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REVIEW

Practice and principle of traditional Chinese medicine for the prevention and treatment of COVID-19

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Abstract **Traditional Chinese medicine (TCM) has played an important role in the prevention and treatment of coronavirus disease 2019 (COVID-19) epidemic in China. The integration of Chinese and Western medicine is an important feature of Chinese COVID-19 prevention and treatment. According to a series of evidence-based studies, TCM can reduce the infection rate of severe acute respiratory syndrome coronavirus 2 in high-risk groups. For patients with mild and moderate forms of COVID-19, TCM can relieve the related signs and symptoms, shorten the period of nucleic-acid negative conversion, and reduce conversion rate to the severe form of the disease. For COVID-19 patients with severe and critical illnesses, TCM can improve inflammatory indicators and blood oxygen saturation, shorten the hospital stay, and reduce the mortality rate. During recovery, TCM can improve patients' symptoms, promote organ function recovery, boost the quality of patients' life, and reduce the nucleic-acid repositive conversion rate. A series of mechanism research studies revealed that capability of TCM to treat COVID-19 through antiviral and anti-inflammatory effects, immune regulation, and protection of organ function via a multicomponent, multitarget, and multipathway approach.**

Keywords traditional Chinese medicine; COVID-19; SARS-CoV-2; clinical evidence-based study; mechanism; integrated traditional Chinese and Western medicine

Introduction

The highly contagious coronavirus disease 2019 (COVID-19) refers to the acute respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Before determining the mechanism by which traditional Chinese medicine (TCM) recognizes and treats COVID-19, we must first gain insights into fundamental concepts regarding how TCM recognizes and treats exogenous heat diseases. In TCM, the Six Qi (wind, cold, heat, dampness, dryness, and fire) refer to the six different types of extreme or erratic climate fluctuations in nature, and they are considered the main causes of exogenous diseases. According to Wu Youke, a Ming dynasty physician, Li Qi was the direct cause of the plague; this belief is similar to the current knowledge indicating that infectious diseases are caused by pathogenic microorganisms. The adjustment of the state of the body's internal environment is the core concept and an important feature of TCM in the treatment of diseases. The treatment of COVID-19 through TCM is based on the therapeutic rule that combines patient symptoms and the core pathogenesis of the disease and its treatment in accordance with the corresponding prescriptions to support the body's positive energy (Qi), change the environment in which the virus multiplies, and eliminate cold, dampness, and other negative conditions Qi rather than directly kill the virus. This principle explains the feasibility of applying TCM in the treatment of COVID-19 patients at an early stage and in response to the different strains of SARS-CoV-2. Practitioners of TCM also believe in the close relation of water metabolism to several internal organs, such as the lungs, spleen, and kidneys. In addition, the impairment of water metabolism

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can result in some pathological consequences, such as phlegm and dampness. Meanwhile, many symptoms, including heavy body, diarrhea, sticky stools, and other pathological conditions, such as pulmonary edema and mucus-like exudates, that were found in the autopsy of COVID-19 patients can be attributed to the manifestation of dampness or phlegm in TCM [1].

According to statistical data, China has had more than 300 major outbreaks of infectious diseases, and a rich experience of using Chinese medicine to control the plague has been accessible. Based on the experience of ancient Chinese physicians in the treatment of infectious diseases, according to the TCM characteristics (cold and dampness syndrome) of the COVID-19 epidemic, and the patients' symptoms, environment, climate, etc., the academician Xiaolin Tong proposed for the first time a theory to explain the characteristics of the COVID-19 epidemic from the TCM perspective of cold-dampness plague (Hanshi plague) and developed treatment methods accordingly [2]. The cold-dampness plague theory has been used throughout the Chinese' three-year history of fighting the COVID-19 epidemic, as reflected in the *Chinese National Diagnosis and Treatment Protocol for COVID-19*. The 4th to 10th editions cover the mild cold-dampness stagnating in the lung pattern, moderate cold-dampness obstructing the lung pattern, severe lung failure by SARS-CoV-2 infection, severe presence of epidemic toxins blocking the lung pattern, critical form of internal block and external collapse pattern, and cold-fluid accumulation in the lung during the recovery period. The cold-dampness plague theory is a complete system of theory, treatment method, prescription, and herbs, and its appropriateness has been confirmed during the three years of the COVID-19 epidemic.

This paper systematically reviews clinical evidence-based studies, mechanism research, and application patterns of Chinese medicine in the prevention and treatment of COVID-19. It also provides a basis for elucidating the clinical evidence chain, therapeutic level, and mechanism of Chinese medicine in the treatment of COVID-19 and references for the improved application of Chinese medicine in the prevention and treatment of acute infectious diseases in the future.

Clinical evidence is obtained in this work, and the efficacy and benefits of TCM in the prevention, treatment, and rehabilitation of COVID-19 patients are determined further. Regarding mechanism, the capability of TCM to inhibit the SARS-CoV-2 virus replication and transcription is explored. TCMs interfere with normal physiological functions of the virus and attenuate various infection-related processes, including anti-inflammatory effects, and monitoring of balanced intestinal flora, improved immune function, and organ protection. Moreover, this paper presents the advantages of using TCM in response to COVID-19 and the value of Wuchang pattern in the prevention and control of new public health emergencies, with the aim of providing a reference for rational TCM remedy for COVID-19 in clinical settings and suggesting potential directions for development in scientific research.

Evidence-based study of TCM for the treatment of COVID-19

As residents of a country with TCM origination, the Chinese generally exudes a positive attitude toward TCM, which was widely used during the COVID-19 epidemic and deeply applied in the prevention, treatment, and rehabilitation of COVID-19 patients. Overall, in China, patients with mild and moderate forms of COVID-19 were treated with Chinese herbal medicine (CHM) and Chinese patent medicine, and those with severe COVID-19 and critically ill were treated mainly with combined Chinese and Western medicine. The treatment methods of TCM, which include Chinese herbal decoction, Chinese patent medicine, and Chinese herbal injection, have yielded a series of positive results for the treatment of COVID-19, which confirm the effectiveness and safety of TCM in the treatment of all types of COVID-19 (Table 1).

Prevention

For disease prevention, Chinese people often include certain herbs in their daily diet to boost their immunity, which reduces the probability of infection. A retrospective analysis of a cohort study based on a large population of 22 975 individuals showed the substantial effect of LHQW on reducing the positive rate of SARS-CoV-2 in close contacts of COVID-19 cases [3]. Information from the Wuchang District Health and Wellness Committee showed that SHHS can reduce the positive detection rate of SARS-CoV-2 among suspected cases and their close contacts. The obtained data revealed that 723 000 doses of SHHS were distributed in Wuhan, which helped more than 50 000 people. Fourteen days after the distribution of the drug, the number of newly confirmed cases drastically dropped for the first time and remained at a low level; this finding confirms that early intervention involving Chinese medicine not only protected a large number of susceptible people but also reduced the disease incidence in high-risk groups [4].

