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Review Article

Chinese herbal injections for coronavirus disease 2019 (COVID-19): A narrative review

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ABSTRACT

Background: The outbreak of Coronavirus disease 2019 (COVID-19) has caused more than 180 million infections and 3.9 million deaths. To date, emerging clinical evidence has shown the synergetic benefits of Chinese herbal injections in treating this contagious respiratory disease. This review aims to summarize and analyze the efficacy and safety of Chinese herbal injections in the therapy of COVID-19.

Methods: The literature from 3 electronic databases, PubMed, CNKI, and Web of Science, were searched using the search terms "COVID-19", "SARS-CoV-2", "traditional Chinese medicine", "herb", "herbal", and "injection". Then the identified articles were comprehensively evaluated.

Results: Limited data demonstrated that Chinese herbal injections could significantly improve the clinical outcomes of COVID-19 patients, especially in combination with conventional treatment strategies. The benefits of which were mainly associated with the relief of symptoms, prevention of secondary infection, regulation of inflammation and immune function. There was also evidence showing the inhibitory effects on SARS-CoV-2 replication *in vitro*. Nevertheless, available real-world data suggested the increased risk of adverse event. Furthermore, the defects of existing researches and the insights for discovering novel antiviral drugs were prospectively discussed.

Conclusion: Evidence-based advances revealed that Chinese herbal injections such as XueBiJing injection and ShenMai injection, exerted potent effects against COVID-19. Further laboratory researches and clinical evaluation are needed to gather scientific evidence on the efficacy and safety.

1. Introduction

Coronavirus disease 2019 (COVID-19), an emerging infectious disease caused by SARS (Severe Acute Respiratory Syndrome) Coronavirus 2 (SARS-CoV-2), has led to more than 180 million infections and 3.9 million deaths till now (https://www.who.int/emergencies/diseases/novel-coronavirus-2019).[1–3] The World Health Organization (WHO) declared that COVID-19 was a public health emergency of international concern on 30 January 2020, and became a pandemic on 11 March 2020.

Patients infected with COVID-19 often had a wide range of pathological symptoms from common features such as fever, cough, and fatigue, to severe illness likely acute respiratory distress syndrome (ARDS) due to the cytokine storm, septic shock, and eventually develop multi-organ failure and death.[4–7] Till now, there was still a very high mortality rate in fighting against COVID-19. The situation to prevent and control COVID-19 is still grim all over the world. However, since the outbreak of COVID-19, China has taken timely interventions to curb its spread, and also achieved rapid and effective containment of COVID-19 infection by early detection, early quarantine, and early treatment.[4,8,9] The treatment strategies for COVID-19 were mainly focused on the relief of

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Table 1
The herbal sources of Chinese herbal injections.

Chinese herbal injections	Herbal sources (Chinese name)	Refs.
XueBiJing injection	Carthamus tinctorius L. (Honghua), Paeonia lactiflora Pall. (Chishao), Ligusticum chuanxiong Hort. (Chuanxiong), Salvia miltiorrhiza Bunge (Danshen), Angelica sinensis (Oliv.) Diels (Danggui)	[28]
XiYanPing injection	Andrographis paniculata (Burm. f.) Nees (Chuanxinlian)	[41]
ReDuNing injection	Artemisia carvifolia Buch.-Ham. ex Roxb. (Qinghao), Lonicera japonica Thunb. (Jinyinhua), Gardenia jasminoides Ellis (Zhizi)	[42]
TanReQing injection	Scutellaria baicalensis Georgi (Huangqin), Selenarctos thibetanus (G. Cuvier) (Xiongdanfen), Naemorhedus goral Hardwicke (Shanyangjiao), Lonicera japonica Thunb. (Jinyinhua), Forsythia suspensa (Thunb.) Vahl. (Lianqiao)	[53]
XingNaoJing injection	Moschus moschiferus L. (Shexiang), Gardenia jasminoides Ellis (Zhizi), Curcuma aromatica Salisb. (Yujin), Dryobalanops aromatica Gaertn.f. (Bingpian)	[55]
ShenFu injection	Radix Ginseng Rubra (Hongshen), Radix Aconiti Lateralis Preparata (Fuzi)	[67]
ShengMai injection	Panax ginseng C. A. Mey. (Renshen), Ophiopogon japonicus (Linn. f.) Ker-Gawl. (Maidong), Schisandra chinensis (Turcz.) Baill. (Wuweizi)	[74]
ShenMai injection	Radix Ginseng Rubra (Hongshen), Ophiopogon japonicus (Linn. f.) Ker-Gawl. (Maidong)	[79]
Shuanghuanglian injection	Lonicera japonica Thunb. (Jinyinhua), Scutellaria baicalensis Georgi (Huangqin), Forsythia suspense (Thunb.) Vahl (Lianqiao)	[82]
YanHuNing injection	Andrographis paniculata (Burm. f.) Nees (Chuanxinlian)	[39]
Baicalin injection	Scutellaria baicalensis Georgi (Huangqin)	[82]
Arctigenin injection	Arctium lappa L. (Niubangzi)	[83]
Protocatechuic aldehyde injection	Salvia miltiorrhiza Bunge (Danshen)	[84]

