Review Article

Narrative review: Chinese medicine against the COVID-19: current status, challenge and perspectives

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Objective: To summarize an evidence-based overview of the literature on the current status of the therapeutic strategy of Chinese medicine (CM) in combating severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and to discuss future perspectives on CM intervention for the treatment of coronavirus disease 2019 (COVID-19).

Background: SARS-CoV-2 is a highly transmissible pathogenic coronavirus that has caused a worldwide pandemic of acute respiratory disease known as COVID-19. The clinical presentations of COVID-19 range from no symptom to mild respiratory tract infections to severe disease with serious lung injury, multi-organ failure, and even death. To date, no clinically proven effective therapy is available for COVID-19. Constant efforts are being made to identify effective anti-SARS-CoV-2 molecules. Whereas CM has been used as a treatment option to successfully fight against various epidemic and pandemic outbreaks, including the current COVID-19 pandemic, in Chinese history.

Methods: The information in this review has been collected systematically from the scientific literature databases including PubMed, Web of science, Google scholar, Springer, China National Knowledge Infrastructure (CNKI), Official website, Published books, and dissertations.

Conclusions: In this paper, we have reviewed the pathogenesis and clinical manifestations of SARS-CoV-2, as well as the corresponding CM treatment for different stages of COVID-19. We also summarized the recent research findings on a number of Chinese herbal formulae and proprietary Chinese medicine products which are recommended by the China National Health Commission for the Treatment of COVID-19. An overview was also conducted on the common herbal components and active ingredients in the mentioned Chinese herbal products. Overall, this review has revealed the valuable role of CM in the fight against COVID-19, and provided a future perspective on the study of effectiveness of CM for COVID-19.

Keywords: SARS-CoV-2; Chinese medicine; coronavirus pneumonia; coronavirus disease 2019 (COVID-19)

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Introduction

A novel coronavirus, later designated as SARS-CoV-2 by World Health Organization, was reported in late 2019 in the city of Wuhan, China, SARS-CoV-2 caused an outbreak of unwanted viral pneumonia (1,2). The clinical manifestations of the SARS-CoV-2-caused disease, now known as coronavirus disease 2019 (COVID-19), range from no symptom to mild respiratory tract infections and

influenza-like illness (mainly fever, cough, and fatigue), to severe disease with severe lung injury and multi-organ failure, and even death (3,4). As of 3 September 2021, there were 218,946,836 confirmed cases of COVID-19 worldwide, with 4,539,723 deaths (5). The COVID-19 pandemic continues to cause havoc to the world and pose an enormous threat to global public health. However, there has not been any evidence-based antiviral therapy for the treatment of COVID-19 to date, much like the fact that there was not effective treatment option for SARS (6) and MERS (7) outbreaks. The lack of effective therapy, together with the high morbidity and fatality rates, highlights an urgent need for novel drug discovery for COVID-19 treatment. The research has shown that the isolated SARS-CoV-2 belongs to beta-coronavirus with a single stranded RNA (8), which closely resembles SARS and MERS. Therefore, the clinical experiences gained in the fight of SARS and MERS may point to possible ways to treat COVID-19 infection effectively.

Chinese medicine (CM) have been used since time immortal to treat various infectious diseases, and previous studies showed that CM had great potential for preventing SARS transmission and had remarkable therapeutic effects against SARS epidemic in 2003 (9,10). Hence, it is rational to postulate that CM is a worthy therapeutic option for enhancing host immunity to combat SARS-CoV-2 infection. According to the "Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia" published in China, CM has been recommended as a formal therapeutic modality for COVID-19, and different CM prescriptions and proprietary Chinese herbal medicine (CHM) has been frequently used in China to treat COVID-19 and reported to achieve satisfactory results (11-13). About 15 trials listed in China's registry expect to enroll a total of more than 2,000 people in studies on a variety of traditional CM for test coronavirus treatment (14). And CM also recommended as a treatment option of COVID-19 in the China National Health Commission (NHC) guidelines (15). The present review aimed to provide a comprehensive evidence-based overview on the current scenario of SARS-CoV-2 infection and the potential use of CM in combating this pandemic of global scale.

We present the following article in accordance with the Narrative Review reporting checklist (available at https://dx.doi.org/10.21037/lcm-21-26).

Methods

This is a narrative overview of the literature synthesizing the findings of research papers retrieved from the computerized databases of PubMed, Web of science, Google scholar, Springer, China National Knowledge Infrastructure (CNKI), Official website, Published books, and dissertations.

Pathogenesis and clinical manifestations of SARS-CoV-2

The SARS-CoV-2 is an enveloped single stranded RNA (ssRNA) virus with spike-like-glycoproteins expressed on the surface forming a "corona" (16). The genome sequences of SARS-CoV-2 attained from patients share 79.6% sequence similarity to that of SARS-CoV, and the virus consists of four major structural proteins (17). The spike (S) protein mainly affects the fusion and cell entry process of the virus, and allows the attachment and entering of SARS-CoV-2 to the host cells. The membrane (M) protein mainly delineates the shape of the viral envelope, while both the envelope (E) and nucleocapsid (N) proteins actively participate in the viral assembly and budding events (18). Angiotensin-converting enzyme 2 (ACE2) is the receptor of SARS-CoV-2, and the S protein of the virus binds to the ACE2 receptor on the host cell surface, accompanied by being further primed by transmembrane protease serine (TMPRSS2) to facilitate its entry to the host cell (19,20).

The SARS-CoV-2 primarily disseminates through the droplets and aerosol caused by sneezing or coughing. It also has the potential to spread from the surfaces contaminated by the virus and the fomites as it is known to survive for hours. The pathogenesis of SARS-CoV-2 in humans manifests itself as mild symptoms to respiratory distress syndrome. By binding to epithelial cells in the respiratory tract, the inhaled SARS-CoV-2 starts replication and migrates to the contacting airways and enters the epithelial cells in the lungs. Contrasted to SARS-CoV, SARS-CoV-2 has inferior severe pathogenesis, but has higher transmission capability, as evidenced by the swiftly increasing number of COVID-19 cases worldwide (21). The early symptoms of COVID-19 include fever, dry cough, fatigue and dyspnea, which are very similar to that of other viral respiratory diseases like common flu (22). Generally, the incubation period for SARS-CoV-2 is around 15 days, but the reported range can be anywhere from 0 to 24 days (23). COVID-19 can be diagnosed by either chest CT radiography or laboratory testing. The typical features on initial CT include ground-glass opacities with a peripheral or multilobar distribution.