Treatment of patients with mild and moderate forms of COVID-19

Chinese patent medicines and herbal prescriptions, such as LHQW, JHQG, QFPD, SHHS decoction/granules (also known as HSY Formula), HSBD, and XFBD are recommended in the *Chinese National Diagnosis and Treatment Protocol for COVID-19* and can be used to

Table 1 Research results on the staging treatment of COVID-19 with TCM

Staging treatment	Representative TCM decoction and Chinese patent medicine
Mild and moderate	Lianhua Qingwen capsules (LHQW), Jinhua Qinggan granules (JHQG), Qingfei Paidu decoction/granule (QFPD), Sanhan Huashi granules (SHHS) decoction/granules (also known as HSY Formula), Huashi Baidu decoction/granules (HSBD), Xuanfei Baidu decoction/granules (XFBD)
Severe and critical	QFPD, HSBD, Xiyanping (XYP) injection, Xuebijing (XBJ) injection, Shenhuang granules
Recovery period	Qimai Feiluoping decoction (QM), recovery using six types of proprietary Chinese medicine (Jinshuibao tablets, Shengmaiyin oral liquid, Shumian capsules, Xiaoyao capsules, Xiangsha Liujun pills, and Ludangshen oral liquid)

treat patients with mild and moderate forms of COVID-19.

A double-blind, placebo, randomized controlled trial (RCT) involving 300 patients with COVID-19 confirmed that JHQG is a safe and effective proprietary Chinese medicine for the treatment of COVID-19; JHQG can relieve symptoms, such as cough, sputum, sore throat, dyspnea, headache, nasal congestion, fatigue, and myalgia, in patients with mild COVID-19 [5]. JHQG granules effectively shortened the period to nucleic-acid negative conversion in COVID-19 patients and promoted the absorption of inflammatory exudates in the lungs, with no notable adverse effects [6]. A retrospective study that included 78 COVID-19 patients revealed that the administration of JHQG considerably reduced the risk of progression to hospitalization and death in older patients with COVID-19 [7]. A real-world clinical study involving 749 COVID-19 patients showed that QFPD reduced hospital stay (in the room), days of nucleic-acid negative conversion, days on medication, and time to resolution of some major symptoms and effectively improved imaging outcomes in lung computed tomography (CT) of patients with mild to moderate COVID-19 [8]. A retrospective cohort study that included 721 patients with mild and moderate COVID-19 revealed that SHHS increased considerably the nucleic-acid negative conversion rate of patients; moreover, none of the 430 patients who took Chinese herbs experienced severe disease compared with the 19 patients included in the control group (19/291, 6.5%) [9]. In addition to age, the year of diagnosis and the duration of SHHS consumption are new prognostic predictors of COVID-19, wherein the later the year of diagnosis and the longer the duration of SHHS consumption, the lower the number of severe cases [10]. In a non-RCT study of COVID-19 patients infected with the Omicron strain, XFBD shortened the period to nucleic-acid negative conversion, promoted the relief of symptoms, such as cough, sputum, throat discomfort, and dry mouth, and exhibited a good safety profile [11]. A meta-analysis of 18 RCT studies involving 2275 patients indicated that the COVID-19 patients treated with CHM benefited in terms of clinical outcomes compared with those treated with conventional Western medicine, with effects including improved clinical symptoms and imaging and laboratory indices, shorter disease duration, and fewer severe cases [12] (Table 2).

According to the above studies, herbal intervention at the early stage of COVID-19 can substantially reduce the incidence of the disease in healthy people, effectively block virus transmission, and provide an invisible protective barrier to susceptible people. For patients with mild to moderate COVID-19, more positive effects were observed in the clinical outcomes of the TCM group compared with those of the control group; these outcomes were mainly manifested as the amelioration of clinical symptoms, improved lung CT imaging results and laboratory indices, shortened disease duration and nucleic-acid negative conversion days, decreased shifting to severe disease, and less difficulty and pressure for late medical treatment, which ultimately imply the tendency toward a good direction. Thus, TCM should be used in the early and rapid intervention of the treatment of COVID-19 patients.

Treatment of severe and critically ill patients with COVID-19

The *Chinese National Diagnosis and Treatment Protocol for COVID-19* recommends the use of Chinese patent medicines and Chinese herbal prescriptions, such as QFPD, HSBD, XYP injection, and XBJ injection, for the treatment of patients with severe and critical COVID-19. Furthermore, to strengthen the guidance on the treatment of severe and critical COVID-19 patients using TCM and facilitate the combined use of Chinese and Western medicine for rescue, the tenth edition of *Chinese National Diagnosis and Treatment Protocol for COVID-19* recommends the inclusion and exclusion of Chinese herbal prescriptions for patients suffering from severe and critical COVID-19 symptoms. A series of evidence-based studies showed the reduced mortality in severe/critically ill COVID-19 patients after TCM application.

A retrospective study was conducted on 662 COVID-19 patients with severe or critical illness. After propensity score matching at a 1:1 ratio, 156 CHM users were matched to 156 non-CHM users. Univariate logistic regression analysis indicated significant differences in the effects of CHM, age, and disease severity on mortality. Meanwhile, multivariate logistic regression analysis revealed considerable differences in the effects of CHM, age, and medical history on mortality. The risk of death was reduced by 88.1% in the CHM group compared with

Table 2 Application of TCM in the treatment of mild and moderate forms of COVID-19