symptoms, reduction of complications, and recovery of injured organs, or based on the clinical experience in treating SARS and influenza. Among which the protocol using traditional Chinese medicine, such as Chinese herbal injections, played indispensable benefits for China's successful battle with COVID-19.[4,10]

For thousands of years, traditional Chinese medicine has played a vital role in facing the prevalence of severe plague as well as developing novel antiviral drugs.[11–14] Growing evidence had showed the benefits of Chinese herbal injections in the treatment of COVID-19. We hope that these updated data will serve as an important complement against COVID-19 and provide valuable lessons for the overall advancement of human medicine.

2. Methods

The literature from 3 electronic databases, PubMed, CNKI, and Web of Science, were searched using the search terms "COVID-19", "SARS-CoV-2", "traditional Chinese medicine", "herb", "herbal", and "injection".

3. Current status of COVID-19 treatment

The rapid development of COVID-19 pandemic has been a vital threat to global health. To conquer such severe epidemic of SARS-CoV-2, great efforts have been made by scientists and researchers to analyze the genetic sequence, epidemiological, laboratory test results, clinical characteristics, as well as novel treatment strategies and clinical outcomes. Screening for existing drugs to see their antiviral potential against SARS-CoV-2 is an important option.

A large amount of research data had showed that COVID-19 involved multiple targets and could lead to multiple organ dysfunction, which brought enormous challenge to manage COVID-19 patients, especially to the severe cases.[15–18] Therefore, the use of multipotent agents for multi-target intervention should be an effective way for drug selection. To fight against the sudden plague, the National Medical Products Administration (NMPA) of China approved several Chinese herbal injections such as ReDuNing injection, TanReQing injection and XingNaoJing injection in clinical use, as showed in **Table 1**.[19] Here we summarized and analyzed recent advances of Chinese herbal injections in fighting COVID-19 to excavate effective strategies for restraining this viral prevalence.

4. Chinese herbal injections for COVID-19

4.1. XueBiJing injection

XueBiJing injection is originally a five-herb medicine for antibiotic-based sepsis care.[20,21] It also has a potential immunoregulation ability, as well as effects on bacteriostasis, anti-endotoxin, and anti-inflammation.[22] Recent clinical randomized controlled trial showed that XueBiJing injection was effective and safe in the treatment of acute exacerbation of chronic obstructive pulmonary disease (AECOPD).[23] It showed protective potential against lung injury in patients who undergo cardiopulmonary bypass surgery due to downregulation of inflammatory mediators, reduction in neutrophil infiltration, and upregulation of IL-10.[24] Moreover, XueBiJing injection (Tianjin Chase Sun Pharmaceutical Co., Tianjin, China) with the dosage of 100 mL (0.1 g/mL) in normal saline 100 mL (every 12 h, intravenous drip) versus placebo could also significantly improve the primary endpoint of the pneumonia severity index, the secondary clinical outcomes of mortality, and the duration of mechanical ventilation and intensive care unit (ICU) stay in critically ill patients with severe pneumonia.[25] These clinical data have revealed its effects in improving severe lung diseases.

