



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

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Review

Potential drugs for the treatment of the novel coronavirus pneumonia (COVID-19) in China

Xiaoqi Pan^{a,1}, Lan Dong^{b,1}, Lian Yang^a, Dayi Chen^a, Cheng Peng^{a,*}^a School of Public Health and School of Pharmacy, Chengdu University of Traditional Chinese Medicine, Chengdu, 611137, China^b The Third People's Hospital of Chengdu, Chengdu, 610031, China

ARTICLE INFO

Keywords:

COVID-19

SARS-CoV-2

Chemical drugs

Traditional Chinese medicines

Biological products

ABSTRACT

The fight against the novel coronavirus pneumonia (namely COVID-19) that seriously harms human health is a common task for all mankind. Currently, development of drugs against the novel coronavirus (namely SARS-CoV-2) is quite urgent. Chinese medical workers and scientific researchers have found some drugs to play potential therapeutic effects on COVID-19 at the cellular level or in preliminary clinical trials. However, more fundamental studies and large sample clinical trials need to be done to ensure the efficacy and safety of these drugs. The adoption of these drugs without further testing must be careful. The relevant articles, news, and government reports published on the official and Preprint websites, PubMed and China National Knowledge Infrastructure (CNKI) databases from December 2019 to April 2020 were searched and manually filtered. The general pharmacological characteristics, indications, adverse reactions, general usage, and especially current status of the treatment of COVID-19 of those potentially effective drugs, including chemical drugs, traditional Chinese medicines (TCMs), and biological products in China were summarized in this review to guide reasonable medication and the development of specific drugs for the treatment of COVID-19.

1. Introduction

The novel coronavirus pneumonia (coronavirus disease 2019, COVID-19) is caused by a novel coronavirus (severe acute respiratory syndrome coronavirus 2, SARS-CoV-2) infection (Chen et al., 2020a, 2020b, 2020c). SARS-CoV-2 that seriously endangers human health has been found throughout China and around the world, including America, Brazil, Russia, India, Peru, England, and other countries (Zhang et al., 2020a,b,c,d). As of April 14, 2020, a total of 83,700 confirmed cases and 3351 deaths in China, and more than 1.85 million of COVID-19 confirmed cases in other countries were reported. According to the speed of SARS-CoV-2 infection, the number of confirmed and deaths of COVID-19 in the world is still increasing. The prevention and treatment of COVID-19 is undoubtedly one of the biggest challenges in the history

of human development. Chinese government formulated quickly strict prevention and control mechanism, issued the "Guidelines for the diagnosis and treatment of novel coronavirus pneumonia (the seventh trial version)", and encouraged the front-line clinical workers to try to use the marketed medicines for COVID-19 treatment (National Health Commission, National Administration of Traditional Chinese Medicine, 2020). Fortunately, as of April 14, 2020, more than 78,000 of patients had been successfully cured in China. A number of drugs exhibit certain inhibitory effects on SARS-CoV-2 in China, which are expected to be specific drugs for the treatment of COVID-19. Meanwhile, a large number of clinical and fundamental studies on these potentially effective drugs are being carried out. Some drugs that have been clinically tested in advance have good curative effects, and some drugs also have shown certain antiviral effects in vitro experiments. However, most of

Abbreviations: COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; RCTs, randomized controlled trials; CNKI, China National Knowledge Infrastructure; NCP, novel coronavirus pneumonia; TCMs, traditional Chinese medicines; SARS-CoV, severe acute respiratory syndrome coronavirus; MERS-CoV, middle east respiratory syndrome coronavirus; ARDS, acute respiratory distress syndrome; HIV, human immunodeficiency virus; RSV, respiratory syncytial virus; DENV, dengue virus; EC50, half effective concentration; RTP, ribofuranosyl-5'-triphosphate; MNV, murine norovirus; GA, glycyrrhizic acid; ACE2, angiotensin converting enzyme II; HXZQ, Huoxiang Zhengqi; JHQG, Jinhua Qinggan Granule; CRP, C-reactive protein; LHQW, Lianhua Qingwen Capsule; Shufeng SFJD, Jiedu Capsule; FFTS, Fangfeng Tongsheng Pill; QFPD, Qingfei Paidu Decoction; TJQW, Toujie Quwen Granule; HSB, Huashi Baidu Prescription; XFBD, Xuanfei Baidu Decoction; COPD, chronic obstructive pulmonary disease; CP, convalescent plasma; IFN- α , interferon- α ; NK, natural killer; MSCs, mesenchymal stem cells

* Corresponding author at: School of Pharmacy, Chengdu University of Traditional Chinese Medicine, Chengdu, Sichuan, 611137 China.

E-mail address: pengchengchengdu@126.com (C. Peng).

¹ These authors contributed equally to this work.

<https://doi.org/10.1016/j.virusres.2020.198057>

Received 20 March 2020; Received in revised form 15 May 2020; Accepted 7 June 2020

Available online 09 June 2020

0168-1702/© 2020 Elsevier B.V. All rights reserved.

these drugs have not yet been tested in standardized clinical studies, especially large sample randomized controlled trials (RCTs).

In the face of the battle between human health and viruses, Chinese scholars should share these potential drugs to cooperate with other countries and regions for resisting this virus attack. This review lists current clinical trial drugs and potential drugs against SARS-CoV-2 in China, including chemical drugs, traditional Chinese medicines (TCMs), and biological products, which is beneficial to promote researchers around the world to discover specific drugs for COVID-19 treatment as soon as possible.

2. Literature search strategy

We searched the official and Preprint websites, PubMed and China National Knowledge Infrastructure (CNKI) databases to identify literature with the following terms: “SARS-CoV-2,” OR “2019-nCoV,” OR “COVID-19,” OR “novel coronavirus pneumonia (NCP)” from December 2019 to April 2020. Those papers with a description with drugs for COVID-19 treatment were selected, including full-length articles, comments, news, correspondences, editorials, reviews, government reports, case reports, and especially clinical or fundamental studies. We screened out chemical drugs, TCMs, and biological medicines that played potentially therapeutic effects on COVID-19 supported by scientific data. The review will be updated and revised with the increasing clinical studies on these drugs for the treatment of COVID-19.

3. SARS-CoV-2

SARS-CoV-2 is a single-stranded RNA virus, whose genetic characteristics are obviously different from severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) (National Health Commission, National Administration of Traditional Chinese Medicine, 2020; Li et al., 2020b). Current research showed that SARS-CoV-2 had more than 85 % homology with bat SARS-like coronavirus (bat-SL-CoVZC45), suggesting that bat is probably the natural host of SARS-CoV-2 (Xu et al., 2020a,b; Zhou et al., 2020). Moreover, many wild animals may become the potential intermediate hosts of SARS-CoV-2, such as swine, bamboo rat, and badger (Li et al., 2020c). In addition to patients with SARS-CoV-2 infection that are the main source of infection, asymptomatic patients may also spread this virus from person to person. Humans are mainly infected by SARS-CoV-2 through respiratory droplets or close contact with patients. Chinese academician Zhong Nanshan's team obtained the latest clinical manifestations of SARS-CoV-2 infected patients by analyzing 1099 cases, which is the largest sample analysis to date. Results pointed out that only 43.8 % showed fever symptom in the early stage, and fever accounted for 87.9 % after hospitalization. Fever and cough are the most common symptoms of COVID-19. A few patients are accompanied by myalgia, diarrhea, and vomiting. The latent period of COVID-19 was 0–24 days. The above symptoms can rapidly develop to acute respiratory distress syndrome (ARDS), septic shock, metabolic acidosis, coagulation dysfunction, or multiple organ failure in severe cases (Huang et al., 2020a,b,c). COVID-19 is classified into mild, common, severe, and critically ill based on the severity of disease symptoms.

4. Potential chemical drugs against SARS-COV-2

At present, COVID-19 is mainly treated with the marketed drugs, which have antiviral effects in previous clinical trials. The early clinical trials have showed that a variety of chemical drugs have certain antiviral effects against SARS-CoV-2. However, these drugs need to be further tested in clinical trials to verify the efficacy and safety. The chemical structures, pharmacological actions, indications, adverse reactions, and general usage of these chemical drugs for COVID-19 treatment were listed in Table 1.

4.1. Lopinavir/ritonavir

Kaletra consists of two kinds of protease inhibitors lopinavir and ritonavir, which both can block the division of Gag-Pol polyproteins and generate non-infectious virus particles to specifically inhibit retroviral infection (van der Laan et al., 2018). Initially, this drug is mainly used to treat human immunodeficiency virus (HIV) infection in adults and children over 2 years of age. Studies in vitro experiments showed that lopinavir and ritonavir could reduce the levels of SARS-CoV and MERS-CoV (Chu et al., 2004). Based on the results of substantial clinical benefits of lopinavir and ritonavir in patients with SARS-CoV infection, scientists speculated that this drug might be effective in patients with SARS-CoV-2 infection (Huang et al., 2020a,b,c). The team in Zhongshan University constructed a structural model of two new coronavirus proteases-coronavirus endopeptidase C30 and papain-like protein through homology modeling, and docked lopinavir/ritonavir with protease models, respectively. Results showed that lopinavir and ritonavir more easily combined with coronavirus endopeptidase C30 compared with papain-like enzymes, which expressed excellent anti-SARS-CoV-2 effects (Lin et al., 2020). However, after using lopinavir/ritonavir tablets in 40 patients diagnosed with COVID-19, 29 cases had adverse reactions related to lopinavir/ritonavir, such as the elevated triglycerides, nausea, and diarrhea (Liang et al., 2020). Therefore, larger clinical trials of this drug should focus on its safety.

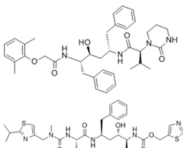
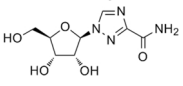
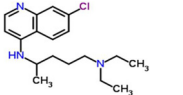
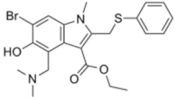
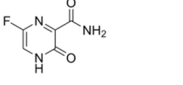
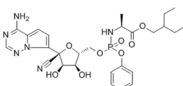
4.2. Ribavirin

Ribavirin, a broad-spectrum antiviral drug, can be phosphorylated in red blood cells to produce ribavirin monophosphate, diphosphate, and triphosphate. Ribavirin monophosphate is a strong inhibitor of inosine monophosphate dehydrogenase, which can inhibit cellular guanylate synthesis, reduce cellular guanylate triphosphate, and block viral nucleic acid synthesis. Ribavirin triphosphate inhibits influenza virus RNA polymerase, thereby interfering with virus replication (Knowles et al., 2003). Oral ribavirin administration with or without intravenous immunoglobulin is a well-tolerated treatment for respiratory syncytial virus (RSV) infection in moderately to severely immunocompromised hosts (Marcelin et al., 2014). In addition, ribavirin was also active against dengue virus (DENV) with the half effective concentration (EC50) of 3 μ mol/L in A549 cells (Chang et al., 2011). When ribavirin was used in combination with IFN- α 2b, anti-MERS-CoV activity of ribavirin was significantly enhanced in rhesus macaques (Falzarano et al., 2013). Ribavirin was shown to inhibit SARS-CoV replication in five different cell types derived from animals or humans at therapeutically achievable concentration (Morgenstern et al., 2005). However, some adverse reactions should be noted during ribavirin application. For example, 61 % of patients developed hemolytic anemia, 58 % hypocalcemia, and 46 % hypomagnesemia in 110 SARS patients treated with ribavirin (Knowles et al., 2003). Given the efficacy of ribavirin in the treatment of diseases caused by SARS-CoV and MERS-CoV, it is expected to become an effective drug for COVID-19 treatment. However, the efficacy of ribavirin for the treatment of COVID-19 is still controversial, which are needed to further confirm in clinical trials.

4.3. Chloroquine

Chloroquine is an anti-malarial and anti-inflammatory drug, which is widely used in the treatment of malaria and rheumatoid arthritis for more than 70 years. Anti-malarial effect of chloroquine may interfere with the replication and transcription of the plasmodium schizont DNA or hinder its endocytosis, thereby leading to the parasite to die due to amino acids deficiency. Chloroquine also has immunomodulatory activity, which can synergistically enhance antiviral effects (Wang et al., 2020a,b,c,d,e). Chloroquine phosphate and hydroxychloroquine destroy the terminal glycosylation of angiotensin converting enzyme II (ACE2) in vitro. Therefore, chloroquine may be potent inhibitors of

Table 1
The potential chemical drugs against SARS-CoV-2.