Study ID	Sample size	Intervention method	Duration of interventions	Primary outcome
Qiao *et al*. [3]	*n* = 22 975 (LHQW, *n* = 18 579; control arm, *n* = 6423)	Retrospective cohort study LHQW (oral, 4 capsules/time, 3 times/day)	The longest duration for taking the medication was 14 days	Reduced the positive rate of SARS-CoV-2 in close contacts of COVID-19 cases
Shah *et al*. [5]	*n* = 300 (JHQG, *n* = 150; control arm, *n* = 150)	RCT JHQG (oral, 5 g/sachet, 3 times/day)	10 days	Improved clinical symptoms and negative result in viral polymerase chain reaction (PCR)
Liu *et al*. [6]	*n* = 80 (treatment arm, *n* = 44; control arm, *n* = 36)	Retrospective cohort study JHQG (oral, 6 g/sachet, 2 times/day)	7 days	Viral nucleic-acid testing and duration of improvement of pneumonia
Lin *et al*. [7]	*n* = 78	Retrospective cohort study JHQG (oral, 5 g/sachet, 3 times/day)		
Li *et al*. [8]	*n* = 749 (CHM arm, *n* = 509; control arm, *n* = 240)	Real-world study Use of "Formula 1," "Formula 2 (QFPD)," or "Formula 3" based on evidence and administration of one dose twice a day or the proprietary Chinese medicine recommended in the program	Median number of medication days: 8.0 (6.0–11.0) days	Severe/critical conversion rate during the observation period
Tian *et al*. [9]	*n* = 721 (treatment arm, *n* = 430; control arm, *n* = 291)	Retrospective cohort study SHHS (including decoction, granules, etc.)		Reduced proportion of mild and moderate COVID-19 patients who progressed to severe disease status
Zhang *et al*. [10]	*n* = 176	Retrospective cohort study SHHS (including decoction, granules, etc.)	Arrival or exceeding 7 days	Reduced proportion of mild to moderate COVID-19 patients who were converted to severe or death status
Pang *et al*. [11]	*n* = 180 (treatment arm, *n* = 120; control arm, *n* = 60)	Non-RCT XFBD (oral, 10 g/sachet, 2 times/day)	14 days	Reduced virus nucleic-acid negative-conversion time and length of hospital stay
Xiong *et al*. [12]	*n* = 2275	Meta-analysis 18 RCTs were enrolled	5–15 days	Improving clinical symptoms, imaging, and laboratory indicators, shortening the course of disease, and reducing the number of severe cases

that in the non-CHM group [13]. Another study showed that the use of TCM considerably reduced all-cause mortality in patients with severe/critical COVID-19 compared with the group without CHM treatment [14]. Another RCT study confirmed that the combined treatment using Western medicine and HSBD effectively reduced the inflammatory response in severe COVID-19 patients and the incidence of adverse effects, such as gastrointestinal bleeding and prolonged clotting time [15]. The combination of HSBD and Chinese herbal injections also substantially reduced the clinical remission time of patients with COVID-19 [16]. XBJ is a Chinese herbal injection based on Xuefu Zhuyu decoction [17], and it is commonly used to treat systemic inflammatory reactions induced by infections and as a supplementary agent in the treatment of impaired organ function among patients with multiorgan dysfunction syndrome [18]. A recent study showed that the expressions of tumor necrosis factor (TNF)-α, interferon-γ-inducible protein-10, macrophage inflammatory protein-1β, and regulated upon activation, normal T cell expressed and secreted factor (RANTES) increased considerably 2 and 3 days after the viral infection of COVID-19 patients; XBJ injection remarkably inhibited the expression of inflammatory mediators on days 7 and 8 of treatment [19]. An open, multicenter, RCT study involving 111 patients with severe/critical COVID-19 unveiled that Shenhuang granules reduced mortality, increased lymphocyte count, and reduced adverse events in COVID-19 patients [20] (Table 3).

According to the above studies, the dosage form of Chinese herbal injection is almost used and/or combined with Western medicine to treat critically ill patients and given the regimen, can reduce adverse effects, shorten the time to clinical remission, and decrease mortality in critically ill patients.

Recovery period

The pharmacological and nonpharmacological components of TCM are useful for the recovery treatment of patients with COVID-19. Chinese patent medicines

Table 3 Application of TCM in the treatment of severe and critical forms of COVID-19

Study ID	Sample size	Intervention method	Duration of interventions	Primary outcome
Chen *et al*. [13]	*n* = 662 (CHM, *n* = 484; control arm, *n* = 178)	Retrospective cohort study CHM (oral, 2 times/day)	The longest duration of taking medication was 14 days	All-cause mortality
Sun *et al*. [14]	*n* = 282 (TCMD, *n* = 186; control arm, *n* = 96)	Retrospective cohort study TCMD (oral, 2 times/day)	10 days	All-cause mortality
Liu *et al*. [15]	*n* = 50 (treatment arm, *n* = 25; control arm, *n* = 25)	HSBD (1–2 doses were taken daily with water decoction, 100–200 mL each time, by oral or nasal feeding, 2–4 times/day)	1 month	Clinical outcome, blood count, inflammatory factor levels, and occurrence of adverse reactions
Shi *et al*. [16]	*n* = 60 (A = 20, B = 20, C = 20)	Non-RCT Group C: HSBD (137 g twice daily, orally), Shenmai injection (60 mL once daily, intravenously), XYP injection (100 mg twice daily, intravenously), and XBJ injection (100 mL twice daily, intravenously)		Clinical remission time and clinical remission rate
Zhou *et al*. [20]	*n* = 111 (SHG arm, *n* = 57; control arm, *n* = 54)	RCT Shenhuang granule (oral, 1 sachet, twice daily)	14 days	Clinical improvement and mortality rate

and herbal prescriptions, which include QM, Jinshuibao tablets, Shengmaiyin oral liquid, Shumian capsules, Xiaoyao capsules, Xiangsha Liujun pills, and Ludangshen oral liquid, are clinically effective in the recovery phase of COVID-19. The effective nonpharmacological therapies include Taichi exercise, Baduanjin exercise, etc.

Pharmacological therapies

QM decoction is a Chinese herbal prescription recommended in the Chinese rehabilitation program for discharged COVID-19 patients with functional disorders, and it is used to treat pulmonary fibrosis in the recovery phase of COVID-19. Clinical findings revealed that QM decoction can effectively improve symptoms, such as fatigue and asthma, and lung function and abnormalities in lung CT, such as ground glass shadow, fibrous cord shadow, and fibrous strip shadow, of patients recovering from COVID-19 [21]. Several randomized, double-blind, placebo-controlled, multicenter clinical trials have reported the following findings on patients recovering from COVID-19: (1) Jinshuibao tablets and Shengmaiyin oral liquid can considerably improve cardiopulmonary function and related symptoms, including shortness of breath, sweating, chest tightness, and dry cough; (2) Shumian capsules can remarkably relieve sleep disorders; (3) Xiangsha Liujun pills and Ludangshen oral liquid can improve digestive functions, including fatigue, loss of appetite, abdominal distention, and loose stools [22,23].

Nonpharmacological therapies

Nonpharmacological therapies in TCM, such as Qigong, Baduanjin exercise, Taichi exercise, acupuncture, and Tuina massage, also play critical roles in COVID-19 treatment, especially in the recovery period.

