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•Review•

Recent advances of traditional Chinese medicine on the prevention and treatment of COVID-19

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[ABSTRACT] Coronavirus disease-2019 (COVID-19) is a new highly infectious disease caused by a novel coronavirus. Recently, the number of new cases infected pneumonia in the world continues to increase, which has aroused great concern from the international community. At present, there are no small-molecule specific anti-viral drugs for the treatment. The high mortality rate seriously threatens human health. Traditional Chinese medicine (TCM) is a unique health resource in China. The combination of TCM and Western medicine has played a positive and important role in combating COVID-19 in China. In this review, through literature mining and analysis, it was found that TCM has the potential to prevent and treat the COVID-19. Then, the network pharmacological studies demonstrated that TCM played roles of anti-virus, anti-inflammation and immunoregulation in the management of COVID-19 *via* multiple components acting on multiple targets and multiple pathways. Finally, clinical researches also confirmed the beneficial effects of TCM on the treatment of patients. This review may provide meaningful and useful information on further drug development of COVID-19 and other viral infectious diseases.

[KEY WORDS] Novel coronavirus pneumonia; Prescription of traditional Chinese medicine; Single Chinese herb; Active ingredients of traditional Chinese medicine; Viral infection

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Introduction

Since December 2019, a novel coronavirus (named “severe acute respiratory syndrome coronavirus 2”, SARS-CoV-2) has erupted around the world. On March 12, 2020, the World Health Organization has officially declared coronavirus disease 2019 (COVID-19) as a global pandemic. According to the epidemic real-time data statistics, as of July 12, a total of 85 522 people have been diagnosed in China, with 4 648 deaths, and 12 756 366 people have been diagnosed abroad, with 562 975 deaths. The study found that the process of infection caused by SARS-CoV-2 is closely related to angiotensin-converting enzyme 2 (ACE2). The spike protein (S protein) of SARS-CoV-2 enters human cells through binding ACE2 receptor and then drives the virus to reproduce and attack new cells^[1,2]. The clinical symptoms of COVID-19 patients mainly include fever, cough, fatigue, myalgia, diarrhea and complications of multiple organ damage^[3,4]. Currently, specific small-molecule anti-viral drugs

have not been available for the treatment. The COVID-19 is still a serious threat to human health, and effective prevention and treatment are crucial in this situation.

COVID-19 has been considered to belong to the category of “epidemic disease” in traditional Chinese medicine. The cause is that the human body feels the external toxin and pathogen. The pathogenesis is mainly “wet, heat, poison, stasis, deficiency” and the lesions are mainly in the spleen, lungs and stomach^[5,6]. Chinese herbalists have accumulated valuable experience and played an essential role in the fight against the disease for thousands of years^[7]. The General Office of the National Health and Health Commission of China and the Office of the State Administration of Traditional Chinese Medicine (TCM) issued “Diagnosis and Treatment of Pneumonia Caused by Novel Coronavirus Infection”, which reflects the characteristics and advantages of TCM in the prevention and treatment of pneumonia^[8,9]. Early intervention of TCM has effectively alleviated the development of the disease. The combination of TCM and Western medicine reduced adverse events and other complications induced by glucocorticoid, anti-biotic and anti-viral treatments^[10].

At present, the published reviews on the research progress of TCM in the prevention and treatment of COVID-19 mainly focus on the following aspects: summarize the under-

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standing of the etiology, pathogenesis and syndrome characteristics of COVID-19 by the theory of TCM [11], review the clinical application [12,13] or explore the rules of TCM [14] and new natural compounds with anti-SARS-CoV-2 activity [15]. Whereas, our present review mainly focuses on the usage of TCM prescriptions, its extracts and active ingredients through literature mining analysis, experimental research and clinical application analysis. What's more, we summarized the names, compositions, specific action pathways and characteristics of TCM which have potential anti-SARS-CoV-2 activity in the form of tables and pictures. This study might provide some support or new clues for the prevention and treatment of COVID-19 and other viral infectious diseases.