XueBiJing injection was also officially recommended to treat severe COVID-19 cases by NMPA of China.[19] There were evidence-based data showing its efficacy in treating COVID-19. As elucidated in a retrospective case-control study, XueBiJing injection combined with routine treatment showed significant improvements in IL-6 level and body temperature in COVID-19 patients.[26] Besides, more cases of improved computerized tomography (CT) imaging results and shorter time taken to produce a negative nucleic acid test were observed in XueBiJing injection group, though the differences were not statistically significant. The network pharmacology and molecular docking studies revealed that quercetin, luteolin, and apigenin in XueBiJing injection could affect the overlapping targets tumor necrosis factor (TNF), epidermal growth factor receptor (EGFR), mitogen-activated protein kinase 1 (MAPK1), Caspase-3, signal transducer and activator of transcription 3 (STAT3), and interleukin (IL)-6, while anhydrosafflor yellow *B* (AHSYB), salvianolic acid *B* (SAB), and rutin could combine with its crucial proteins, and thus played anti-inflammatory, antiviral, and immune roles to treat COVID-19.[27,28]

Ma et al. showed that XueBiJing injection could protect cells from SARS-CoV-2-induced cell death and inhibit the average size

and plaque number in vitro, which was attributed to the inhibition of virus proliferation, and the upregulated expression of pro-inflammatory cytokines.[29] Another clinical study showed that XueBiJing injection could effectively increased white blood cell count and lymphocyte count, and decreased the levels of C-reactive protein (CRP) and erythrocyte sedimentation rate, which were more obviously improved in XueBiJing injection 100 mL group than that of 50 mL group.[30] As elucidated in a prospective randomized controlled trial, the treatment with routine medication plus Xuebijing injection significantly suppressed the secretion of IL-6, IL-8, and TNF-α, reduced the CRP level, and increased the lymphocyte level.[31] After 14 days of treatment, the rate of mechanical ventilation and septic shock, the proportion of patients became critically ill, the duration of main clinical symptoms, and the length of ICU hospitalization stay were significantly improved.[31] Nevertheless, Xuebijing injection treatment did not significantly reduce the 28-day mortality.[31] In a centralized monitoring study of 31913 patients using XueBiJing injection, 0.3% of them had adverse reactions which were stated in the drug instructions such as skin pruritus, rash, chest tightness, and fever, but were disappeared or relieved after drug withdrawal or symptomatic treatment.[29]

These findings suggested that the routine treatment in combination with XueBiJing injection is beneficial to improve the clinical outcomes of COVID-19 patients. Though the investigations of XueBiJing injection in COVID-19 were few, its clinical benefits were encouraging. Further evaluation is still needed to clarify its pharmacological mechanisms and toxicological evidence.

4.2. XiYanPing injection

XiYanPing injection (medicinal composition: andrographolide sulfonate) is one of the products of Chinese herbal injections used against acute respiratory infections, tonsillitis, chronic obstructive pulmonary disease (COPD), influenza, hand-foot-mouth disease (a common childhood infectious disease caused by a variety of enteroviruses), bronchiolitis, mumps, herpangina, infectious mononucleosis, and psychosis.[32,33] Andrographolide had been demonstrated to ameliorate lung injury via suppression of NLRP3 inflammasome activation, NF-κB signaling, and pyroptosis.[34–36] It was also effective to enhance cytotoxic T cells, NK cells, phagocytosis, and antibody-dependent cell-mediated cytotoxicity.[32,37] The network meta-analysis showed that XiYanPing injection in combination with Western medicine obviously reduced the time for the disappearance of lung rales in patients with community-acquired pneumonia compared to Western medicine alone.[38] Panraksa et al. showed that andrographolide, the medicinal composition of XiYanPing injection, had significant anti-dengue virus (DENV) activity by reducing the levels of cellular infection and virus output in HepG2 and HeLa, respectively.[39] These properties form the foundation of XiYanPing injection to regulate immune function and restrain virus-induced pathogenesis. Rajagopal et al. found that andrographolide was significantly binding with the active site of SARS-CoV-2 main protease when compared to hydroxychloroquine and nelfinavir, which may produce significant activity.[40]

In severe COVID-19 patients, XiYanPing injection (100 mg, iv, bid), XueBiJing injection (100 mL, iv, bid), and ShenMai injection (60 mL, iv, qd) combined with Huashi Baidu granule (137 g, po, bid) could shorten the median time of SARS-CoV-2 RNA clearance, showed more widely lung lesion opacity absorption, and decreased CRP, erythrocyte sedimentation rate, serum ferritin, and myoglobin, with no case of death, transferred to ICU, or received invasive mechanical ventilation.[41] XiYanPing injection was officially recommended to treat severe COVID-19 cases by NMPA of China.[19] Further evidence is needed to clarify its benefits and safety for COVID-19 treatment.