A RCT study of 128 COVID-19 patients confirmed that Qigong exercise and acupoint Tuina combined with standard therapy methods can improve lung function, relieve symptoms, such as dyspnea and cough, and shorten the hospital stay of severe COVID-19 patients [24]. A controlled pre- and postclinical study involving 33 discharged COVID-19 patients confirmed that Liuzijue alleviated dyspnea, depression, and anxiety [25]. A randomized controlled study involving 87 patients with COVID-19 revealed that Baduanjin combined with auricular acupressure improved sleep quality, anxiety–depression status, and TCM symptoms in COVID-19 patients with insomnia and attained a higher efficacy than oral eszopiclone [26]. In a meta-analysis of nine RCT studies involving 571 participants, Taichi reduced remarkably the levels of inflammatory markers, such as C-reactive protein, TNF-α, and interleukin-6 (IL-6), which provided a rationale for its use as an adjunctive treatment for COVID-19 [27]. Altogether, Qigong, Taichi, and Baduanjin can remarkably improve the patients' quality of life from three dimensions, i.e., physical, social, and emotional functions, and are feasible and acceptable for rehabilitation after COVID-19 and the treatment of long COVID-19 symptoms [28,29]. An integrated TCM intervention therapy (including Baduanjin exercise, foot baths, moxibustion and acupoint application, Tongzhi granule, and Wuhan Kangyi decoction) can promote the rehabilitation of clinical symptoms and reduce the occurrence of nucleic-acid positive relapse in patients recovering from COVID-19. The corresponding mechanism may be related to the improved immune function and rapid elimination of residual viral particles from the body. This finding

suggests the potential of TCM comprehensive intervention therapy in the prevention and treatment of resurgery [30]. The guide on TCM rehabilitation for the recovery period of COVID-19 (for trial implementation) recommends the implementation of acupuncture strategies [31]. Furthermore, the guide on acupuncture for COVID-19 issued by the Chinese Acupuncture Association highlights the crucial role of acupuncture in the recovery period of COVID-19 [32]. A RCT study that included 60 patients reported that Shugan Tiaoshen acupuncture combined with Western medicine improved the depressed mood and sleep quality of patients with depressive insomnia comorbidities due to their experience of isolation during the COVID-19 epidemic [33]. After the infection with SARS-CoV-2, the acquired immune function of an individual is impaired for a certain period; however, early rehabilitation and conditioning through the administration of Chinese medicine, respiratory training, and physical exercise can considerably alleviate the impairment of the acquired immune function after infection and accelerate recovery [34]. Therefore, the application of TCM drugs together with nondrug therapies should be emphasized during the period of recovery from SARS-CoV-2 infection.

The above studies revealed the efficacy of TCM treatment in the recovery period of COVID-19 infection. In addition, a combination regimen of Chinese medicine, acupuncture, Tuina, and Qigong can exert evident effect thresholds.

Treatment of COVID-19 with TCM in children

TCM benefits the treatment of pediatric diseases. The 10th edition of the *Chinese National Diagnosis and Treatment Plan for COVID-19* supports and provides guidance regarding the use of TCM in the treatment of children with COVID-19. According to a retrospective analysis of 346 children infected with the Omicron strain of SARS-CoV-2, LHQW reduced the time to nucleic-acid negative conversion and hospitalization duration of children with COVID-19 [35]. HSBD was also used effectively in the treatment of children infected with the Omicron strain of SARS-CoV-2; it reduced the time to nucleic-acid negative conversion and improved the overall symptom scores [36]. Table 4 shows the details of the recovery period and treatment of children.

The above studies preliminarily revealed that the combined protocol of Chinese and Western medicine is safe and effective for the treatment of COVID-19 in children and may provide a basis to guide doctors

Table 4 Application of TCM in the recovery period and treatment of children with COVID-19

Study ID	Sample size	Intervention method	Duration of interventions	Primary outcome
An *et al*. [26]	*n* = 1200 (100 individuals in each control and experimental groups for six Chinese patent medicines)	RCT		
An *et al*. [27]	*n* = 200 (treatment arm, *n* = 100; control arm, *n* = 100)	RCT Ludangshen oral liquid (10 mL/time, twice daily)	14 days	Observation of changes in gastrointestinal and respiratory symptoms
He *et al*. [30]	*n* = 420 (treatment arm, *n* = 325; control arm, *n* = 95)	Observational study Comprehensive interventions (Baduanjin exercise, foot baths, moxibustion with acupoint application, Tongzhi granule, and Wuhan Kangyi decoction)		Reverse transcription-PCR results
Yan *et al*. [33]	*n* = 60 (treatment arm, *n* = 30; control arm, *n* = 30)	RCT Shugan Tiaoshen acupuncture (1 session/2 days, 3 times a week)	8 weeks	Depressed mood and quality of sleep
Xu *et al*. [35]	*n* = 2808 (treatment arm, *n* = 346; control arm, *n* = 346)	Retrospective cohort study Prescribed doses of LHQW granules were 3 g for children of 3–6 years old, 4.5 g for children of 7–9 years old, and 6 g for children of 10–17 years old, three times daily. LHQW capsule doses were 1 capsule for children of 3–6 years old, 2 capsules for children of 7–9 years old, and 4 capsules for children of 10–17 years old, three times daily. Children under 2 years of age received 1 g LHQW granules three times daily		Negative conversion time of nucleic acid
Feng *et al*. [36]	*n* = 108 (HSBD, *n* = 72; control arm, *n* = 36)	RCT Intervention group patients were given HSBD the day after randomization, with a dose of 2.5 g for children aged 3–6 years old, 5 g for children aged 7–12 years old, and 10 g for children aged 13–18 years old, twice daily for 5 consecutive days	5 days	Duration for SARS-CoV-2 nucleic-acid negative conversion after randomization

regarding the clinical use of medication and a reference for policy development related to the prevention and treatment of special populations of patients with COVID-19 using Chinese medicine.

Efficacy of integrated TCM and Western medicine on patients with COVID-19

The combined application of Chinese and Western medicine is a major feature of the prevention and control of COVID-19 in China. This type of treatment is mainly used on patients with severe and critical illnesses.

The combination of JHQG granules and Western medicine can relieve clinical symptoms, such as fever, cough, sputum, fatigue, and loss of appetite, in COVID-19 patients and reduce anxiety and the use of antibiotics compared with Western medicine alone [37,38]. A randomized controlled study involved 120 patients assigned to a control group and a test group at a ratio of 1:2; the control group received standard Western medicine treatment alone for 2 weeks, and the test group received a combination of the standard Western medicine and CHM treatment for 2 weeks. Compared with the control group, the test group exhibited shorter symptom recovery period, greater improvement in lung CT imaging findings, shorter periods to fever reduction and cough relief, higher discharge rate, shorter mean length of stay, mMRC scale score, clinical cure rate, and better laboratory test results. A higher clinical efficacy was observed with the application of combined Chinese and Western medicine treatment regimen in patients with the moderate form of COVID-19 compared with patients who received a Western medicine treatment regimen alone [39].