Literature analysis of the potential efficacy of the TCM for the prevention and treatment of COVID-19

It is found that TCM has anti-virus, anti-inflammation, immunoregulation functions through literature mining and analysis. Hence, they are considered to have the potential to treat COVID-19. The Office of the State Administration of TCM has selected Qingfei Paidu Decoction (QFPD) as a general prescription for the prevention and treatment of COVID-19. This prescription is based on Mahuang Decoction (MHD), Xiaochaihu Tang (XCHT), Wuling Powder (WLP), Shegan Mahuang Decoction (SGMHD) and Ju-Zhi-Jiang Decoction (JZJD), and is suitable for patients with mild symptoms, critical and convalescent patients. QFPD could play a rapid antiviral effect and shorten the treatment time of patients through the TCM theoretical analysis combined with the initial clinical observations [16]. It was believed that Huashibaidu prescription (HSBD) could regulate the *qi* of the lung through the literature analysis. Hence, it was recommended for the treatment of severe pneumonia through multiple targets [17]. Symptoms of *qi* deficiency often appear in convalescent patients. Shengmai San (SMS) is a classic prescription that can be applied to the diseases of *qi* and *yin*-deficiency and also has pharmacological effects such as anti-fibrosis. What's more, it could accelerate the recovery time of patients and prevent the occurrence of sequelae [18]. At the same time, literature demonstrated that the Yiqi Fumai Lyophilized Injection (YQFM) could treat COVID-19 with cardiovascular disease [19]. Additionally, Xuebijing injection (XBJ) contains Chinese herbal extracts of *Carthamus tinctorial*, *Radix Paeoniae Rubra*, *Ligusticum chuanxiong Hort*, and *Salvia*. According to the current clinical basis of XBJ, it has in-depth research value in the treatment of severe pneumonia patients [20]. In the trial version seven, Huoxiang Zhengqi Powder (HXZQ), Jinhua Qinggan Granules (JHQG), Lianhua Qingwen Capsules (LHQW), Shufeng Jiedu Capsules (SFJD), Reduning Injection (RDN) and other Chinese patent medicines were also mentioned. HXZQ is a frequently-used damp-clearing prescription and has efficacy of reliving superficialities, dispersing dampness, and harmonizing stomach. Combined with HXZQ, it not only has anti-bacterial and anti-vir-

al effects but also could regulate gastrointestinal function and the body's immunity. It is considered that it has the potential to treat COVID-19 with the digestive tract as the first symptom [21]. At the same time, it is found that HXSQ, JHQW, LHQW and SFJD have a potential role to improve the symptoms of fever, fatigue and gastrointestinal discomfort in COVID-19 patients during medical observation period discovered by searching and analyzing Chinese and English databases [22]. Another report showed that the volatile oil of TCM has the functions of anti-tussive, expectorant, anti-viral and immune regulation. Chinese herbal medicines such as *Agastache rugosa*, tangerine peel, *Atractylodes Rhizoma* and *Atractylodes macrocephala* may be potentially beneficial for the treatment of COVID-19 [23]. Besides, compound glycyrrhizin has anti-viral, anti-inflammatory and hormone-like effects. Literature analysis found that it could reduce the incidence of a late hormone withdrawal syndrome in patients with COVID-19 [24]. Through the analysis of the above literature, the potential feasibility of the TCM prescriptions for the treatment of COVID-19 was elucidated. More experimental and clinical research are still needed to prove the safety and effectiveness of single Chinese herbs and natural active ingredients.

Network pharmacological studies of the TCM for the prevention and treatment of COVID-19

Amounts of network pharmacological studies have suggested that the possible mechanisms of TCM for the treatment of COVID-19 include anti-virus, anti-inflammation, immunoregulation, and others through multiple components acting on multiple targets and multiply pathways. The relevant studies were summarized as follows.

Anti-virus pathways

Existing researches showed that SARS-CoV-2 3CL hydrolase (Mpro) is vital for the replication of SARS-CoV-2 and plays an indispensable role in the proteolytic processing of viral polyproteins (essential proteins for viral replication and function) [25]. Therefore, TCM with the capacity to target Mpro or ACE2 holds the promise to prevent the infection of SARS-CoV-2. Through network pharmacology and molecular docking methods, Mpro and ACE2 were used as targets to determine the binding energy, and it was found that HXZQ [26], JHQG [27], LHQW [28], XBJ [29], Tanreqing Injection (TRQ) [30] had a good binding force and exerted a therapeutic role by inhibiting virus entry and replication. Other literature indicated that the phosphatidylinositol-3 kinase (PI3K)/total protein kinase B (AKT) pathway could regulate various types of angiogenesis and cell proliferation, which was related to the replication, assembly and pathogenicity of SARS-CoV-2 [31]. Network pharmacological analysis indicated that HXZQ [32], QingfeiPaidu Decoction (QFPD) [33] and XBJ [29,34] could also play a therapeutic role by regulating PI3K-Akt to inhibit virus invasion and replication.