Chemical drugs	Chemical structures	Pharmacological effects	Indications	Adverse reactions	General usage (For reference only)
Lopinavir/ Ritonavir		Anti-virus: HIV protease inhibitor	AIDS	Diarrhea, nausea, vomiting, liver damage, etc	200 mg/50 mg/capsule, 2 capsules each time, 2 times per day, and the course of treatment does not exceed 10 days
Ribavirin		Broad spectrum anti-virus: viral RNA polymerase inhibitor	Hepatitis C	Hemolytic anemia	It is recommended to be combined with IFN- α or lopinavir/ritonavir, 500 mg/time for adults, 2–3 intravenous infusions daily, and the course of treatment does not exceed 10 days
Chloroquine		Anti-malaria, anti-inflammation: autophagy	Malaria, rheumatoid arthritis	Headache, dizziness, gastrointestinal reactions, tinnitus, itchy skin, etc	Suitable for adults aged 18–65. wt > 50 kg, 500 mg/time, 2 times per day, 7 days of the course of treatment; weight < 50 kg, on the first and second day, 500 mg/time, 2 times per day, and on the third to 7 th day, 500 mg/time, one time per day
Arbidol		Broad spectrum anti-virus: block the fusion of the virus with the host cell	Upper respiratory tract infection caused by influenza A and B viruses	Nausea, diarrhea, dizziness and elevated serum transaminase	200 mg/time for adults, 3 times per day, and the course of treatment should not exceed 10 days
Favipiravir		Anti-virus: viral RNA polymerase inhibitor	Influenza a, EBOV infection	Increased uric acid, diarrhea, neutropenia, increased AST and ALT	The first dose for adults is 1600 mg (1 time/12 h). Starting the next day, the maintenance dose is 600 mg (1 time/12 h), and the course of treatment is 7–10 days. Favipiravir can be used in combination with IFN- α atomization inhalation
Remdesivir		Broad spectrum anti-virus : viral RNA polymerase inhibitor	SARS-CoV and MERS-CoV infection	Undefined	Undefined

Note: The interaction of chemical drugs with other drugs for the treatment of COVID-19 should be noted. The efficacy and safety of these drugs should be further evaluated during clinical application. The combination of three or more antiviral drugs is not recommended. If intolerable side effects occur, please stop drugs.

SARS-CoV-2 infection. Based on the results of previous studies, chloroquine phosphate has a therapeutic effect on COVID-19 in vitro (Wang et al., 2020a,b,c,d,e). At present, several clinical trials were successively announced. The results of an open-label non-randomized clinical trial revealed that hydroxychloroquine was significantly associated with viral load reduction or disappearance in patients with COVID-19 (Philippe et al., 2020). Similarly, another randomized clinical trial also confirmed the efficacy of hydroxychloroquine on COVID-19, which are manifested with the shortening of the body temperature recovery time and the cough remission time of patients with COVID-19 (Chen et al., 2020a, 2020b, 2020c). Preliminary evidence from a multicenter prospective observational study showed that the median time to undetectable viral RNA was shorter in chloroquine than in non-chloroquine, and no serious adverse reactions were observed in the chloroquine group (Huang et al., 2020a,b,c). In contrast, the results of some clinical studies showed negative for the treatment of COVID-19 with chloroquine or hydroxychloroquine. For example, an open-label, randomized, controlled trial indicated that hydroxychloroquine did not result in a higher negative conversion probability than standard-of-care alone in mild to moderate COVID-19 patients, and adverse events, especially diarrhea, were higher after receiving hydroxychloroquine (Tang et al., 2020). Another randomized, double-blinded, phase IIb clinical trial showed that the high dosage chloroquine phosphate group (total 12 g) presented more QTc > 500 ms and higher mortality rate (17 %) than the low dosage group (total 2.7 g) (Mayla et al., 2020). Hence, the safety and efficacy of chloroquine for the treatment of COVID-19 still need to be testified by more and bigger clinical trials.

4.4. Arbidol

Arbidol inhibits the fusion between viral envelope and cell membrane of the target cells, thereby preventing the virus from entering the

target cells (Teissier et al., 2011). Arbidol is often used to resist influenza viruses in Russia and China, which has not yet been approved for marketing in other countries. In vitro and in vivo studies have shown that arbidol has antiviral activity against influenza virus, RSV, rhinovirus, coxsackie virus, coxsackie virus B5, and adenovirus (Shi et al., 2007; Zhong et al., 2009). Previous studies have shown that arbidol can inhibit RNA viruses and filoviridae, such as SARS-CoV and MERS-CoV (Guan et al., 2018; Hulseberg et al., 2019). Chinese scientists found that arbidol could effectively inhibit the pathological effects of SARS-CoV-2 at a concentration of 10–30 $\mu\text{mol/L}$ with 60 times of viral load in vitro through screening a variety of antiviral drugs. At present, two RCTs have been initiated to evaluate the efficacy and safety of arbidol in the treatment of COVID-19 in China.

4.5. Favipiravir

Favipiravir is a viral RNA polymerase inhibitor, which can be mediated by its metabolite ribofuranosyl-5'-triphosphate (RTP) that inhibits influenza virus RNA polymerase activity. Favipiravir was urgently used and presented good inhibitory effects on Ebola virus in 2014 (Nagata et al., 2015). Despite of fairly modest antiviral activity, favipiravir could completely inhibit murine norovirus (MNV) replication at a concentration of 100 $\mu\text{g/mL}$ with little or no side effects on cells (cell survival rate > 80 %) (Rocha-Pereira et al., 2012). Favipiravir is proven to protect mice from lethal infection with various influenza viruses (Furuta et al., 2013). However, previous reports showed that favipiravir might have a prolonged QT interval during treatment, which should be paid attention to monitoring during medication (Kumagai et al., 2015). Favipiravir has been officially approved by Chinese Medical Products Administration for marketing and formally put into production in China. Favipiravir is the first approved drug with the potential curative effect on COVID-19 in China, which will play an

important role in prevention and control of SARS-CoV-2 infection.

4.6. Remdesivir

Remdesivir produced by Gilead Sciences Inc. is mainly used as a test drug against Ebola virus. One review suggested that remdesivir might be more suitable against coronaviruses (John, 2020). Remdesivir has a strong anti-filovirus effect in vitro and a certain anti-coronavirus effect through inhibiting RNA-dependent RNA synthetase in animal experiments (Wang et al., 2020b; Zumla et al., 2016). Subsequent research found that remdesivir was not only effective against Ebola virus, but also inhibits respiratory syncytial virus, coronavirus, nipah virus, and hendra virus (Warren et al., 2016). Researchers reported that the first COVID-19 patient in the United States recovered after receiving remdesivir treatment (Holshue et al., 2020). In November 2019, the results of a phase II clinical trial showed that 175 of 681 Ebola patients were treated with remdesivir, following 29 serious adverse reactions, only one of which was related to remdesivir (Mulangu et al., 2019). Research showed that giving remdesivir could prevent rhesus macaques from getting sick before MERS-CoV infection and improve their symptoms after being infected (de Wit et al., 2020). Furthermore, remdesivir treatment initiated early during infection had a clear clinical benefit in SARS-CoV-2-infected rhesus macaques, which predicted that early remdesivir treatment initiation in COVID-19 patients might prevent progression to severe pneumonia (Brandi et al., 2020). Chinese scientists have found that EC50 of remdesivir against SARS-CoV-2 is 0.77 $\mu\text{mol/L}$ in Vero E6 cells, and the selection index SI is greater than 129, indicating that this drug can effectively inhibit SARS-CoV-2 infection in vitro (Wang et al., 2020a,b,c,d,e). Preliminary results from a clinical trial conducted by the National Institute of Allergy and Infectious Diseases (NIAID) in USA showed that the patients who received remdesivir had 31 % faster time to recovery than those who received placebo, indicating that remdesivir has a significant positive effect in reducing recovery time for patients with COVID-19. In addition, Gilead Sciences Inc. also announced that similar clinical improvements after the 5-day and 10-day remdesivir administration in patients with severe COVID-19 were found even without a placebo control. However, a randomized, double-blinded, placebo-controlled, multicentre clinical trial conducted by Chinese scientists revealed that remdesivir did not accelerate recovery or reduce the mortality in patients with severe COVID-19 compared with the placebo group. The rate of early discontinuation due to adverse events, including nausea, vomiting, and cardiopulmonary failure, was higher in the group receiving remdesivir than that in the placebo group (11.6 % versus 5.1 %). Although this is the first high-quality clinical trial of remdesivir in the treatment of COVID-19 so far, only 237 samples are included in the clinical trial (Wang et al., 2020a,b,c,d,e). Therefore, the antiviral efficacy and safety of remdesivir still need to be supported by more high-quality and larger sample clinical studies.

5. Potential TCMs for prevention and treatment of COVID-19

In China, the practice of fighting against SARS-CoV-2 in the past four months has fully confirmed that TCMs play an important role in prevention and treatment of COVID-19 before successful development of specific medicines and vaccines. The combination treatment methods of TCMs and chemical drugs improved clinical efficacy, shortened the length of hospital stay, and reduced the critical mortality rate (Xia et al., 2020). Therefore, those TCMs, including Chinese herbal compound prescriptions, injection preparations, and active ingredients of TCMs, with certain effects for prevention and treatment of COVID-19 should be summarized and shared. Chinese herbal compound prescriptions and injection preparations that were tried to prevent and treat COVID-19 in China were listed in Table 2.

5.1. Active ingredients of TCMs

Glycyrrhizic acid (GA) is the principal bioactive ingredient isolated from Chinese herb *Glycyrrhizae Radix et Rhizoma*. The latest glycyrrhizic acid preparations are oral GA and pure alpha GA preparation. GA has a direct antiviral effect on hepatitis B virus via affecting the hepatitis B surface antigen to extracellular secretion. GA can significantly inhibit HIV proliferation through immune activation (Sun et al., 2019). A study published by Stanford University and the University of Hong Kong proved that GA could bind to ACE2, which testified that GA preparation might have potential value in preventing SARS-CoV-2 infection. Studies have shown that GA can not only exert antiviral effects by regulating immune function, but also has a clear anti-inflammatory mechanism (Li et al., 2017). A number of experts in Hubei province of China said that patients with severe COVID-19 could trigger an inflammatory storm, leading to multiple organ failure. GA derivatives also presented the antiviral activity against SARS-CoV (Hoever et al., 2005). A clinical retrospectively analysis of 73 SARS patients showed that compound glycyrrhizin could improve the symptoms of dry cough, chest tightness, shortness of breath, and other symptoms, which is believed that compound glycyrrhizin has a certain effect on SARS-CoV (Lu et al., 2003). At present, the commonly used oral GA + vitamin C for the treatment of COVID-19 has been approved in a clinical trial in China.

In addition, a study revealed that several active natural products and TCMs might have therapeutic effects on COVID-19 through screening the self-built "Highly Pharmaceutical Compound Database" and "Medicinal Plant-Derived Compound Component Database". The active ingredients of TCMs, such as deoxyrhapontin in *Rhei Radix et Rhizoma*, chalcone in *Sophorae tonkinensis Radix et Rhizoma*, polydatin in *Polygoni cuspidate Rhizoma et Radix*, and shikonin in *Arnebiae Radix*, have good inhibitory effects against SARS-CoV-2. Although clinical studies about these active ingredients of TCMs have not been conducted, this discovery provides strong evidence for clinical research and treatment of COVID-19 with TCMs.

5.2. Chinese herbal compound prescriptions

Chinese herbal compound prescription refers to a prescription consisting of two or more components for the treatment of a relatively certain disease and syndrome, which has a relatively prescribed processing method and usage method. Each herb in Chinese herbal compound prescription has specific curative effect, which cooperates with each other to increase the curative effect or reduce toxicity and adverse reactions. Chinese herbal compound prescriptions are widely applied in clinical practice, which has overall comprehensive effects of broad-spectrum antibacterial, antiviral, and immune function regulation.

Huoxiang Zhengqi (HXZQ) is used as a common Chinese herbal compound prescription to improve the symptoms of headache, dizziness, nausea and vomiting, fatigue, and gastrointestinal discomfort in Chinese families. There are different dosage forms on the market, such as water, capsule, and pill. Clinical reports showed that HXZQ powder treated 22 cases of infectious diarrhea caused by Norwalk virus, with the results of 100 % effective rate (Wang, 2010). HXZQ oral solution could bind to ACE2 to target PTGS2, HSP90AB1, AR, CAMSAP2, and other targets through the network pharmacology and molecular docking, thus playing a role in prevention and control of COVID-19 (Deng et al., 2020). Adverse reactions caused by HXZQ preparations are diverse, such as skin damage being the most, followed by circulatory system, respiratory system, and nervous system symptoms (Fang et al., 2015).

Jinhua Qinggan Granule (JHQQ) is used to treat fever caused by external infections, including H1N1 influenza infection in 2009. JHQQ can reduce serum C-reactive protein (CRP) and IFN- γ levels in patients with influenza, thus improving the immune function (Li et al., 2013; Qi et al., 2016). 300 major active ingredients of JHQQ for COVID-19 treatment were predicted through network pharmacology analysis,

Table 2
The potential TCMs for prevention and treatment of COVID-19.