A randomized controlled clinical trial study showed the advantages of combined Huoxiang Zhengqi dropping pills and Lianhua Qingwen granules in the treatment of nausea, vomiting, and limb soreness; such treatment also reduced the utilization rate of anti-infective drugs in patients [40]. A prospective, multicenter, open-label, RCT revealed that XYP injection shortened considerably the time to fever resolution, cough recovery, and virus clearance, and reduced the proportion of patients with worsening clinical symptoms [41]. A RCT showed that the combination of TCM and Western medicine treatment can improve effective and discharge rates [42]. Two RCTs revealed that the combination of TCM and Western medicine treatment can improve clinical symptoms, such as fever and cough in patients, and increase the improvement rate of lung CT [43,44]. In another RCT, the integration treatment involving TCM and Western medicine can reduce the proportion of patients progressing to severe cases and improve clinical symptoms [45].

In clinical practice, the combination of Chinese and Western medicine has played a major role in the treatment of severe/critical COVID-19 patients at high risk of death. A systematic evaluation study comprising 6 RCT and 15 observational studies, which included 12 981 patients with severe/critical COVID-19, showed the reduced risk of death, critical case conversion rate, and use of mechanical ventilation after the supplementation with TCM; in addition, revealed remarkable benefits in terms of shorter hospital stay, virus clearance time, and symptom regression compared with conventional supportive care alone [46]. A meta-analysis that included 29 RCTs involving 3060 patients and 28 retrospective studies involving 12 460 patients reported that the integration of TCM and Western medicine reduced the proportion of patients that progressed to severe disease by 55% and the mortality rate of patients with severe or critical illness by 49% [47]. A meta-analysis of 19 RCT studies involving 1474 patients revealed that the combination of Chinese and Western medicine for treating COVID-19 was associated with effective symptom control and reduced disease progression [48]. Another meta-analysis confirmed the safety of combined treatment with Chinese and Western medicine for COVID-19 patients [49]. A retrospective analysis on 50 patients with severe COVID-19 treated with QFPD combined with conventional Western medicine showed that combination treatment can effectively improve the clinical symptoms in such patients [50]. A single-center retrospective study indicated that a combination of Chinese and Western medicine can relieve symptoms and promote recovery in hemodialysis patients with COVID-19 [51]. Therefore, the combination of conventional medicine with Chinese medicine may provide better results in the treatment of critically ill patients with COVID-19 [52] (Table 5).

Compared with the use of Western medicine alone, the combination of TCM and Western medicine has greater benefits for patients with COVID-19. Thus, we should further strengthen the related mechanism to reinforce the integration of TCM and Western medicine and further improve the mechanism for the governance of TCM and Western medicine in response to major public health emergencies.

Potential mechanisms of TCM in the treatment of COVID-19

The anti-SARS-CoV-2 effect of TCM was studied in SARS-CoV-infected (hACE2) transgenic mice and Vero E6, Huh7, and other cell lines. Lipopolysaccharide (LPS)-induced acute lung injury (ALI/sepsis, etc.), bleomycin-induced pulmonary fibrosis, and dextran sulfate sodium salt-induced colitis models were used to study the anti-inflammatory effects of TCM and its effects on intestinal flora changes, immune function improvement, organ

Table 5 Integration of TCM and Western medicine

Study ID	Sample size	Intervention method	Duration of interventions	Primary outcome
An *et al*. [38]	*n* = 123 (JHQG, *n* = 92; control arm, *n* = 31)	RCT JHQG (oral, one sachet, three times/day)	14 days	Symptom improvement rate and symptom disappearance rate after 14 days of treatment
Duan *et al*. [38]	*n* = 123 (JHQG, *n* = 82; control arm, *n* = 41)	RCT JHQG (oral, 6 g/sachet, three times/day)	5 days	Symptom improvement rate and symptom disappearance rate
Wenguang *et al*. [39]	*n* = 108 (treatment arm, *n* = 73; control arm, *n* = 35)	RCT TCM decoction (1 total dose daily, 400 mL, twice in the morning/day)		Time to complete recovery and lung CT findings
Xiao *et al*. [40]	*n* = 124 (treatment arm, *n* = 61; control arm, *n* = 63)	RCT Huoxiang Zhengqi dropping pills (one bag, 2 times/day) and Lianhua Qingwen granules (one bag, 3 times/day)	14 days	Clinical symptom improvement and disappearance rates after 14 days of treatment
Zhang *et al*. [41]	*n* = 130	Multicenter, prospective, open-label RCT XYP injection (10 mg/kg once per day, maximum daily dosage 500 mg)	7–14 days	Time from the start of studying medicine to complete symptom resolution, including fever resolution and cough recovery
Fu *et al*. [42]	*n* = 73 (treatment arm, *n* = 37; control arm, *n* = 36)	RCT Toujie Quwen granules (one bag, 2 times/day)	15 days	Proportion of patients progressing to severe cases, total effective rate, and discharge rate
Qiu *et al*. [43]	*n* = 50	RCT Maxing Xuanfei Jiedu decoction (150 mL, 3 times/day)	10 days	Proportion of patients progressing to severe cases; lung CT improvement rate, disappearance time of fever, and disappearance time of cough
Sun *et al*. [44]	*n* = 57 (treatment arm, *n* = 32; control arm, *n* = 25)	RCT Lianhua Qingke granules (1 bag, 3 times/day)	14 days	Proportion of patients progressing to severe cases; lung CT improvement rate, symptom disappearance rate
Yu *et al*. [45]	*n* = 295 (treatment arm, *n* = 147; control arm, *n* = 148)	RCT Lianhua Qingwen granules (6 g, 3 times/day)	7 days	Proportion of patients progressing to severe cases; total effective rate and lung CT improvement rate
Li *et al*. [46]	*n* = 12 981	Meta-analysis of 21 studies (6 RCTs and 15 observational studies)		
Kang *et al*. [47]	*n* = 15 520	Meta-analysis of 57 studies (28 RCTs and 29 retrospective studies)		
Luo *et al*. [48]	*n* = 1474	Meta-analysis of 19 RCTs		
Liu *et al*. [49]	*n* = 982	Meta-analysis of 11 studies (4 RCTs and 7 case-control studies)		
Wang *et al*. [50]	*n* = 50	Retrospective cohort study		Efficacy and safety indicators
Huang *et al*. [51]	*n* = 53 (treatment arm, *n* = 31; control arm, *n* = 22)	A single-center, retrospective study	5 days	Clinical outcomes (i.e., discharge, mortality, and length of stay)

protection, and other aspects. Fig. 1 shows the mechanism by which TCM affects COVID-19.

