

Review

Application of Chinese Herbal Medicine in COVID-19

Yehong Tian*, Xiaowei Qiu*, Xin Jiang, Jinchang Huang, Fengyu Zhang

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ABSTRACT

Traditional Chinese herbal medicine has a long history in treating febrile diseases, according to *the Shang Han Lun*, a classical theory of traditional Chinese medicine developed by Zhang Zhongjing in the *Han* Dynasty. Some herbs have been formulated as prescription formulae or manufactured as finished medicine such as pills, capsules, or injections. The Chinese government has recommended specific TCM prescriptions alone or combined with Western medicine to treat patients with COVID-9. Here, we introduce three prescription formulae, *Qingfei Paidu* Decoction, *Huashi Baidu* Formula, and *Xuanfei Baidu* Formula, three finished medicines, *Lianhua Qingwen* Capsule, *Jinhua Qinggan* Granule, and *Xuebijing* Injection; following this, several single herbs such as *Ephedra herba*, *Honeysuckle*, *Scutellaria*, *Glycyrrhizae radix*, *Armeniacae semen*, *Sophorae flavescentis radix*, and *Curcuma longa*. We review existing evidence of these traditional medicines and herbs for their related antiviral activities, efficacy, and underlying mode of action in virus-related diseases. Most of these drugs have been traditionally used in Chinese medicine for over a thousand years, and they have been proved to be safe in treating flu-like virus infections. It will be adequate to further test for their efficacy for COVID-19 and understand the underlying molecular mechanism.

KEYWORDS

COVID-19, SARS-CoV-2, Traditional Chinese medicine, herbal medicine

INTRODUCTION

Traditional Chinese medicine (TCM) alone and combined with Western medicine (TCWM) have shown benefits in the prevention and treatment of Coronavirus infection disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Despite the lack of formal clinical trials, TCM has an excellent potential to complement the treatment of patients with COVID-19 through shortening viral shedding, mitigating clinical symptoms from deterioration, restoring normal laboratory parameters, reverting radiological changes, and reducing case fatality (1-5). According to the clinical data disclosed by related departments of the Chinese govern-

ment, there was a positive correlation between cure rate and use of TCM in patients with COVID-19 (4). In the *Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia* (DTPNCP) issued by the National Health Commission (NHC) and State Administration of Traditional Chinese Medicine (SATCM), some specific schemes for TCM treatment have emerged as the protocol revision from version 3 to 7 (6).

Several TCM regimens are recommended for treating COVID-19 in the Trial Version 7 of the DTPNCP (**Table 1**). The prescription herbs seemed to vary with severity, stage, and clinical manifestation of COVID-19. According to the clinical classification (6), the Institute of Chinese Materia

* Authors contributed equally to this work.

Correspondence to: J Huang; email: zyhhuang@163.com or F Zhang; email: zhangfy@gcatresearch.org.

Medica at the Chinese Academy of Chinese Medical Sciences has established a human coronavirus 229E mouse model (BALB/c) of cold and dampness syndrome which is appropriate for studying human coronavirus pneumonia with lung syndrome (7). Based on the mouse model, investigators have found that several Chinese herbal prescriptions could significantly reduce viral load, inflammatory cytokine levels, and inflammatory lung injury but improve the immune cells in the peripheral blood (7-9).

COVID-19 belongs to the “plague” (Yi Bing, 疫病) or epidemic or endemic disease category in the TCM theory (10). TCM has been historically documented with more than 3000 years of use in treating epidemic diseases. Existing evidence suggests that TCM combined with Western medicine seemed superior in treating COVID-19 (11). Besides asymptomatic infection, patients with

COVID-19 are classified into mild, moderate, severe, and critically ill based on the clinical symptom severity (12). The “three prescriptions and three finished medicines” were commonly applied for the treatment of COVID-19. Three prescriptions refer to *Qingfei Paidu Decoction* (QFPDD), *Huashi Baidu Formula* (HSBDF), and *Qingfei Paidu Decoction* (QFPDD); three finished medicines refer to *Jinhua Qinggan Granule* (JH-G), *Lianhua Qingwen Capsule* (LH-C), and *Xuebijing Injection* (XBJ) that have been on the market. Of three prescription formulae, XFBDF is recommended for moderate cases, HSBDF is for severe cases, but QFPDD is for all cases of COVID-19. Among three finished medicines, JH-G and LH-C are for mild cases, and XBJ injection is for severe and critically ill cases. This review introduces the “three prescription and three finished medicines” and some individual herbs that may hold promise for treating patients with COVID-19.

Table1. Recommended Prescriptions in Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Version 7).