Traditional Chinese medicines	Compositions	Indications	Adverse reactions	General usage (Forreferenceonly)
Huoxiang Zhengqi preparations (capsule, pill, water, oral liquid)	13 types of herbs: <i>Pogostemonis Herba</i> , <i>Perillae Folium</i> , <i>Angelicae dahuricae Radix</i> , <i>Atractylodis macrocephalae Rhizoma</i> , <i>Citri reticulatae Pericarpium</i> , <i>Pinelliae Rhizoma Praeparatum</i> , <i>Magnoliae officinalis Cortex</i> , <i>Portia</i> , etc.	Migraine, influenza, acute upper respiratory tract infection, heat stroke, functional dyspepsia, etc	Few people may have skin damage, flushing, palpitation, dizziness, rash, itching, disulfiram-like reaction if combined with cephalosporins, etc	Oral Huoxiang Zhengqi water or solution is 5–10 mL once, twice a day. Pills are 2.5–5 g once, twice a day. Capsules are 4 capsules once, twice a day. Diet should be light during medication
Jinhua Qinggan Granule	<i>Lonicerae japonicae Flos</i> , <i>Fritillariae thunbergii Bulbus</i> , <i>Scutellariae Radix</i> , <i>Arcatii Fructus</i> , <i>Artemisiae annuae Herba</i> , etc.	Various influenza : influenza a (H1N1)	Undefined	Take a bottle of boiled water, one sachets at a time, twice a day, for 3–5 days, or as directed by your doctor. Avoid spicy, cold, greasy food
Lianhua Qingwen Capsule (granule)	13 types of herbs: <i>Forsythiae Fructus</i> , <i>Lonicerae japonicae Flos</i> , <i>Ephedrae Herba</i> , <i>Artemisiae semen Anarum</i> , <i>Gypsum Fibrosum</i> , <i>Isatidis Radix</i> , <i>Dryopteridis crassirhizomatis Rhizoma</i> , <i>Houttuyniae Herba</i> , <i>Pogostemonis Herba</i> , etc.	Influenza	Mostly occurs after the first medication, such as nausea, vomiting, bloating, diarrhea, rash, itching, etc	Oral administration, 4 capsules or one granules at a time, thrice a day. 7–10 days as a course for mild and common COVID-19
Shufeng Jiedu Capsule (granule)	<i>Polygoni cuspidate Rhizoma et Radix</i> , <i>Forsythiae Fructus</i> , <i>Isatidis Radix</i> , <i>Bupleuri Radix</i> , <i>Parinariae Herba</i> , <i>Verbenae Herba</i> , <i>Phragmitis Rhizoma</i> , <i>Glycyrrhizae Radix et Rhizoma</i>	Acute upper respiratory infection	Occasionally nausea, rash, dizziness, headache, increased blood pressure, etc	Oral administration, 4 tablets at a time, thrice a day
Fangfeng Tongsheng Pill (granule)	17 types of herbs: <i>Saposhnikovia Radix</i> , <i>Schizonepetae Spica</i> , <i>Menthae haplocalycis Herba</i> , <i>Ephedrae Herba</i> , <i>Rhei Radix et Rhizoma</i> , <i>Narri Sulfas</i> , <i>Gardeniae Fructus</i> , etc	Hives, eczema, constipation	Occasionally allergic rash	Oral administration, one pill at a time, twice a day
Toujie Quwen Granule (Pneumonia NO. 1 prescription)	16 types of herbs: <i>Scutellariae Radix</i> , <i>Forsythiae Fructus</i> , <i>Lonicerae japonicae Flos</i> , and <i>Isatidis Folium</i> , etc.	Antiviral	Undefined	Oral administration, 2 sachets at a time, 11 g each sachet, twice a day
Qingfei Paidu Decoction	21 types of herbs: <i>Ephedrae Herba</i> , <i>Artemisiae semen Amarum</i> , <i>Gypsum Fibrosum</i> , <i>Asari Radix et Rhizoma</i> , <i>Bupleuri Radix</i> , <i>Scutellariae Radix</i> , and <i>Citri reticulatae Pericarpium</i> , etc.	Measles, pneumonia	Possibly occurs after unreasonable medication, such as excessive sweating, epigastric discomfort, diarrhea, and elevated blood pressure	One dose daily, once in the morning and evening (40 min after a meal), take in warm water, three doses as a course. If possible, add half a bowl of rice soup after each serving
Huashi Baidu Prescription	14 types of herbs: <i>Ephedrae Herba</i> , <i>Pogostemonis Herba</i> , <i>Gypsum Fibrosum</i> , <i>Artemisiae semen Amarum</i> , <i>Pinelliae Rhizoma Praeparatum</i> , <i>Rhei Radix et Rhizoma</i> , and <i>Glycyrrhizae Radix et Rhizoma</i> , etc.	Pneumonia	Undefined	1–2 doses daily, decoction, 100–200 mL each time, 2–4 times per day, oral or nasal feeding
Xuanfei Baidu Decoction	13 types of herbs: <i>Ephedrae Herba</i> , <i>Artemisiae semen Amarum</i> , <i>Gypsum Fibrosum</i> , <i>Pogostemonis Herba</i> , <i>Artemisiae annuae Herba</i> , and <i>Glycyrrhizae Radix et Rhizoma</i> , etc.	Pneumonia	Undefined	One dose daily, decoction 400 mL, take 200 mL in the morning and evening, respectively
Xiyanping injection	<i>Andrographolide</i> total ester sulfonate	Acute viral upper respiratory tract infection, viral bacterial pneumonia, influenza, acute and chronic bronchitis	Digestive symptoms, such as nausea and vomiting	Viral infection or combined mild bacterial infection: 0.9 % sodium chloride injection 250 mL + Xiyanping injection 100 mg bid
Xuebijing injection	<i>Carthami Flos</i> , <i>Paeoniae Radix Rubra</i> , <i>Chuanxiong Rhizoma</i> , <i>Salviae miltiorrhizae Radix et Rhizoma</i> , and <i>Angelicae sinensis Radix</i>	Pulmonary infection	Chest tightness, rash, anaphylactic shock, fever, abdominal pain, nausea, vomiting, blood pressure drop, etc.	Systemic inflammatory response or multifunctional organ failure: 0.9 % sodium chloride injection 250 mL + xuebijing injection 100 mL bid
Shenfu injection	<i>Ginseng Radix et Rhizoma rubra</i> and <i>Aconiti lateralis Radix praeparata</i> extract	Septic, hemorrhagic, and dehydration shock	Undefined	Shock: 0.9 % sodium chloride injection 250 mL + Shenfu injection 100 mL bid
Shengmai injection	<i>Ginseng Radix et Rhizoma rubra</i> , <i>Ophiopogonis Radix</i> , and <i>Schisandrae chinensis Fructus</i>	Septic shock, coronary heart disease, angina pectoris, epidemic hemorrhagic fever, arrhythmia	Allergic rash, back pain	Immunosuppression: glucose injection 250 mL + Shengmai injection 20–60 mL bid
Reduning injection	<i>Artemisiae annuae Herba</i> , <i>Lonicerae japonicae Flos</i> , and <i>Gardeniae Fructus</i>	Upper respiratory infection	Individual patients may experience dizziness, chest tightness, dry mouth, diarrhea, and nausea and vomiting. Occasional allergic reactions, such as redness, itching, or rashes throughout the body.	Viral infection or combined mild bacterial infection: 0.9 % sodium chloride injection 250 mL + Reduning injection 20 mL bid
Tanreqing injection				

(continued on next page)

Table 2 (continued)

Traditional Chinese medicines	Compositions	Indications	Adverse reactions	General usage (Forreferenceonly)
Xingnaojing injection	<i>Scutellariae Radix</i> , <i>Pulsifellis Ursi</i> , <i>Goat horn</i> , <i>Lonicerae japonicae Flos</i> , and <i>Forsythiae Fructus</i>	Acute bronchitis, acute pneumonia (early stage)	Allergies, anaphylactic shock, dizziness, nausea, vomiting, itchy skin, rash, high fever, abnormal heart and kidney function, etc.	Viral infection or combined mild bacterial infection: 0.9 % sodium chloride injection 250 mL + Tanreqing injection 40 mL bid
	<i>Moschus</i> , <i>Gardeniae Fructus</i> , <i>Curcuma Radix</i> , and <i>Borneolum Syntheticum</i>	Epidemic B encephalitis, hepatic coma	Occasional allergic reactions, including skin itching, rash, and fever. Occasionally, adverse symptoms such as chest tightness, belching, rapid breathing, and rapid heartbeat	High fever with disturbance of consciousness: 0.9 % sodium chloride injection 250 mL + Xingnaojing injection 20 mL bid
Shenmai injection	<i>Ginseng Radix et Rhizoma rubra</i> and <i>Ophiopogonis Radix</i>	Shock, coronary heart disease, viral myocarditis, chronic corpulmonale, granulocytopenia	Occasional allergic reactions, such as palpitation, shortness of breath, chest tightness, flushing of the face, etc. Occasional anaphylactic shock, dyspnea, and heart failure.	Immunosuppression: glucose injection 250 mL + Shenmai injection 100 mL bid

Note: Drugs with similar efficacy can be selected according to individual conditions, or can be used in combination with another TCM. Injections should be used following the principle of starting with low doses and adjusting gradually according to clinical symptoms, which can be in combination with decoctions. Clinical application of the above TCMs requires special attention to drug contraindications, especially allergic constitution. The above usage of TCMs is for reference only, which should be adjusted appropriately according to the patient's symptoms.

involving 414 target proteins, 47 of which are potential targets for COVID-19 treated with JHQQ (Mao et al., 2020). Lianhua Qingwen Capsule (LHQQ) are applied to relieve fever or high fever and cough caused by influenza, which can inhibit the proliferation of various influenza viruses and reduce IL-6, IL-8, and TNF- α levels, thereby exerting antiviral effects (Ding et al., 2017; Dong et al., 2014). LHQQ significantly enhanced the efficacy of conventional antiviral drugs, and improved fever, cough, and fatigue symptoms in a clinical study of 63 suspected COVID-19 cases (Lv et al., 2020). In addition, a retrospective clinical study of LHQQ combined with conventional treatment patients, LHQQ could significantly improve fever, fatigue, cough, sputum, shortness of breath, chest tightness, and appetite in patients with common COVID-19, and reduce the proportion of common to severe (Cheng et al., 2020). Clinical study of 42 patients with common COVID-19 treated with LHQQ found that compared with the control group, the disappearance rate of fever symptoms increased from 57.1 % to 85.7 %, and the disappearance rate of cough symptoms increased from 5.6 % to 46.7 %. The duration of fever was shortened by 1.5 days, the disappearance rate of expectoration increased from 9.1 % to 64.3 %, and the disappearance rate of shortness of breath symptoms increased from 0 to 77.8 % (Yao et al., 2020). LHQQ prescription for the treatment of mild and common COVID-19 has been approved to be added to drug instruction in China.

Shufeng Jiedu Capsule (SFJD) can prevent acute upper respiratory tract infection, and also has good curative effects on fever, cough, and headache. Studies showed that SFJD significantly reduced the serum levels of PGE2, IL-1 β , and TNF- α in rats with acute pharyngitis (Qian, 2019). SFJD combined with arbidol could significantly improve clinical symptoms, including the increased white blood cells and lymphocytes, and the absorption of chest CT image in 100 patients with mild COVID-19 (Xiao et al., 2020). Fangfeng Tongsheng Pill (FFTS) can effectively reduce serum TNF- α level, thus exerting anti-inflammatory, anti-allergic and immune-regulating effects (Jin et al., 2017; Wang et al., 2018). SARS-CoV-2 infection is easy to cause symptoms, such as fatigue, gastrointestinal upset, and fever during the observation period. Chinese herbal compound prescriptions can reduce the levels of related inflammation-related factors, exert anti-inflammatory and improve immunity, and ultimately alleviate the symptoms of patients with COVID-19 (Zhang et al., 2020b).

Qingfei Paidu Decoction (QFPD) is mainly used to control lung infection in clinical practice. The active ingredients of QFPD for the treatment of COVID-19 were predicted by network pharmacology methods, including quercetin, luteolin, kaempferol, naringenin, and isorhamnetine (Xu et al., 2020a,b). QFPD combined with antiviral drugs could significantly shorten the hospitalization time, clinical symptom improvement time, and lung CT improvement time of COVID-19 patients by retrospectively evaluating the treatment of 60 COVID-19 patients (Li et al., 2020a,b,c,d,e). Results of clinical studies in four pilot provinces of China showed that QFPD achieved a total effective rate of more than 90 % during the treatment of 214 patients with COVID-19 for 3 days as a course of treatment, 60 % of which had significantly improved symptoms and imaging performance and 30 % were stable without exacerbation (He et al., 2020). But patients need to drink half a bowl of rice soup after taking the medicine to relieve the adverse reaction. Toujie Quwen Granule (TJQW) (Pneumonia No.1 prescription), a Chinese clinical experience prescription, contains 16 types of drugs, such as *Scutellariae Radix*, *Forsythiae Fructus*, *Lonicerae japonicae Flos*, and *Isatidis Folium*. After treatment with TJQW, the symptoms of two patients were significantly improved, including temperature return to normal, inflammation absorption, and the negative viral nucleic acid test results (Fu et al., 2020). TJQW has been approved for application in 30 designated hospitals in China for the clinical treatment of COVID-19 in combination with chemical drugs.