Antiviral effect of TCM

SARS-CoV-2 has a spike (S) protein that attaches to angiotensin-converting enzyme 2 (ACE2) on the cell membrane and then penetrates the host cell. Therefore, strategies that were developed to inhibit viral infection and replication have focused on targets, such as S proteins and nonstructural proteins, including the highly conserved RNA-dependent RNA polymerase (RdRp), main protease (SARS-CoV-2 $3CL^{pro}$ or M^{pro}), and papain-like protease, and indirect selection to target host-cell recognition systems, such as ACE2 and transmembrane protease [53]. Previous studies have shown that some TCM compounds and single Chinese medicine, and monomer components of TCM (Table 6) can exert an anti-SARS-CoV-2 effect by blocking the binding of the S protein to the ACE2 receptor and inhibiting the activity of M^{pro} and $3CL^{pro}$.

TCM formulas: The anti-SARS-CoV-2 effect of LHQW is manifested through the inhibition of SARS-CoV-2 replication and reducing host-cell release of cytokines [54]. Leupeptin in QFPD plays an anti-SARS-CoV-2 role by inhibiting the activity of M^{Pro} [55]. XBJ exerts an anti-SARS-CoV-2 effect by blocking the proliferation of SARS-CoV-2 and inhibiting the upregulation of SARS-CoV-2-induced pro-inflammatory cytokines [56].

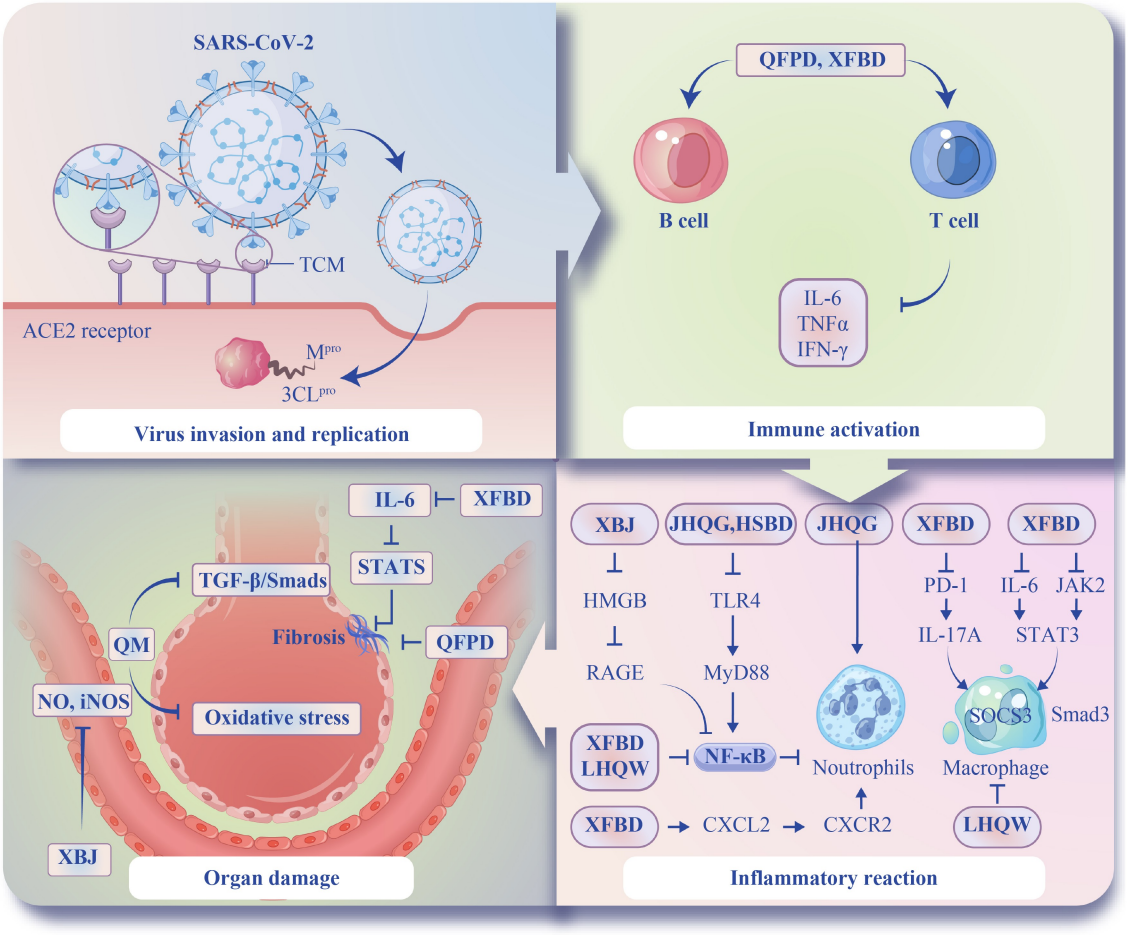

Fig. 1 Potential mechanism of TCM in the treatment of COVID-19.

Single Chinese medicine: Aqueous extracts of Jinyinhua (*Lonicera japonica* Thunb.) and Huangqi (*Astragalus mongholicus* Bunge) suppressed SARS-CoV-2 entry to host cells and COVID-19-related cytokine storm *in vitro* [57]. Zisuye (*Perilla frutescens* (L.) Britt) can inhibit SARS-CoV-2 replication by inactivating virions [58].

Monomer components of TCM: Given the complexity of TCM compounds, the effective TCM components that show antiviral and anti-inflammatory effects must be screened. Luqi Huang *et al*. observed the dose-dependent inhibitory effects of magnolol, glycyrrhisoflavone, licoisoflavone A, emodin, echinatin, and quercetin in HSBD on SARS-CoV-2 [59]. Ephedrine, the active ingredient of Mahuang (*Ephedra sinica* Stapf), inhibited the entry of SARS-CoV-2 pseudovirus into ACE2 (h) cells and reduced its entry rate [60]. Glycyrrhizin, the main active ingredient of Gancao (*Glycyrrhiza glabra* L.), can prevent SARS-CoV-2 from entering host cells and replicating through the reduced ACE2 expression and inhibition of the interaction between the RBD of the S protein and ACE2 [61]; glycyrrhizin can also inhibit the activity of S protein [62]. Salvianolic acid C can inhibit the formation of the six-helix bundle by specifically binding to the HR1 region in the S2 subunit of the S protein, which effectively blocks S protein-mediated membrane fusion and viral infection [63]. Honokiol derivatives can inhibit the entry of SARS-CoV-2 pseudovirus into HEK-293T-ACE2h cells [64]. Baicalein can inhibit the M^{pro} activity of SARS-CoV-2 [65].