SARS-CoV-2 infection is primarily associated with

Table 1 Clinical manifestations of different stages of COVID-19

Stage of disease	Clinical manifestations
Medical observation period	Fatigue with gastrointestinal discomfort
	Fatigue with fever
Clinical treatment period	
Mild case	Fever and respiratory tract symptoms (fatigue, cough), sputum, body aches, chest tightness, suffocation, appetite, nausea, sticky stool
Moderate case	Fever, cough with little sputum or yellow sputum, chest tightness, shortness of breath, abnormal distention, constipation, swelling, nausea, loose stools
Severe case	Fever, flushing, cough, yellow and sticky sputum, or blood in the sputum, shortness of breath, fatigue, dry mouth, sticky mouth, nausea, inability to eat, poor bowel movements, short red urine, delirium, wrong vision, or spotted rash, or vomiting, or twitching of the limbs
Critical case	Difficulty in breathing, frequent wheezing or need for mechanical ventilation, accompanied by dizziness, irritability, sweating, cold limbs, dark purple tongue, thick or greasy fur, and large floating five roots
Recovery stage	Fatigue, shortness of breath, dry mouth, thirst, heart palpitations, excessive sweating, poor appetite, low or no fever, dry cough and less phlegm, thready pulse and feeble pulse

pneumonia, and the disease is also named severe specific contagious pneumonia, and in some patients, the infection could lead to acute respiratory distress syndrome (ARDS). The blood biochemistry indexes, such as albumin, lactate dehydrogenase, C-reactive protein, lymphocytes (percent) and neutrophils (percent), can give an idea about the disease severity (24). COVID-19 patients may present hypoalbuminemia, leukocytosis, leukopenia with lymphopenia and an increase in aspartate transaminase, lactate dehydrogenase, alanine aminotransferase, bilirubin and specially, D-dimer (25,26). The ARDS in COVID-19 is now known to be caused by cytokine storms, and the rapid replication of SARS-CoV-2 in the lungs may elicit a strong immune response. Cytokine storms with ARDS could result in respiratory failure, which is believed to be the main cause of death in COVID-19. Patients of older than 60 years old and those with underlying medical conditions such as cancer, diabetes, cardiovascular disease and chronic respiratory disease have a greater risk of developing ARDS and death (27,28). Multiple organ failure has also been reported in some COVID-19 cases (29,30).

The specific symptoms and the corresponding treatment methods have been provided in the NHC guidelines. According to the latest 8th edition of the Guideline (15), COVID-19 is divided into the observation stage and clinical treatment stage (mild, moderate, severe, critical and recovery stage) according to different clinical manifestations during the disease development (*Table 1*).

Application of CM for the treatment of COVID-19

The past two years have witnessed a substantially increased application of CM-based herbs and formulations for the treatment of COVID-19 (31). A total of 15 CM formulae or proprietary CM products are recommended, of which 7 are oral medications while 8 belong to injection fluids according in the NHC guidelines (*Table 2*). The main constituents of these herbal preparations are summarized in *Table 3*.

Oral CM for the treatment of COVID-19

Lian-Hua-Qing-Wen Capsules (granule)

Lian-Hua-Qing-Wen Capsule (LHQWC), a Chinese medicine formula originally developed for the treatment of SARS, is commonly used to treat respiratory tract infection in China. The Capsule consists of 13 herbs, including *Lonicerae Japonicae Flos* (Jinyinhua), *Forsythiae Fructus* (Lianqiao), *Houttuyniae Herba* (Yuxingcao), *Armeniacae Semen Amarum* (Kuxingren), *Isatidis Radix* (Banlangen), *Ephedrae Herba* (Mahuang), *Pogostemonis Herba* (Guanghuoxiang), *Crassirhizomatis Rhizoma* (Mianmaguanzhong), *Rhodiolae Crenulatae Radix et Rhizoma* (Hongjingtian), *Rhei Radix et Rhizoma* (Dahuang), *l-menthol* (Bohenao), *Glycyrrhizae Radix et Rhizoma* (Gancao) and *Gypsum Fibrosum* (Shigao) (60,61). LHQWC can be used as a remedy to treat clinical symptoms such as fever, cough, and fatigue in patients with mild and common types of COVID-19. LHQWC has been shown to ameliorate the

Table 2 The CHM recommended for COVID-19 by the China National Health Commission treatment guidelines (Version 8)