4.3. ReDuNing injection

ReDuNing injection is a patented Chinese medicine used for common cold and lung infection in clinic.[42] It could alleviate paraquat-induced lung injury by increasing superoxide dismutase activity, and suppressing myeloperoxidase activity, wet/dry ratio, and the amounts of total leukocytes, neutrophils, and malondialdehyde.[42] A randomized, double-blind, double-dummy, oseltamivir controlled clinical trial showed that the effect of ReDuNing injection (Jiangsu Kangyuan Pharmaceutical Co., LTD., China) with the dosage of 20 mL in normal saline 250 mL (once a day, intravenous drip) was not worse than oseltamivir on the alleviation of influenza symptoms such as fever, aversion to cold, sore throat, and nasal obstruction score in the treatment of seasonal influenza.[43] The combination of ReDuNing injection with ribavirin was effective for severe H1N1 treatment due to the synergistic effect of antiviral and antiinflammation.[44] Besides, ReDuNing injection combined with loratadine treatment showed better results than acetaminophen alone in the reduction of DENV threats by decreasing the concentrations of cytokines and interleukin parameters including TNF-α, IFN-γ, TGF-β1, IL-4, IL-6, and IL-12.[45] Another study showed that atomized ReDuNing showed significantly decreased mortality, prolonged survival time, and reduced cough rate, in influenza virus PR8-infected mice.[46]

In Vero E6 cells, ReDuNing injection could regulate the proteases including angiotensin-converting enzyme 2 (ACE2), Mpro, and PLP in COVID-19, and affected cytokine levels, reduced inflammation, and displayed antipyretic activity by regulating the expression of MAPKs, PKC, and p65 NF-κB.[47] Recently, a randomized, open-labeled, multicenter, controlled trial from 12 general hospitals of China was published.[48] The study reported that the symptom resolution rate was higher, and the median time to resolution of the clinical symptoms, nucleic acid test turning negative, hospital stay, and time to defervescence was shorter with Reduning injection (20 mL/day for 14 days) treatment than the routine treatment only.[48]

These data reveal the lung protection, anti-inflammation, and antiviral effects of ReDuNing injection, which supported its use in COVID-19 therapy. In addition, its atomized inhalation method may increase the efficacy and reduce the safety risks associated with injections. Further improvement of the dosage form of ReDuNing are also attractive.

4.4. TanReQing injection

TanReQing injection is a classical compound herbal recipe commonly used to treat lung diseases and serious influenza in China.[49,50] It has been proven to have effects of clearing heat, eliminating phlegm, detoxification, reducing inflammation, and alleviating cough.[50] Li and partners had found that TanReQing injection (Kaibao Pharmacy Co., LTD., China) with the dosage of 20 mL (once a day, intravenous infusion) could improved the Chinese medical signs and symptoms in the patients with AECOPD via decreasing plasma levels of IL-8 and neutrophil elastase, and then could improve response to airway inflammation and mucus hypersecretion.[49] A meta-analysis shown that TanReQing injection combined with conventional therapy (levofloxacin, cefuroxime, or cefoperazone sodium and sulbactam sodium) was superior to conventional therapy in terms of higher cure rate in treating acute exacerbation of chronic bronchitis patients.[51] As a therapy for acute bronchitis, TanReQing injection also had potentially beneficial effect in reducing the time to resolution of fever, cough, crackles, and absorption of shadows on X-ray.[52]

It was also reported that TanReQing injection combined with Western medicine was the most advantageous in shortening the time for defervescence and the average hospitalization time in

treating community-acquired pneumonia.[38] A retrospective cohort study showed that TanReQing had significant reduction in the negative conversion time and duration of fecal nucleic acid with increased level of immune indicator $CD3^+$ T cells in patients with mild and moderate COVID-19, but it was the oral dosage form.[53] Recently, Huang et al.[54] demonstrated that Tanreqing injection combined with α-interferon significantly improved symptoms, blocked deterioration, and promoted rehabilitation by increasing the symptom score and effective rate three, five and seven days after the treatment in patients with confirmed and suspected COVID-19. The clinical data for TanReQing injection use in COVID-19 patients are eagerly awaited.