Huashi Baidu Prescription (HSBD) that is developed by Chinese academicians Huang Luqi's team can improve fever, promote blood circulation to remove blood stasis, and improve the immunity function.

An analysis of 44,672 confirmed cases with COVID-19 by Chinese Center for Disease Control and Prevention showed that the crude mortality rate of critical cases was 49 % (Epidemiology working group for NCIP epidemic response, Chinese Center for Disease Control and Prevention, 2020). Severe COVID-19 is easy to develop into critical illness, which greatly increases the mortality rate. Clinical studies have confirmed that the application of HSBD following the guidance of traditional theories can effectively relieve the symptoms of severe COVID-19 and reduce the conversion rate and mortality rate of critical illness. However, the dosage of HSBD needs to be adjusted according to clinical symptoms of severe COVID-19. HSBD can also be used in combination with Chinese medicine injection preparations, such as Xiyanning, Xuebijing, Xingnaojing, Tanreqing, Shenmai, and Shenfu injections, to increase the efficacy against SARS-CoV-2 (Zhao et al., 2020). Xuanfei Baidu Decoction (XFBD) that is developed by Chinese academician Zhang Boli and Professor Liu Qingquan's team is also used for the treatment of COVID-19. XFBD was clinically applied in several hospitals in Wuhan, such as Wuhan Hospital of Traditional Chinese Medicine, Hubei Provincial Hospital of Integrated Chinese & Western Medicine, and Jiangxia Shelter Hospital. Results of the relevant cohort studies on COVID-19 treated with XFBD are being sorted out. XFBD can significantly reduce fever, cough, fatigue and other symptoms of the mild and common patients, and prevent mild to severe in preliminary clinical studies. The important targets of XFBD are mainly enriched in the pathways related to viral infection and lung injury through network pharmacology analysis, suggesting that the mechanism of XFBD for the treatment of COVID-19 is mainly related to combating viral infection and repairing lung injury (Wang et al., 2020b).

Shuanghuanglian is composed of *Lonicerae japonicae Flos*, *Scutellariae Radix*, and *Forsythiae Fructus*, which has been used to prevent infection for more than 2000 years in China. The common formulations on the market include granule, oral solution, and injection. Shuanghuanglian has multiple pharmacological activities, including antibacterial, antiviral, and immune-enhancing functions. Previous studies have shown that Shuanghuanglian injection has obvious antiviral effects against influenza A virus H5N1 in vivo and in vitro (Tang et al., 2018). A systematic review of RCTs suggested that Shuanghuanglian could be applied for the treatment of acute upper respiratory tract infection (Zhang et al., 2013). Preliminary studies in vitro found that Shuanghuanglian oral solution inhibited SARS-CoV-2. But whether Shuanghuanglian is effective against COVID-19 requires a large number of clinical trials to confirm. At present, Shuanghuanglian has been clinically studied in Shanghai Public Health Clinical Center and Tongji Hospital affiliated to Huazhong University of Science and Technology. Shanghai Institute of Materia Medica has negotiated and reached a cooperation agreement with relevant companies to jointly conduct in-depth research on the antiviral efficacy of Shuanghuanglian.

5.3. Chinese medicine injection preparations

Chinese medicine injection preparation is a sterilized solvent, powder or concentrated solution, which can be applied for injecting into the body through extracting the active ingredients from TCMs by the modern techniques and methods. The active component of Xiyanning injection is andrographolide total ester sulfonate. Xiyanning injection that is commonly used clinically for respiratory infections, pneumonia, and gastroenteritis has anti-inflammatory, blood coagulation regulation, vascular endothelial protection, immunity-enhancing and other functions through the "multi-components, multi-targets, and multi-pathways" mechanism (Ma et al., 2009, 2015). Xuebijing injection is mainly used for anti-infective treatment, which can antagonize endotoxin and inflammatory mediators and improve lung and systemic inflammation in the treatment of coronavirus (Li et al., 2020a,b,c,d,e). In clinical application, Xuebijing injection had a significant effect on inflammation storm and low blood oxygen saturation caused by SARS-CoV-2 infection. A retrospective analysis of 44 patients with common

COVID-19 found that Xuebijing treatment could promote the absorption of lung infection lesions, thereby improving the efficacy. But Xuebijing had no obvious efficacy on inflammatory indexes, including white blood count, lymphocyte count, percentage of lymphocytes, CRP, and ferritin (Zhang et al., 2020a,b,c,d). Few patients may experience itchy skin after injecting Xuebijing injection. The incidence of Xuebijing injection is reported differently, probably between 2.68 % and 4% (Lu and Fan, 2013). The components of Shenfu injection that is used clinically to treat septic shock include *Ginseng Radix et Rhizoma rubra* and *Aconiti lateralis Radix praeparata* extract, which contain the active ingredients ginsenosides and water-soluble alkaloids. Occasionally, allergic reactions may occur after Shenfu injection treatment. An analysis on 23 RCTs containing 1804 participants showed that the combination of Shengmai injection and chemical drugs could achieve a better effect than drugs alone in terms of improving the clinical total effective rate, pulmonary function, blood gas index, immunoglobulin and CRP levels, and the lung rale disappearance time of chronic obstructive pulmonary disease (COPD) (Huang et al., 2019). But Shengmai injection may cause adverse reactions, such as allergic rash and severe back pain. The ingredients of Reduning injection are *Artemisiae annuae Herba*, *Lonicerae japonicae Flos*, and *Gardeniae Fructus*, which are used for relieving symptoms caused by upper respiratory tract infection, such as high fever, headache, and cough. Reduning injection rescued death triggered by Enterovirus 71 infection in Vero cells and in mice (Cao et al., 2015). Severe pneumonia induced by H1N1 influenza a virus could be reversed by the combination of ribavirin and Reduning administration (Ma et al., 2016). Tanreqing injection is mainly used for the treatment of acute and chronic bronchitis, pneumonia, and upper respiratory tract infections caused by bacteria or viruses. Xingnaojing injection is well known for treating stroke in Chinese clinic. Animal experiments showed that Xingnaojing injection improved cerebral ischaemia/reperfusion injury through inhibiting inflammatory response (Zhang et al., 2020c). A study revealed that Xingnaojing had a positive effect on patients with fever, poisoning, and stroke-induced consciousness disturbance (Wu et al., 2016). Shenmai injection is increasingly used in tumor therapy, which can obviously improve the immune function of tumor patients. For example, Shenmai injection improved the postoperative immunological function of papillary thyroid carcinoma patients by inhibiting differentiation into Treg cells (Fang et al., 2018). When combined with chemotherapeutic drugs, Shenmai injection reduces adverse reactions caused by chemotherapeutic drugs. At present, these Chinese medicine injection preparations are mainly tried to treat middle and severe COVID-19 cases in clinical trials.

6. Biological products for COVID-19 treatment

As the global epidemic situation of COVID-19 becomes more and more serious, many countries and regions have begun to develop biological products for the treatment of COVID-19. Biological products mainly stimulate immune system to produce immune substances that presents antiviral efficacy. As one of the first countries to conduct the prevention and treatment of COVID-19, China has launched the development of biological products against SARS-CoV-2, such as IFN, vaccines, stem cells, and convalescent plasma (CP).

6.1. Interferon- α

Recombinant human interferon- α (IFN- α), including IFN- α 1b and IFN- α 2b, exerts broad-spectrum antiviral, antitumor, cell proliferation inhibition, and immunity improvement on patients. IFN- α binding to cell surface receptors induces cells to produce a variety of antiviral proteins, which inhibits viral proliferation in cells and improves immune ability through enhancing the phagocytosis of macrophages, the cytotoxicity of lymphocytes to target cells, and the vitality of natural killer (NK) cells (Chen et al., 2016; Sugita et al., 1987). IFN- α 2b is widely used to treat some viral diseases, such as acute and chronic viral

hepatitis, shingles, and genital warts. However, IFN may have adverse reactions, such as fever, fatigue, headache, myalgia, arthralgia, loss of appetite, and nausea at the early stage of medication (Wang et al., 2020c). Study showed that IFN- α 2b and ribavirin for the treatment of MERS-CoV infected rhesus macaques reduced virus replication, moderated the host response, and improved clinical outcome (Falzarano et al., 2013). In vivo studies also showed that IFN- α played an effective role in promoting prognosis of MERS-CoV infection (Momattin et al., 2013). By comparing the clinical effects of combined IFN- α with glucocorticoid alone in treating patients with SARS-CoV infection, the results showed that lung image remission time was reduced by 50 %, and oxygen saturation was significantly improved in IFN- α treatment group (Loutfy et al., 2003). At present, IFN- α nebulized inhalation combined with other antiviral drugs, such as ribavirin, has been clinically tested for the treatment of COVID-19, which achieved a good therapeutic effect. However, it is necessary to be alert to the microbial aerosols that may be generated during IFN- α nebulized inhalation due to the possibility of aerosol transmission in SARS-CoV-2 infection (Chen et al., 2020a, 2020b, 2020c). Some medical protection and disinfection should be done to reduce the risk of infection by medical staff. Chinese Clinical Trial Registry announced that clinical trial comparing the efficacy of new recombinant high-efficiency compound IFN and IFN- α for the treatment of COVID-19 has been registered.

6.2. Vaccines

Vaccines treatment is an effective method to prevent infection or improve the severity of diseases (Wang and Wang, 2020). Previous evidence showed that various vaccines were designed and synthesized to effectively prevent SARS-CoV and MERS-CoV infection (de Wit et al., 2016). Development of vaccines need to take a long time, involving virus strain isolation and selection, in vitro experiments, animal experiments, clinical trials, and administrative approval. As of April 8, 2020, a total of 115 COVID-19 vaccine candidates in the world are under development, 78 of which have been confirmed. 73 of the 78 confirmed projects are currently in the exploratory or preclinical stage. Five fastest-growing vaccine candidates have entered clinical development stage (Thanh Le et al., 2020). Inactivated vaccines, recombinant protein vaccines, adenovirus vector vaccines, attenuated influenza virus vector live vaccines, and nucleic acid vaccines against SARS-CoV-2 are being developed vaccines in China. Inactivated vaccines are the most effective path of vaccine development for newly emerging infectious diseases. The latest reports indicated that Chinese Medical Products Administration has approved two clinical trials of inactivated vaccine against SARS-CoV-2 developed by Wuhan Institute of Biological Products Co., LTD combined with Wuhan Institute of Virology and Sinovac Research & Development Co., LTD, respectively. During recombinant protein vaccine development, the construction of virus species has been completed, and cell and virus species identification and genetic stability inspection, animal experiments and safety evaluation testings currently are being carried out in China. The adenoviral vector vaccine developed by Chinese academician Chen Wei's team was the first vaccine to be approved for clinical research. Currently, the vaccination of the phase I clinical trial subjects of this vaccine has been completed, and volunteers of the phase II clinical trial are being recruited, which is the first vaccine strain against SARS-CoV-2 to launch the phase II clinical trial in the world. Moreover, China has also completed the construction of attenuated influenza virus vector vaccine strains and the establishment of quality inspection methods, following the quality process research and quality identification. Meanwhile, animal experiments and safety evaluation experiments are also carried out. In nucleic acid vaccine development process, animal effectiveness and safety evaluation, and the preparation and quality verification of clinical samples are being carried out.

6.3. Stem cells

Stem cell therapy can promote endogenous injury repair by regulating the immune system and improving the microenvironment, and inhibit the progression of acute inflammation in the lungs, thereby relieving symptoms of respiratory distress. Studies have shown that mesenchymal stem cells (MSCs) can be effectively used for the treatment of MERS-CoV (Zumla et al., 2015). At present, stem cell therapy of COVID-19 is mainly focused on MSCs and NK cells, of which the most used is MSCs. On the basis of conventional treatment, a 70 years old female patient with severe COVID-19 was intravenously infused with allogeneic human umbilical cord MSCs. Results showed that the main inflammatory factors IL-6 and CRP levels decreased, the ratio of neutrophils to lymphocytes continuously decreased, and the absolute values of T cells, NK cells, and B cells continued to rise. Results of CT imaging revealed that inflammation in the lungs gradually subsided without any adverse reaction (Gu et al., 2020). Thus, MSCs were shown to be safe and effective for critically ill patients with COVID-19. Up to now, a number of medical institutions, scientific research units and enterprises have launched related clinical research projects of MSCs treatment of COVID-19 in China (Ju, 2020). Although stem cell therapy presents certain advantage against COVID-19, more data and results are still needed to support the safety and efficacy of COVID-19 treatment.