CM formular	Clinical function	Stage	Therapeutical efficacy
Lian-Hua-Qing-Wen Capsule (granule)	Clear heat and detoxify, removes lung hotness. Anti-inflammatory, antipyretic, antibacterial, antiviral	Medical observation period	Ameliorate the clinical symptoms for instance fever, fatigue, cough and shortness of breath of COVID-19 (32,33)
Jin-Hua-Qing-Gan Capsule (granule)	Disperse wind and lungs, clear away heat and detoxify	Medical observation period	Improve the fever, fatigue, cough, anxiety, sputum (34)
Shu-Feng-Jie-Du Capsule	Clearing away the plague and detoxify, and relieving lung heat	Medical observation period	Decreased the clinical recovery time and fatigue, as well as cough (35)
Shuang-Huang-Lian	Clear heat and detoxify, remove lung hotness	Medical observation period	–
Qing-Fei-Pai-Du Decoction	Clearing the lungs and purging heat, detoxifying, and removing blood stasis, resolving phlegm and relieving cough	Mild stage	Shorten the patient's hospitalization time, improve the lung CT and the clinical symptom (36)
Ma-Xing-Shi-Gan Decoction	Facilitate the flow of the lung "qi" and clear away heat	Moderate stage	Disappearance rates of fever, fatigue and cough (37)
Xue-Bi-Jing Injection	Detoxification and stasis removal	Severe and critical stage	Enhanced the lymphocyte count (LYM) and white blood cell count (WBC), decrease the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) of COVID-19 patients (38)
Xi-Yan-Ping injection	Clear heat, detoxify, reduce swelling	Severe stage	Decrease inflammation and enhance such symptoms as cough, fever, and rales in the lungs in COVID-19 patients (39)
Re-Du-Ning injection	Clear heat, relieve wind, and detoxify, antibacterial and antiviral	Severe and critical stage	Ameliorating blood gas indexes, improving clinical symptoms and lung function of patients', and decreasing serum inflammatory factor levels (40,41)
Tan-Re-Qing injection	Clear heat, resolve phlegm and detoxify	Severe and critical stage	Improve clinical symptoms, impede deterioration and promote rehabilitation in COVID-19 patients (42)
Xing-Nao-Jing injection	Rejuvenate the mind and resuscitate, clear heat and phlegm, promote qi and blood circulation, detoxify and relieve pain	Severe and critical stage	Improve the immune function and inflammatory response in body (43)
Shen-Fu injection	Rescuing adversity, replenishing qi and solidifying	Critical stage	Shorten the sequential organ failure assessment score, ICU stay time, total length of hospitalization, ventilator application days, and mortality rate. Improve the prognosis of patients' (44)
Shen-Mai injection	Invigorate qi and solidify, nourish yin, nourish body fluid	Critical stage	Improve the clinical symptoms and signs of patients with ventilator-associated pneumonia, reduce the inflammatory response, and achieved better clinical outcomes (45)
Sheng-Mai injection	Invigorate qi and nourish yin, restore pulse and solidify	Critical stage	Enhanced pulmonary function, oxygen saturation, and IgG indexes, as well as shortened the time for disappearance of lung rales (46)

Table 3 The main constituents of CHM used for the treatment of CDVID-19

CM formular	Constituents	Active ingredients (source)	Cov type	Ref.
Lian-Hua-Qing-Wen Capsule (granule)	*Lonicerae Japonicae Flos (Jinyinhua), Forsythiae Fructus (Lianqiao), Houttuyniae Herba (Yuxingcao), Armeniacae Semen Amarum (Kuxingren), Isatidis Radix (Banlangen), Dryopteridis Ephedrae Herba (Mahuang), Pogostemonis Herba (Guanghuoxiang), Crassirhizomatis Rhizoma (Mianmaguanzhong), Rhodiolae Crenulatae Radix et Rhizoma (Hongjingtian), Rhei Radix et Rhizoma (Dahuang), I-menthol (Bohenao), Glycyrrhizae Radix et Rhizoma (Gancao)* and *Gypsum Fibrosum (Shigao)*	beta-carotene, kaempferol, luteolin, naringenin, quercetin and wogonin	COVID-19; SARS-CoV-2	(47)
Jin-Hua-Qing-Gan Capsule (granule)	*Glycyrrhizae Radix et Rhizoma (Gancao), Lonicerae Japonicae Flos (Jinyinhua), Armeniacae Semen Amarum (Kuxingren), Gypsum Fibrosum (Shigao), Anemarrhenae Rhizoma (Zhimu), Ephedrae Herba (Mahuang), Scutellariae Radix (Huangqin), Forsythiae Fructus (Lianqiao), Arctii Fructus (Niubangzi), Artemisiae Annuae Herba (Qinghao), Menthae Haplocalycis Herba (Bohe), Fritillariae Thunbergii Bulbus (Zhebeimu)* and *Thlaspi Arvense Linn (Baijiangcao)*	Kaempferol (Niubangzi), baicalein (Huangqin) and oroxylin A (Huangqin)	COVID-19	(48)
Shu-Feng-Jie-Du Capsule	*Polygoni Cuspidati Rhizoma et Radix (Huzhang), Forsythiae Fructus (Lianqiao), Isatidis Radix (Banlangen), Bupleuri Radix (Chaihu), Verbenae Herba (Mabiancao), Phragmitis Rhizoma (Lugen), Thlaspi Arvense Linn (Baijiangcao)* and *Glycyrrhizae Radix et Rhizoma (Gancao)*	Quercetin (Huzhang; Lianqiao), Luteolin (Huzhang; Chaihu; Mabiancao; Baijiangcao), Wogonin (Lianqiao)	COVID-19	(49)
Shuang-Huang-Lian	*Lonicerae Japonicae Flos (Jinyinhua), Scutellariae Radix (Huangqin)* and *Forsythiae Fructus (Lianqiao)*	Chlorogenic acid (Lianqiao), phillyrin (), baicalin; baicalein (Huangqin)	COVID-19; SARS-CoV-2	(50)
Qing-Fei-Pai-Du Decoction	*Bupleuri Radix, Ephedrae Herba (Mahuang), Glycyrrhizae Radix et Rhizoma (Gancao), Cinnamomi Cortex (Rougui), Alismatis Rhizoma (Zexie), Polyporus (Zhuling), Poria (Fuling), Atractylodis Macrocephalae Rhizoma (Baizhu), Bupleuri Radix (Chaihu), Scutellariae Radix (Huangqin), Lonicerae Japonicae Flos (Jinyinhua), Belamcandae Rhizoma (Shegan), Pogostemonis Herba (Guanghuoxiang), Asari Radix et Rhizoma (Xixin), Zingiberis Rhizoma Recens (Shengjiang), Radix Asteris (Ziyuan), Aurantii Fructus Immaturus (Zhishi), Gypsum Fibrosum (Shigao), Pinelliae Rhizoma (Banxia), Dioscoreae Rhizoma (Shanyao), Armeniacae Semen Amarum (Kuxingren), Citri Reticulatae Pericarpium (Chenpi)* and *Farfarae Flos (Kuandonghua)*	Baicalein (Huangqin), Patchouli alcohol (Huoxiang), Shionone (Ziwan) and Ergosterol (Zhuling)	COVID-19; SARS-CoV-2	(51)
Ma-Xing-Shi-Gan Decoction	*Ephedrae Herba (Mahuang), Armeniacae Semen Amarum (Kuxingren), Gypsum Fibrosum (Shigao)* and *Glycyrrhizae Radix et Rhizoma (Gancao)*	Quercetin; Kaempferol; Herbacetin; Delphinidin; Resivit (Mahuang), Estrone; Stigmasterol; CLR; Sitosterol (Xing Ren), Isotrifoliol; Inflacoumarin A; Kanzonol F; Quercetin, Formononetin (Gancao), CaSO4; CaSO4; Fe; Mn; Zn (Shigao)	COVID-19	(52)

