COVID-19 patients (Table 1) (Zikuan Leng et al., 2020). Adoptive MSC transfer might therefore be a valuable treatment option for COVID-19.

9. Inhaled nitric oxide (iNO)

Nitric oxide (NO) is a key endogenous molecule implicated in a variety of physiological and pathological processes including smooth muscle relaxation, immune responses and antimicrobial activities (Saura et al., 1999; Schmidt and Walter, 1994). Due to its potent and selective pulmonary vasodilation, iNO has been extensively applied to treat pulmonary hypertension, ARDS and other respiratory diseases with a relative good safety profile (Fig. 3) (Griffiths and Evans, 2005; Pepke-Zaba et al., 1991). Of note, previously published *in-vitro* studies indicated NO possessed inhibitory effects on SARS-CoV replication (Fig. 2) (Akerström et al., 2005; Keyaerts et al., 2004a). Moreover, a small-sample clinical study testing the efficacy of iNO in the treatment of SARS showed, 6 severely infected patients receiving iNO therapy presented with improved arterial oxygenation and reduction in a need for ventilator support (Chen et al., 2004). In view of the high incidence of pulmonary complications in COVID-19 infected patients, iNO therapy may serve as a promising candidate for treating severe cases of COVID-19 via alleviating lung damage. Currently, a related phase II clinical trial testing iNO is underway in COVID-19 infected patients complicated with ARDS (NCT04306393 and NCT04305457).

10. Traditional Chinese medicine treatment

Traditional Chinese medicine (TCM) is a unique and well-established system of medicine widely employed for thousands of years to prevent and treat numerous diseases in China. In the battle to stop the epidemic situation of COVID-19, the integration of traditional Chinese and western medicine is a unique scheme in China. Approximately 85% of Chinese COVID-19 patients underwent TCM treatment as reported by XuNanping, the vice minister of Science and Technology of China (China's State Council, 2020). In clinical practice, several kinds of TCM have demonstrated their beneficial effects in treating patients with COVID-19 pneumonia (Ren et al., 2020). Lianhua Qingwen (LHQW) has a broad-spectrum antiviral effect on a host of influenza viruses, such as influenza A (H1N1), and HPAI A (H7N9) viruses, by inhibiting viral propagation and regulating immune function (Fig. 3) (Ding et al., 2017; Dong et al., 2014). LHQW has been commonly used for treating viral influenza clinically and played a key role in controlling SARS-CoV during the 2003 outbreak. Recently, LHQW was reported to have inhibitory activity against SARS-CoV-2 and anti-inflammatory effects *in vitro* (Table 1) (Runfeng et al., 2020).

Xuebijing (whose chemical composition includes safflower yellow A, paginin, ferulic acid, and salvianolic acid B) functions as an endotoxin antagonist, anti-inflammatory agent, and anticoagulant (He et al., 2013; Sun et al., 2010; Xu et al., 2009; Zhang et al., 2006) and has been widely used in China as a therapy for sepsis (Fig. 3) (Chen et al., 2018). A clinical trial showed that injecting Xuebijing improved the symptoms of severe pneumonia (Wang et al., 2016). Given the cytokine storms in severe COVID-19 infection, administering Xuebijing could turn critically ill cases into mild ones by attenuating the overactivated immune responses and preventing progressive pathological deterioration. Two clinical trials aimed at testing the efficacy and safety of Xuebijing injection for COVID-19 have been registered in the Chinese Clinical Trial Registry (ChiCTR2000030388 and ChiCTR2000029381) (Table 1).

In addition to LHQW and Xuebijing, the Chinese clinical guidelines for COVID-19 pneumonia treatment have included Jinhua Qinggan granules, Shufeng Jiedu capsules, and Lung Cleansing and Detoxifying Decoction, given their potential efficacy and few adverse effects in clinically treating COVID-19 infection (NHPFC, 2020).