6.4. Convalescent plasma

CP therapy is applied for treating patients with infectious diseases through extracting the cured patients' plasma, serum or immunoglobulin, which was widely used in infectious diseases outbreaks in recent years, such as pandemic influenza, SARS, and MERS (Arabi et al., 2015; Cheng et al., 2005; Leider et al., 2010). A systematic review showed that early treatment with CP might be more effective than late treatment with that (Mair-Jenkins et al., 2015). In theory, most of the patients with COVID-19 will produce specific antibodies against SARS-CoV-2 after the recovery, which can kill and clear the virus. Preliminary clinical studies also confirmed that CRP and IL-6 levels in 3 severe COVID-19 patients after plasma exchange therapy were significantly reduced, lymphocytes and prothrombin time were improved, but inflammatory factors in patients treated with tocilizumab did not decrease (Luo et al., 2020). The clinical symptoms improved significantly, oxygen saturation and oxygenation index tended to improve, and inflammation indicators also improved within 72 h after CP infusion for a severe COVID-19 patient (Li et al., 2020b). Severe illness is the leading cause of COVID-19-induced death. Therefore, CP therapy may be an effective method to reduce mortality of severe COVID-19 patients with serious inflammatory response in the absence of specific treatments. In China, CP therapy has been added to the "Diagnosis and Treatment Plan for the Novel Coronavirus Infected Pneumonia (trial edition 7)", which is applicable to the treatment of cases with rapid progression, severe or critically ill. However, CP must be collected at an appropriate time and has a higher neutralizing antibody titer (Bai et al., 2020).

7. Discussion

At present, a worldwide outbreak of COVID-19 seriously affects people's health and economic development. SARS-CoV-2 infection has been widely caused in the general population and medical staff. Development of specific medicines or vaccines for the treatment of COVID-19 is quite urgent. Chinese scientists tried various marketed drugs, especially chemical drugs and TCMs, for the treatment of COVID-19. A number of drugs with good effects against SARS-CoV-2 in vitro or preliminary clinical trials have emerged. However, there is still insufficient evidence to support the efficacy and safety of these drugs against SARS-CoV-2. Some shortcomings exist in previous studies, such as unreliable in vitro results, non-standard clinical trials, small sample size. Hence, it is necessary to summarize these potential therapeutic

drugs to ensure clinical medication safety and guide further standardized clinical research.

Chemical drugs have the advantages of clear composition, rapid onset of action, and strong antiviral ability. Due to the urgency of COVID-19 treatment, kalectra, ribavirin, chloroquine, remdesivir, arbidol, and favipiravir were clinically used to antagonize SARS-CoV-2 in China (National Health Commission, National Administration of Traditional Chinese Medicine, 2020). Most of the above drugs show good antiviral effects during the treatment of SARS-CoV and MERS-CoV. Ribavirin, favipiravir, and remdesivir directly inhibit the viral RNA polymerase, leading to the premature termination of RNA transcription. Arbidol inhibits the fusion between viral envelope and cell membrane of the target cell, preventing the virus from entering the target cell. Kaletra consists of two protease inhibitors that prevent the cleavage of Gag-Pol polyproteins, resulting in the production of non-infectious virions. Chloroquine can interfere with the replication and transcription of pathogen DNA. Although these chemical drugs have significant antiviral effects, drug safety is an important factor to be considered in clinical application. The latest clinical studies showed that lopinavir, ritonavir, and arbidol had no significant improvement on symptoms (such as elevated body temperature) or the shortening of the negative time of respiratory virus nucleic acid effect, compared with the absence of any antiviral drugs. In contrast, the incidence of adverse reactions in the lopinavir and ritonavir groups was higher than that in the control group without antiviral drugs. Chloroquine and remdesivir are regarded as the promising chemical drugs against SARS-CoV-2. However, the dosage and cycle of chloroquine need further clinical trials to confirm. The clinical pharmacokinetic reports indicated that the oral half-life of chloroquine was as long as 5–60 days, the median half-life is 21–30 days, and the clinical lethal dose is 3–5 g. Therefore, the clinical dosage of chloroquine needs to be adjusted according to individual differences of body weight and age. The efficacy and safety of remdesivir for COVID-19 treatment still lack more high-quality evidence. Therefore, the application of these chemicals in the treatment of COVID-19 should pay special attention to the latest clinical trials and drug safety studies.

TCM has been practiced clinically in China for thousands of years to relieve the symptoms of diseases and regulate immunity. TCM is of great value in prevention and treatment of COVID-19. The therapeutic effects of TCMs, including active ingredients of TCMs, Chinese herbal compound prescriptions, and Chinese medicine injection preparations, on COVID-19 have been extensively studied. Currently, active ingredients of TCMs against SARS-CoV-2 are only studied in vitro or by computer simulation. Some studies have pointed out that GA can bind to ACE2 by the molecular docking methods, suggesting that GA preparations have potential application value for preventing SARS-CoV-2 infection. There was a study that screened several TCMs ingredients with anti-SARS-CoV-2 activity through virtual screening and enzymatic testing, including emodin, polydatin, chalcone, and shikonin. However, these active ingredients of TCMs need to pass clinical trials to further confirm their efficacy against COVID-19. HXZQ, JHQG, LHQW, SFJD, FFTS, TJQW, and QFPD suggested by Chinese health authorities have all been tried in clinical trials, all of which have shown good curative effects, such as shorten the time for the patient to heal and relieve the development from mild to severe (Xue et al., 2020). HXZQ can alleviate fatigue and gastrointestinal discomfort in patients with COVID-19. JHQG, LHQW, and SFJD have similar effects, which can improve the symptoms of fatigue and fever in COVID-19 patients. JHQG has a definite effect on the treatment of mild and common patients with COVID-19, which can shorten the time of fever, improve the normalization rate of lymphocytes and leukocytes, and promote immunological function. LHQW also shows good curative effect on mild and common patients with COVID-19, which is manifested with relieving fever, cough, fatigue and other symptoms, and effectively reducing the conversion rate of mild/common to severe.

QFPD has a total effective rate of more than 90 % in the early

clinical treatment of COVID-19, which is suitable for mild, common, and severe patients (He et al., 2020). QFPD showed an important role in blocking the development of mild, common to severe and critically ill and rescuing severe and critical illness. HSB and XFBD both are effective prescriptions summarized by Chinese medical teams in the front-line clinical treatment of COVID-19 based on clinical observations in Wuhan, which have good effects in blocking the progression of disease and improving symptoms, especially in shortening the course of COVID-19. In a clinical study of 50 mild COVID-19 patients with TJQW oral administration, the temperature of all patients returned to normal, cough symptoms disappeared in 50 % of patients, symptoms of sore throat disappeared in 52.4 %, and symptoms of fatigue in 69.6 % disappeared. Chinese medicine injections have also been clinically tested for severe and critically ill patients with COVID-19. Xiyanning, Reduning, and Tanreng injections that all have anti-inflammatory and antibacterial effects can be used to treat patients with viral infection and mild bacterial infection. Xingnaojing injection has the effects of reducing fever, resuscitating and refreshing the brain, which is mainly aimed at patients with high fever following unconsciousness. Xuebijing injection can improve the cure rate and discharge rate of patients with COVID-19, reduce the chance of conversion from severe to critically ill, and promote the elimination of inflammatory factors. Shenmai injection can provide the immunity of patients, which is mainly used to treat the immunosuppressed patients. Shenfu injection has the effect of resuscitating for patients with shock. Arachidonic acid metabolism pathway is involved in cytokine production (Xiao et al., 2005). The latest research showed that serum levels of inflammatory factors in patients with SARS-CoV-2 infection significantly increased, suggesting that SARS-CoV-2 infection may involve "cytokine storm" (Alimuddin et al., 2020). Studies have screened 338 active ingredients of TCMs that have potential inhibitory effects on the arachidonic acid metabolism pathway through the pharmacophore technology (Ren et al., 2020). Interestingly, the above active ingredients existed in HXZQ, JHQG, LHQW, QFPD, Xuebijing injection, Reduning injection, and Tanreng injection, which suggested that the above TCMs may resist SARS-CoV-2 infection by inhibiting the "cytokine storm". Although TCMs are effective and relatively safe for prevention and treatment of COVID-19, clinical medication needs to be administered under the guidance of an experienced physician, thereby avoiding adverse reactions due to overdose or misuse of TCMs. Moreover, clinical medication based on different symptoms and the severity of the disease is an important principle during the treatment of COVID-19 with TCMs. For example, preliminary clinical studies showed that LHQW was effective for the treatment of mild or common patients with SARS-CoV-2 infection, which is manifested with the improvement of fever, cough, and diarrhea. Xuebijing had a wonderful effect on the treatment of severe and critically ill patients with COVID-19.

Both TCMs and chemical drugs can complement each other rather than replacing each other, which has been fully demonstrated in prevention and control of this outbreak of COVID-19. TCM with a relatively wide range of treatment can improve the immunity and relieve symptoms in mild cases with COVID-19, such as fever, cough, fatigue, and sore throat. In terms of severe COVID-19, TCM can also reduce the progression from severe to critical illness, thereby reducing the mortality rate. Chemical drugs have clear chemical composition and significant antiviral effect, which can quickly inhibit SARS-CoV-2 infection. The latest clinical evidence showed that the integrated traditional and western medicine for the treatment of COVID-19 could significantly reduce the clinical symptoms of patients, shorten the course of disease, and improve the clinical cure rate (Xia et al., 2020). A retrospective analysis of 71 discharged patients with COVID-19 showed that the combination therapy of IFN- α , arbidol, high-dose of vitamin C, and TCMs was effective against SARS-CoV-2 (Huang et al., 2020a,b,c). A systematic review showed that LHQW combined with western medicines significantly improved fever symptoms with good clinical safety (Qi et al., 2020). Zhang Boli's team observed the clinical effect of

integrated traditional Chinese and western medicine in the treatment of COVID-19. The results showed that compared with the pure western medicine group (13 cases of common type, 4 cases of severe, and 1 case of critically ill), the average days of treatment in the integrated traditional Chinese and western medicine treatment group (27 cases of common type, 6 cases of severe, and 1 case of critically ill) was shortened from 7.15 days to 5.15 days, the average recovery time of body temperature was shortened from 4.38 days to 2.64 days, the average time of hospital stay was shortened from 9.59 days to 7.38 days, the improvement rate of CT imaging was increased from 68.8 % to 88.2 %, clinical cure rate was increased from 61.1 % to 94.1 %, the conversion rate of common to severe and critically ill was reduced from 35.3 % to 5.9 % (Xia et al., 2020).

Biological products are currently an important means for treating severe COVID-19, which can effectively relieve patients' symptoms to reduce mortality. Development of biological products mainly includes IFN- α , vaccines, stem cells, and CP. Although the theoretical incidence of adverse events induced by IFN- α nebulized inhalation may be lower than that of traditional administration routes, the relevant medication monitoring should still be done (Wu et al., 2020). IFN- α is often used clinically in combination with other antiviral drugs to treat COVID-19, such as ribavirin and favipiravir. The dosage, drug stability, adverse reactions, and the risk of secondary infection should be fully considered during IFN aerosol inhalation. Vaccine treatment is an effective method to prevent and treat COVID-19, but the development of vaccines needs to take a long time. The safety and effectiveness of drugs in vaccine development process require sufficient clinical data to verify. Fortunately, the adenoviral vector vaccine that is independently developed by China's team has entered the phase II clinical trials. Stem cell therapy also shows certain potential for COVID-19 treatment. The application of MSCs will give new clinical plan for COVID-19 treatment. Preliminary clinical studies have shown that CP therapy has good efficacy for severe COVID-19 treatment, but CP with high-quality antibody titers is difficult to obtain. In the absence of specific drugs, CP therapy can become a first-aid method for COVID-19 patients with severe or critically ill.

8. Conclusions

China has accumulated a bit of experience during the prevention and treatment of SARS-CoV-2 infection with the above drugs, including chemical drugs, TCMs, and biological products. Although these drugs are expected to be specific drugs for the treatment of COVID-19, the adoption of these drugs without adequate evidence of efficacy and safety must be careful. Nowadays, these potential drugs have been used to treat COVID-19 by many countries and regions due to the outbreak of COVID-19. The basic characteristics of these drugs, including pharmacological effects, indications, and adverse reactions, and especially advance on the treatment of COVID-19, should be understood to promote reasonable medication and guide further basic research and clinical trials.

Declaration of Competing Interest

The authors have no conflict of interest.

Acknowledgments

This work was supported by National Natural Science Foundation of China (81891010, 81891012, 81630101), China Postdoctoral Science Foundation (2018M631070), Sichuan Science and Technology Agency Foundation (2018JZ0081), and Xinlin Scholar Research Promotion Project of Chengdu University of Traditional Chinese Medicine.