Moreover, some natural products such as baicalin, hes-

peridin, glycyrrhizin and nicotinamide could play an antiviral effect of COVID-19 through the ACE2 receptor^[35].

Anti-inflammation pathways

The “cytokine storm” is one of the main pathogenic mechanisms of COVID-19^[36]. It means that the body will produce and release a variety of inflammatory factors after being infected, such as Tumor Necrosis Factor- α (TNF- α), Interleukin-1 (IL-1), Interleukin-6 (IL-6), Interleukin-12 (IL-12) and Interferon- α (IFN- α), Interferon- β (IFN- β). The release of “inflammatory” cytokines will induce new cytokine production and release which will in turn cause cell and organ damage. Therefore, improving the body’s cytokine storm and oxidative stress status presumably could reduce the severity and mortality rate. HXZQ^[37], JHOG^[38,39], Shengjiang powder (SJS)^[40], HSB^[41], QFPD^[42,43], Moxing Shigan Decoction (MXSG)^[44], XCHD^[45], XBJ^[46], RDN^[47], Xiyanning Injection (XYP)^[35], a TCM composition^[48] containing *Agastache rugosa*, *Chrysanthemi Indici Flos*, *Moslae Herba*, and *Artemisia annua* could act on TNF, MAPK, NF- κ B such signaling pathways to suppress the elevated cytokine levels. Additionally, vitamin C, curcumin and glycyrrhizin exerted a potential protective effect on SARS-CoV-2 infection by preventing cytokine storms^[49]. It is worth noting that the arachidonic acid (AA) metabolic pathway can mediate the production of multiple inflammatory factors^[50], such as monocyte chemoattractant protein-1 (MCP-1), TNF, IL and IFN *etc.* Therefore, it is considered to be closely related to the occurrence and development of inflammation. Cluster model analysis revealed that HXZQ, JHOG, LHQW, QFPD, XBJ, RDN and TRQ have potential inhibitory effects on AA pathway to treat pneumonia caused by SARS-CoV-2 through alleviating “cytokine storm”^[51].

Immunoregulation pathways

Virus-infected cells release signals to recruit and activate immune cells. These immune cells secrete a variety of cytokines and chemokines to recruit more immune cells to the lesion site. However, this can lead to excessive immune responses and damage the body. TCM could alleviate excessive immune responses to restore normal physiological functions of the body. Based on the network pharmacology, LHQW was reported to have 55 common targets with SARS-CoV-2^[52], which were enriched in immunity (mainly the innate immune pathway induced by type I interferon) and inflammation (TNF, IL-17, Toll-like receptors)^[28]. The significant pathways of TRQ included Th17 cell differentiation pathway, MAPK, EGFR and TNF signaling pathway, which could alleviate excessive immune response, inhibit activated cytokines and eliminate inflammation^[30]. A TCM prescription containing *Tripterygium Wilfordii* could regulate immunity against viruses^[53].

Others

To date, other potential targets and pathways of Chinese

herbal medicine prescriptions were predicted through network pharmacological analysis. For example, the increase of creatine kinase (CK) and lactate dehydrogenase (LDH) is related to lung cell damage and systemic symptoms^[3], thus, HXZQ^[54] may treat COVID-19 by reducing CK and LDH levels to improve oxygenation index and systemic symptoms. The potential signal pathways of Shufeng Jiedu Capsule (SFJD) for preventing and treating COVID-19 were IL-17, HIF-1 and Toll-like receptors, and the targets were IL-10, IL-6, prostaglandin-endoperoxide synthase (PTGS), Glycogen synthase-3 (GSK3B), transcription activator-1 (STAT-1)^[55,56]. HSB^[41] showed 49 potential targets for COVID-19 including IL-6, TNF, MAPK1, MAPK8 and IL-1 β ^[57]. Shengmai injection (SMI) treated COVID-19 through caspase (CASP), PTGS, NOS and other signaling pathways^[58], and YQFM played a role in the early therapy of COVID-19 by inhibiting microvessel exudation, invigorating *qi*, astringing and solidifying^[59], it was also helpful for acute and severe cardiopulmonary patients^[19].

There is a myriad of literature on network pharmacology analysis of single Chinese herbs and natural products. For example, *Agastache rugosa* showed 16 active ingredients and 10 related targets, which were acted on Toll, MAPK and other signaling pathways^[60]. Seven effective compounds, forty-nine corresponding targets and thirty-one pathways were screened from *Rhubarb* and illustrated that it could treat COVID-19 through multi-component and multi-target^[61]. Moreover, Quercetin and (-)-Epigallocatechin gallate and other 12 TCM monomers showed similar affinity to IL-6, ACE2 and SARS-CoV-2 as recommended medicines, and thus played a vital role in the treatment of COVID-19^[62].