4.5. XingNaoJing injection

XingNaoJing injection, an another well-known traditional Chinese patent medicine, is derived from An-Gong-Niu-Huang pill widely used for cerebral ischemia injury with anti-inflammatory action.[55] Low quality evidence showed that patients with viral encephalitis used combination of XingNaoJing injection and conventional treatment, had higher cured rate and less mortality rate with shorter average difference of time for fever, conscious, or convulsive recovery.[56] In treating acute infective fever patients, XingNaoJing injection (Wuxi Jimin Credible Shanhe Pharmaceutical Co., LTD., China) with the dosage of 20 mL in normal saline (or 5% glucose) 250 mL (once or twice a day, intravenous drip) could depress the fever induced by viral infection effectively and rapidly, reduce the course of treatment, and interfere the course of fever induced by viral infection.[57] Ribavirin aerosol assisted XingNaoJing injection combined with vidarabine therapy in children with hand-foot-mouth disease had significantly increased cure rate compared with ribavirin.[58]

A network pharmacological analysis and mechanism prediction study showed that the core compounds of XingNaoJing injection could regulate the inflammatory response, oxidative stress, angiogenesis, and other processes to improve the neurological damage caused by SARS-CoV-2, inhibit virus replication, and prevent infection of the host cell by binding with ACE2 (one receptor of SARS-CoV-2).[59] These data support the potential antiviral effects of XingNaoJing injection, but few direct evidence have shown its role in COVID-19 patients.

4.6. ShenFu injection

ShenFu injection is mainly used to treat heart failure, shock, arrhythmia, acute myocardial infarction, dilated cardiomyopathy, viral myocarditis, pulmonary heart disease, and other cardiovascular diseases.[60] It could improve the survival rate of endotoxin shock in a rat model of acute lung injury through inhibiting the HMGB1-NF-κB pathway and preventing cytokine storm.[61] In addition, ShenFu injection (Ya'an San-jiu Pharmaceutical Co., LTD., Sichuan, China) with the dosage of 100 mL (12 h a day, intravenous drip) also significantly improved hemodynamic indices such as cardiac index, global end diastolic volume index, mean arterial pressure, and heart rate, in early volume resuscitation treated septic shock patients.[62] Combined metabolic pathway enrichment and topology analyze indicated that the mechanisms of ShenFu injection against coxsackievirus B3-induced acute viral myocarditis might be due to modulating the disordered homeostasis of sphingolipid metabolism, arachidonic acid metabolism, glycerophospholipid metabolism, tryptophan metabolism, and TCA cycle.[63] In vivo work showed that ShenFu injection not only inhibited NF-κB activity, but also reduced TNF-α and IL-6 expressions in systemic inflammatory response syndrome rats.[64] In patients with nonsmall cell lung cancer, adjuvant treatment with ShenFu injection was confirmed to enhance the quality of life, ameliorate the chemotherapy-induced gastrointestinal toxicities, and bone marrow suppression, and thus improve patients compliance to chemotherapy.[65] These studies suggest the benefits of ShenFu injection in modulating cytokine release, antiviral activity, and lung protection.

Network pharmacology study showed that Shenfu injection may treat COVID-19 combined with acute kidney injury through combating cytokine storm, improving body immunity, resisting oxidative stress, and reducing hypoxia-reoxygenation injury.[66] A recent structured study protocol for a randomized controlled trial is expected to recruit 150 severe or critical COVID-19 patients by receiving 100 mL ShenFu injection twice a day for seven consecutive days, the primary endpoint of which is a composite of newly developed or exacerbated organ dysfunction.[67] It may provide reliable clinical evidence of ShenFu injection for COVID-19 treatment soon.