References

- Alimuddin, Z., David, S.H., Esam, I.A., Ziad, A.M., Markus, M., 2020. Reducing mortality from COVID-19: host-directed therapies should be an option. *Lancet* 395 (10224), e35–e36. [https://doi.org/10.1016/S0140-6736\(20\)30305-30306](https://doi.org/10.1016/S0140-6736(20)30305-30306).
- Arabi, Y., Balkhy, H., Hajeer, A.H., Bouchama, A., Hayden, F.G., Al-Omari, A., Al-Hameed, F.M., Taha, Y., Shindo, N., Whitehead, J., Merson, L., Al-Johani, S., Al-Khairi, K., Carson, G., Luke, T.C., Hensley, L., Al-Dawood, A., Al-Qahtani, S., Modjarrad, K., Sadat, M., Rohde, G., Leport, C., Fowler, R., 2015. Feasibility, safety, clinical, and laboratory effects of convalescent plasma therapy for patients with Middle East respiratory syndrome coronavirus infection: a study protocol. *SpringerPlus* 4, 709.
- Bai, W.D., Cai, W., Chen, S.F., Chen, Y.Q., 2020. The present situation and Prospect of Convalescent Plasma Treatment: taking novel coronavirus pneumonia for example. *Chin. J. Virol.* (病毒学报). <https://doi.org/10.13242/j.cnki.bingduxuebao.003672>. [2020-03-27].
- Brandi, N.W., Friederike, F., Benjamin, S., Kimberly, M.W., Danielle, P.P., Jonathan, S., Neeltje, v.D., Ian, L., Claude, K.Y., Lizzette, P.P., Atsushi, O., Jamie, L., Patrick, W.H., Greg, S., Catharine, M.B., Sarah, A., Kent, B., Tomas, C., Craig, M., Dana, P.S., Vincent, J.M., Emmie, d.W., 2020. Clinical benefit of remdesivir in rhesus macaques infected with SARS-CoV-2. *bioRxiv*. <https://doi.org/10.1101/2020.04.15.043166>.
- Cao, Z.Y., Chang, X.J., Zhao, Z.P., Cao, L., Xiao, W., 2015. Antiviral effects of reduning injection against Enterovirus 71 and possible mechanisms of action. *Chin. J. Nat. Med.* (中国天然药物) 13 (12), 881–888.
- Chang, J., Schul, W., Butters, T.D., Yip, A., Liu, B., Goh, A., Lakshminarayana, S.B., Alonzi, D., Reinkensmeier, G., Pan, X., Qu, X., Weidner, J.M., Wang, L., Yu, W., Borune, N., Kinch, M.A., Rayahin, J.E., Moriarty, R., Xu, X., Shi, P.Y., Guo, J.T., Block, T.M., 2011. Combination of alpha-glucosidase inhibitor and ribavirin for the treatment of dengue virus infection in vitro and in vivo. *Antiviral Res.* 89 (1), 26–34.
- Chen, Y., Zhu, W., Shu, Y., 2016. [Research progress on antiviral activity of interferon-induced transmembrane proteins]. *Chin. J. Virol.* 32 (2), 222–228.
- Chen, Y.W., Tang, L.Q., Zhang, S.Y., Wang, M., Shen, A.Z., 2020a. Rational administration and pharmaceutical care of interferon alpha nebulization therapy in corona virus disease 2019. *Chin. J. Hosp. Pharm.* (中国医院药学杂志) [2020-02-25]. <http://kns.cnki.net/kcms/detail/42.1204.R.20200224.1905.007.html>.
- Chen, N., Zhou, M., Dong, X., Qu, J., Gong, F., Han, Y., Qiu, Y., Wang, J., Liu, Y., Wei, Y., Xia, J., Yu, T., Zhang, X., Zhang, L., 2020b. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 395 (10223), 507–513.
- Chen, Z.W., Hu, J.J., Zhang, Z.W., et al., 2020c. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. *medRxiv*. <https://doi.org/10.1101/2020.03.22.20040758>.
- Cheng, Y., Wong, R., Soo, Y.O., Wong, W.S., Lee, C.K., Ng, M.H., Chan, P., Wong, K.C., Leung, C.B., Cheng, G., 2005. Use of convalescent plasma therapy in SARS patients in Hong Kong. *Eur. J. Clin. Microbiol. Infect. Dis.* 24 (1), 44–46.
- Cheng, D.Z., Wang, W.J., Li, Y., Wu, X.D., Zhou, B., Song, Q.Y., 2020. Analysis of the efficacy of Chinese medicine Lianhua Qingwen in 51 cases of new coronavirus pneumonia patients: a multi-center retrospective study. *Tianjin J. Tradit. Chin. Med.* (天津中医药) [2020-03-11]. <http://kns.cnki.net/kcms/detail/12.1349.R.20200310.1024.004.html>.
- Chu, C.M., Cheng, V.C., Hung, I.F., Wong, M.M., Chan, K.H., Chan, K.S., Kao, R.Y., Poon, L.L., Wong, C.L., Guan, Y., Peiris, J.S., Yuen, K.Y., Group, H.U.S.S., 2004. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. *Thorax* 59 (3), 252–256.
- de Wit, E., van Doremalen, N., Falzarano, D., Munster, V.J., 2016. SARS and MERS: recent insights into emerging coronaviruses. *Nature reviews. Microbiology* 14 (8), 523–534.
- de Wit, E., Feldmann, F., Cronin, J., Jordan, R., Okumura, A., Thomas, T., Scott, D., Cihlar, T., Feldmann, H., 2020. Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. *Proc. Natl. Acad. Sci. U. S. A.* 117 (12), 6771–6776.
- Deng, Y.J., Liu, B.W., He, Z.X., Liu, T., Zheng, R.L., Yang, A.D., Huang, A., Li, Y.T., Xu, Y.L., 2020. Study on active compounds from Huoxiang Zhengqi Oral Liquid for prevention of novel coronavirus pneumonia (COVID-19) based on network pharmacology and molecular docking. *Chin. Tradit. Herbal Drugs (中草药)* 1–10. [2020-2003-2015]. <http://kns.cnki.net/kcms/detail/2012.1108.R.20200224.20202202.20200002.html>.
- Ding, Y., Zeng, L., Li, R., Chen, Q., Zhou, B., Chen, Q., Cheng, P.L., Yutao, W., Zheng, J., Yang, Z., Zhang, F., 2017. The Chinese prescription lianhuqingwen capsule exerts anti-influenza activity through the inhibition of viral propagation and impacts immune function. *BMC Complement. Altern. Med.* 17 (1), 130.
- Dong, L., Xia, J.W., Gong, Y., Chen, Z., Yang, H.H., Zhang, J., He, J., Chen, X.D., 2014. Effect of lianhuqingwen capsules on airway inflammation in patients with acute exacerbation of chronic obstructive pulmonary disease. *Evid. Complement. Alternat. Med.* 2014, 637969.
- Wang, Y., Tian, D.L., Sun, Y.Y., Bai, Y.L., Zhu, L.Q., 2020e. Pharmaceutical care for children in therapy of novel coronavirus pneumonia. *Chin. J. Hosp. Pharm.* (中国医院药学杂志). <https://doi.org/10.13286/j.1001-5213.2020.06.01>. [2020-02-19].
- Epidemiology working group for NCIP epidemic response, Chinese Center for Disease Control and Prevention, 2020. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China. *Chin. J. Epidemiol.* (中华流行病学杂志) 41 (2), 145–151.
- Falzarano, D., de Wit, E., Rasmussen, A.L., Feldmann, F., Okumura, A., Scott, D.P., Brining, D., Bushmaker, T., Martellaro, C., Baseler, L., Benecke, A.G., Katze, M.G., Munster, V.J., Feldmann, H., 2013. Treatment with interferon-alpha2b and ribavirin improves outcome in MERS-CoV-infected rhesus macaques. *Nat. Med.* 19 (10),