Additionally, there are still many TCM prescriptions in the experimental research stage. For example, A centralizing and lung-saving medicine composition might reverse the progression of COVID-19 and reduce the deterioration rate^[63]. There are some TCM sachets^[64], nebulizers^[65], fumigation preparations^[66] and aromatherapy^[67] with disinfection function under research which could help stop the spread of the epidemic.

Clinical study of the TCM for the prevention and treatment of COVID-19

A randomized clinical trial on LHQW of 284 COVID-19 patients is useful to confirm the beneficial effect of TCM. In the trial, 142 patients were given LHQW for 14 consecutive days (4 capsules, three times a day), the results manifested that the recovery rate (91.5% vs 82.4%), the improvement rate (83.8% vs 64.1%) and the clinical cure rate (78.9% vs 66.2%) of the treatment group were higher than the control group, with no serious adverse reactions^[68]. This trial showed that LHQW could be considered to ameliorate clinical symptoms of COVID-19. Furthermore, 22 065 subjects were given HXZQ and Jinhao Jierye Granules (JHJR) for preventive administration for 5 consecutive days with the protection rate of the intervention group was 91.8%, which indicated that

they provided effective protection for the community^[69]. Then, 123 COVID-19 patients were additionally given JHQG for 5 consecutive days^[70], and the disappearance rate of fever symptoms in the treatment group was about 85.0%, which was 27.0% higher than that in the control group, and the Hamilton anxiety score decreased significantly in the treatment group (6.37) than in the control group (4.88), indicating that JHQG could effectively relieve the symptoms and anxiety of patients. A retrospective analysis of 68 patients found that the effective rate (91.2%) of the treatment group combined with the SFJD for 7 days was dramatically higher than that of the control group (70.6%, $P < 0.05$), and no adverse events occurred^[71]. The analysis revealed that the combined use of SFJD was effective and safe.

On the other hand, 214 confirmed cases in four pilot provinces were treated with QFPD (3 days as a course of treatment), which showed a total effective rate of more than 90%^[72]. Among these, 98 patients were treated for 9 days and the total effective rate was 92.09%, of which the recovery rate was 41.13%, the significant efficiency was 26.92%, and the effective rate was 24.04%^[73]. These trials provided strong evidence for the clinical application of QFPD. Furthermore, 80 patients were given MXSG for 5–7 days, the effective rate was 95%^[74]. Forty patients were given MXSG combined with conventional treatment for 7 days, and the disappearance rates of the main clinical symptoms (fever, fatigue, cough) were 96.8% (30/31), 100.0% (28/28) and 81.8% (18/22) respectively^[75]. It showed that the combined use of MXSG could effectively improve the symptoms of patients. And 44 patients were given XBJ treatment for 7 consecutive days, which indicated that the overall effectiveness of the intervention group (68.2%) was slightly higher than that of the control group (50.0%), and no serious adverse reactions occurred^[76]. The clinical trials showed that XBJ also had a certain therapeutic effect. Nevertheless, there are dozens of TCM are conducting clinical trials at present, certain specific Chinese medicines are also incorporated (Table 3).

Discussion and Summary

TCM has accumulated thousands of years' experience in the treatment of pandemic and endemic diseases. Literature analysis has indicated the potential feasibility of QFJD, HSBD, XBJ and other Chinese herbal preparations to treat COVID-19. Although its safety and effectiveness need to be clarified, it can provide a theoretical basis for subsequent experiments and clinical research. At present, most of the TCM preparations have been explored their potential mechanisms and targets by network pharmacology and molecular docking. The results showed that some TCM preparations could inhibit virus entry and replication *in vivo* by binding to Mpro and ACE2 targets, such as HXZQ, JHQG, LHQW, XBJ, TRQ and XYP. Also, they could play an anti-inflammatory role by acting on TNF, MAPK, Toll, NF- κ B, IL-17, HIF-1 and other signaling pathways, which embodied the unique characteristics and advantages in the improvement of multiple organ