4.7. ShengMai injection

ShengMai injection is a classical Chinese herbal injections officially recorded in Chinese Pharmacopoeia (version 2015) and has long been used to treat heart failure.[68] ShengMai injection could protect against ischemia-reperfusion injury by modulating myocardial energy metabolism to improve cardiac efficiency via multiple myocardial energy metabolism pathways including stimulating glucose metabolism and restraining fatty acid metabolism.[69] On the basis of Western medicine routine treatment, ShengMai injection (Suzhong Pharmaceutical Group Co. LTD., Jiangsu, China) with the dosage of 50 mL (twice a day, intravenous injection) could significantly improve hemodynamic indexes, and enhance cardiac function of the patients with cardiac insufficiency after cardiopulmonary resuscitation.[70]

It plus supportive therapy also showed a significant effect on the abnormal levels of creatine phosphokinase, lactate dehydrogenase, and myocardial enzyme creatine kinase isoenzyme MB, and also improved the quality of life in the treatment of viral myocarditis.[71] Recent meta-analysis showed that ShengMai injection in combination with Western medicine for treating COPD could achieve a better effect than Western medicine alone in improving the clinical total effective rate, lung function, blood gas index, immunoglobulin levels, CRP levels and the lung rale disappearance time, with significantly reduced COPD assessment test score and average hospitalization time, as well as improved dyspnea index.[72] ShengMai injection add-on therapy also appeared to be more effective in improving quality of life and reducing chemotherapy-induced adverse effects in non-small cell lung cancer patients.[73] The network pharmacology and molecular docking analysis showed that a total of 22 active compounds and 16 common targets with COVID-19 including ACE were obtained from Shengmai injection, which exerts the role of anti-inflammatory, immunomodulatory, anti-shock, and blood oxygen saturation increase.[74] These representative studies indicate potential benefits of multi-organ protection of ShengMai injection. But further evidence is anticipated in patients with COVID-19.

4.8. ShenMai injection

ShenMai injection is mainly used for the treatment of atherosclerotic coronary heart disease and viral myocarditis as well as an organ protector.[75–77] It could decrease inflammatory cytokine levels and suppress the expression of IKK-α and iNOS, and also restore heart dysfunction in doxorubicin-induced acute cardiotoxicity mice.[76] ShenMai injection also alleviated the decrease of key enzymes and transporters, reduced the utilization of metabolic

Table 2
Studies of Chinese herbal injections in COVID-19 patients.

Chinese herbal injections	Clinical/biological effects	Study type	References
XueBiJing injection	Normalized body temperature, IL-6 ↓, improved CT imaging results, negative time for nucleic acid testing ↓	Retrospective case-control study	[26]
	Pneumonia severity index and score ↓, oxygenation index ↑, PaCO2 ↑, lymphocyte ↑, TNF-α ↓, IP-10 ↓, MIP-1β ↓, RANTES ↓	Single-center retrospective study	[29]
	White blood cell ↑, lymphocyte ↑, CRP ↓, erythrocyte sedimentation rate ↓	Randomized controlled study	[30]
	IL-6 ↓, IL-8 ↓, TNF-α ↓, CRP ↓, lymphocyte ↑, mechanical ventilation rate ↓, septic shock rate ↓, disease deterioration ↓, ICU hospitalization stay ↓	Prospective randomized controlled trial	[31]
XiYanPing injection	Time of SARS-CoV-2 RNA clearance ↓, lung lesion opacity absorbed ↑, CRP ↓, erythrocyte sedimentation rate ↓, serum ferritin ↓, myoglobin ↓	Retrospective case series study	[41]
ReDuNing injection	Symptom resolution rate ↑, time to clinical symptoms resolution ↓, time to nucleic acid test turning negative ↓, hospital stay ↓, time to defervescence ↓	Randomized, open-labeled, multicenter, controlled study	[48]
TanReQing injection	Pathological symptoms ↓, disease deterioration ↓, effective rate ↑	Single-center retrospective study	[54]
ShenMai injection	SARS-CoV-2 RNA clearance time ↓, CRP level ↓, erythrocyte sedimentation rate ↓, serum ferritin ↓, myoglobin ↓, improvement rate of chest CT manifestations ↑	Retrospective case series study	[41]