Anti-inflammatory effect of TCM

XFBD can inhibit the overactivation of complement by inhibiting the Janus kinase 2/signal transducer and activator of transcription 3 (STAT3)/suppressor of cytokine signaling 3 (SOCS3) and nuclear factor (NF)-κB signaling pathways, and subsequently alleviate IgG immune complex-induced ALI [66]. XFBD can also regulate the formation of neutrophil extracellular traps by inhibiting the NF-κB signaling pathway [67] and the CXCL2/CXCR2 signaling pathway [68], which alleviated LPS-induced ALI in mice. Molecular docking and dynamics studies revealed that I-SPD, pachypodol, and vestitol, which are important active components of XFBD, can reduce inflammatory response and apoptosis

Table 6 Antiviral targets of TCM

Herbal/compound	Active ingredients	Cells	Mechanisms of action
LHQW [55]		Vero E6 and Huh-7 cells	Inhibition of viral replication and reduction of cytokines released by host cells
QFPD [55]	Leupeptin	Vero cells	Inhibition of M^{pro}
XBJ [56]		Huh-7 cells	Blockage of virus proliferation
Honeysuckle [57]		BHK-21 cells	Inhibition of M^{pro}
Huangqi [57]		BHK-21 cells	Inhibition of M^{pro}
Perilla frutescens (L.) Britt [58]	Perilla leaf extract	Vero E6and Huh7 cells	Prevents SARS-CoV-2 from entering host cells
HSBD [59]	Glycyrrhisoflavone and licoisoflavone A		Inhibition of RdRp
HSBD [59]	Echinatin and quercetin		Inhibition of M^{pro}
Ephedra	Ephedrine [60]	ACE2(h) cells	Inhibition of SARS-CoV-2 spike pseudovirus entry into ACE2 (h) cells
Licorice	Glycyrrhizin [61,62]	Vero E6	Decreases ACE2 expression and inhibits the interaction between the S protein receptor binding domain (RBD) and ACE2/inhibition of spike proteins
Salvia miltiorrhiza	Salvianolic acid C [63]	Vero E6 and HEK85T cells	Inhibition of spike proteins
Magnolia officinalis	Honokiol derivatives [64]	HEK-293 T-$ACE2^h$	Blocking the binding of SARS-CoV-2 to host ACE2 receptors
Radix Scutellariae	Baicalein [65]		Inhibition of M^{pro}

by inhibiting NLR family pyrin domain-containing 3 activation and reduce the production of inflammatory factors and chemokines of inflammatory cells by inhibiting CSF2 activation [69]. LHQW also considerably inhibited NF-κB expression, reversed SOCS3 expression, and regulated c-Jun N-terminal kinase-activator protein-1 in inflammatory macrophages, thereby exerting anti-inflammatory effects. JHQG can reduce LPS-induced lung inflammation and alleviate ALI in mice by promoting the apoptosis of neutrophils and inhibiting the Toll-like receptor (TLR) 4/MyD88/NF-κB pathway [70]. The anti-inflammatory role of XBJ is manifested through the regulation of the NF-κB signaling pathway [71]. It can also regulate the balance of regulatory T and T helper 17 cells by inhibiting the secretion of proinflammatory cytokines mediated by the high mobility group box-1 protein (HMGB1), thus improving the survival rate of mice with septic shock [72]. The purine, glutathione, sphingomyelin, arachidonic acid, and phospholipid metabolism pathways can be potential pathways through which XBJ exerts its effects for the treatment of sepsis-induced ALI [73]. HSBD can inhibit cytokine storm and relieve inflammation by regulating the TLR4/NF-κB and phosphatidylinositol-3 kinase/Akt pathways [74]. QFPD can inhibit the M2 polarization of macrophages in lung tissues of mice treated with bleomycin [75].

Immunity and organ protection effect of TCM

BALB/c mice were infected with human coronavirus HCoV-229E and stimulated in cold and damp environments to construct a mouse model of coronavirus-induced viral pneumonia. Experiments revealed that QFPD can increase the percentage of $CD4^+$ T, $CD8^+$ T, and B cells in the peripheral blood of mice, reduce the level of inflammatory cytokines, such as IL-6, TNF-α, and interferon (IFN)-γ, restore the abnormal communication between cells, and considerably improve liver purine metabolism. These findings indicate the capability of QFPD to regulate the immune function of the body and reduce liver damage and inflammation induced by coronavirus [76]. QFPD restored the richness and diversity of intestinal microflora, improved the immune function, and reduced the inflammation level in a pneumonia mouse model by altering the intestinal microflora and host metabolism [77]. XFBD also exhibited effects similar to those of QFPD [78,79]. XFBD regulated the infiltration of neutrophils and macrophages by inhibiting the programmed cell death protein 1/IL-17A signaling pathway, balancing immune cell homeostasis, and reducing hyperinflammatory responses, which alleviated LPS-induced ALI [80]. XFBD treatment can remarkably inhibit weight loss, increase spleen and thymus indices, improve pathological manifestations, and alleviate the decreased serum levels of TNF-α, IFN-γ, IgG, and IgM and the expressions of IL-2, IL-4, and IL-6 in the spleen. In the XFBD group, the reduction of $CD4^+$ T and $CD8^+$ T cells caused by cyclophosphamide treatment was also recovered. This finding suggests that XFBD can be a potential candidate for immune response modification and therapy [81]. XBJ inhibits NO production and inducible nitric oxide synthase protein expression in vascular endothelial cells, which implies its better protective effect on endothelial cells [82]. XFBD

can reduce bleomycin-induced pulmonary fibrosis by inhibiting IL-6/STAT3 activation and associated macrophage infiltration [83]. QFPD can also effectively alleviate bleomycin-induced lung inflammation and collagen deposition and notably reduce the extent of pulmonary fibrosis in mice [84]. QM can inhibit the oxidative stress-mediated mitochondrial complex I and the transforming growth factor-β/Smad3 pathway, which reduces the epithelial–mesenchymal transition and promotes the degradation of the extracellular matrix to induce an antipulmonary fibrosis effect [21].

