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REVIEW

Traditional Chinese Medicine

Traditional Chinese medicine for treatment of coronavirus disease 2019: a review

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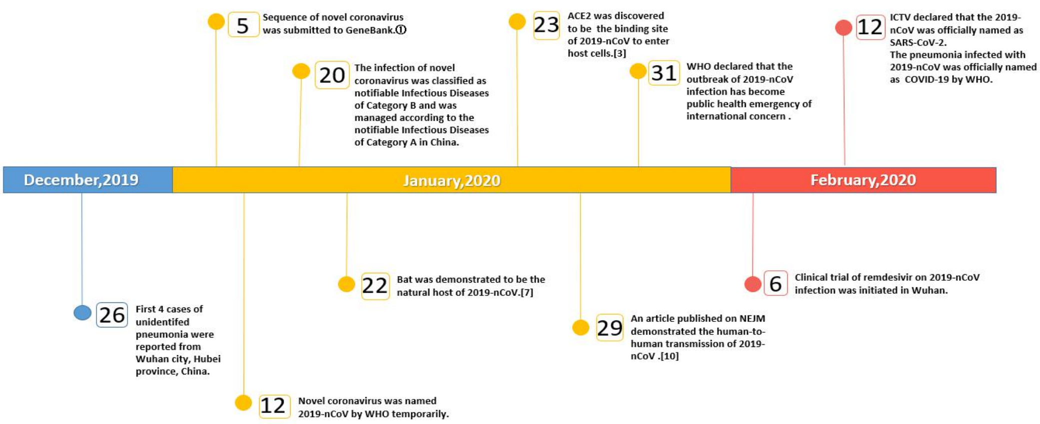
Highlights

Coronavirus disease 2019 (COVID-19) has recently become a public health concern worldwide. The use of traditional Chinese medicine (TCM) may have substantial impact on COVID-19. In this review, we summarize the disease pathogenesis, clinical outcomes, and current applications of TCM for the treatment of COVID-19.

Traditionality

The pathogenesis and clinical symptoms related to severe respiratory disease were described many years ago in TCM texts. The ancient book of TCM *Huang Di Nei Jing* (*Inner Canon of Huangdi*) was written during the Western Han Dynasty of China (dated approximately 99 B.C.E.–26 B.C.E.); the text recorded a plague that could transmit disease from human-to-human with symptoms that were similar to those described for COVID-19. Three additional texts, notably *Shang Han Za Bing Lun* (*Treatise on Cold Damage Diseases*) written by Zhang Zhongjing (200 C.E.–210 C.E.), *Wen Yi Lun* (*Theory of Plague*) and *Wen Re Lun* (*Translated Theory of Warm*) written by Wu Youke (1642 C.E.), recorded therapies and formulas that were effective at treating infectious diseases; among them, the classical prescription Da Yuan Yin and the use of human variolation were considered as means to prevent smallpox. Currently, the use of TCM has resulted in remarkable improvement and alleviation of symptoms in COVID-19 patients.



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Abstract

Since late December in 2019, the coronavirus disease 2019 has received extensive attention for its widespread prevalence. A number of clinical workers and researchers have made great efforts to understand the pathogenesis and clinical characteristics and develop effective drugs for treatment. However, no effective drugs with antiviral effects on severe acute respiratory syndrome coronavirus 2 have been discovered currently. Traditional Chinese medicine (TCM) has gained abundant experience in the treatment of infectious diseases for thousands of years. In this review, the authors summarized the clinical outcome, pathogensis and current application of TCM on coronavirus disease 2019. Further, we discussed the potential mechanisms and the future research directions of TCM against severe acute respiratory syndrome coronavirus 2.

Key words: Severe acute respiratory syndrome coronavirus 2, Coronavirus disease 2019, Clinical outcome, Angiotensin-converting enzyme 2, Traditional Chinese medicine

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***Abbreviations*:**

COVID-19, coronavirus disease 2019; SARS, severe acute respiratory syndrome; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; MERS, Middle East respiratory syndrome; ARDS, acute respiratory distress syndrome; TCM, traditional Chinese medicine; ACE2, angiotensin-converting enzyme 2; S protein, spike protein; HR, heptad repeat; SARS-CoV, severe acute respiratory syndrome coronavirus; MERS-CoV, Middle East respiratory syndrome coronavirus.