Severity	Syndrome	Recommended prescription
Mild	M moderate and severe cases. Critical cases in necessity.	<i>Qingfei Paidu decoction</i> : Ephedra 9g, Honey-fried Licorice 6g, Almonds 9g, Gypsum 15-30g (decocted firstly), Cassia Twig 9g, Alisma 9g, Grifola 9g, Atractylodes 9g, Poria 15g, Radix Bupleuri 16g, Scutellaria baicalensis 6g, Ginger Pinellia 9g, Ginger 9g, Aster Tataricus 9g, Flos Farfarae 9g, Blackberrykiky Rhizome 9g, Asarum 6g, Chinese Yam 12g, Citrus aurantium 6g, Tangerine Peel 6g, Agastache Rugosus 9g.
Mild	Cold dampness and stagnation lung syndrome	<i>Raw Ephedra</i> 6g, <i>Raw Gypsum</i> 15g, <i>Almond</i> 9g, <i>Notopterygium Root</i> 15g, <i>Semen Lepidii</i> 15g, <i>Cyrtomium Fortunei</i> 9g, <i>Lumbricus</i> 15g, <i>Paniculate Swallowwort Root</i> 15g, <i>Agastache rugosa</i> 15g, <i>Peran</i> 9g, <i>Atractylodes (Cang Zhu)</i> 15g, <i>Poria</i> 45g, <i>Raw Atractylodes (Bai Zhu)</i> 30g, <i>Charred Triplet</i> 9g, <i>Magnolia Officinalis</i> 15g, <i>Betel Nut</i> 9g, <i>Fructus Tsaoko</i> 9g, <i>Ginger</i> 15g.
Mild	Dampness and heat-accumulation lung syndrome	<i>Betel Nut</i> 10g, <i>Fructus Tsaoko</i> 10g, <i>Magnolia Officinalis</i> 10g, <i>Anemarrhena</i> 10g, <i>Scutellaria</i> 10g, <i>Radix Bupleuri</i> 10g, <i>Red Peony Root</i> 10g, <i>Forsythia</i> 15g, <i>Artemisia Annua</i> 10g (decocted later), <i>Atractylodes (Cang Zhu)</i> 10g, <i>Folium Isatidis</i> 10g, <i>Raw Licorice</i> 5g.
Moderate	Dampness and stagnation lung syndrome	<i>Raw Ephedra</i> 6g, <i>Bitter Almond</i> 15g, <i>Raw Gypsum</i> 30g, <i>Raw Coix Seed</i> 30g, <i>Atractylodes (Cang Zhu)</i> 10g, <i>Agastache Rugosus</i> 15g, <i>Artemisia Annua</i> 12g, <i>Polygonum Cuspidatum</i> 20g, <i>Verbena</i> 30g, <i>Dried Reed Root</i> 30g, <i>Semen Lepidii</i> 15g, <i>Exocarpium</i> 15g, <i>Raw Licorice</i> 10g.
Moderate	Cold dampness lung syndrome	<i>Atractylodes (Cang Zhu)</i> 15g, <i>Pericarpium Citri Reticulatae</i> 10g, <i>Magnolia Officinalis</i> 10g, <i>Agastache Rugosus</i> 10g, <i>Fructus Tsaoko</i> 6g, <i>Raw Ephedra</i> 6g, <i>Notopterygium Root</i> 10g, <i>Ginger</i> 10g, <i>Betel Nut</i> 10g.
Severe	Plague poison and lung-closing syndrome	<i>Raw Ephedra</i> 6g, <i>Almond</i> 9g, <i>Raw Gypsum</i> 15g, <i>Licorice</i> 3g, <i>Agastache Rugosus</i> 10g (decocted later), <i>Magnolia Officinalis</i> 10g, <i>Atractylodes (Cang Zhu)</i> 15g, <i>Fructus Tsaoko</i> 10g, <i>Pinellia</i> 9g, <i>Poria</i> 15g, <i>Raw Rhubarb</i> 5g (decocted later), <i>Semen Lepidii</i> 10g, <i>Red Peony</i> 10g.
Severe	Syndrome of flaring heat in Qifen and Yingfen	<i>Raw Gypsum</i> 30-60g (decocted firstly), <i>Anemarrhena</i> 30g, <i>Raw Rehmannia</i> 30-60g, <i>Buffalo Horn</i> 30g (decocted firstly), <i>Red peony Root</i> 30g, <i>Radix Scrophulariae</i> 30g, <i>Forsythia</i> 15g, <i>Peony Bark</i> 15g, <i>Coptis</i> 6g, <i>Bamboo Leaves</i> 12g, <i>Semen Lepidii</i> 15g, <i>Raw Licorice</i> 6g. Finished patent medicine: <i>Xiyanping</i> injection, <i>Xuebijing</i> injection, <i>Reduning</i> injection, <i>Tanreqing</i> injection, <i>Xingnaojing</i> injection.
Critical	Syndrome of inner blocking causing a collapse	<i>Ginseng</i> 15g, <i>Radix Aconiti Carmichaeli</i> 10g (decocted firstly), <i>Dogwood</i> 15g, delivered with <i>Suhexiang</i> Pill or <i>Angong Niu Huang</i> Pill. Finished patent medicines: <i>Xuebijing</i> injection, <i>Reduning</i> injection, <i>Tanreqing</i> injection, <i>Xingnaojing</i> injection, <i>Shenfu</i> injection, <i>Shengmai</i> injection, <i>Shenmai</i> injection.
Convalescent	Lung and spleen Qi deficiency syndrome	<i>Pinellia</i> 9g, <i>Pericarpium Citri Reticulatae</i> 10g, <i>Codonopsis</i> 15g, <i>Sunburn Astragalus</i> 30g, <i>Atractylodes (Baizhu)</i> 10g, <i>Poria</i> 15g, <i>Agastache Rugosus</i> 10g, <i>Amomum Villosum</i> 6g (decocted later), <i>Licorice</i> 6g.
Convalescent	Qi and Yin deficiency syndrome	<i>Radix Adenophorae</i> 10g, <i>Radix Glehniae</i> 10g, <i>ophiopogonis</i> 15g, <i>American Ginseng</i> 6g, <i>Schisandra</i> 6g, <i>Raw Gypsum</i> 15g, <i>Bamboo Leaves</i> 10g, <i>Mulberry Leaves</i> 10g, <i>Rhizoma Phragmitis</i> 15g, <i>Salviae Miltiorrhiza</i> 15g, <i>Raw Liquorice</i> 6g.

Note: Disease severity was classified into mild, moderate, severe, critical, and convalescent

REPRESENTATIVE PRESCRIPTIONS

Qingfei Paidu Decoction (QFPDD, 清肺排毒汤)

QFPDD is a specified formula recommended for treating patients with COVID-19 (6). It includes five TCM prescription formulae, *Ma Xing Shi Gan decoction* (MXSGD, 麻杏石甘汤) (13), *She Gan Ma Huang decoction* (SGMHD, 射干麻黄汤) (14), *Xiao Chai Hu decoction* (XCHD, 小柴胡汤) (15) and *Wu Ling San* (WLS, 五苓散) (16), and other herbs. These five formulae or TCM prescriptions constitute five functional units (FUs) in line with traditional Chinese medicine's compatibility theory. According to the *Treatise*

on Cold-induced Disease (*Shang Han Lun*, 伤寒论), all classic prescriptions treat exogenous febrile disease developed in the Han Dynasty. In total, QFPDD contains 21 Chinese herbs (Table 2), and notably, is recommended for confirmed cases with COVID-19 across all types of severity (6, 17). A clinical retrospective study evaluated the effectiveness of QFPDD combined with Western medicine in patients with COVID-19 and demonstrated significant anti-inflammatory and metabolic effects, whereas Western medicine alone failed to show a statistically significant effect (18). The other two studies also showed that QFPDD improved laboratory test markers and clinical symptoms (19, 20).