Table 3 (*continued*)

Table 3 (*continued*)

CM formular	Constituents	Active ingredients (source)	Cov type	Ref.
Xue-Bi-Jing Injection	*Carthami Flos (Honghua), Paeoniae Radix Rubra (Chishao), Chuanxiong Rhizoma (Chuanxiong), Salviae Miltiorrhizae Radix et Rhizoma (Danshen)* and *Angelicae Sinensis Radix (Danggui)*	Quercetin, gallic acid, luteolin, rosmarinic acid, rutin, kaempferol hlorogenic acid, tanshinone II A, hydroxysafflor yellow A, and paeoniflorin	COVID-19; SARS-CoV-2	(53)
Xi-Yan-Ping injection	*Andrographolides (Chuanxinlianneizhi)*	Total sulfonate of andrographolide	COVID-19	(39)
Re-Du-Ning injection	*Lonicerae Japonicae Flos (Jinyinhua), Artemisiae Annuae Herba (Qinghao)* and *Gardeniae Fructus (Zhizi)*	Quercetin, luteolin, and kaempferol	SARS-CoV-2	(54)
Tan-Re-Qing injection	*Lonicerae Japonicae Flos (Jinyinhua), Forsythiae Fructus (Lianqiao) Scutellariae Radix (Huangqin)* and *Ursi fellis pulvis (Xiongdanfen)*	Kaempferol; quercetin; luteolin (Jinyinhua, Lianqiao), baicalein (Huangqin), and wogonin (Huangqin, Lianqiao)	SARS-CoV-2	(55)
Xing-Nao-Jing injection	*Moschus (Shexiang), Curcumae Radix (Yujin), Gardeniae Fructus (Zhizi)* and *Borneolum Syntheticum (Bingpian)*	Divanillalaceton and Q27139023 (Yujin)	COVID-19; SARS-CoV-2	(56)
Shen-Fu injection	*Ginseng Radix et Rhizoma Rubra (Hongshen)* and *Aconiti Lateralis Radix Praeparata (Fuzi)*	Kaempferol, beta-sitosterol, stigmasterol and fumarine	COVID-19	(57)
Shen-Mai injection	*Ginseng Radix et Rhizoma Rubra (Hongshen)* and *Ophiopogonis Radix (Maidong)*	Diosgenin, stigmasterol, beta-sitosterol and ginsenoside Rh1_qt	COVID-19	(58)
Sheng-Mai injection	*Ginseng Radix et Rhizoma Rubra (Hongshen), Ophiopogonis Radix (Maidong)* and *Schisandrae Chinensis Fructus (Wuweizi)*	Schisanlactone E (Wuweizi), stigmasterol (Maidong), N-trans-feruloyltyramine (Maidong)	COVID-19	(59)

clinical symptoms such as fever, fatigue and shortness of breath in 63 patients with COVID-19 (32). A randomized controlled trial on the effectiveness of LHQWC in 284 (142 each in treatment and control group) confirmed cases of COVID-19 demonstrated that the patients treated with LHQWC for 2 weeks resulted in a significantly higher recovery rate (91.5% *vs.* 82.4%, P=0.022), a dramatically shorter median time to symptom recovery (7 *vs.* 10 days, P<0.001), as well as a markedly shorter time to recovery of fever (2 *vs.* 3 days), coughing (7 *vs.* 10 days), and fatigue (3 *vs.* 6 days) (P<0.001 for all) compared to the control group. The results of this clinical trial fully testified the efficacy and safety of LHQWC for patients with COVID-19 (62). A multi-center retrospective analysis of the therapeutic effect of LHQWC in 51 patients with COVID-19 was conducted to assess the disappearance rate, duration, and effectiveness in alleviating the main symptoms (fever, fatigue and cough), and the results showed that combined application of LHQWC more significantly improved cough, fever, fatigue, shortness of breath, anorexia, chest distress and other clinical symptoms of COVID-19 than the control group (33).

Jin-Hua-Qing-Gan Capsule (granule)

Jin-Hua-Qing-Gan Capsule (JHQGC) is another patented Chinese medicine frequently prescribed for the treatment of COVID-19. It comprises *Glycyrrhizae Radix et Rhizoma* (Gancao), *Lonicerae Japonicae Flos* (Jinyinhua), *Armeniacae Semen Amarum* (Kuxingren), *Gypsum Fibrosum* (Shigao), *Anemarrhenae Rhizoma* (Zhimu), *Ephedrae Herba* (Mahuang), *Scutellariae Radix* (Huangqin), *Forsythiae Fructus* (Lianqiao), *Arctii Fructus* (Niubangzi), *Artemisiae Annuae Herba* (Qinghao), *Menthae Haplocalycis Herba* (Bohe), *Fritillariae Thunbergii Bulbus* (Zhebeimu) and *Thlaspi Arvense Linn* (Baijiangcao) (63). The study evaluated the duration of detectable viral nucleic acid and pneumonia

absorption improvement in 80 cases of COVID-19 patients, and the results showed that the 7-day viral clearance rate was dramatically higher in the JHQGC treated group than the control group (P=0.009), and the pneumonia recovery time revealed by chest CT was 8±4 d in the JHQGG group, which was markedly shorter than the control group (10±5 d) (P=0.021) (63). Clinical studies have also shown that JHQGC possesses therapeutic efficacy in treating H1N1 influenza virus infection (64). In another study on 123 COVID-19 patients who were randomized into a JHQGC combined with routine treatment group for 5 days (n=82) and a routine treatment as a control group (n=41). The addition of JHQGC more significantly relieved fever, fatigue, cough, anxiety, sputum and the hospitalization rate than the control group (34).