***Competing interests*:**

The authors declare that they have no conflict of interest.

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Background

Coronavirus disease 2019 (COVID-19) has received extensive attention for its increasing incidence and widespread prevalence [1, 2]. On January 31, 2020, World Health Organization declared that the outbreak of COVID-19 had become public health emergency of international concern. According to statistics from National Health Commission of the People's Republic of China, by February 16, 2020, a total of 70,548 confirmed cases and 1,770 fatal cases of COVID-19 had been reported in China. At this writing, cases of COVID-19 infection have been reported in more than 20 countries and in regions worldwide [3].

Given the recent advances in research and biotechnology, a virus believed to be the etiologic agent of COVID-19 was isolated and the sequence of virus genome was revealed using high-throughput sequencing [4]. Currently, this virus is named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [5] and the disease resulting SARS-CoV-2 was officially named COVID-19 by World Health Organization [6]. Bats have been identified as the possible animal host of SARS-CoV-2 [7] and a mechanism for SARS-CoV-2 infection has been postulated. The timeline of important events marking the SARS-CoV-2 outbreak since the report of the first case on December 26, 2019 is shown in Figure 1. Traditional Chinese medicine (TCM) has a thousand-year history of experience with all types of infectious diseases and has been employed previously as effective treatments for severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) [8]. We report here that TCM is currently in wide use for the treatment of COVID-19. In this review, we summarize the clinical outcome, pathogenesis and current application of TCM for the treatment of COVID-19.

Epidemiology of COVID-19

Zhou et al. found that the genome sequence of a coronavirus isolated from a bat showed 96% similarity with the sequence of SARS-CoV-2; these results suggested that bat species might be a host of SARS-CoV-2. In addition, the earliest cases of COVID-19 were all individuals who reported direct contact with the Huanan Seafood Market in Wuhan, China [9]. Many wild animals such as hedgehog, badger, snake and birds are sold for human consumption at this market, although bats are not typically included in this group. Researchers from South China Agricultural University declared the intermediate host of SARS-CoV-2 could be the Chinese pangolin (*Manis pentadactyla*) although this has not been confirmed at this date.

An article published on *New England Journal of Medicine* on January 29, 2020, reported human-to-human transmission of SARS-CoV-2 [10]. Recent epidemiology studies by Guan et al. [11] documented that only a few COVID-19 patients (1.18%) were in contact with wildlife, while 31.8% of COVID-19 patients traveled to Wuhan recently and 71.80% of COVID-19 patients had recent contact with people from Wuhan.