Table 2. List of TCM drugs in QFPDD

No	Chinese pinyin	Chinese	Latin	Alternative name in the guide	Dose
1	Ma Huang	麻黄	<i>Ephedra herba</i>	<i>Ephedrae Herba</i>	9g
2	Zhi Gan Cao	炙甘草	<i>Glycyrrhizae Radix</i>	<i>Glycyrrhizae Radix</i>	6g
3	Xing Ren	杏仁	<i>Amygdalus communis</i>	<i>Armeniacae Semen</i>	9g
4	Bai zhu	白术	<i>Atractylodes macrocephala Koidz</i>	<i>Atractylodis macrocephalae Rhizoma</i>	9g
5	Chai HU	柴胡	<i>Radix Bupleuri</i>	<i>Bupleuri Radix</i>	16g
6	Huang Qin	黄芩	<i>Scutellaria baicalensis</i>	<i>Scutellariae Radix</i>	6g
7	Jiang Ban Xia	姜半夏	<i>Pinellia ternata</i>	<i>Pinellinae Rhizoma Praeparatum</i>	9g
8	Zi Wan	紫菀	<i>Aster Tataricus</i>	<i>Asteris Radix</i>	9g
9	Kuan Dong Hua	款冬花	<i>Flos Farfarae</i>	<i>Farfarae Flos</i>	9g
10	Xi Xin	细辛	<i>Asarum</i>	<i>Asari Radix et Rhizoma</i>	6g
11	She Gan	射干	<i>Blackberry Lily Rhizome</i>	<i>Belamcandae Rhizoma</i>	9g
12	Shan Yao	山药	<i>Dioscorea polystachya</i>	<i>Dioscoreae Rhizoma</i>	12g
13	Zhi Shi	枳实	<i>Citrus aurantium</i>	<i>Aurantii Fructus immaturus</i>	6g
14	Huo Xiang	藿香	<i>Agastache Rugosus</i>	<i>Pogostemonis Herba</i>	9g
15	Sheng Jiang	生姜	<i>Zingiber officinale rosc</i>	<i>Zingiberis Rhizoma recens</i>	9g
16	Fu Ling	茯苓	<i>Wolfiporia cocos</i>	<i>Poria</i>	15g
17	Chen Pi	陈皮	<i>Pericarpium citri reticulatae</i>	<i>Citri reticulatae Pericarpium</i>	6g
18	Sheng Shi Gao	生石膏	<i>Gypsum fibrosum</i>	<i>Gypsum fibrosum (decocted first)</i>	15-30g
19	Gui Zhi	桂枝	<i>Cinnamomum cassia presel</i>	<i>Cinnamomi Ramulus</i>	9g
20	Ze Xie	泽泻	<i>Alismatis</i>	<i>Alismatis Rhizoma</i>	9g
21	Zhu Ling	猪苓	<i>Polyporus frondosus (Fr)</i>	<i>Polyporus</i>	9g

Chen et al. (21) screened the QFPDD compounds by all five FUs to identify active compounds and understand the mode of action underlying the efficacy. Using network pharmacology (22), they integrated drugs, targets, pathways, and diseases into a biological network from a holistic perspective. Five formulae yielded 67 active compounds, in which four specific compounds and five common ones in QFPDD presented optimal molecular dockings with SARS-CoV-2 viral structural and non-structural proteins. Remarkably, all the nine compounds showed some optimal docking consistently with papain-like protease (PL^{pro}, nsp3), RNA-dependent RNA polymerase (RdRP, nsp12), and N7-guanine methyltransferase (nsp14), suggesting that these compounds might have the potentials for inhibiting viral replications. Of note, RdRP, the critical enzyme of replicase-transcriptase complex (12), has been a target by approved antiviral drugs such as remdesivir (23). Each formula may have an independent protective effect on COVID-19. The formulae-target-based pathway

analysis indicates that these compounds are related to bacterial and viral responses, immune response, signaling transduction (21).

Other studies predicting potential mechanism using network pharmacology suggest that QFPDD may have functions of anti-virus, anti-inflammatory, and enhancing immunity. The network regulation mechanism with multi-component and multi-target is evaluated at a molecular network level, which may provide a theoretical basis of QFPDD to treat COVID-19 (24-26). Also, Wu et al. (27) selected 24 compounds for molecular docking with 3C-like protease (3CL^{pro}, also the main protease, M^{pro}) and angiotensin-converting enzyme 2 (ACE2) receptors, respectively. They demonstrated that 22 of 24 compounds had a particular affinity to 3CL^{pro} and ACE2, in which Ergosterol, a sterol found in the membrane of animal cells, could form hydrogen bonds with the 3CL^{pro} of SARS-CoV-2 (27).

Yang et al. (28) performed an *in-silico* analysis and experimental study of a rat model to identify the chemical compounds of QFPDD and reveal potential mechanisms underlying treatment effect on COVID-19. Putatively, 129 compounds were identified through liquid chromatography coupled with high-resolution mass spectrometry, and they are mainly classified into flavonoids, glycosides, carboxylic acids, and saponins. The target network model indicated that MXSGD might play a pivotal role in the therapeutic efficacy of QFPDD. In the rat model of LPS-induced pneumonia treated with MXSGD, they performed a transcriptomic analysis and found that thrombin and Toll-like receptor (TLR) signaling pathway seemed essential pathways MXSGD mediated anti-inflammatory effects. They also validated one primary compound in MXSGD, glycyrrhizic acid from *glycyrrhizae radix*, inhibiting TLR agonist induced IL6 production in macrophages.

Liu et al. (29) performed a study to detect the critical chemical compounds of QFPDD using high-performance liquid chromatography-quadrupole-orbitrap high-resolution mass spectrometry. A total of 39 chemical compounds were identified in the blood sample. When injected in mice, nine compounds were quickly absorbed and distributed to multiple tissues. Eight of which were peaked within 0.5 h when the observed exposure levels of the compounds in

the lung tissue from high to low were ephedrine, prunasin, pseudoephedrine, amygdalin, hesperidin, risflorentin, baicalin, hyperoside, liquiritin.