damage. HSBD might act on the RIG-1/IRF/IFN- β , NF- κ B/TNF-1L signaling pathways to reduce the release of inflammatory factors to alleviate lung injury. LHQW possibly modulated AGE/RAG1/ROS, PI3K/AKT and other signaling pathways to reduce kidney damage caused by inflammation. QFPD, MXSG potentially reduced the heart and brain damage linked with Caspase-3/Bcl-2, TNF-R1/MAPK and other signaling pathways. Compared with Western medicine treatment, TCM has its unique treatment concepts and principles. For example, QFPD is a common and core prescription in the prevention and treatment of COVID-19, and patients can be treated based on syndrome differentiation individually following the TCM theory^[77]. Also, HXZQ could not only act on the main pathogenesis of “wet poison”, but also restore the *qi* mechanism to improve patients' symptoms^[37]. LHQW is a representative Chinese drug for treating viral infection-related diseases and has a broad clinical application basis^[78]. XBJ showed no immunosuppressive effects in the treatment of clinical severe and critical COVID-19 patients. What's more, the incidence of adverse reactions was low and the clinical effect was remarkable^[47]. These findings have shown that compounds and preparations of TCM have their unique characteristics and potential advantages in treating COVID-19 (Fig. 1) and also provided a clinical basis for the follow-up TCM treatment plan and new drug development. Among them, the TCM composition and the action pathways for the prevention and treatment of the COVID-19 are shown in Table 1.

Moreover, literature mining and big data analysis showed that some natural products including quercetin, puerarin, porphyrin, quercetin-7-O- β -D-glucoside and patchouli alcohol in Patchouli have a better combination with Mpro, which could reduce virus replication. Seven effective compounds such as β -sitosterol and aloe-emodin in Rhubarb purportedly had the anti-viral, anti-inflammatory, anti-oxidative stress, anti-apoptosis and regulation of body immunity effects through multiple pathways and multiple targets. Meanwhile, the active ingredients of TCM such as glycyrrhizin and baicalin could inhibit the virus activity. For the experimental study of single Chinese herbs or extracts, Rhubarb, *Scutellaria baicalensis* Geor, *Coptidis Rhizoma*, *Flos Loniceræ*, *Folium isatidis* and other antipyretics or antidotes have a certain therapeutic effect, which could provide a reference for the new combination of TCM. For example, there are some TCM sachets and sprays which have applied for patents to help reduce the prevalence and mortality. The effective components and action pathways of single TCM and natural active components for anti-SARS-CoV-2 are shown in Table 2.

The above summary suggests that TCM and its preparations showed the unique superiority of a full course of treatment and a full range of treatments. Early prevention and early treatment could reduce the mortality rate, improve symptoms, decrease the occurrence of complications and recurrence, which showed broad application prospects. The network pharmacological analysis indicates that the possible