Shu-Feng-Jie-Du Capsule

Shu-Feng-Jie-Du Capsule (SFJDC) is a well - known Chinese herbal preparation and mainly used to treat acute upper respiratory tract infections (65). It encompasses 8 medicinal herbs, including *Forsythiae Fructus* (Lianqiao), *Polygoni Cuspidati Rhizoma et Radix* (Huzhang), *Isatidis Radix* (Banlangen), *Bupleuri Radix* (Chaihu), *Verbenae Herba* (Mabiancao), *Phragmitis Rhizoma* (Lugen), *Thlaspi Arvense Linn* (Baijiangcao) and *Glycyrrhizae Radix et Rhizoma* (Gancao) (66). SFJDC has the therapeutic effects of clearing away the plague and detoxification, and relieving lung heat, and is recommended for the treatment of COVID-19 patients with fever during medical observation period (67). Clinical data showed that addition of SFJDC to standard antiviral therapy (AVT) more significantly decreased the clinical recovery time and fatigue (from 3.55±4.09 to 1.19±2.28 days), as well as cough (from 5.67±5.64 to 3.47±3.75) when compared to AVT alone. SFJDC treatment was more effective when used within the first 8 days following the onset of symptoms (35). SFJDC might be a promising herbal drug for the treatment of COVID-19, but large-scale randomized, placebo-controlled, double-blinded and multicenter studies are needed to establish clinical evidence on its efficacy and safety.

Shuang-Huang-Lian oral liquid

Shuang-Huang-Lian (SHL) oral liquid is a CM preparation composed of 3 herbs, i.e., *Lonicerae Japonicae Flos* (Jinyinhua), *Forsythiae Fructus* (Lianqiao) and *Scutellariae Radix* (Huangqin). It is officially recorded in the Chinese Pharmacopeia and has the therapeutic functions of removing toxic heat and inducing diaphoresis. Multiple pharmacological activities of SHL, involving antiviral, antibacterial, anti-inflammatory action and immune enhancement, have been reported. It has been broadly used for treating various infectious diseases caused by bacteria or viruses in the respiratory tract (68). However, so far, no clinical study of SHL on the COVID-19 treatment has been reported. The 3CL protease (3CLpro) is a highly conserved protease which is indispensable for CoVs replication, and is a promising target for development of broad-spectrum antiviral drugs. A pharmacological research showed that SHL dose-dependently suppressed SARS-CoV-2 3CLpro as well as the replication of SARS-CoV-2 in Vero E6 cells (50).

Qing-Fei-Pai-Du Decoction (QFPDD)

QFPDD is perhaps the most commonly prescribed Chinese herbal formula for the treatment of COVID-19 in China. QFPDD is composed of *Bupleuri Radix*, *Ephedrae Herba* (Mahuang), *Glycyrrhizae Radix et Rhizoma* (Gancao), *Cinnamomi Cortex* (Rougui), *Alismatis Rhizoma* (Zexie), *Polyporus* (Zhuling), *Poria* (Fuling), *Atractylodis Macrocephalae Rhizoma* (Baizhu), *Bupleuri Radix* (Chaihu), *Scutellariae Radix* (Huangqin), *Lonicerae Japonicae Flos* (Jinyinhua), *Belamcandae Rhizoma* (Shegan), *Pogostemonis Herba* (Guanghuoxiang), *Asari Radix et Rhizoma* (Xixin), *Zingiberis Rhizoma Recens* (Shengjiang), *Radix Asteris* (Ziyuan), *Aurantii Fructus Immaturus* (Zhishi), *Gypsum Fibrosum* (Shigao), *Pinelliae Rhizoma* (Banxia), *Dioscoreae Rhizoma* (Shanyao), *Armeniacae Semen Amarum* (Kuxingren), Citri Reticulatae Pericarpium (Chenpi) and Farfarae Flos (Kuandonghua). The prescription has multiple functions, including antiviral, anti-inflammatory, immune regulatory, and antipyretic effects. It has also been clinically proven to have good therapeutic effects on COVID-19 (69). Clinical studies on QFPDD with different dosage forms in the treatment of COVID-19 showed that QFPDD could effectively ameliorate the symptoms and the effective rate was above 80% (70). The modified QFPDD in combination with western medicine such as chloroquine phosphate, alpha-interferon, arbidol, oseltamivir and ribavirin in the treatment of COVID-19 was found to be more effective when compared to the treatment of western medicine alone, and the combined treatment could dramatically shorten the patient's hospitalization time, the time of lung CT improvement and the time of clinical symptom improvement (36). QFPDD was used clinically for 3 consecutive days as a course of treatment to treat 214 confirmed COVID-19 cases in four different provinces, and the results showed that the overall effective

rate was more than 90%; among them more than 60% of the cases showed significant improvement in symptoms and imaging manifestations and 30% of the patients showed stability of symptoms without deterioration or worsening (71). Currently the use of QFPDD has been extended to treat suspected cases of COVID-19.

Ma-Xing-Shi-Gan Decoction (MXSGD)

MXSGD consists of *Glycyrrhizae Radix et Rhizoma* (Gancao), *Ephedrae Herba* (Mahuang), *Gypsum Fibrosum* (Shigao) and *Armeniacae Semen Amarum* (Kuxingren) (72,73). It has multiple functions such as antiviral, anti-inflammatory, immune regulatory, and anti-pyretic effects. Clinical studies have shown that MXSGD had a marked effect on the treatment of viral influenza (74). Clinical research on 40 cases of COVID-19 patients treated with a combination of MXSGD and western medicine routine treatment showed that after treatment for seven days, the disappearance rates of fever, fatigue and cough were 96.8% (30/31), 100.0% (28/28), 81.8% (18/22), respectively. Aspartate transaminase (AST), alanine transaminase (ALT) and creatinine (Scr) in these patients were normal. MXSGD combined with the western medicine routine treatment has a remarkable clinical curative effect on common COVID-19 without obvious damage on liver and kidney function (37). Its therapeutic effect may be attributed to its anti-inflammatory and antiviral effects. In clinical practice, MXSGD is commonly use in the national and provincial prevention and treatment programmes and is extensively prescribed for both suspected and confirmed cases of COVID-19. To date, MXSGD is one of the core prescriptions for the treatment of various kinds of pulmonary infection.