In summary, QFPDD seemed to have a multi-compound synergistic effect on COVID-19; these studies provide intriguing evidence for subsequent pharmacodynamics and mode of action for a formal clinical investigation.

Huashi Baidu Formula (HSBDF, 化湿败毒方)

HSBDF is the core prescription formula specifically refined for COVID-19 by the national medical team of traditional Chinese medicine, according to the early clinical practice of the national diagnosis and treatment plan at Jinyintan Hospital in Wuhan. In the sixth trial edition of the DTPNCP, HSBDF is recommended for the severe COVID-19 with TCM characteristic of plague poison and lung-closing syndrome (30). HSBDF consists of component herbs (Table 3), which have been included in individual formulae of MXSGD, *Tingli Dazao Xiefei* decoction (TLDZXF, 葶藶大枣泄肺汤), *Xuanbai Chengqi* decoction (XBCQD, 宣白承气汤), *Huopu Xialing* decoction (HPXLD, 藿朴夏苓汤) and *Leishi Xuantou Moyuan* decoction (LSXTMYD, 雷氏宣透膜原法) (31).

Table 3. List of TCM drugs in HSBDF

No	Chinese pinyin	Chinese	Latin	Alternative name in the guide	Dose
1	Sheng Ma Huang	生麻黄	<i>Ephedra herba</i>	<i>Herba Ephedrae</i>	6g
2	Gan Cao	甘草	<i>Glycyrrhizae Radix</i>	<i>Glycyrrhizae Radix</i>	3g
3	Xing Ren	杏仁	<i>Armeniacae Semen</i>	<i>Amygdalus communis</i>	9g
4	Sheng shi gao	生石膏	<i>Gypsum fibrosum</i>	<i>Gypsum fibrosum (decocted first)</i>	15g
5	Huo Xiang	藿香	<i>Agastache Rugosus</i>	<i>Pogostemonis Herba</i>	10g
6	Hou Po	厚朴	<i>Magnolia Officinalis Rehd Et Wils</i>	<i>Cortex Magnoliae Officinalis</i>	10g
7	Fa Ban Xia	法半夏	<i>Pinellia ternata</i>	<i>Pinellinae Rhizoma Praeparatum</i>	9g
8	Cang zhu	苍术	<i>Atractylodes Lancea</i>	<i>Rhizoma Atractylodis</i>	15g
9	Cao guo	草果	<i>Amomum Tsao-Ko Crevostet</i>	<i>Tsaoko Amomum Fruit</i>	10g
10	Fu Ling	茯苓	<i>Wolfiporia cocos</i>	<i>Poria</i>	15g
11	Sheng da huang	生大黄	<i>Rhei Radix Et Rhizoma</i>	<i>Chinese rhubarb</i>	5g
12	Sheng huang qi	生黄芪	<i>Astragali Radix</i>	<i>Milkvetch Root</i>	10g
13	Ting li zi	葶苈子	<i>Lepidii Semen Descurainiae Semen</i>	<i>Pepperweed Seed</i>	10g
14	Chi shao	赤芍	<i>Radix Paeoniae Rubra</i>	<i>Red Paeony Root</i>	15g

HSBDF has been demonstrated with therapeutic efficacy for COVID-19. A non-randomized controlled trial has shown that HSBDF can enhance the therapeutic effect of Lopinavir-Ritonavir on the remission time of patients with COVID-19 (32). A retrospective case series study showed that HSBDF combined with other traditional Chinese medicine had improved effects on SARS-CoV-2 RNA clearance, lung lesion opacity absorption, and inflammation resolution in severe COVID-19 patients (33) and was safe for severe cases to reduce mortality. Several studies combined network pharmacology and molecular docking (34). Tao et al. (35) showed that the top two HSBDF compounds baicalein and quercetin had a high affinity with ACE2. HSBDF may regulate multiple signaling pathways through ACE2 to play a therapeutic role in COVID-19. Zhu

et al. (36) found that four critical Chinese herbal medicines (*Glycyrrhizae Radix*, *Ephedra herba*, *Atractylodes macrocephala* Koidz, and *Astragalus membranaceus*) and 11 main active compounds (quercetin, luteolin, kaempferol, naringenin, β -sitosterol, delphinidin, isorhamnetin, aloemodin, irisolidone, baicalein, and catechin) may play a vital role in the therapeutic effect on severe COVID-19. Lai et al. (37) predicted that HSBDF contained some main compounds such as quercetin, luteolin, kaempferol, begonianin, naringenin, β -sitosterol, and baicalein, of which quercetin, luteolin, and kaempferol had optimal binding with ACE2.

XuanFei Baidu formula (XFBDF, 宣肺败毒方)

XFBD is a prescription formula defined by Academician Zhang Boli and Dr. Liu Qingquan Liu to treat COVID-19 with damp toxins and lung depression syndromes. It consists of four traditional formulae of MXSGD, *Maxingyigan* decoction (MXSGD, 麻杏薏甘汤), *Qianjinweijing* decoction (QJWD, 千金苇茎汤), TLDZXF, in total 13 traditional Chinese medicines (Table 4). XFBD has been demonstrated with therapeutic effect on COVID-19 in clinical practice, and it can significantly shorten the disease course, especially reducing the progression of mild patients to severe patients. In a pilot randomized clinical trial, XFBD combined with conventional treatment had significant improvement of clinical symptoms, white blood cells and lymphocytes, immunity, C-reactive protein, and erythrocyte sedimentation rate than conventional treatment alone (38).

Network pharmacology indicates that the therapeutic mechanism of XFBD in COVID-19 is through a multidrug, multicomponent, and multitarget pattern. Through regulating a series of biological pathways closely related to the pathophysiology of COVID-19, XFBD can play a key role in balancing immunity, anti-inflammatory and regulating liver function, bile metabolism, and restoring the balance of energy metabolism (39). Molecular docking analysis showed that the active XFBD compounds, such as luteolin, β -sitosterol, formononetin, and pterocarpin, were closely related to viral protein 3CL^{pro} and host cellular receptor ACE2. By regulating IL6, MAPK3, MAPK1, IL1, CCL2, EGFR, NOS2, and other key targets, XFBD may have anti-inflammatory, antioxidant, and regulating the host immunity to treat COVID-19 (40).