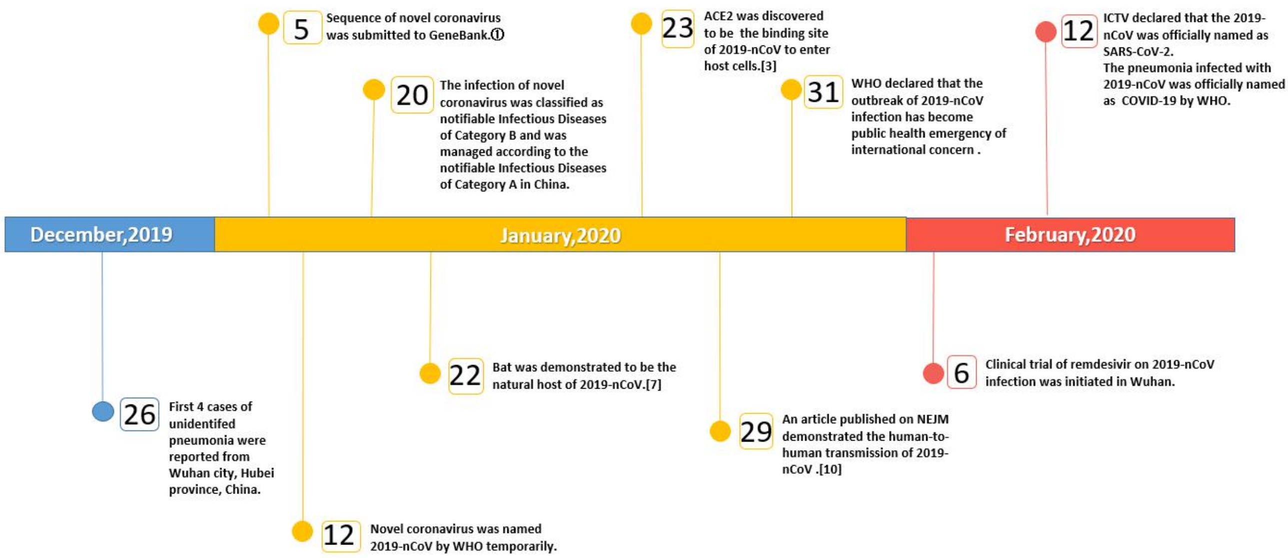

Figure 1 Timeline of important events during SARS-CoV-2 outbreak. COVID-19, coronavirus disease 2019; ACE2, angiotensin-converting enzyme 2; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WHO, World Health Organization; ICTV, International Committee on Taxonomy of Viruses ; NEJM, New England Journal of Medicine; 2019-nCoV, 2019 novel coronavirus; ①, https://www.ncbi.nlm.nih.gov/nuccore/MN908947.

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Respiratory and contact transmission are the main transmission routes of SARS-CoV-2. SARS-CoV-2 RNA is also detected in feces of COVID-19 patients, suggesting the possibility of fecal-oral transmission as another potential transmission route [12–14]. Aerosol and transplacental transmission routes are also regarded as among important possibilities to consider, although there is no substantial research supporting this hypothesis at this time.

Clinical symptoms of COVID-19

The asymptomatic incubation period of SARS-CoV-2 is 0 to 24 days, with a median incubation period of 3 days [11]. Once the disease has taken hold, most of the patients report symptoms including fever, cough, dyspnea, muscle soreness and/or fatigue. Some patients also reported sputum production, headache, hemoptysis and/or diarrhea. Patients with mild symptoms develop low-grade fevers and mild fatigue but no symptoms suggestive of pneumonia. By contrast, patients with severe disease experience dyspnea and hypoxemia which can develop into acute respiratory distress syndrome (ARDS), septic shock, severe metabolic acidosis and coagulation disorders [9–11, 15]. The epidemiology of severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV-2 and clinical features of three different coronavirus syndromes (SARS, MERS and COVID-19) are listed in Table 1 and Table 2, respectively.

Table 1 Epidemiology of SARS-CoV, MERS-CoV and SARS-CoV-2

	SARS-CoV [16, 17]	**MERS-CoV** [17–19]	**SARS-CoV-2** [3, 11, 20]
Date of first detection	November, 2002	June, 2012	December, 2019
Location of first detection	Guangdong province, China	Jeddah, Saudi Arabia	Wuhan city, Hubei province, China
Epidemiological distribution	Large outbreaks of imported cases in South China, Canada and Asia	27 countries and regions in the Middle East, Europe, Africa, Asia and North America	Outbreak in China, imported cases in more than 20 countries and regions such as Japan, Singapore, Thailand and others.
Onset season	Winter	Breeding season of camels	Winter
Natural host	*Rhinolophus sinicus*	Bat (?) [a]	Bat (?) [a]
Intermediate host	Wild mammals (civet in South China)	Camels (Middle East and Africa)	*Manis pentadactyla* (?) [a]
Route of transmission	Droplets, contact	Droplets, contact, airborne (?) [a]	Droplet, contact, fecal-oral (?) [a], aerosol (?) [a], transplacental (?) [a]
Main form of transmission	Human-to-human, animal-to-human	Animal-to-human, human-to-human	Human-to-human, animal-to-human
Incubation period (days)	1.9–14.7	2–14, occasionally up to 21 days	0–24
Age, years (range)	39.9 (1–91)	56 (14–94)	47 (35–48)
Male : female sex ratio	1 : 1.25	3.3 : 1	1.39 : 1
Confirmed cases	8,096	2,494	70,548
Fatal cases	774	858	1,770
Basic reproductive number (R0)	0.3–4.1	0.3–1.3	2.68

The statistical characteristics associated with SARS-CoV-2 were derived from the 1099 patients (as of January 29, 2020) reported by the team of Zhong Nanshan. The number of confirmed cases and deaths was determined by the National Health Commission of the People's Republic of China (information presented as reported through February 16, 2020).