11. Immunoenhancers

11.1. Interferons

IFNs are large families of numerous type I species (IFN-α, IFN-β, IFN-ε, IFN-κ, and IFN-ω) and one type II species (IFN-γ) (Liu, 2005; Parkin and Cohen, 2001). Type I IFNs have demonstrated inhibitory effects on a wide range of viruses including SARS-CoV (Fig. 3) (Minagawa et al., 1987; Sperber and Hayden, 1989; Ströher et al., 2004; Tan et al., 2004). When they encounter viruses, host cells form and release IFNs, which protect the original and adjacent cells against attack. The antiviral state produces its effects by several means, such as inhibiting viral RNA transcription, protein translation, and post-translational modification (Fig. 2 and Fig. 3) (De Andrea et al., 2002). To date, the clinical effect of IFN intervention in COVID-19 infection is ambiguous. Previous evidence confirmed IFN efficacy in inhibiting SARS-CoV (Cinatl et al., 2003; Sainz et al., 2004). IFN-α showed *in vitro* inhibitory effects on SARS-CoV at concentrations of 1000 IU/ml (Ströher et al., 2004). Interestingly, recombinant human IFN-β1a within a safe dose range exhibited more potent activity on SARS-CoV (Hensley et al., 2004). As a registered agent for chronic hepatitis C, IFN-α2b was reported to protect type 1 pneumocytes against SARS coronavirus infection in macaques (Haagmans et al., 2004). Combined treatment of IFN-α-2a and ribavirin was shown to have antiviral effects on MERS-CoV (Falzarano et al., 2013). In addition to their antiviral activity, IFNs show an immunomodulatory capability; type I interferons can enhance natural killer (NK)-cell cytotoxicity, enhance the expression of major histocompatibility complex I proteins, as well as promote IFN production and the proliferation of NK cells and macrophages (De Andrea et al., 2002; Goodbourn et al., 2000; Sen, 2001). IFN-α in conjunction with corticosteroids were shown to improve oxygen saturation and facilitate more rapid resolution of radiographic lung abnormalities in SARS infection (Loutfy et al., 2003). A study using a MERS-CoV infection mouse model indicated that early application of exogenous IFN-β facilitated virus clearance and protected against fatal lung infection, while delayed IFN-β administration tended to elevate damaging proinflammatory cytokine responses and led to deleterious outcomes (Channappanavar et al., 2019). Given the inconclusive effects of IFNs in treating viral infectious diseases, IFNs and combined therapy should be prudently employed with COVID-19 infection (Table 1).

11.2. Intravenous gamma globulin

Intravenous gamma globulin (IVIG) as purified IgG products prepared from pooled human plasma has been widely used for treating numerous inflammation-related diseases including heart failure, adult respiratory distress syndrome, and vasculitis (Jolles et al., 2005). IVIG demonstrates its passive immunity and anti-inflammatory effects by supplying idiotypic antibodies (Kaveri et al., 1991), binding to Fc receptors (Fehr et al., 1982), suppressing pathogenic cytokines (Andersson and Andersson, 1990; Andersson et al., 1993), preventing formation of membranolytic attack complexes (Lutz et al., 1996), and modulating T-cell function (Fig. 3) (Marchalonis et al., 1992). Transchromosomic bovine-produced human polyclonal immunoglobulin G antibodies inhibited MERS-CoV in murine models and *in vitro* assays (Luke et al., 2016). Due to the scarcity of human-derived IgG products (or convalescent plasma), therapeutic immunoglobulin might provide insights for COVID-19 treatment (Table 1). However, IVIG should be carefully administered given its numerous adverse effects (e.g., myalgia, fever, renal failure (Achiron, 1997; Bertorini et al., 1996; Wajanaponsan and Cheng, 2004), and venous thromboembolism (Hoffmann and Enk, 2019). Thromboembolism was found in a third of patients with SARS who underwent IVIG treatment during the SARS outbreak in Singapore (Lew et al., 2003).

11.3. Natural killer (NK) cell therapy

NK cells, a small subset of peripheral white blood cells, serve as an essential part of innate immune response. NK cells can elicit rapid and robust protective effects in defense against viral infections through direct cytotoxicity and immunomodulatory capability (Fig. 3) (Vivier et al., 2008). Once recognizing infected host cells, NK cells trigger targeted cell apoptosis by perforin- and granzyme B-mediated pathways and secrete multiple cytokines involved in regulation of innate and adaptive immune responses, which facilitate viral clearance (Iannello et al., 2008). NK cell-based immunotherapies have long been investigated for treating malignancies, albeit with limited clinical practice due to the difficulty to obtain sufficient cell numbers for adoptive transfer (Lee, 2019). Recently, CYNK-001, an investigational allogeneic NK cell therapy derived from placental hematopoietic stem cells, has passed through an investigational new drug application approved by FDA (Celularity, 2020). As a NK cell product, CYNK-001 harbors the potential for inhibiting viral infection through direct killing SARS-CoV-2 infected host cells and indirect inducing immune responses. However, there exists controversy about whether the elicited strong inflammatory responses are favorable or detrimental for patients infected with severe COVID-19. The efficacy and safety of NK cell therapy for COVID-19 require to be tested by ongoing related clinical trials.