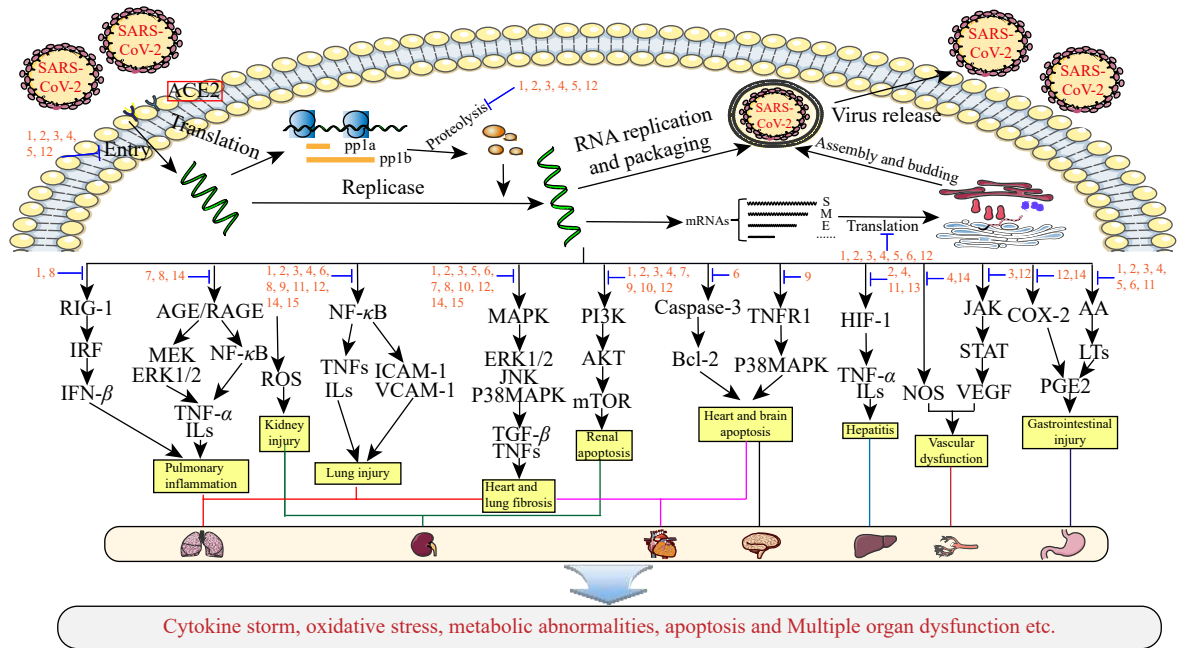


Fig. 1 Schematic diagram of possible action pathways of traditional Chinese medicine for prevention and treatment of COVID-19. 1 HXZQ; 2 JHQG; 3 LHQW; 4 XBJ; 5 TRQ; 6 QFPD; 7 SJS; 8 HSB; 9 MXSG; 10 XCHT; 11 RDN; 12 XYP; 13 SFJD; 14 SMI; 15 YQFM

Table 1 Chinese herbal compound for anti-COVID-19

Name	Composition	Treatment approach	References
Huoxiang Zhengqi Oral Liquid (HXZQ)	Patchouli oil, Perilla leaf oil, <i>Angelica dahurica</i> , <i>Atractylodes lancea</i> , <i>Magnolia officinalis</i> (processing with Zingiber officinale), Born Pinellia ternate, Indian Bread, Tangerine peel, Arecae Pericarpium, Licorice extract	Inhibit virus entry and replication; inhibit inflammation, and cytokine storm	[26, 37]
Jinhua Qinggan Granules (JHQG)	Flos Lonicerae, Gypsum Fibrosum, honey-prepared Herba Ephedrae, Armeniaca Semen Amarum, <i>Scutellaria baicalensis</i> Geor, Fructus Forsythiae, Fritillaria thunbergii, <i>Anemarrhena asphodeloides</i> , <i>Arctium lappa</i> , Artemisia annua, Herba Menthae, Radix Glycyrrhizae	Inhibit virus, regulate immunity, inflammation and apoptosis	[27, 38, 39]
Lianhua Qingwen Prescription (LHQW)	Fructus Forsythiae, Flos Lonicerae, <i>Ephedra sinica</i> , Armeniaca Semen Amarum, Gypsum Fibrosum, Isatis indigotica, Dryopteris crassirhizoma, Houttuynia cordata, Pogostemon cablin, Rheum palmatum, Rhodiola rosea, <i>Mentha haplocalyx</i> , Radix Glycyrrhizae	Inhibit viral replication and reduce cytokine release from host cells; regulate immunity	[28]
Shengjiang powder (SJS)	<i>Bombyx batryticat</i> , <i>Cryptotympana pustulata ecdysis</i> , <i>Curcuma longa</i> , <i>Rheum palmatum</i>	Intervene in virus invasion and suppress stress response	[40]
Huashibaidu prescription(HSBD)	Raw ephedra, Armeniaca Semen Amarum, Gypsum Fibrosum, Radix Glycyrrhizae, Agastache rugosa, Magnoliae Officinalis Cortex, <i>Atractylodes lancea</i> , <i>Amomum tsao-ko</i> , Rhizoma Pinellinae Praeparata, <i>Poria cocos</i> , Rhubarb, Astragali radix, <i>Draba nemorosa</i> , <i>Paeonia lactiflora</i>	Inhibit inflammation, improve cytokine storm	[41, 57]
Qingfei Paidu Decoction(QFPD)	Ephedrae Herba, Fried Glycyrrhiza uralensis, Armeniaca Semen Amarum, Gypsum Fibrosum, Cinnamomun cassia, Alismaorientalein, <i>Polyporus umbellatus</i> , <i>Atractylodes macrocephala</i> , <i>Poria cocos</i> , Bupleuri Radix, <i>Scutellaria baicalensis</i> Geor, ginger-processed Pinelliaternata, Ginger, Aster tararicus, Farfarae Flos, Belamcandae Rhizoma, Asari Radix et Rhizoma, Dioscorea opposite Rhizoma, Aurantii Fructus Immaturus, Tangerine peel, Agastache rugosa	Inhibit virus invasion and replication; inhibit inflammation, improve cytokine stormy	[33, 42]