CM injections for the treatment of COVID-19

Xue-Bi-Jing Injection (XBJI)

XBJI is an intravenous herbal preparation made from 5 Chinese herbs, comprising *Carthami Flos* (Honghua), *Salviae Miltiorrhizae Radix et Rhizoma* (Danshen), *Paeoniae Radix Rubra* (Chishao), *Chuanxiong Rhizoma* (Chuanxiong) and *Angelicae Sinensis Radix* (Danggui) (75). Clinically, XBJI is mainly applied for the treatment of sepsis, infection-caused systemic inflammatory response syndrome, and multiple organ dysfunction syndrome (76,77). Clinical research showed that 42 COVID-19 patients treated with XBJI combined with routine symptomatic treatment exhibited more significant improvements in IL-6 level and body temperature in the treatment group than that in the control group. Especially in severe cases, the reduction in body temperature was greater in the treatment group as compared with the control group (P<0.05). A higher number of COVID-19 patients in the treatment group showed improved CT imaging than in the control group, and the time taken to have a negative nucleic acid test was shorter in the treatment group than in the control group (76).

In a retrospective study, 60 severe cases of COVID - 19 patients were randomly assigned to 20 cases in each group to receive routine treatment group, XBJ 50 mL group and XBJ 100 mL group, respectively. On the basis of routine treatment, XBJI was given twice a day for 7 days in both of the XBJ 50 mL and XBJ 100 mL groups. The blood routine test, erythrocyte sedimentation rate (ESR), C - reactive protein (CRP) and chronic health evaluation II score, SARS-CoV-2 nucleic acid test and disease classification of three groups were evaluated. Following the treatment, the lymphocyte count (LYM) and white blood cell count (WBC) of three groups were enhanced, while ESR and CRP decreased. When compared with the conventional treatment group, the WBC count of the XBJ 100 mL group was dramatically increased (1×10^9/L: 7.12±0.55 *vs.* 5.67±0.51, P<0.05), while the levels of ESR and CRP in the XBJ 50 and 100 mL groups markedly declined [ESR (mm/1 h): 45.9±5.7, 40.5±7.4 *vs.* 55.3±6.6; CRP (mg/L): 32.3±4.6, 28.0±6.2 *vs.* 37.3±5.9, all P<0.05]. When compared with the XBJ 50 mL group, the increases in WBC, ESR and CRP were more significant in the XBJ 100 mL group [WBC ($\times10^9$/L): 7.12±0.55 *vs.* 5.82±0.49, ESR (mm/1 h): 40.5±7.4 *vs.* 45.9±5.7; CRP (mg/L): 28.0±6.2 *vs.* 32.3±4.6, all P<0.05]. The clinical symptoms of the patients in the XBJI 100 mL group were improved more markedly than that of the XBJI 50 mL and routine groups (38). Currently, XBJI is recommended for the treatment of critical cases of COVID-19 by the NHC guidelines.

Xi-Yan-Ping injection (XYPI)

XYPI is commonly applied for the treatment of bronchitis, bacillary dysentery, hand-foot-mouth disease and other infectious diseases in China (78). Andrographolides, which is the sole active ingredient of XYPI, is a diterpenoid lactone isolated from Chinese herb *Andrographis paniculata* (Chuanxinlian) (79). Data have demonstrated the effectiveness of this sulfonated andrographolide in sepsis and acute lung injury (80). XYPI was able to decrease inflammation in COVID-19 patients and enhance such symptoms as cough, fever, and rales in the lungs. A

retrospective analysis found that XYPI was more effective than Ribavirin in improving clinical symptoms of 92 patients with viral pneumonia (81).

Re-Du-Ning injection (RDNI)

RDNI, composed of *Lonicerae Japonicae Flos* (Jinyinhua), *Artemisiae Annuae Herba* (Qinghao) and *Gardeniae Fructus* (Zhizi), is commonly used for the upper respiratory tract infection (exogenous wind heat syndrome) manifesting high fever, chills, headache and body pain, cough with yellow phlegm (82,83). It is one of the patented Chinese medicine preparations recommended in the "New Coronavirus Pneumonia Diagnosis and Treatment Plan" (Trial Versions 6 and 7), and is especially recommended for severe cases (84). RDNI combined with biapenem has been shown to have a better clinical effect on severe pneumonia, as it is capable of ameliorating blood gas indexes, improving patients' clinical symptoms and lung function, and decreasing serum inflammatory factor levels (40,41). RDNI was able to regulate ACE2, Mpro and PLP in COVID-19 patients. The underlying mechanisms of RDNI in the treatment of COVID-19 may be associated with modulation of the cytokine production, while its antipyretic activity may be achieved via regulating the expression of p65, PKC, MAPKs and nuclear factor NF-κB (84).

Tan-Re-Qing injection (TRQI)

TRQI consists of *Forsythiae Fructus* (Lianqiao), *Scutellariae Radix* (Huangqin), *Lonicerae Japonicae Flos* (Jinyinhua) and *Ursi fellis pulvis* (Xiongdanfen), and has a marked curative effect on the diseases of the upper respiratory tract (85). Clinical studies have shown that TRQI was efficacious against infectious diseases, such as viral pneumonia, human infection with H7N9 avian influenza, community acquired pneumonia (CAP), acute bronchitis, acute attack of chronic bronchitis, tuberculosis accompanied with infection (86). A systematic assessment showed that administration of TRQI on top of antibiotics for the treatment of CAP markedly improved clinical symptoms, and the duration of fever was shortened, and the cough with expectoration ameliorated, while the recovery of chest radiography and hemogram improved without any significant adverse reactions (86). A total of 118 patients who met the diagnostic criteria of COVID-19 were divided into treatment group (58 cases treated with TRQI combined with α-interferon) and control group (60 cases without treatment of TRQI combined with α-interferon). The symptom score and the effective rate were observed at 3, 5 and 7 days after the treatment, respectively. The results revealed that the effective rate and symptom scores of the treatment group were dramatically higher than the control group ($P<0.05$). TRQI combined with α-Interferon could significantly improve clinical symptoms, impede deterioration and promote rehabilitation in patients with confirmed and suspected cases of COVID-19 (42).