12. Corticosteroids

Due to their excellent anti-inflammatory, antifibrotic properties and

ability to suppress collagen deposition, corticosteroids are frequently used to treat ARDS and sepsis (Fig. 3) (Heming et al., 2018; Rhen and Cidlowski, 2005; Thompson, 2003). Despite the long history of administering corticosteroids, their therapeutic effectiveness and safety remain controversial. Several clinical trials and *meta*-analyses have indicated that corticosteroids are associated with increased mortality, a tendency for requiring mechanical ventilation therapy, and relatively longer hospitalizations for SARS, MERS, and H1N1 infections (Arabi et al., 2018; Han et al., 2011; Stockman et al., 2006). These adverse events are partly due to the suppression of normal host immune responses and impeded viral clearance. Numerous studies have, however, demonstrated corticosteroids' beneficial effects on physiologic outcomes in virus-associated respiratory diseases, supporting the proper application of corticosteroids in these cases, especially critical cases (Li et al., 2017; Siemieniuk et al., 2015). A retrospective study of 401 patients with SARS showed that corticosteroids reduced case fatality rates and shorten hospital stays (Chen et al., 2006). An accurate conclusion regarding the therapeutic effect of corticosteroids in treating COVID-19 cannot therefore be drawn (Table 1). High corticosteroid doses are closely associated with adverse events such as secondary infections, delayed viral clearance, and emergence of viral resistance. According to the Guidelines for the Diagnosis and Treatment of COVID19 (7th edition) in China (NHPFC, 2020), however, prudent low-to-moderate doses of corticosteroids could yield potential therapeutic benefits for a subset of seriously ill patients with COVID-19 pneumonia, recommendations in line with the interim clinical management guidance for COVID-19 released by the World Health Organization, which advised against routinely administering corticosteroids except for clinical indications such as exacerbated chronic obstructive pulmonary disease and septic shock (WHO, 2020b).

13. Anticoagulants

Tang et al. (2020b) investigated the effects of anticoagulant heparin in patients with severe COVID-19. The D-dimer, prothrombin time and age were positively, and platelet count was negatively correlated with 28-day mortality. There was no difference on 28-day mortality between heparin users and nonusers. However, the 28-day mortality of heparin users was lower than nonusers. This study suggests that anticoagulant therapy with heparin appears to be associated with better prognosis in severe COVID-19 patients (Tang et al., 2020b). Interestingly, patients with severe pneumonia by COVID-19 had higher platelet count than those induced non-COVID-19, and only the former with markedly elevated D-dimer may benefit from anticoagulant therapy (Yin et al., 2020). Future study using a large sample size is needed to confirm the effects of heparin in the management of COVID-19 patients.

A recent study demonstrated the interaction between the SARS-CoV-2 spike S1 protein receptor binding domain (SARS-CoV-2 S1 RBD) and heparin, suggesting the development of heparin-based therapeutics (Microft-West et al., 2020). It is of great interest to develop the novel heparin-based compounds for COVID-19.

14. Vitamins

14.1. Vitamin C

Vitamin C has pleiotropic roles in modulating the immune system (Carr and Maggini, 2017) and is known for its antioxidant properties, and antioxidants are generally accepted as an adjuvant therapy for critically ill patients, whose vitamin C levels are markedly decreased (Carr et al., 2017; Nakano and Suzuki, 1984). Vitamin C exerts positive effects on the immune system by stimulating IFN production, supporting lymphocyte proliferation, and boosting neutrophil phagocytic capability (Fig. 3) (May and Harrison, 2013; Oudemans-van Straaten et al., 2014; Wilson, 2013). In acute lung injury and ARDS, excessive neutrophil accumulation in inflammatory loci results in lung tissue damage through the release of necrotic cell contents (known as neutrophil extracellular traps) (Papayannopoulos, 2018; Weiss, 1989), and vitamin C is reported to prevent this process (Mohammed et al., 2013). In animal models of sepsis, vitamin C was shown to protect lung barrier function and reduce lung vascular injury through diminishing inflammatory responses and coagulant changes (Fisher et al., 2012; Fisher et al., 2011). A phase I trial in patients with critically severe sepsis reported that high doses of vitamin C reduced the extent of multiple organ failure and mitigated circulating injury biomarker levels (Fowler et al., 2014). Placebo-controlled trials have shown that vitamin C could reduce the duration of colds (Hemilä and Chalker, 2013). Given that COVID-19 patients frequently present lung damage, vitamin C could be a promising candidate (Table 1).