Continued

Name	Composition	Treatment approach	References
Maxing Shigan Decoction(MXSG)	Ephedra, Armeniaceae Semen Amarum, Gypsum Fibrosum, Radix Glycyrrhizae	Inhibit inflammation; improve cytokine stormy and pulmonary interstitial edema	[44]
Xiaochaihu Tang(XCHT)	Bupleuri Radix, <i>Scutellaria baicalensis</i> Geor, Pinellia ternate, Ginger, Ginseng Radix et Rhizoma, Radix Glycyrrhizae, Jujube	Inhibit inflammation;Reduce the temperature	[45]
Xuebijing injection(XBJ)	<i>Carthamus tinctorius</i> , Radix Paeoniae Rubra, <i>Ligusticum chuanxiong</i> Hort, <i>Salvia miltiorrhiza</i> , <i>Angelica sinensis</i>	Inhibit viral invasion and replication; inhibit inflammation	[29, 46, 47]
Reduning Injection(RDN)	Artemisia annua, Flos Lonicerae, Gardeniae Fructus	Inhibit inflammation	[47]
Shengmai injection(SMI)	Ginseng Radix et Rhizoma, Ophiopogonis Radix, <i>Schisandra chinensis</i>	Inhibit inflammation and oxidative stress; improve pulmonary fibrosis and microcirculation; regulate immune function	[58]
Yiqi Fumai Lyophilized Injection(YQFM)	Red ginseng, Ophiopogonis Radix, <i>Schisandra chinensis</i>	Inhibit inflammation and oxidative stress; improve pulmonary fibrosis and microcirculation; regulate immune function	[59]
Tanreqing Injection(TRQ)	<i>Scutellaria baicalensis</i> Geor, Bear Bile Powder, Caprae hircus cornu, Flos Lonicerae, Fructus Forsythiae	Inhibit inflammation;regulate immunity	[30]
Xiyanping Injection(XYP)	<i>Andrographis Herba</i>	Inhibit inflammation;regulate immunity	[35]
Shufeng Jiedu Capsules(SFJD)	<i>Polygonum cuspidatum</i> , Fructus Forsythiae, <i>Isatis indigotica</i> , Bupleuri Radix, Herba Patriniae, Verbenae Herba, Rhizoma Phragmitis, Radix Glycyrrhizae	Inhibit inflammation and virus infection;	[55, 56]
Chinese medicine composition	Agastache rugosa, Chrysanthemi Indici Flos, Moslae Herba, Artemisia annua	Inhibit inflammation and virus infection;	[49]
Chinese medicine aromatherapy air disinfectant	<i>Artemisia argyi</i> , <i>Isatidis Radix</i> , <i>Folium Isatidis</i> , <i>Dryopteris crassirhizoma</i> Nakai, Flos Lonicerae, Fructus Forsythiae, <i>Scutellaria baicalensis</i> Geor, Herba Menthae, <i>Atractylodis Rhizoma</i> , <i>Aquilariae Lignum Resinatum</i> , <i>Viola yedoensis</i> , Chrysanthemi Indici Flos, <i>Houttuynia cordata</i>	Sterilization, inbit virus	[67]
Chinese medicine composition sachet	<i>Syzygium aromaticum</i> , <i>Platycladus orientalis</i> , <i>Angelica dahurica</i> , Flos Lonicerae, Agastache rugosa, <i>Eupatorium fortune</i> , <i>Cinnamomum cassia</i> , Camphor, <i>Saposhnikovia divaricata</i> , <i>Isatidis Radix</i> , <i>Artemisia argyi</i> , borneol	Inhibit bacterial and viral infection	[64]
Chinese medicine atomizing agent	Qingai Oil, Artemisia annua oil, Ginseng oil, Astragalus oil, <i>Rhodiola rosea</i> , Grape seed oil	Inhibit virus; improve immunity;improve fatigue	[65]
Chinese medicine fumigating bath preparation	Semiliquidambar Cathayesis, <i>Cinnamomum camphora</i> roots, <i>Cymbopogon citratus</i> , <i>Scutellaria barbata</i> , <i>Polygonum Cuspidatum</i> , <i>Caulis Lonicerae</i> , Fructus Forsythiae, Dandelion, Bupleuri Radix, <i>Cynanchi Stauntonii</i> , Armeniaceae Semen Amarum, Aster tararicus, Rhizoma Phragmitis, <i>Gaultheria yunnanensis</i>	Promote metabolism and circulation;improve human immunity; inhibit virus	[66]
Fuzheng lung-saving medicine composition	<i>Aconitum carmichaelii</i> , Dried ginger, Honey-fried Licorice, Flos Lonicerae, Spina Gleditsiae, <i>Ipomoea cairica</i> , <i>Pogostemon cablin</i> , Tangerine peel	Inhibit inflammation and virus infection;Improve body immunity	[63]
Chinese medicine composition	<i>Tripterygium wilfordii</i> , Gypsum Fibrosum, <i>Dioscorea opposite</i> Rhizoma, <i>Scrophulariae Radix</i> , Fructus Forsythiae, <i>Cryptotympana pustulata</i> ecdysis, <i>Codonopsis pilosula</i> , Herba Menthae, <i>Arctium lappa</i> , Haematitum	Inhibit virus; regulate immunity; reduce temperature	[53]