Innovative practice of TCM community prevention and control—Wuchang pattern

The "Wuchang pattern" uses the TCM cure party + community + Internet mode; based on the epidemic situation and under government support, a large number of universal prescriptions were distributed to patients or residents of the community through a special app or scanning a WeChat QR code on the Chinese medicine bag for feedback in medication results; experts then adjusted the diagnosis and treatment plan based on feedback prescription [85,86]. SHHS decoction/granules were distributed in Wuchang District in Wuhan City and reduced disease incidence in high-risk groups and the proportion of mild and moderate COVID-19 patients turning to severe status. Thus, this strategy showed excellent efficacy in epidemic prevention and treatment. The application of Wuchang pattern in the absence of specific drugs enabled the prompt treatment of many patients, demonstrated the efficacy of TCM, and contributed Chinese knowledge and treatment approaches to the global fight against the COVID-19 pandemic.

Discussion

Main findings

Following the onset of COVID-19 pandemic, TCM has been systematically used in China to prevent and control the spread of COVID-19. A series of scientific research studies and innovative approaches enabled China to develop effective TCM patent medicines for COVID-19, such as QFPD, XFBD, HSBD, and SHHS granules, which meet the requirements of clinical and domestic use. In addition, the Chinese model of diagnosis and treatment involving the integration of TCM and modern Western medicine has been used to treat severe and critical COVID-19 patients and has played a decisive role in the victory against the COVID-19 pandemic. The TCM community epidemic prevention model, which is represented by the Wuchang pattern, has gained rich experience for the further application of TCM in the management of emerging infectious diseases in the future.

In the present study, we performed a systematic review of the results of evidence-based clinical and basic research on various TCM formulations and Chinese patent medicines for the treatment of COVID-19, as recommended in the *Chinese National Diagnosis and Treatment Protocol for COVID-19*. The effectiveness and safety of TCM in the treatment of COVID-19 of varying severities and the related mechanisms were demonstrated from multiple perspectives. In general, the preventive use of TCM can enhance immunity and reduce infection rates. For patients with mild and moderate forms of COVID-19, TCM can relieve related signs and symptoms, shorten the time of nucleic-acid negative conversion, and reduce the rate of conversion to the severe form. For COVID-19 patients with severe and critical illnesses, TCM can improve inflammatory indicators and blood oxygen saturation, shorten the length of hospital stay, and reduce the mortality rate. In the recovery period, TCM can improve patients' symptoms and quality of life, promote organ function recovery, and reduce the recurrence rate. Furthermore, a series of basic research studies showed the feasibility of using TCM in the treatment of COVID-19 by inducing antiviral and anti-inflammatory effects, facilitating immune regulation, and protecting organ function through multicomponent, multitarget, and multipathway approaches. Some monomer components discovered based on TCM have a high application value in the research and development of new drugs for COVID-19 treatment. Baicalin is a new inhibitor of SARS-CoV-2 $3CL^{Pro}$ [87]. Several monomer components of HSBD can also effectively inhibit the replication of SARS-CoV-2.

Evidence gaps

The current research encountered several limitations regarding the application of TCM in the treatment of COVID-19. In terms of clinical research, although TCM formulas or Chinese patent medicines recommended by the *Chinese National Diagnosis and Treatment Protocol for COVID-19* have certain clinical effects, a limited number of prescriptions or TCM prescriptions have been considered clinical basis for COVID-19 treatment. In addition, several clinical studies used small sample sizes and presented poor quality of evidence. Therefore, more standardized and strict high-quality clinical research is needed to provide a high-level clinical basis for treatment of COVID-19 using TCM. In terms of mechanism, the mechanism of most TCM prescriptions for COVID-19 are based on network pharmacology prediction and macromolecular docking analysis. However, these mechanisms are not confirmed by relevant experiments. In this review, these mechanisms based on network pharmacology and macromolecular docking prediction have not been discussed. In addition, animal experimental

models have low correlation with TCM theory and clinical research. This requires the establishment of animal models that combine disease and syndrome based on modern medical research, and combined with the theory of TCM, preserve the characteristics of TCM research by appropriately utilizing modern science and technology, and clarify the principles of TCM for treating diseases. At present, these restrictions hinder the implementation of TCM on a global scale, and further research is needed to address this issue in the future. The Chinese medicine phenomics research seeks to identify potential mechanisms of TCM at different scales and based on a personal, precise, and promising approach to provide novel insights into TCM research in the future. Integrative pharmacology-based TCM is also an important reference strategy [88,89].

Future directions

With the advent of major public health emergencies, Wuchang has created the "Wuchang pattern" in the context of an imperfect conventional medical system. This innovative model utilizes the role of TCM in the prevention and control of the epidemic. The practice of the Wuchang pattern has exemplary importance in responding to major public health events in the future. Its timely dissemination can provide new "solutions" for the medical management of new and sudden major public health accidents.

In COVID-19 pandemic, the integration regimen of TCM and Western medicine exhibited a crucial role in combating the epidemic; it opened up and enriched the research on the "Chinese way" and "Chinese characteristics" of health and epidemic prevention. In the future, studies should focus on the further enhancement of the role of TCM in the management mechanism of major public health emergencies to better utilize the advantages of TCM and Western medicine. A management mechanism with Chinese characteristics must be developed to respond to major public health emergencies and prevent and resolve the risks of major public health emergencies.

In the early intervention stage, comprehensive intervention and classified treatment, TCM has made an important and lasting contribution to the prevention and control of COVID-19. Only China and South Korea have developed relevant guidelines for the use of TCM as a treatment tool. However, such achievements still prove to be inadequate. Better guidelines and deeper public medical education can help TCM practitioners and patients in the appropriate use of TCM, which reduces the damage to people's health caused by sudden public health events. Therefore, international cooperation with other countries and regions is recommended. In addition, international guidelines must be developed, and a complete evidence chain for the prevention, treatment, and rehabilitation of TCM for patients around the world must be provided.

Conclusions

Encouraging evidence reveals that TCM is beneficial and safe in the prevention of and treatment of COVID-19. The current findings need to be confirmed by rigorous mechanism research and clinical trials. Meanwhile, we need to further develop and promote the "Wuchang pattern," the management mechanism, and guidelines for the integration of TCM and Western medicine.

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Compliance with ethical guidelines

Conflicts of Interests Linhua Zhao, Chuanxi Tian, Yingying Yang, Huifang Guan, Yu Wei, Yuxin Zhang, Xiaomin Kang, Ling Zhou, Qingwei Li, Jing Ma, Li Wan, Yujiao Zheng, and Xiaolin Tong declare that they have no competing interests.

This manuscript is a review article and does not involve a research protocol that requires the approval of relevant institutional review board or ethics committee.

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