14.2. Vitamin D

Vitamin D is known to modulate the innate and adaptive immune system, and its deficiency is associated with increased autoimmunity as well as in an increased susceptibility to infection (Aranow, 2011). Grant et al. (2020) pointed the role of vitamin D in reducing the risk of respiratory tract infections by COVID-19. Actions of mechanism of vitamin D include the induction of antimicrobial peptides (i.e., cathelicidins and defensins) that can reduce viral replication rate and impeding pro-inflammatory cytokines. Several clinical trials of vitamin D in patients with COVID-19 (i.e., NCT04334005, NCT04344041) are underway.

15. Non-steroidal anti-inflammatory drugs (NSAIDs)

The non-steroidal anti-inflammatory drugs (NSAIDs) including ibuprofen have been widely used to treat fever or pain. In March 11, 2020, Fang et al. (2020) reported the hypothesis that ibuprofen can increase the risk of developing severe and fatal COVID-19 since ibuprofen is known to upregulate ACE2 receptors. However, there is no evidence indicating that ibuprofen worsens the clinical symptoms of COVID-19 infected patients (FitzGerald, 2002; Kakodkar et al., 2020). In March 23, 2020, US FDA announced that it is not aware of any evidence that NSAIDs such as ibuprofen could worsen COVID-19.

16. Vaccine

There is no specific vaccine currently available for containing COVID-19 infection. To meet the urgent need for an effective vaccine in the context of active SARS-CoV-2 transmission, companies and institutions worldwide have been working on a SARS-CoV-2 vaccine through various approaches, resulting in a series of vaccine candidates (Routley, 2020). One of the most promising one of them is mRNA-1273, which is developed by National Institute of Allergy and Infectious Disease scientists together with biotechnology company Moderna (Fig. 3) (Moderna, 2020a; NIH, 2020). As an mRNA vaccine, mRNA-1273 embedded in lipid nanoparticles encodes viral S proteins of SARS-CoV-2 and then delivers the antigen into human cells to elicit SARS-CoV-2-specific neutralizing antibodies and potent immune responses, thereby protecting healthy individuals against COVID-19 infection (Fig. 3). mRNA vaccine is superior to other conventional vaccines, given its high potency, short production cycles and safety as lack of actual viral genome (Ahn et al., 2020). A phase I, open-label, dose-ranging trial of mRNA-1273 was conducted in 45 healthy adult volunteers aged 18 to 55 years with three different doses of mRNA-1273 to assess its efficacy and appropriate effective dose (Table 1) (NCT04283461). On April 16, 2020, Moderna received the award from US Government Agency BRADA for up to $483 million to accelerate development of mRNA-1273 against COVID-19 (Moderna, 2020b).

mRNA-1273 was the first vaccine to be tested in a clinical trial, followed closely by another promising candidate called Ad5-nCoV, which was jointly developed by Tianjin-based biotechnology company

Cansino and the Institute of Biotechnology of the Academy of Military Medical Sciences. Developed with Cansino's adenovirus-based viral vector vaccine technology platform, Ad5-nCoV uses replication-defective adenovirus type 5 as a vector to load SARS-CoV-2 gene fragments onto it to express the SARS-CoV-2 S protein (Fig. 3) (Shi et al., 2020b). According to Cansino, preclinical data in animal models demonstrated that Ad5-nCoV can elicit robust immune responses and a favorable safety profile (Mak, 2020). Currently, the phase I clinical trial evaluating the safety and efficacy of Ad5-nCoV has been initiated in Wuhan (Table 1) (Shi et al., 2020b).

A recently published study in *the Lancet* introduced a newly developed potentially effective SARS-CoV-2 vaccine named PittCoVacc, short for Pittsburgh Coronavirus Vaccine, developed by University of Pittsburgh School of Medicine scientists (Kim et al., 2020). PittCoVacc uses S-protein fragments of SARS-CoV-2 to stimulate the generation of specific antibodies (Fig. 3). PittCoVacc is delivered with a novel technique known as microneedle array, a fingertip-sized patch of 400 tiny needles. This strategy can elicit more potent immune responses than conventional subcutaneous needle injection and has been demonstrated to be sufficiently safe. PittCoVacc has been tested immunogenicity in mice with the emergence of substantial SARS-CoV-2 antibodies within 2 weeks after prime immunization. The research team hoped to test PittCoVacc in humans in clinical trials in the next few months (Table 1) (ScienceDaily, 2020).