- 1313–1317.
- Fang, Z.X., Liu, R.L., Wu, H., Wang, J.B., 2015. Literature analysis of adverse reactions induced by Huoxiang Zhengqi preparation. *Henan Tradit. Chin. Med. (河南中医)* 35 (6), 1434–1436.
- Fang, T., Li, J., Wu, X., 2018. Shenmai injection improves the postoperative immune function of papillary thyroid carcinoma patients by inhibiting differentiation into Treg cells via miR-103/GPER1 axis. *Drug Dev. Res.* 79 (7), 324–331.
- Fu, X.X., Lin, L.P., Tan, X.H., 2020. 2 cases reports of Corona Virus Disease 2019 treated by Tiejiequwen granules. *J. Jinan Univ. (Nat. Sci. Med. Ed.) (暨南大学学报(自然科学与医学版))* 1–6. [2020-2003-2015]. <http://kns.cnki.net/kcms/detail/2044.1282.N.20200310.20201720.20200002.html>.
- Furuta, Y., Gowen, B.B., Takahashi, K., Shiraki, K., Smee, D.F., Barnard, D.L., 2013. Favipiravir (T-705), a novel viral RNA polymerase inhibitor. *Antiviral Res.* 100 (2), 446–454.
- Gu, L.M., Li, T., Zeng, Y., Chen, J.H., Wang, F.P., Hao, Y.L., Wu, H.Y., Ruan, J.Y., Li, Y.J., Chen, Y., Xia, J., Sun, J., Hu, J.Y., Li, W., Yu, C.T., Ma, Z.X., Qian, C.Y., Hu, M., 2020. Human umbilical cord mesenchymal stem cells treatment combined with anti-virus and other treatments for COVID-19. *J. Kunming Med. Univ. (昆明医科大学学报)* 41 (3), 96–100.
- Guan, W.D., Du, Q.L., Jiang, H.M., Zhao, J.C., Yang, Z.F., 2018. Comparison of inhibitory effects of arbidol and Lianhuaqingwen Capsules on Middle East respiratory syndrome coronavirus in vitro and in vivo. *Guangdong Med. J. (广东医学)* 39 (23), 3454–3458.
- He, Q.H., Liu, Y.K., Sun, X.R., Sun, Y.K., Sun, G.R., 2020. Traditional Chinese medicine against the new coronavirus pneumonia—the significance and function of "Qingfei Jiedu decoction" issued by the National Administration of Traditional Chinese Medicine. *J. Tradit. Chinese Med.* 1–4. [2020-2002-2025]. <http://kns.cnki.net/kcms/detail/2011.2166.R.20200224.20201038.20200008.html>.
- Hoever, G., Baltina, L., Michaelis, M., Kondratenko, R., Baltina, L., Tolstikov, G.A., Doerr, H.W., Cinatl Jr., J., 2005. Antiviral activity of glycyrrhizic acid derivatives against SARS-coronavirus. *J. Med. Chem.* 48 (4), 1256–1259.
- Holshue, M.L., DeBolt, C., Lindquist, S., Lofy, K.H., Wiesman, J., Bruce, H., Spitters, C., Ericson, K., Wilkerson, S., Tural, A., Diaz, G., Cohn, A., Fox, L., Patel, A., Gerber, S.I., Kim, L., Tong, S., Lu, X., Lindstrom, S., Pallansch, M.A., Weldon, W.C., Biggs, H.M., Uyeki, T.M., Pillai, S.K., Washington State -nCoV, V.C.I.T., 2020. First case of 2019 novel coronavirus in the United States. *N. Engl. J. Med.* 382 (10), 929–936.
- Huang, X., Duan, X., Wang, K., Wu, J., Zhang, X., 2019. Shengmai injection as an adjunctive therapy for the treatment of chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Complement. Ther. Med.* 43, 140–147.
- Huang, L.J., Chen, F.C., Jiang, X.Q., Li, Z.H., Wang, W., Liu, Y.W., 2020a. Clinical characteristics and therapy of novel corona virus pneumonia: 71 cases retrospective analysis. *Central South Pharm. (中南药学)* [2020-04-07]. <http://kns.cnki.net/kcms/detail/43.1408.R.20200403.1618.002.html>.
- Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., Zhang, L., Fan, G., Xu, J., Gu, X., Cheng, Z., Yu, T., Xia, J., Wei, Y., Wu, W., Xie, X., Yin, W., Li, H., Liu, M., Xiao, Y., Gao, H., Guo, L., Xie, J., Wang, G., Jiang, R., Gao, Z., Jin, Q., Wang, J., Cao, B., 2020b. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 395 (10223), 497–506.
- Huang, M.X., Li, M., Xiao, F., 2020c. Preliminary evidence from a multicenter prospective observational study of the safety and efficacy of chloroquine for the treatment of COVID-19. *al., e. medRxiv*. <https://doi.org/10.1101/2020.04.26.20081059>.
- Hulseberg, C.E., Feneant, L., Szymanska-de Wijs, K.M., Kessler, N.P., Nelson, E.A., Shoemaker, C.J., Schmaljohn, C.S., Polyak, S.J., White, J.M., 2019. Arbidol and other low-molecular-weight drugs that inhibit lassa and ebola viruses. *J. Virol.* 93 (8).
- Jin, X., Hou, R.F., Tao, F., Lu, H., 2017. Research progress on the regulation of body weight and body fat with Fangfeng Tongsheng San. *World J. Integr. Tradit. Western Med. (世界中西医结合杂志)* 12 (10), 1472–1476.
- John, C., 2020. Can an anti-HIV combination or other existing drugs outwit the new coronavirus? *Science*. <https://www.sciencemag.org/news/2020/2001/can-anti-hiv-combination-or-other-existing-drugs-outwit-new-coronavirus>.
- Ju, X.L., 2020. The potential mechanism and research progress of mesenchymal stem cells in the treatment of 2019 novel coronavirus pneumonia. *J. Shandong Univ. (Health Sci. (山东大学学报(医学版)))* [2020-03-05]. <http://kns.cnki.net/kcms/detail/37.1390.r.20200304.1426.002.html>.
- Knowles, S.R., Phillips, E.J., Dresser, L., Matukas, L., 2003. Common adverse events associated with the use of ribavirin for severe acute respiratory syndrome in Canada. *Clin. Infect. Dis.* 37 (8), 1139–1142.
- Kumagai, Y., Murakawa, Y., Hasunuma, T., Aso, M., Yuji, W., Sakurai, T., Noto, M., Oe, T., Kaneko, A., Yu, T., Xia, J., Wei, Y., Wu, W., Xie, X., Yin, W., Li, H., Liu, M., Xiao, Y., Gao, H., Guo, L., Xie, J., Wang, G., Jiang, R., Gao, Z., Jin, Q., Wang, J., Cao, B., 2020b. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 395 (10223), 497–506.
- Leider, J.P., Brunker, P.A., Ness, P.M., 2010. Convalescent transfusion for pandemic influenza: preparing blood banks for a new plasma product? *Transfusion* 50 (6), 1384–1398.
- Li, G.Q., Zhao, J., Tu, Z.T., Li, J.B., Liu, Q.Q., Shi, L.Q., Miao, Q., Yuan, H.Q., Liu, X.Q., Long, Y.Y., Liu, Z.G., Zhao, T., Li, L., Tang, Q.H., He, Y.C., Bian, Y.J., Hu, J.Q., 2013. Treating influenza patients of wind-heat affecting Fei syndrome by Jinhua Qinggan Granule: a double-blinded randomized control trial. *Chin. J. Integr. Med.* 33 (12), 1631–1635.
- Li, Y., Sun, F., Jing, Z., Wang, X., Hua, X., Wan, L., 2017. Glycyrrhizic acid exerts anti-inflammatory effect to improve cerebral vasospasm secondary to subarachnoid hemorrhage in a rat model. *Neurol. Res.* 39 (8), 727–732.
- Li, K.Y., An, W., Xia, F., Chen, M., Yang, P., Liao, Y.L., Xu, X., Zhou, Q., Fang, S.S., Zhang, M.W., 2020a. Observation on clinical effect of modified Qingfei paidu decoction in treatment of COVID-19. *Chin. Tradit. Herbal Drugs (中草药)* [2020-04-08]. <http://kns.cnki.net/kcms/detail/12.1108.R.20200407.1425.011.html>.
- Li, Y., Zhang, S.C., Zhang, S.Q., Cheng, C., Wang, H.Y., 2020b. An analysis of the curative effect of convalescent plasma on one cases of new coronavirus pneumonia. *J. Clin. Transfusion Lab. Med. (临床输血与检验)* [2020-04-16]. <http://kns.cnki.net/kcms/detail/34.1239.R.20200415.1851.002.html>.
- Li, C.Y., Zhang, X.Y., Liu, S., Shang, H.C., 2020c. Evidence and research on Xuebijing injection in the treatment of pneumonia with novel coronavirus infection (COVID-19). *Modernization of Traditional Chinese Medicine and Materia Medica-World Science and Technology (世界科学技术-中医药现代化)*. pp. 1–6. [2020-2003-2015]. <http://kns.cnki.net/kcms/detail/2011.5699.R.20200217.20201242.20200002.html>.
- Li, X., Wang, W., Zhao, X., Zai, J., Zhao, Q., Li, Y., Chailion, A., 2020d. Transmission dynamics and evolutionary history of 2019-nCoV. *J. Med. Virol.* 92 (5), 501–511.
- Li, X., Zai, J., Zhao, Q., Nie, Q., Li, Y., Foley, B.T., Chailion, A., 2020e. Evolutionary history, potential intermediate animal host, and cross-species analyses of SARS-CoV-2. *J. Med. Virol.* 92 (6), 602–611.
- Liang, J., Zheng, T., Wang, Q.B., Dong, Y.C., Yu, Z.Z., 2020. Safety Analysis of lopinavir/ritonavir tablets in 40 hospitalized patients with Coronavirus Disease 2019. *Chinese J. Hosp. Pharm. (中国医院药学杂志)* 1–4. [2020-04-10]. <http://kns.cnki.net/kcms/detail/44.1204.R.20200410.0820.002.html>.
- Lin, S., Shen, R.N., He, J.D., Li, X.H., Guo, X.S., 2020. Molecular modeling evaluation of the binding abilities of ritonavir and lopinavir to wuhan pneumonia coronavirus proteases. *bioRxiv*. <https://doi.org/10.1101/2020.01.31.929695>.
- Loutfy, M.R., Blatt, L.M., Siminovich, K.A., Ward, S., Wolff, B., Lho, H., Pham, D.H., Deif, H., LaMere, E.A., Chang, M., Kain, K.C., Farcas, G.A., Ferguson, P., Latchford, M., Levy, G., Dennis, J.W., Lai, E.K., Fish, E.N., 2003. Interferon alfacon-1 plus corticosteroids in severe acute respiratory syndrome: a preliminary study. *Jama* 290 (24), 3222–3228.
- Lu, H.R., Fan, L.Q., 2013. Evidence-based application, adverse drug reactions and pre-caution of Xuebijing injectio. *Chin. J. New Drugs (中国新药杂志)* 22 (20), 2449–2452.
- Lu, H.Y., Huo, N., Wang, G.F., Li, H.C., Nie, L.G., Xu, X.Y., 2003. Clinical observation of the therapeutic effect of compound glycyrrhizin on SARS. *China Pharm. (中国药房)* 14 (10), 34–36.
- Luo, S., Yang, L.J., Wang, C., Liu, C.M., Li, D.M., 2020. Clinical observation of 6 severe COVID-19 patients treated with plasma exchange or tocilizumab. *J. Zhejiang Univ. (Med. Sci.) (浙江大学学报(医学版))* [2020-03-17]. <http://kns.cnki.net/kcms/detail/33.1248.R.20200317.1146.002.html>.
- Lv, R.B., Wang, W.J., Li, X., 2020. Clinical observation on treating 63 suspected cases of new coronavirus pneumonia with Chinese medicine Lianhua Qingwen. *J. Tradit. Chin. Med.* 1–5. [2020-2003-2015]. <http://kns.cnki.net/kcms/detail/2011.2166.R.20200215.20201633.20200004.html>.
- Ma, S.T., Liu, P.X., Long, W., Yu, J., Xu, Y., 2009. Effects of the multi-target capability of Xuebijing and its inflammatory pharmacodynamic material basis. *Chin. J. Chem. Phys. (物理化学学报)* 25 (10), 2080–2086.
- Ma, S.T., Yu, H., Zhang, X.L., Xiong, Y.Y., 2015. Potency material bases of Xuebijing formula and its multi-target effects on Sepsis. *Chin. J. Integr. Med. (中国中西医结合杂志)* 35 (11), 1351–1355.
- Ma, Y., Zhang, W., Zhao, Z., Li, M., Liu, J., Wang, Y., 2016. Combination of ribavirin and reduning protects mice against severe pneumonia induced by H1N1 influenza a virus. *J. Tradit. Chinese Med.* 36 (2), 181–186.
- Mair-Jenkins, J., Saavedra-Campos, M., Baillie, J.K., Cleary, P., Khaw, F.M., Lim, W.S., Makki, S., Rooney, K.D., Nguyen-Van-Tam, J.S., Beck, C.R., Convalescent Plasma Study, G., 2015. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. *J. Infect. Dis.* 211 (1), 80–90.
- Mao, Y., Su, Y.X., Xue, P., Li, L.L., Zhu, S.J., 2020. Discussion on the mechanism of Jinhua Qinggan Granule in the treatment of novel coronavirus pneumonia. *J. Chin. Med. Mater. (中药材)* [2020-04-09]. <http://kns.cnki.net/kcms/detail/44.1286.R.20200408.1725.002.html>.
- Marcelin, J.R., Wilson, J.W., Razonable, R.R., Mayo Clinic, H.O., Transplant Infectious Diseases, S., 2014. Oral ribavirin therapy for respiratory syncytial virus infections in moderately to severely immunocompromised patients. *Transpl. Infect. Dis.* 16 (2), 242–250.
- Mayla, G.S.B., Fernando, d.A.V., Vanderson, S.S., et al., 2020. Chloroquine diphosphate in two different dosages as adjunctive therapy of hospitalized patients with severe respiratory syndrome in the context of coronavirus (SARS-CoV-2) infection: preliminary safety results of a randomized, double-blinded, phase IIb clinical trial (CloroCovid-19 Study). *medRxiv*. <https://doi.org/10.1101/2020.04.07.20056424>.
- Momattin, H., Mohammed, K., Zumla, A., Memish, Z.A., Al-Tawfiq, J.A., 2013. Therapeutic options for Middle East respiratory syndrome coronavirus (MERS-CoV)—possible lessons from a systematic review of SARS-CoV therapy. *Int. J. Infect. Dis.* 17 (10), e792–798.
- Morgenstern, B., Michaelis, M., Baer, P.C., Doerr, H.W., Cinatl Jr., J., 2005. Ribavirin and interferon-beta synergistically inhibit SARS-associated coronavirus replication in animal and human cell lines. *Biochem. Biophys. Res. Commun.* 326 (4), 905–908.
- Mulangu, S., Dodd, L.E., Davey Jr., R.T., Tshiani Mbaya, O., Proschan, M., Mukadi, D., Lusakibanza Manzo, M., Nzolo, D., Tshomba Oloma, A., Ibanda, A., Ali, R., Coulibaly, S., Levine, A.C., Grais, R., Diaz, J., Lane, H.C., Muyembe-Tamfum, J.J., Group, P.W., Sivahara, B., Camara, M., Kojan, R., Walker, R., Dighero-Kemp, B., Cao, H., Mukumbayi, P., Mbala-Kingebeni, P., Ahuka, S., Albert, S., Bonnett, T., Crozier, I., Duvenhage, M., Proffitt, C., Teitelbaum, M., Moench, T., Aboulhab, J., Barrett, K., Cahill, K., Cone, K., Eckes, R., Hensley, L., Herpin, B., Higgs, E., Ledgerwood, J., Pierson, J., Smolskis, M., Sow, Y., Tierney, J., Sivapalasingam, S., Holman, W., Gettinger, N., Vallee, D., Nordwall, J., Team, P.C.S., 2019. A randomized, controlled trial of ebola virus disease therapeutics. *N. Engl. J. Med.* 381 (24), 2293–2303.
- Nagata, T., Lefor, A.K., Hasegawa, M., Ishii, M., 2015. Favipiravir: a new medication for the Ebola virus disease pandemic. *Disaster Med. Public Health Prep.* 9 (1), 79–81.
- National Health Commission, National Administration of Traditional Chinese Medicine,