Table 4. List of TCM drugs in XFBD.

No	Chinese pinyin	Chinese	Latin	Alternative name in guide	dose
1	Sheng Ma Huang	生麻黄	<i>Ephedra herba</i>	<i>Ephedrae Herba</i>	8g
2	Sheng Gan Cao	生甘草	<i>Glycyrrhizae</i>	<i>Raw licorice</i>	10g
3	Ku Xing Ren	苦杏仁	<i>Amygdalus communis</i>	<i>Armeniacae Semen</i>	9g
4	Sheng shi gao	生石膏	<i>Gypsum fibrosum</i>	<i>Gypsum fibrosum</i>	30g
5	Guang Huo Xiang	藿香	<i>Agastache Rugosus</i>	<i>Pogostemonis Herba</i>	15g
6	Sheng Yi Yi Ren	生薏苡仁	<i>Semen Coicis</i>	<i>Coix Seed</i>	30g
7	Hu Zhang	虎杖	<i>Polygoni Cuspidati Rhizoma Et Radix</i>	<i>Polygonum cuspidatum</i>	20g
8	Mao Cang zhu	茅苍术	<i>Rhizoma Atractylodes Lancea</i>	<i>Swordlike Rhizoma Atractylodis</i>	10g
9	Ma bian cao	马鞭草	<i>Verbenae Herb</i>	<i>Herba Verbenae</i>	30g
10	Qing hao cao	青蒿草	<i>Artemisiae Annuae Herba</i>	<i>Artemisia Annu L</i>	25g
11	Gan mao gen	干茅根	<i>Radix Couchgrass</i>	<i>Couchgrass root</i>	30g
12	Ting li zi	荳蔻子	<i>Lepidii Semen Descurainiae Semen</i>	<i>Pepperweed Seed</i>	15g
13	Hua ju hong	化橘红	<i>Citri Grandis Exocarpium</i>	<i>Pummelo Peel</i>	20g

FINISHED PATENT MEDICINES

Lianhuaqingwen capsule (LH-C, 莲花清瘟胶囊)

LH-C, a repurposed finished Chinese medicine approved on the market, has been officially recommended for treating patients with COVID-19 (6). LH-C includes 13 herbs (41) from two prescription formulae of MXSGD and *Yinqiao* decoction (YQD). MXSGD is a component of QFPDD described above, while YQD is from the TCM monograph *Wenbing Tiaobian*, further developed from *Shang Han Lun* by *Wu Jutong* in the *Qing* Dynasty. YQD was used to treat "Warm disease", characterized by fever, thirst, and headache, and often occurs in the Spring season. LH-C has been used for common seasonal flu and influenza (42). *In vitro*, LH-C can inhibit the viral proliferation of several influenza strains (e.g., H1N1, H3N2) and block viral replication in the early stages of infections (41), probably through inhibiting the export of viral RNA nucleocapsid protein. Another study showed that LH-C inhibiting influenza viral replication could reduce critical protease expression by multiple targets (43). Also, LH-C can suppress in mice virus-induced NF- κ B signaling and gene expressions of cytokine and chemokine IL6, IL8, TNF- α , IP10, and MCP-1, which excessive expression could lead to cytokine storm (41).

Recently, LH-C was shown to ameliorate the cardinal symptoms such as fever, cough, fatigue and shorten the disease course in patients with COVID-19 (44-46). A multicenter open-label randomized controlled trial (47), with 284 patients, 142 in each treatment and control group, showed that COVID-19 patients treated with LH-C addition had a significant symptom recovery compared to the conventional treatment. Meanwhile, LH-C had a favorable safety profile in the treatment of COVID-19 (47).

In vitro studies showed that LH-C had an inhibitory effect on SARS-CoV-2 viral replication (48, 49) and reduced proinflammatory cytokine gene expression (49). Chen et al. (50) provided chemical and biochemical evidence for the mechanisms of LH-C therapeutic effects on COVID-19 patients, based on the compounds exposed to humans. They detected 132 LH-C prototypes and metabolites in human plasma and urine, using a combination of HRMS and an untargeted data-mining approach. Eight compounds in LH-C exposed to humans had the potential ability to target ACE2, and of which rhein, forsythoside A, forsythoside I, neochlorogenic acid, and its isomers exhibited a high inhibitory effect on ACE2.

Jinhua Qingan Granules (JH-G, 金花清感颗粒)

JH-G is the first finished Chinese patent medicine shown efficacy on influenza A (H1N1) in 2009 (42). The fifth trial version of DTPNCP first recommended JH-G for individuals in the observation period for COVID-19, and, later, it was recommended as a therapeutic drug for mild cases. A retrospective analysis of 80 COVID-19 patients indicated that JH-G could effectively shorten viral shedding and promote pneumonia inflammatory exudate absorption

without obviously adverse reactions (51). A clinical study showed that treatment with JH-G was more effective than the conventional treatment in improving clinical symptoms, including fever (80.3% vs. 53.1%), fatigue (77.6% vs. 53.8%), cough (66.1% vs. 42.9%), and expectoration (85.3% vs. 46.2%). Meanwhile, the adverse reactions were fewer than those in conventional treatment (52).

Table 5. List of TCM drugs in JH-G.