The US-based company Novavax has identified a vaccine candidate NVX-CoV2373, a stable, prefusion protein developed through the advanced nanoparticle technology (Table 1 and Fig. 3). The Matrix-M adjuvant will be incorporated with NVX-CoV2373 to enhance immune responses and stimulate increased levels of neutralizing antibodies (Novavax, 2020). A first-in-human trial will be started in May 2020.

Other types of vaccines (e.g., DNA, RNA, vector, whole-cell killed and live-attenuated vaccines) are in the rapid development process (Routley, 2020). A phase 1 study of the novel DNA vaccine INO-4800 (NCT04336410) is underway (Inovio, 2020). Despite the seriousness of the pandemic ravaging the world, researchers should take the time to assess the safety and efficacy of vaccines in animal models and then conduct related human clinical trials to prevent more harm than good from occurring with hastily produced vaccines.

17. Zinc

Zinc, a trace mineral, is necessary for the immune system since zinc-deficient patients had severe immune dysfunctions (Prasad, 2008). Interestingly, there are numerous reports showing the loss of sense of smell and taste in the early stages of COVID-19 infected people (Keyhan et al., 2020; Lechien et al., 2020). It is well known that zinc deficiency is associated with loss of taste, and that zinc supplementation has beneficial effects in subjects with loss of taste (Doty, 2019; Heyneman, 1996; Yagi et al., 2013). Collectively, it is likely that zinc deficiency in patients with COVID-19 infection may be associated with the loss of smell and taste in these patients.

Importantly, zinc is a potent inhibitor of various RNA viruses such as SARS-CoV (te Velthuis et al., 2010). Given the inhibiting action of zinc in the replication of coronavirus, it is possible that zinc may have beneficial effects for COVID-19 infection since zinc supplement is available in the world. First clinical trial of intravenous zinc in COVID-19 patients is underway in Australia (ACTRN12620000454976). Furthermore, several clinical trials of the combination of zinc and other candidates (i.e., HCQ, vitamin D, vitamin C) in patients with COVID-19 are underway (NCT04326725, NCT04351490, NCT04342728).

18. Others

The findings of a recent *in vitro* study by Australian researchers are notable. They found that ivermectin (an anti-parasitic drug) could effectively block SARS-CoV-2 growth in cell cultures within 48 h, even at a single dose (Fig. 2). However, the mechanism though which ivermectin exerts its antiviral action is unknown. This study only demonstrated the effectiveness of ivermectin for the control of SARS-CoV-2 *in vitro* (Caly et al., 2020). Further study of its efficacy and safety for inhibiting SARS-CoV-2 in humans or animals needs to be investigated.

19. Conclusion

The COVID-19 pandemic is an unprecedented crisis for public health and world economy and has had a huge impact not only on China but other countries. In the fight against COVID-19, we should unite and understand that benefiting one benefits all, whereas harming one harms all. Scientists worldwide struggle to seek efficacious COVID-19 treatments. Learning from previous experience in coping with SARS and MERS, a series of existing drugs have been used in clinical practice to treat COVID-19 infection and clinical trials evaluating their efficacy and safety for COVID-19 are ongoing. Given the unique viral structure and distinct pathogenesis, there is an urgent need for novel COVID-19-specific therapies, including vaccines and antivirals. As discussed above, there are many different candidates for COVID-19 infected patients. Part of patients with COVID-19 infection have been medicated with other drugs for their illness. Therefore, potential drug- drug interactions should be considered for the combination (Zhang et al., 2020b).

Research teams from China, Singapore and the United States published a new study on the preprint website BioRxiv (Anderson et al., 2020). Through systematic and comprehensive screening of more than 20,000 genes in bat cells, the teams identified MTHFV1, a gene indispensable for viral replication in bat and human cells and found that carolacton, a host protein MTHFV1 inhibitor, could effectively inhibit replication of several RNA viruses including SARS-CoV-2, suggesting that carolacton (a natural bacteria-derived product) could be a novel therapeutic drug for COVID-19.

Finally, further understanding of SARS-CoV-2 mechanisms in humans could help in developing novel therapeutic drugs for COVID-19. We must protect ourselves against COVID-19 infection until the aforementioned candidates for COVID-19 are approved.

20. Authors' contributions

JZ and BX performed the study design, data collection, data analysis, data interpretation, and writing. KH performed the study design, data interpretation, and writing. All authors approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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