Xing-Nao-Jing injection (XNJI)

XNJI mainly consists of *Moschus* (Shexiang), *Curcumae Radix* (Yujin), *Gardeniae Fructus* (Zhizi) and *Borneolum Syntheticum* (Bingpian) (56). It is widely used clinically for pneumonia, viral encephalitis, craniocerebral injury, pulmonary encephalopathy, acute poisoning, acute cerebrovascular disease, respiratory failure, and sepsis. In a clinical study in which 82 patients with severe pneumonia hospitalizing in the ICU were randomly divided into study group and control group. On top of conventional antibacterial therapy, patients in the study group were treated with XNJI, and the effects of different treatment regimens on severe pneumonia and serum cytokine content were compared. The effective rate in the study group was significantly higher than that in the control group ($\chi^2=5.479$, $P<0.05$). XNJI was found to regulate cellular immune function, effectively suppress the inflammatory response in the body, thereby improving the clinical response (43).

Shen-Fu injection (SFI)

SFI comprises *Ginseng Radix et Rhizoma Rubra* (Hongshen) and *Aconiti Lateralis Radix Praeparata* (Fuzi), and is commonly applied in the treatment of cardiovascular and cerebrovascular diseases (87,88). Pharmacological studies have shown that it could elevate blood pressure and improve microcirculation against inflammatory reaction. It can be used alone or as an adjuvant to treat severe pneumonia, multiple organ dysfunction and sepsis. Treatment with SFI in 80 elderly patients with severe pneumonia significantly reduced the levels of NT-pro BNP. The total effective rate of the study group was 95.0%, which was higher than that of the control group at 77.50% ($P<0.05$). The results indicate that SFI could improve the therapeutic efficacy of elderly patients with severe pneumonia (89). In another clinical study, 30 cases of pneumonia patients were randomized into the SFI treatment group and conventional treatment group. The blood gas indicators, ventilator and antibiotics use days, and sequential organ failure assessment scores between the two groups were compared. The results showed that the arterial oxygen partial pressure (PaO_2, Hac)

of the patients in the SFI treatment group was significant better than that of the control group. The sequential organ failure assessment score, ICU stay time, total length of hospitalization, ventilator application days, and mortality rate of the SFI group were lower than those of the control group (P<0.05). The effective rate of the treatment group was better than that of the control group (P<0.05). The treatment of elderly patients with severe pneumonia with SFI could significantly shorten the number of days of antibiotics use and ventilator application, maintain the blood gas index, and improve the prognosis of the patients (44).

Shen-Mai injection (SMI)

SMI, consisting of *Ginseng Radix et Rhizoma Rubra* (Hongshen) and *Ophiopogonis Radix* (Maidong), is commonly used in coronary heart disease and chronic pulmonary heart disease treatment (90,91). One study randomly assigned 46 patients with severe pneumonia into control and treatment groups, and the control group received conventional treatment, while the treatment group received 60 mL of SMI in addition to the conventional treatment. The results demonstrated that the patients who received SMI had dramatically higher total effective rate than that of the control group (P<0.05), and the average length of hospitalization in the treatment group was shorter than that of the control group (P<0.05). SMI adjuvant treatment of severe pneumonia could improve the clinical symptoms and immune function of the patients (92). In another study, 62 patients with ventilator-associated pneumonia were randomly divided into treatment group and control group. Patients in the control group were given antibiotics, cardiotonic and diuretics to correct water and electrolyte and acid-base disorders. In addition to the above treatment, the treatment group was given 50 mL of SMI intravenously once daily. The results show that after treatment, the acute physiology and chronic health status score II and oxygenation index of the observation group were compared with those of the control group, and the differences were statistically significant (P<0.05); SMI could improve the clinical symptoms and signs of patients with ventilator-associated pneumonia, reduce the inflammatory response, and achieved better clinical outcomes (45).

Sheng-Mai injection (SGMI)

SGMI is composed of *Ginseng Radix et Rhizoma Rubra* (Hongshen), *Ophiopogonis Radix* (Maidong) and *Schisandrae Chinensis Frucyus* (Wuweizi). Pharmacological studies have shown that SGMI has the therapeutic functions of protecting the heart and lung function and the organism from inflammatory shock, and immunoregulation. It is widely used in various cardiovascular diseases (93). In a clinical study, 33 patients with systemic inflammatory response syndrome were randomized into a routine Western medicine treatment group and SGMI + routine treatment group. SGMI combined with conventional treatment could significantly enhance the plasma prostacyclin (PGI2) and PGI2/TXA2, decrease the endothelin (ET) and atrial natriuretic peptide (ANP) level and improve pulmonary and cardiovascular microcirculation. SGMI has also been found to play a protective role in various organs (94). Randomized controlled trials were conducted on 1,804 participants to evaluate the impact of SGMI on chronic obstructive pulmonary disease (COPD). The results showed that SGMI not only improved the overall clinical response rate, but also enhanced pulmonary function, oxygen saturation, and IgG indexes, as well as shortened the time for disappearance of lung rales. The results suggested that SGMI in combination with routine Western medicine had a positive effect in the treatment of COPD (46).

Common herbal components and active ingredients of CM for the treatment of COVID-19

CHMs are usually composed of various herbs and contain many active ingredients that can target different molecular pathways for a given medical condition. We compared the herbs and active constituents in the aforementioned CHM for COVID-19 treatment. Network pharmacology analysis was usually used to identify the common active ingredients in CM formulae that have been proven to be effective for COVID-19 treatment (*Table 4*). *Glycyrrhizae Radix et Rhizoma* (Gancao), *Dryopteridis Ephedrae Herba* (Mahuang), *Forsythiae Fructus* (Lianqiao), *Lonicerae Japonicae Flos* (Jinyinhua) and *Armeniacae Semen Amarum* (Kuxingren) are the common herbal components in the proprietary Chinese herbal products including LHQWC, JHQGC, QFPDD. *Forsythiae Fructus* (Lianqiao), *Scutellariae Radix* (Huangqin) and *Lonicerae Japonicae Flos* (Jinyinhua) are the common herbs in SHL and TRQI. *Glycyrrhizae Radix et Rhizoma* (Gancao), *Dryopteridis Ephedrae Herba* (Mahuang) and *Armeniacae Semen Amarum* (Kuxingren) are the common herbs of MXSGD. Radix *Ophiopogonis Radix* (Maidong) is the common herb in the SFI, SMI and SGMI. Among these common herbs, *Glycyrrhizae Radix et Rhizoma* (Gancao) is the herb used most frequently in the treatment