No	Chinese pinyin	Chinese	Latin	Name in the guide
1	Jin yin hua	金银花	<i>Lonicerae Japonicae Flos</i>	Honeysuckle
2	Shi gao	石膏	<i>Radix Paeoniae Rubra</i>	Red Paeony Root
3	Ma Huang	麻黄	<i>Ephedra herba</i>	<i>Ephedrae Herba</i>
4	Zhi Gan Cao	炙甘草	<i>Glycyrrhizae Radix</i>	<i>Glycyrrhizae Radix</i>
5	Xing Ren	杏仁	<i>Amygdalus communis</i>	<i>Armeniaca Semen</i>
6	Qing hao	青蒿	<i>Artemisiae Annuae Herba</i>	<i>Artemisia Annuua L</i>
7	Huang Qin	黄芩	<i>Scutellaria baicalensis</i>	<i>Scutellariae Radix</i>
8	Lian Qiao	连翘	<i>Forsythiae Fructus</i>	<i>Fructus Forsythiae</i>
9	Zhe bei mu	浙贝母	<i>Fritillariae Thunbergii Bulbus</i>	<i>Thunberg Fritillary Bulb</i>
10	Zhi Mu	知母	<i>Anemarrhenae Rhizoma</i>	<i>Rhizoma Anemarrhenae</i>
11	Niu bang zi	牛蒡子	<i>Fructus Arctii</i>	<i>Arctii Fructus</i>
12	Bo He	薄荷	<i>Menthae Herba</i>	<i>Menthae Haplocalycis Herba</i>

Xuebijing Injection (XBJ, 血必净注射液)

XBJ is developed by Dr. Wang Jinda based on 30 years of experience and research under the comprehensive therapeutic theory of "bacteria, toxin, and inflammation." It consists of five Chinese herbs (Table 6). Previously, a meta-analysis showed that XBJ had significant clinical efficacy in patients with sepsis (53). In a randomized controlled trial, treatment of XBJ plus conventional therapy can significantly reduce the conversion from severe to critically ill COVID-19 and shorten the ICU stay (54). A retrospective case-control study also shows that XBJ can significantly improve IL6 levels and body temperature in the observation group than the control

group, particularly the body temperature reduction in severe COVID-19 patients (55). The main compounds in XBJ injection include quercetin, gallic acid, luteolin, rosmarinic acid, rutin, kaempferol, chlorogenic acid, tanshinone IIA, hydroxysafflor yellow A and paeoniflorin. Network pharmacology shows that the mechanism of action may be related to PTGS-2, PTGS-1, CASP-3, RELA, TNF, MAPK-1, IL2, IL6, and IL10 (56). Another network pharmacology analysis showed that the key targets participated in extracellular signal-regulated kinase 1 and 2 cascades, the T-cell receptor signaling pathway, activation of MAPK activity, cellular response to lipopolysaccharide, and other inflammation- and immune-related biological process (57).

Table 6. List of TCM drugs in XBJ injection.

No	Chinese pinyin	Chinese	Latin	Alternative name in guide
1	Hong hua	红花	<i>Carthami Flos</i>	Safflower
2	Chi shao	赤芍	<i>Radix Paeoniae Rubra</i>	Red Paeony Root
3	Chuna xiong	川芎	<i>Ligusticum wallichii</i>	Sichuan lovase rhizome
4	Dan shen	丹参	<i>Salviae Miltiorrhizae Radix et Rhizoma</i>	<i>Salviae Miltiorrhizae</i>
5	Dang gui	当归	<i>Angelicae Sinensis Radix</i>	<i>Angelica sinensis</i>

OTHER CHINESE HERBS

Modern pharmacological studies have shown that some individual herbs have viral inhibitory properties. The antiviral pathways can directly inhibit viruses, which most Chinese herbs may have through clearing away heat and detoxification. The other antiviral pathways include indirectly inhibit the virus or affect virus-mediated inflammation by regulating host immune functions. Here

we described some representative Chinese herbs that may have potential effects on COVID-19.

Ephedra herba (Ma Huang, 麻黄)

The *Ephedra herba* is the dry stem of the plant *Ephedra sinica* Stapf (Cao ma huang), *Ephedra intermedia* Schrenk (Zhong ma huang), or *Ephedra equisetifolia* (Mu zei ma huang). It has functions of sweating, relieving the exterior, dispersing the lungs, relieving asthma, promoting diuresis

and detumescence. The main chemical components of *Ephedra* are alkaloids, flavonoids, volatile oil, organic acids, amino acids, polysaccharides, and tannins. The volatile oil has anti-inflammatory, antiviral, antipyretic, expectorant, sweating, antiasthma effects (58). *Ephedra herba* is one of the TCMs that has been successfully used for patient therapy during the 2002/2003 SARS epidemic.

Ephedra herba has a potent antiviral activity, and its mechanism may be partly related to the catechins of the tannins that inhibit the growth and development of influenza virus A/PR/8/34 in MDCK cells. Sun et al. (59) found that a particular concentration of *Ephedra* extract had antiviral effect, likely through inhibiting respiratory syncytial virus (RSV) syncytium formation. Wei et al. (60) screened out the compounds in *Ephedra herba* and explored their potential mechanism of antiviral activities. They showed that methylephedrine, l-Ephedrine, and d-pseudoephedrine could inhibit influenza A virus proliferation *in vitro*. The mechanism of action might be related to inhibiting virus replication, regulating inflammatory response, host TLR, and retinoic acid-inducible gene-1-like receptors (RIRs). Ephedrine, pseudo-ephedrine, and methyl-ephedrine have potential therapeutic effects on respiratory tract viral infection (61).

Honeysuckle (Jin Yin Hua, 金银花)

Honeysuckle is the dried or incipient flowers of *Lonicerae Japonicae Flos*. Its main active compounds include chlorogenic acids, triterpenoid saponins, flavonoids, inorganic elements, and volatile oils, and they may play some roles in antiviral, anti-inflammatory response, and antibiotics (62). Chlorogenic acid (CHA), one of the active compounds of *honeysuckle*, has been found to induce IFN- α in human peripheral blood leukocytes *in vitro* (63) to activate host cell response to virus infections and immunomodulation to synergize antiviral and antibacterial effects. CHA was shown concentration-dependent in inhibiting apoptosis of Hep-2 cells induced by herpes simplex virus. CHA, rich in *honeysuckle*, was reported to reduce serum hepatitis B virus (HBV) and HBsAg production (64). It also acts as a neuraminidase (Sialidase) blocker to inhibit influenza A virus in cellular and animal models (65), mainly in the late stage of the viral replication cycle through downregulating viral nucleoprotein expression and blocking the release of newly formed viral particles from the infected cells.