CRP, C-reactive protein; CT, computerized tomography; ICU, intensive care unit; IL, interleukin; IP-10, interferon-inducible protein-10; MIP-1β, macrophage inflammatory protein 1β; $PaCO_2$, partial pressure of carbon dioxide in arterial blood; RANTES, regulated on activation normal T-cell expressed and secreted chemokine; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; TNF, tumor necrosis factor.

substrates, prevented aberrant apoptosis, and restored the depleted ATP following ischemia-reperfusion rats.[75] ShenMai injection (Qing Chunbao Pharmaceutical Co., LTD., Hangzhou, China) with the dosage of 100 mL (once a day, intravenous drip) combined with continuous ShenMai capsule (Xinbang Pharmaceutical Co., LTD., Guizhou, China) treatment had been reported to improve the exercise tolerance in the early stage of the cardiac rehabilitation for patients received coronary artery bypass grafting.[78] ShenMai injection also protected lung injury induced by intestinal ischemia/reperfusion through inhibiting the activation of p38MAPK, improving the ratio of Bcl-2 to Bax, and reducing lung apoptosis.[77] To explore the possible targets and mechanism of ShenMai injection for COVID-19 and myocarditis, 17 targets were screened, which mainly regulated immune function through potential targets such as BCL2, MAPK3, IL-6, and regulate signal pathways such as TNF and IL-17, revealing the multi-level, multi-target, and multi-channel mechanism of shenmai injection.[79]

Besides, ShenMai injection was widely used in clinical pediatrics for conditions such as viral myocarditis, pneumonia, neonatal hypoxic ischemic encephalopathy, neonatal scleroderma, diarrhea, and other diseases.[80] Recent report showed that Shenmai injection (60 mL, iv, qd) combined with other Chinese medicine could decreased the median time of SARS-CoV-2 RNA clearance, CRP level, erythrocyte sedimentation rate, serum ferritin, and myoglobin when compared with that of conventional western therapy alone.[41] Besides, Shenmai injection treatment also increased the improvement rate of chest CT manifestations.[41] Further studies on COVID-19 will provide more detailed clinical reference for ShenMai injection.

4.9. Other Chinese herbal injections

Shuanghuanglian preparation is a Chinese traditional patent medicine used for the treatment of acute respiratory tract infections since 1973 in China.[81] Recent study showed that Shuanghuanglian injection or its bioactive components (baicalin and baicalein) dose-dependently inhibited SARS-CoV-2 3CLpro as well as the replication of SARS-CoV-2 in Vero E6 cells, revealing potential effects on COVID-19.[81] YanHuNing injection, extracted from the plant Andrographis paniculata (Burm. f.) Nees (Chuanxinlian), was clinically used for viral pneumonia and viral upper respiratory tract infection in China.[38] In the treatment of community-acquired pneumonia, YanHuNing injection combined with Western medicine had obvious superiorities in the clinical effective rate, time for the disappearance of cough and level of CRP compared to Western medicine alone.[38] Baicalin is the major component found in Scutellaria baicalensis Georgi (Huangqin), and exhibits anti-viral activity.[82] In vivo, the endothelial protective effect of baicalin injection form under hyperglycemia condition was shown to down-regulate reactive oxygen species and inflammation. Arctigenin is a phenylpropanoid dibenzylbutyrolactone lignan extracted from the traditional herb Arctium lappa L. (Niubangzi) with anti-viral and anti-inflammatory effects.[83] Its injection could significantly inhibit porcine circovirus type 2 proliferation in the lungs, spleens, and inguinal lymph nodes with an effect similar to ribavirin.[83] Protocatechuic aldehyde is derived from the Chinese herb Salvia miltiorrhiza Bunge (Danshen) and its injected intraperitoneally efficiently inhibited duck hepatitis B virus replication in vivo.[84] These injections owning lung protection or/and antiviral actions, and warrant further investigations as potential therapeutic agents for SARS-CoV-2 infection.

5. Future perspectives and concluding remarks

Respiratory disease is one of leading cause of death all over the world, and has brought great challenges to human health.[85,86] COVID-19 is a novel identified viral infectious diseases characterized by varying degrees of respiratory symptoms. It has significantly impacted human health and slowed down the development of the world. COVID-19 pandemic has resulted in the need for urgent development of drugs and the conduction of clinical trials to fight the outbreak.