(?) [a], presents the result of current hypotheses but without strong evidence at this time; SARS-CoV, severe acute respiratory syndrome coronavirus; MERS-CoV, Middle East respiratory syndrome coronavirus; COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 2 Clinical characteristics of SARS, MERS and COVID-19

	SARS [17]	MERS [19]	COVID-19 [11]
Common symptoms	Hyperpyrexia (more than 38 °C)	Fever, cough, polypnea	Fever, cough, fatigue
Common extrapulmonary symptoms	Diarrhea	Acute renal failure, diarrhea	Diarrhea, emesis
Imaging features	Interstitial ground-glass changes in lung, parenchymal lesions in mediastinum	Interstitial ground-glass changes in lung, parenchymal lesions in lung	Ground-glass opacity in lung, bilateral patchy opacity in lung
Common complications	ARDS	ARDS, renal failure, disseminated intravascular coagulation and pericarditis	Pneumonia, ARDS, shock
Blood routine and serological tests	Decrease of white blood cells, lymphocytes and blood platelets, increase of ALT and AST	Decrease of white blood cells, lymphocytes and blood platelets in early stage and increase of white blood cells and neutrophil during disease progression, increase of ALT and AST and renal dysfunction	Normal or decrease of white cells, decrease in lymphocytes in mild cases, persistent decrease of lymphocytes in severe cases, increase of ALT, AST, LDH, CK-MB, CRP and ESR in mild cases, increase of cTn in severe cases

SARS, severe acute respiratory syndrome; MERS, Middle East respiratory syndrome; COVID-19: corona virus disease 2019; ARDS, acute respiratory distress syndrome; CK-MB, creatine kinase isoenzyme-MB; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; cTn, cardiac troponin.

Angiotensin-converting enzyme 2: the receptor for SARS-CoV-2 on target cells

During the pandemic phases of SARS-CoV in 2003, angiotensin-converting enzyme 2 (ACE2) was identified as the SARS-CoV receptor on target host cells [21]. DNA sequencing revealed that SARS-CoV-2 genome shares 89% similarity with that of SARS-CoV, suggesting that the mechanisms for SARS-CoV-2 infection of target cells may be similar to that already identified for SARS-CoV [9, 22, 23]. Zhou et al. [9] demonstrated that ACE2 was the cell entry receptor for SARS-CoV-2 in in vitro infectivity studies. Specifically, Hela cells that were genetically modified to express ACE2 from different species including human, Chinese horseshoe bats, civets, pigs and mice were infected with SARS-CoV-2 in vitro. The results demonstrated that ACE2 proteins from all species tested except mice could serve as entry receptors for SARS-CoV-2. Results from experiments using Hela cells expressing human ACE2, or other known coronavirus receptors, including aminopeptidase N and dipeptidyl peptidase 4, revealed that only ACE2 was effective as an entry receptor for SARS-CoV-2 in vitro.

ACE2 is a type I transmembrane protein composed of 805 amino acids and is primarily expressed in the gastrointestinal tract, heart, kidney and lung. As a negative regulator of the renin-angiotensin system, ACE2 plays an important role in maintaining homeostasis of cardiovascular system and regulating absorption of amino acids in kidney and gastrointestinal tract [24]. Genetic studies also reveal the role of ACE2 in preventing stroke [25].

Coronavirus invasion of host cells depends on the actions of the spike protein (S protein) on virus surface. The SARS-CoV S protein includes 2 subunits [26]. The receptor binding domain (RBD) on the S1 subunit interacts with ACE2 to form a virion-ACE2 complex. The virion-ACE2 complex is then transported and enters the endosome of target cells. Subsequently, the structure domain of heptad repeats (HR)1 and HR2 in S proteins interact with one another to form a six-helix bundle core. This core promotes fusion of the viral envelope with cellular membrane. The RNAs of virus are then released into the cytoplasm of target cells (Figure 2) [27, 28]. SARS-CoV virions may also enter the target cell via plasma membrane fusion, via a means similar to that used by human immunodeficiency virus [29].