In addition, *honeysuckle* extract may improve pathological lung injury by inhibiting IL1, IL6, and TNF- α production induced by lipopolysaccharide in a rat model of the alveolar lavage fluid of acute respiratory distress syndrome (66). Luo et al. (67) performed an interventional study in mice with viral myocarditis induced by Coxsackievirus B3 and found that *honeysuckle* solution significantly inhibited caspase-3 and NF- κ B expression in myocardial tissue. Zhang et al. (68) also prepared *honeysuckle* mother liquor with a concentration of 0.6g/mL by water extraction and alcohol precipitation. They observed that *honeysuckle* inhibited human RSV type 3 in human cervical cancer cells

(Hela), likely through directly inactivating virus attachment and inhibiting biosynthesis.

Also, *honeysuckle* polysaccharides can promote the secretion of IFN- γ to regulate immune functions and enhance the host immune response (69); *honeysuckle* significantly increased the survival time of mice infected with the FM1 influenza virus strain and reduced mortality and lung tissue lesions.

In summary, *honeysuckle* may mainly induce IFN- α , reduce pro-inflammatory cytokines (IL1 and IL6), inhibit the NF- κ B signaling pathway, and regulate non-specific immunity to inhibit or block virus replication or synthesis. These pieces of evidence may indicate that *honeysuckle* has potential antiviral activity for SARS-CoV-2. However, research on the direct mechanism against SARS-CoV-2 lacks, and further study of the molecular mechanisms is warranted.

Scutellariae (Huang Qin, 黄芩)

Scutellariae is a perennial herb, and its roots have medicinal value. The main chemical compounds responsible for biological activity are flavonoids, such as baicalin, wogonin (70); others include terpenoids, volatile oil, and trace elements, having an antipyretic, anti-inflammatory, and antimicrobial effect (71). Rao et al. (72) developed methods to obtain extracts from multiple *Scutellaria* species and screened compounds for the SARS-CoV M^{pro} inhibitor; baicalin and its modified derivatives might become effective drugs for the treatment of SARS-CoV. By comparing the structural differences and inhibitory activities of baicalin and oroxylin, the general structural formula of flavonoids with the inhibitory activity of the SARS-CoV M^{pro} was derived, and the flavonoid mother nucleus has adjacent free hydroxyl groups. They then found that the flavonoids with a high content of adjacent free hydroxyl, *scutellarin*, *marigold*, *myricetin*, and *Robinia pseudoacacia*, can also inhibit the SARS-CoV M^{pro}.

To explore the anti-SARS-CoV activity of baicalin, baicalein, and wogonin in *Scutellaria radix in vitro*, Wu et al. (73) added three kinds of flavonoid solutions with different concentrations to MDCK cell line infected by influenza virus FM1 (Asian strain). With ribavirin as the positive control, the antiviral activity of three flavonoids was detected by MTT assay, a colorimetry assay to assess cell metabolic activity. They showed that baicalin had a significant increase in cell survival and antiviral activity than the other two flavonoids, suggesting that baicalin is the main effective compound of *Scutellaria* against the influenza virus. Xu et al. (74) used the influenza FM1 strain-induced pneumonia mouse model to study the mode of action for *Scutellaria*, and found that *Scutellaria* could inhibit the overexpression of proinflammatory cytokines and stimulate antiviral factor IFN- γ .

Glycyrrhizae radix (Gan Cao, 甘草)

Glycyrrhizae radix is the dry root and rhizome of *Glycyrrhiza uralensis*, *Glycyrrhiza inflata*, or *Glycyrrhiza glabra*.

It is a typical Chinese herbal medicine and has a flat nature and sweet taste. Its active components, glycyrrhizic acid (GA), glycyrrhetic acid, glycyrrhiza polysaccharide, have strong antiviral effects (75). The effects of *Glycyrrhiza* on COVID-19 include downregulating proinflammatory cytokines, reducing intracellular reactive oxygen species accumulation, and excessive production of airway exudates (76). ACE2 is a critical host cellular receptor for SARS-CoV-2 spike protein binding to enter the host cell (77). GA may down-regulate the ACE2 expression by inhibiting an enzyme 11-beta-hydroxysteroid dehydrogenase induced high aldosterone levels (78), suggesting that GA may have potential prophylaxis of SARS-CoV-2 infections. In addition, the glycyrrhizin or its metabolite GA has been shown *in vitro* to have a direct antiviral effect on SARS-related coronaviruses (79). Glycyrrhizin also has an anti-inflammatory effect through reducing expression of TLR4 signaling (80), which may have implications for therapeutics of COVID-19 and other pathogen-associated infections in heart, lung, and other systems (78, 80, 81). Literature mining and molecular docking analysis showed that glycyrrhizin and other compounds such as *saiko-saponin* (E, B1, D, F, B2, C2) and 6-(3-oxoindolin-2-ylidene) indolo [2,1-b] quinazolinone (板蓝根) have optimal binding with the SARS-CoV-2 M^{pro}, with the lowest binding energy (less than -38) (82), suggesting they may inhibit the viral replications.

Armeniacae Semen (Ku Xing Ren, 苦杏仁)

Armeniacae Semen is the dry and mature seeds of *Prunus armeniaca* L. var *ansu* Maxim, *Prunus sibirica* L., *Prunus mandshurica* L., *Prunus armeniaca* L. According to TCM, it belongs to the lung and intestine meridians and functions moistening the lung, relieving cough and asthma, moistening the intestines, and defecating. *Armeniacae Semen* mainly contains fatty acids, protein, polyphenols, and mineral elements, in which the main chemical components are bitter almond oil, amygdalin, amygdaline, amygdalinase (83). Modern pharmacological studies have shown that almond has anti-inflammatory and analgesic, antioxidant, antitussive and anti-asthmatic, immune regulation, and antitumor (84). In a network pharmacology study, the amygdalin was selected as the optimal candidate for potential inhibitors of host cellular receptor ACE2 and viral proteins M^{pro} and RdRP. Therefore, it is expected to be a potential anti-coronavirus drug candidate (85).