Table 4 The common herbs and active ingredients in the CHM for the treatment of COVID-19

Components	Active ingredients	CM formular
Glycyrrhizae Radix et Rhizoma (Gancao)	Glycyrrhizin	LHQWC; JHQGC; SFJDC; QFPDD; MXSGD
Ephedrae Herba (Mahuang)	Kaempferol	LHQWC; JHQGC; QFPDD; MXSGD
Forsythiae Fructus (Lianqiao)	Quercetin, wogonin	LHQWC; JHQGC; SFJDC; SHL; TRQI
Scutellariae Radix (Huangqin)	Baicalin, baicalein	JHQGC; SHL; QFPDD; TRQI
Lonicerae Japonicae Flos (Jinyinhua)	Luteolin	LHQWC; JHQGC; SHL; QFPDD; RDNI; TRQI
Armeniacae Semen Amarum (Kuxingren)	Sitosterol	LHQWC; JHQGC; QFPDD; MXSGD
Ophiopogonis Radix (Maidong)	Stigmasterol	SFI; SMI; SGMI

of COVID-19 patients at different stages, including mild, moderate, severe and recovery stages. *Forsythiae Fructus* (Lianqiao) and *Scutellariae Radix* (Huangqin) are frequently used to treat COVID-19 patients at mild and moderate stage, *Dryopteridis Ephedrae Herba* (Mahuang) and *Armeniacae Semen Amarum* (Kuxingren) are used extensively to treat mild, moderate and severe stages of COVID patients (95).

Network pharmacology analysis indicates that the active ingredients in those common herbal components include glycyrrhizin, kaempferol, quercetin, wogonin, baicalin, baicalein, luteolin, sitosterol and stigmasterol which possess wide range of pharmacological activities, including anti-inflammatory, anti-oxidant, anti-microbial, anti-cancer, cardioprotective, neuroprotective, anti-osteoporotic, anti-diabetic, anxiolytic, analgesic and anti-allergic effects (96,97). COVID-19 is known to involve multiple pathological mechanisms such as respiratory disorders, inflammation in the immune system, cardiopulmonary and nervous system dysfunction (57,98). The main active ingredients in these CHM are known to be effective anti-inflammatory agents, which could protect the cardiovascular system and improve dyspnea, respiratory distress syndrome, hypoxemia, and acute septic.

Discussion and future perspectives

Coronavirus, influenza virus, respiratory syncytial virus, and rhinovirus are among the most common viruses that can cause upper respiratory symptoms similar to that of seasonal flu. These RNA viruses can also cause lower respiratory tract infections, leading to pneumonia and bronchiolitis. Young children, the elderly and patients with pulmonary, compromised cardiac or immune systems are particularly at higher risk for severe disease caused by these RNA viruses. Furthermore, avian influenza viruses, together with SARS-associated and MERS coronaviruses, represent critical pandemic threats to the general population. COVID-19, which is currently causing a pandemic of global scale, is the third highly pathogenic human coronavirus disease identified to date. Although less deadly than SARS and MERS, the rapid spread of this contagious disease has posed the gloomiest threat to global health for the past several decades. Great efforts have been devoted to find effective antiviral agents for the treatment of COVID-19. However, results of many clinical studies on antiviral therapy for this virus-induced respiratory infection have not been satisfactory. For example, nucleoside analogs such as ribavirin were once thought to be beneficial for the treatment of COVID-19; however, several clinical studies indicated that ribavirin did not confer clinical any benefit to COVID-19 patients, while it also had severe side effects such as anemia (99).

CM has always been a valuable tool for fighting against pandemics in the long history of Chinese civilization. Indeed, many CM products have been shown to possess potent anti-inflammatory and immunomodulatory effects. CM is now considered to be a promising adjuvant therapy for coronavirus disease in light of its good safety and clinical efficacy. As reviewed in this paper, many CM formulae and products have been demonstrated to be effective in clinical studies in fighting against the current COVID-19 pandemic. For example, LHQWC and JHQGC were shown to be efficacious when they were used during the medical observation period and early stage of COVID-19. While XYPI fluid and XBJI fluid were effective in treating COVID-19 with mild bacterial infections and multiple organ failure. In this review, we also briefly reviewed the common herbal components and active ingredients of those CHM for their known therapeutic efficacy. The

results summarized in this paper collectively attest that CM is a valuable therapeutic option for the prevention and treatment of COVID-19.

However, it should be pointed out that the current clinical evidence level concerning the efficacy of Chinese medicine for COVID-19 is relatively weak, as many clinical studies cited in this review were of low methodological quality. These insufficiencies include (I) most, if not all, of these studies only recruited small number of participants and the sample size for the trials were often small; (II) the trial design for most of these studies were not able to incorporate double-blind and placebo control elements, therefore, the clinical evidence on effectiveness and safety of the CM intervention could not be robustly established; and (III) few studies actually incorporate the mechanistic investigation into outcome measures, thus how CM works for COVID-19 remain largely unknown.

In view of the apparent methodological flaws in many of the clinical studies on Chinese medicine for COVID-19, it is strongly recommended that robust trial design should be adopted in future clinical studies so to accrue quality evidence about the effectiveness and safety of Chinese medicine intervention for COVID-19. As COVID-19 is under good control in China, fewer COVID-19 patients are available for clinical study, and this certainly would pose daunting challenge to the researchers who want to engage in COVID-19 clinical research. Because of the wide spread of occurrence of SARS-Cov-2 virus mutation in many parts of the world, the current vaccination programmes may not confer total protection to those who are at risk of infection. The effective treatment modalities for COVID-19 are still urgently needed. In this regard, Chinese medicine continues to be a valuable armament to fight mutated corona viruses. Research on effectiveness and safety of CHM for COVID-19 will remain a worthy scientific pursuit for many years to come.

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