mechanisms of TCM were anti-virus, anti-inflammation, immune regulation, and organ protection through multiple components acting on multiple targets or pathways for the treatment of COVID-19. Different TCM may act on the same or

similar targets or pathways. Nevertheless, the current understanding of the mechanisms of TCM is mainly produced from virtual simulation through molecular docking and network pharmacology analysis. To confirm these predicted mechan-

Table 2 Single traditional Chinese medicine and natural active ingredients for anti-COVID-19

Name	Composition	Treatment approach	References
Pogostemonis Herb	Quercetin, Genkwanin, Quercetin-7-O- β -D-glucoside <i>ect.</i>	Act on Toll, NOD, RIG-I-like receptor signaling pathway, MAPK signaling pathway, T cell receptor signaling pathway	[60]
Rhubarb	β -sitosterol, Aloe-emodin, Rhein, Catechins	Inhibit virus; Inhibit inflammation, oxidative stress, and apoptosis; regulate body immunity	[61]
Natural active ingredients	Baicalin, Hesperidin, Glycyrrhizin, Nicotinamide	Bind with ACE2 enzyme, act on ACE2 receptor to prevent and treat pneumonia	[35]
	Quercetin, (-)-Epigallocatechin gallate	Act on IL-6 target protein, inhibit cytokine storm	[62]
Natural active compound combinations	Vitamin C, Curcumin, Glycyrrhizin	Regulate immune response; inhibit CoV infection; suppresses excessive inflammation and prevents cytokine storms	[49]

Table 3 The representative clinical trials of TCM for anti-COVID-19

No.	Registration number	Scientific title	Date of Registration
1	ChiCTR2000029434	A randomized, open-label, blank controlled trial for Lian-Hua Qing-Wen Capsule/Granule in the treatment of 2019-nCoV pneumonia (novel coronavirus pneumonia, NCP)	2020-02-01
2	ChiCTR2000033133	A randomized, open-label, blank-controlled, multicenter trial for Shuang-Huang-Lian oral solution in the treatment of novel coronavirus pneumonia (COVID-19)	2020-05-21
3	ChiCTR2000035633	Clinical study of safety, tolerance, and pharmacokinetics of nebulizer (INF-K + anti-inflammatory factor TFF2) in healthy volunteers and exploration of PK/PD fitting modeling in clinical trials of Novel Coronavirus Pneumonia (COVID-19) patients	2020-08-15
4	ChiCTR2000032767	A Medical Records Based Study for Clinical Efficacy and Safety of “clear lung detoxification soup” in the treatment of Novel Coronavirus Pneumonia (COVID-19)	2020-05-09
5	ChiCTR2000032205	A multicenter randomized, double-blind, placebo-controlled trial for Sheng-Mai-Yin for improvement of the pulmonary heart function related symptoms of convalescence patients of new coronavirus pneumonia	2020-04-23
6	ChiCTR2000030545	Efficacy and safety of honeysuckle oral liquid in the treatment of novel coronavirus pneumonia (COVID-19): a multicenter, randomized, controlled, open clinical trial	2020-03-16
7	ChiCTR2000030388	Efficacy and safety of Xue-Bi-Jing injection in the treatment of severe cases of novel coronavirus pneumonia (COVID-19)	2020-03-01

isms, well designed *in vitro* cell experiments and *in vivo* animal studies based on these predictions are needed. Furthermore, many clinical studies and statistical methods still have deficiencies such as limited sample size and nonstandard trial methods *etc.* Therefore, the safety and effectiveness of TCM used in the treatment of emerging coronavirus infections should be carefully evaluated. The mechanism of action to improve COVID-19 remained not clear. It is worth to further evaluate its clinical efficacy for COVID-19, explore its potential molecular mechanism to improve multiple organ damage and identify their substance basis of the possible drug by multiple modern science and technology. Hopefully, the present study will provide reference and lay the foundation for the further development of new drugs for the prevention and treatment of COVID-19 and other viral infectious diseases.

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