Sophorae flavescentis radix (Ku Shen, 苦参)

Sophorae flavescentis radix is the dried root of the leguminous plant *Sophora flavescent* Ait. Matrine is one of the main active compounds with the highest content in *Sophora flavescent* and has a wide range of antiviral effects. Zhao et al. (86) showed *in vitro* that matrine inhibited porcine reproductive and respiratory syndrome virus (PRRSV) by directly killing or interfering with virus replication. Matrine-type alkaloids had an anti-HBV effect in HepG2.2.15 cells, in which sophoridine showed a more potent anti-HBV effect than other matrine-type alkaloids, likely through the sophoridine-mediated reduction of p38 MAPK and TRAF6 levels (87).

Sun et al. (88) from the China Academy of Chinese Medical Sciences established a mouse model combining the human coronavirus pneumonia with cold-dampness pestilence attacking the lung for the first time. The therapeutic effect of matrine sodium chloride injection was evaluated based on immune regulation and inflammation damage. Intraperitoneal injection of the high-dose (36.67 mL·kg⁻¹·d⁻¹) and low-dose (18.33 mL·kg⁻¹·d⁻¹) of matrine sodium chloride injection significantly improved the pathological damage of lung tissue and reduced lung index. The lung index inhibition rates were 86.86% and 76.53% for high- and low-dose injection. The production of IL6, IL10, TNF-α, IFN-γ, and the viral load in lung tissue were significantly reduced; the percentage of CD4⁺T cells, CD8⁺T cells, and B cells in peripheral blood increased. These suggest that the matrine sodium chloride injection may have an evident therapeutic effect, and its mechanism is likely related to the inhibition of virus replication, regulation of immune function, and inhibition of inflammatory factor release.

Yang et al. (89) performed a retrospective analysis of 40 confirmed cases with COVID-19 admitted to an infectious disease hospital from January 30, 2020, to March 21, 2020. All patients (5 severe, one mild, and 34 moderate cases) were treated with matrine sodium chloride injection combined with other Chinese and Western medicines. More than 50% of patients had lung CT lesion absorption after treatment, and the clinical symptoms were significantly improved, and no patients died. The mean time for negative conversion of viral nucleic acid testing was 16.6 days, and the mean hospital stay was 25.9 days.

Kurarione, another flavonoid isolated from the roots of *Sophora flavescent*, has been shown to have a potent antioxidant and immunosuppressive effect (90). Min et al. (34) examined the antiviral impact of kurarinone against infection with the human coronavirus, HCoV-OC43, and found that kurarinone inhibited HCoV-OC43 infection in human lung fibroblast MRC-5 cells in a dose-dependent manner and acted at an early stage of virus infection by impairing the virus-induced autophagic flux to inhibit viral replication.

Curcuma longa (Jiang Huang, 姜黄)

Curcuma longa is the dried rhizome of *Curcuma longa* L., which affects breaking blood and promoting Qi and inducing menstruation to relieve pain. It can be used for various symptoms of blood stasis and Qi stagnation. Curcumin is an effective compound of *Curcuma longa*, which has attracted much attention because of its anti-tumor, anti-inflammatory, immune regulation, antioxidant, anti-virus, and other biological functions (91, 92). Of note, curcumin has been demonstrated to inhibit the proliferation of various viruses such as dengue virus (93), hepatitis-B-virus (94), and Zika virus (95). A recent study (96) showed that curcumin inhibited the proliferation and survival of α-coronavirus in multiple ways. In a porcine transmissible gastroenteritis virus (TGEV) model, curcumin was shown to strongly inhibit TGEV proliferation and viral protein expression in a dose-dependent manner and could kill TGEV directly in a dose, temperature, and time-

dependent manner. Time curve measurement shows that curcumin mainly acts on the early stage of virus replication in various action modes. It can kill the virus directly before the virus infects the cell or combines with the virus envelope to inactivate the virus and alter the cell metabolism to prevent the virus from entering.

CONCLUSION

This article introduces several Chinese medicines and herbs for potential application in preventing or treating COVID-19. These shreds of evidence are primarily from *in vitro* and *silico* studies or animal models. While observed results seemed promising, formal clinical investigations are necessary for obtaining solid evidence from human patients to establish clinical guidance. Patient-based clinical and molecular studies may provide a more rigorous approach to investigating the mechanism underlying the efficacy and provide precision therapeutics.

ABBREVIATIONS

3CL^{pro}, 3C-like protease.
ACE2, angiotensin-converting enzyme 2.
CHA, Chlorogenic acid.
COVID-19, coronavirus infection disease 2019.
DTPNCP, Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia.
FUs, functional units.
HBV, hepatitis B virus.
HPXLD, Huopu Xialing Decoction.
LSXTMYD, Leishi Xuantou Moyuan decoction.
M^{pro}, the main protease.
MXSGD, Ma Xing Shi Gan decoction.
MXYG, Maxingyigan decoction.
NHC, National Health Commission.
JH-G, Jinhua Qinggan granule.
HSBDF, Huashi Baidu formula.
LH-C, Lianhua Qingwen capsule.
PRRSV, porcine reproductive and respiratory syndrome virus.
QJWJD, Qianjinweijing decoction.
QFPDD, Qingfei Paidu decoction.
RdRP, RNA-dependent RNA polymerase.
RSV, respiratory syncytial virus.
SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.
SATCM, State Administration of Traditional Chinese Medicine.
SGMHD, She Gan Ma Huang decoction.
TCM, traditional Chinese medicine.
TCWM, Traditional Chinese-Western medicine.
TGEV, transmissible gastroenteritis virus.
TLDZXF, Tingli Dazao Xiefei decoction.
WLS, Wu Ling San.
XBCQD, Xuanbai Chengqi Decoction.
XBJ, Xuebijing.
XCHD, Xiao Chai Hu Decoction.
YQD, Yinqiao decoction.

CONFLICT OF INTEREST

The authors declare no conflict of interest regarding the publication of this article.

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Author information

The Third Affiliated Hospital, Beijing University of Chinese Medicine, Beijing, China (Yehong Tian, Xiaowei Qiu, Xin Jiang, Jinchang Huang); Global Clinical and Translational Research Institute, Bethesda, MD, USA (Fengyu Zhang); Beijing Huilongguan Hospital & Peking University Huilongguan Clinical Medical Institute, Beijing, China (Fengyu Zhang); Institute of Acupuncture and Moxibustion, Shaanxi University of Chinese Medicine, Shaanxi, China (Yehong Tian)

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