The discovery of potent drugs on the market becomes the advantageous way to dig antiviral drugs for COVID-19 treatment. Traditional Chinese medicine is one of the most important parts of medical practice which exerts wider action spectrum in treating human diseases.[12] Chinese herbal injections were recommended for the treatment of COVID-19 after the outbreak of COVID-19 officially in China.[87] Up to now, cumulative clinical research progress has demonstrated the synergistic benefits of Chinese herbal injections in combination with Western medicine on reducing the time of SARS-CoV-2 RNA clearance, increasing the improvement rate of chest CT manifestations, as well as improving multiple other clinical outcomes (**Table 2**). The pharmacological mechanisms mainly attributed to the antiviral activity, regulation of immunity, and inhibition of inflammatory storm.

Nevertheless, there are limitations and challenges on the agenda to conquer COVID-19. First of all, though the Chinese herbal injections were recommended to be used in COVID-19, such as in China, the data were mostly from the clinical trials on other dis-

eases or the experience on the pharmacological mechanisms of the included herbs. In addition, the existing clinical evidence on COVID-19 was mostly from retrospective studies and combination of multiple therapeutic agents. Therefore, their benefits and mechanisms against COVID-19 should be further illustrated by the well-designed fundamental studies and clinical trials.

Second, there are network pharmacology analysis showing that Chinese herbal injections may prevent COVID-19 by regulating several attractive targets and signaling pathways. Nevertheless, the clinical effects and safety of the herbal injections or its components on COVID-19 are rare to be studied with observational studies or clinical trials. Besides, the network pharmacology assessments seem redundant as they mainly identify largely the same candidate molecules and genetic targets. The same molecules being repeatedly found in different Chinese herbal injections may not indicate a genuine result, but rather due to non-specific interactions by particular molecules. Furthermore, those studies may not provide the common and consistent English names, Latin binomials, and the Chinese language name (in both Roman characters and Chinese characters) of each herbal component. Besides, the selection of some candidate herbs was based on the qi and damp-heat, which were non-scientific concepts in modern medical science. Further researches are urgently needed to screen effective antiviral agents and identify the importance of different targets, which will substantially promote the development of COVID-19 treatment.

Third, though Chinese herbal injections combined with traditional strategies could improve the clinical outcomes during antiviral therapy, the evidence is weak due to the small sample of included patients and the lack of the classification of COVID-19 severity. Fourth, the published clinical trials were mainly from China, the data from different countries will further enrich the clinical treatment experience. However, there were no foreign approval of these herbal injection medications yet, thus these agents would be hardly used in countries other than China. The international approval of these herbal injections or some of them to be used in clinical, by international cooperation and exchange of medication experience, should be encouraged to deal with such severe viral prevalence.

Great attention had been paid to the application of antiviral agents for COVID-19 treatment in the real-world, there were also growing concerns related to the toxicity or inevitable adverse reactions of Chinese herbal injections. It was reported that Chinese herbal injections might be involved in varying degrees of adverse drug reactions due to contraindications, irregular medication of elders and children, as well as improper choice of solvent.[30,88,89] The complex components of Chinese herbal injections may indicates more risk of drug-drug interactions. The clinical pharmacists should play crucial role in the guarantee of medication safety and provide available pharmaceutical care to improve the rational use of Chinese herbal injections.

6. Conclusion

This review has introduced the updated evidence of Chinese herbal injections in organ protection and COVID-19 treatment. Besides, the insights for further antiviral drug development are provided. To offer scientific references for the international health systems, further extensive evidence was still needed to support existing therapies of Chinese herbal injections for COVID-19.

Author contributions

Conceptualization: LDK. Formal investigation: LHS, LCL, LL. Data analysis: LHS, LCL, LL. Writing original draft: LCL, XBZ, MG. Writing review and editing: ZHZ, LJZ, CLS, YY, MG. All authors read and approved the final version of this manuscript.

Conflict of interests

The authors declare that they have no conflicts of interest.

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Ethical statement

Not applicable.

Data availability

This review used published literature as sources and the data are included in this article.

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