2020. Guidelines for the diagnosis and treatment of novel coronavirus pneumonia (the seventh trial version). *J. Lanzhou Univ. (Med. Sci.)* (兰州大学学报(医学版)) 46 (2), 1–7.
- Philippe, G., Jean, C.L., Philippe, P., et al., 2020. Hydroxychloroquine and Azithromycin as a treatment of COVID-19: preliminary results of an open-label non-randomized clinical trial. *medRxiv*, 105949. <https://doi.org/10.1101/2020.03.16.20037135>.
- Qi, J.P., Qi, X.Y., Wang, X.J., 2016. Clinical efficacy of different doses of Jinhuaqinggan granule on influenza and serum levels of cytokines. *Modern Med. J. (现代医学)* 44 (12), 1664–1669.
- Qi, G.D., Qi, W., Jiang, Q., Shen, K.Q., Zhang, X., Zhang, L., 2020. The efficacy of Lianhua Qingwen combined with western medicine scheme on COVID-19 general type patients: a systematic review. *Clin. J. Tradit. Chin. Med. (中医药临床杂志)* [2020-04-10]. <http://kns.cnki.net/kcms/detail/34.1268.r.20200410.0909.002.html>.
- Qian, Y.Q., 2019. Effects of Shufeng Jiefu capsule on PGE-2, IL-1 β , and TNF- α in serum of rats with acute pharyngitis and its clinical efficacy. *Anhui Univ. Chin. Med. (安徽中医药大学)*.
- Ren, Y., Yao, M.C., Huo, X.Q., Gu, Y., Zhu, W.X., Qiao, Y.J., Zhang, Y.L., 2020. Study on treatment of "cytokine storm" by anti-SARS-CoV-2 prescriptions based on arachidonic acid metabolic pathway. *China J. Chin. Mater. Med. (中国中药杂志)* 1–8 [2020-2003-2015]. <https://doi.org/10.19540/j.cnki.cjcm.20200224.20200405>.
- Rocha-Pereira, J., Jochmans, D., Dallmeier, K., Leyssen, P., Nascimento, M.S., Neyts, J., 2012. Favipiravir (T-705) inhibits in vitro norovirus replication. *Biochem. Biophys. Res. Commun.* 424 (4), 777–780.
- Shi, L., Xiong, H., He, J., Deng, H., Li, Q., Zhong, Q., Hou, W., Cheng, L., Xiao, H., Yang, Z., 2007. Antiviral activity of arbidol against influenza A virus, respiratory syncytial virus, rhinovirus, coxsackie virus and adenovirus in vitro and in vivo. *Arch. Virol.* 152 (8), 1447–1455.
- Sugita, K., Miyazaki, J., Appella, E., Ozato, K., 1987. Interferons increase transcription of a major histocompatibility class I gene via a 5' interferon consensus sequence. *Mol. Cell. Biol.* 7 (7), 2625–2630.
- Sun, Z.G., Zhao, T.T., Lu, N., Yang, Y.A., Zhu, H.L., 2019. Research progress of glycyrrhizin acid on antiviral activity. *Mini Rev. Med. Chem.* 19 (10), 826–832.
- Tang, Y., Wang, Z., Huo, C., Guo, X., Yang, G., Wang, M., Tian, H., Hu, Y., Dong, H., 2018. Antiviral effects of Shuanghuanglian injection powder against influenza A virus H5N1 in vitro and in vivo. *Microb. Pathog.* 121, 318–324.
- Tang, W., Cao, Z.J., Han, M.F., et al., 2020. Hydroxychloroquine in patients mainly with mild to moderate COVID-19: an open-label, randomized, controlled trial. *medRxiv* 369, m1849. <https://doi.org/10.1101/2020.04.10.20060558>.
- Teissier, E., Zandomenighi, G., Loquet, A., Lavillette, D., Laverne, J.P., Montserret, R., Cosset, F.L., Bockmann, A., Meier, B.H., Penin, F., Pecheur, E.L., 2011. Mechanism of inhibition of enveloped virus membrane fusion by the antiviral drug arbidol. *PLoS One* 6 (1), e15874.
- Thanh Le, T., Andreadakis, Z., Kumar, A., Gomez Roman, R., Tollefsen, S., Saville, M., Mayhew, S., 2020. The COVID-19 vaccine development landscape. *Nat. Rev. Drug Discov.* 19 (5), 305–306.
- van der Laan, L.E., Garcia-Prats, A.J., Schaaf, H.S., Tikiso, T., Wiesner, L., de Kock, M., Winckler, J., Norman, J., McIlleron, H., Denti, P., Hesselink, A.C., 2018. Pharmacokinetics and drug-drug interactions of lopinavir-ritonavir administered with first- and second-line antituberculosis drugs in HIV-infected children treated for multidrug-resistant tuberculosis. *Antimicrob. Agents Chemother.* 62 (2).
- Wang, M.Y., 2010. Huoxiang Zhengqi Powder in treating 22 cases of norovirus infectious diarrhea. *Nei Mongol J. Tradit. Chin. Med. (内蒙古中医药)* 29 (06), 8.
- Wang, H.R., Wang, X., 2020. Advances in research of novel coronavirus related drugs and biological products. *Acta Pharm. Sin. (药学报)* 55 (3), 349–354.
- Wang, Y.F., Wang, L., Zhao, F., Li, G.D., Wang, C.H., 2018. Effects of fangfeng tongsheng granule on chronic UrUcarle model rats. *Chin. J. Integr. Med. (中国中西医结合杂志)* 38 (11), 1374–1378.
- Wang, M., Cao, R., Zhang, L., Yang, X., Liu, J., Xu, M., Shi, Z., Hu, Z., Zhong, W., Xiao, G., 2020a. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res.* 30 (3), 269–271.
- Wang, Y., Zhou, Y.Z., Zhu, Y.Y., Xiao, T.T., Huang, C., Yang, K., Ye, J., Wu, Z.Z., Xiao, Y.H., 2020b. Remdesivir prospect of anti-coronavirus effect. *Chinese journal of antibiotics (中国抗生素杂志)* (02), 103–112.
- Wang, Y.M., Zhang, D.Y., Du, G.H., et al., 2020c. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet* 395 (10236), 1569–1578. [https://doi.org/10.1016/S0140-6736\(1020\)31022-31029](https://doi.org/10.1016/S0140-6736(1020)31022-31029).
- Wang, Y., Li, X., Zhang, J.H., Xue, R., Qian, J.Y., Zhang, X.H., Zhang, H., Liu, Q.Q., Fan, X.H., Zhang, B.L., 2020d. Mechanism of Xuanfei Baidu Tang in treatment of novel coronavirus pneumonia based on network pharmacology. *China J. Chin. Mater. Med. (中国中药杂志)*. <https://doi.org/10.19540/j.cnki.cjcm.20200325.401>. [2020-03-27].
- Warren, T.K., Jordan, R., Lo, M.K., Ray, A.S., Mackman, R.L., Soloveva, V., Siegel, D., Perron, M., Bannister, R., Hui, H.C., Larson, N., Strickley, R., Wells, J., Stuthman, K.S., Van Tongeren, S.A., Garza, N.L., Donnelly, G., Shurtleff, A.C., Retterer, C.J., Gharaibeh, D., Zamani, R., Kenny, T., Eaton, B.P., Grimes, E., Welch, L.S., Gomba, L., Wilhelmsen, C.L., Nichols, D.K., Nuss, J.E., Nagle, E.R., Kugelman, J.R., Palacios, G., Doerffler, E., Neville, S., Carra, E., Clarke, M.O., Zhang, L., Lew, W., Ross, B., Wang, Q., Chun, K., Wolfe, L., Babusis, D., Park, Y., Stray, K.M., Trancheva, I., Feng, J.Y., Barauskas, O., Xu, Y., Wong, P., Braun, M.R., Flint, M., McMullan, L.K., Chen, S.S., Fearn, R., Swaminathan, S., Mayers, D.L., Spiropoulou, C.F., Lee, W.A., Nichol, S.T., Cihlar, T., Bavari, S., 2016. Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys. *Nature* 531 (7594), 381–385.
- Wu, L., Zhang, H., Xing, Y., Gao, Y., Li, Y., Ren, X., Li, J., Nie, B., Zhu, L., Shang, H., Gao, Y., 2016. Meta-analysis of the effects of xingnaojing injection on consciousness disturbance. *Medicine* 95 (7), e2875.
- Wu, B., Xiao, G.R., Luo, M., Hu, Q.Z., Wu, F.B., Xu, T., 2020. Data mining and safety analysis of drugs for novel coronavirus pneumonia treatment based on FAERS: alpha interferon. *Herald Med. (医药导报)* 1–16. [2020-2003-2015]. <http://kns.cnki.net/kcms/detail/2042.1293.R.20200225.20200949.20200004.html>.
- Xia, W.G., An, C.Q., Zheng, C.J., Zhang, J.X., Huang, M., Wang, Y., Yang, F.W., Duan, C., Li, Z.L., Liu, Q.Q., Zhang, B.L., 2020. Clinical study of 34 cases of new coronavirus pneumonia treated by Chinese and western medicine. *J. Tradit. Chin. Med. (中医杂志)* 61 (05), 375–382.
- Xiao, Y.J., Mu, Y.M., Zhan, X.R., Li, M., Lu, Z.Q., Lu, J.M., Pan, C.Y., 2005. Inhibitory effects of arachidonic acid on the expressions of monocyte chemoattractant protein-1 (MCP-1) and intercellular adhesion molecule-1 (ICAM-1) in vascular endothelial cells treated with palmitic acid. *Chin. J. Diabetes (中华糖尿病杂志)* (04), 299–301.
- Xiao, Q., Jiang, Y.J., Wu, S.S., Wang, Y., An, J., Xu, W.P., Wu, J.J., 2020. Analysis of the value of chinese medicine shufeng jiedu capsule combined with abidor in treating mild new coronavirus pneumonia. *J. Emerg. Tradit. Chin. Med.* [2020-03-10]. <http://kns.cnki.net/kcms/detail/50.1102.R.20200309.1528.004.html>.
- Xu, X., Chen, P., Wang, J., Feng, J., Zhou, H., Li, X., Zhong, W., Hao, P., 2020a. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. *Sci. China Life Sci.* 63 (3), 457–460.
- Xu, D.Y., Xu, Y.L., Wang, Z.W., Lv, Y.L., Zhu, H.L., Song, T., 2020b. Mechanism of qingfeipaidu decoction on COVID-19 based on network pharmacology. *Pharmacol. Clin. Chin. Mater. Med. (中药药理学与临床)* 36 (1), 26–32.
- Xue, B.S., Yao, K.W., Xue, Y.X., 2020. Theoretical analysis of Chinese medicine for the rapid and effective treatment of new coronavirus pneumonia by Qingfei Jiedu decoction. *J. Tradit. Chin. Med. (中医杂志)* 1–2. [2020-2003-2015]. <http://kns.cnki.net/kcms/detail/2011.2166.R.20200216.20200204.20200002.html>.
- Yao, K.T., Liu, M.Y., Li, X., Huang, J.H., Cai, H.B., 2020. Retrospective clinical analysis on treatment of coronavirus disease 2019 with traditional Chinese medicine Lianhua Qingwen. *Chin. J. Exp. Tradit. Med. Formulae (中国实验方剂学杂志)*. <https://doi.org/10.13422/j.cnki.syfjx.20201099>. [2020-02-06].
- Zhang, H., Chen, Q., Zhou, W., Gao, S., Lin, H., Ye, S., Xu, Y., Cai, J., 2013. Chinese medicine injection shuanghuanglian for treatment of acute upper respiratory tract infection: a systematic review of randomized controlled trials. *Evid. Complement. Alternat. Med.* 2013, 987326.
- Zhang, L.H., Li, B.H., Jia, P., Pu, J., Bai, B., Li, Y., Zhu, P.J., L. L. Zeng, G.J., Zhao, X., Dong, S.S., Liu, M.H., Zhang, N., 2020a. An analysis of global research on SARS-CoV-2. *J. Biomed. Eng. (生物医学工程学杂志)* 37 (2), 1–14. [2020-2003-2015]. <http://kns.cnki.net/kcms/detail/2051.1258.R.20200311.20201129.20200002.html>.
- Zhang, Y., Tang, D.Z., Shu, B., Li, W.X., Zhang, J.L., Li, Y., Ding, F., Feng, R., He, M.C., Chen, N., Shi, Q., Wang, Y.J., 2020b. Study on the mechanism of the new coronavirus pneumonia intervened by traditional Chinese medicine based on the literature. *J. Tradit. Chin. Med. (中医杂志)* 1–8. [2020-2003-2015]. <http://kns.cnki.net/kcms/detail/2011.2166.R.20200224.20200938.20200002.html>.
- Zhang, Y.M., Qu, X.Y., Tao, L.N., Zhai, J.H., Gao, H., Song, Y.Q., Zhang, S.X., 2020c. XingNaoJing injection ameliorates cerebral ischaemia/reperfusion injury via SIRT1-mediated inflammatory response inhibition. *Pharm. Biol.* 58 (1), 16–24.
- Zhang, C.Y., Zhang, S., Wang, W., Jiang, X.Q., 2020d. Clinical observation of Xuebijing in the treatment of COVID-19. *Chin. J. Hosp. Pharm. (中国医院药学杂志)* [2020-04-10]. <http://kns.cnki.net/kcms/detail/42.1204.r.20200409.1637.002.html>.
- Zhao, Y.S., Hou, X.Y., Gao, Z.H., Wang, T., 2020. Research on medication for severe type of COVID-19 based on Huashi Baidu prescription. *Chin. Arch. Tradit. Chin. Med. (中华中医药学刊)* [2020-03-31]. <http://kns.cnki.net/kcms/detail/21.1546.R.20200330.1632.002.html>.
- Zhong, Q., Yang, Z., Liu, Y., Deng, H., Xiao, H., Shi, L., He, J., 2009. Antiviral activity of Arbidol against Coxsackie virus B5 in vitro and in vivo. *Arch. Virol.* 154 (4), 601–607.
- Zhou, P., Yang, X.L., Wang, X.G., Hu, B., Zhang, L., Zhang, W., Si, H.R., Zhu, Y., Li, B., Huang, C.L., Chen, H.D., Chen, J., Luo, Y., Guo, H., Jiang, R.D., Liu, M.Q., Chen, Y., Shen, X.R., Wang, X., Zheng, X.S., Zhao, K., Chen, Q.J., Deng, F., Liu, L.L., Yan, B., Zhan, F.X., Wang, Y.Y., Xiao, G.F., Shi, Z.L., 2020. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 579 (7798), 270–273.
- Zumla, A., Azhar, E.I., Arabi, Y., Alotaibi, B., Rao, M., McCloskey, B., Petersen, E., Maeuer, M., 2015. Host-directed therapies for improving poor treatment outcomes associated with the middle east respiratory syndrome coronavirus infections. *Int. J. Infect. Dis.* 40, 71–74.
- Zumla, A., Chan, J., Azhar, E., Hui, D., Yuen, K., 2016. Coronaviruses-drug discovery and therapeutic options. *Nat. Rev. Drug Discov.* 15, 327–347.