After entering the target cells, the SARS-CoV RNA genome interacts in a complex with the viral RNA replicase and transcription enzymes. The minus strands of viral RNA are transcribed and are ultimately translated into structural proteins [30]. The cytoplasmic viral RNAs and structural proteins are packaged to form new viruses which are released from infected cells and go on to infect other available target cells in the immediate environment.

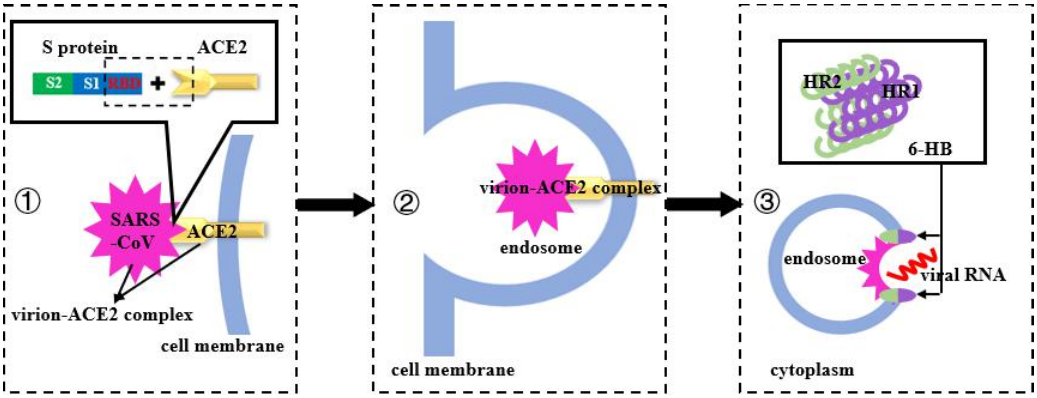

Figure 2 SARS-CoV binds to ACE2 and enters target cell through endosomal membrane fusion. ① The receptor binding domain (RBD) on S1 protein may bind with ACE2 on cell membrane to form virion-ACE2 complex. ② The virion-ACE2 complex is transported and enters the endosome of target cells. ③ The structure domain of heptad repeat (HR) 1 and HR2 in S protein interact with one another to form a six-helix bundle core, which promotes fusion between the viral envelope and the cellular membrane. The virus RNAs are then released into the cytoplasm of target cells.
ACE2, angiotensin-converting enzyme 2; S protein, spike protein; RBD, receptor binding domain; SARS-CoV, severe acute respiratory syndrome coronavirus; HR, heptad repeat; 6-HB, six-helix bundle.

In vivo studies were also carried out to investigate the role of ACE2 in a respiratory disease model. ACE2 gene-deleted mice exhibited severe lung injury and dysfunction of renin-angiotensin system in a model of lung injury induced by cationic polyamidoamine dendrimer nanoparticles; likewise, treatment with an angiotensin II type I receptor antagonist suppressed the sequelae of nanoparticle-induced lung injury in wild-type mice [31]. Creation of an in vivo infection model for SARS-CoV and SARS-CoV-2 was not straightforward, as neither interacts with mouse ACE2. Perlman and colleagues established a human ACE2 transgenic mice model. With this transgenic mouse model, SARS-CoV could be detected in the pulmonary alveoli. It is conceivable that the human ACE2 transgenic mouse model can be an important tool for conducting SARS-CoV-2 infection experiments and for identifying new drugs that would be effective for the treatment of COVID-19 [32, 33].

Role of TCM on treating COVID-19

In TCM, the term “plague” is used to denote infectious disease. From the earliest times, the Chinese people have understood the severity underlying this disease process and have searched for improved understanding. The ancient book of TCM *Huang Di Nei Jing* (*Inner Canon of Huangdi*) was written during Western Han Dynasty in China (approximately 99 B.C.E.–26 B.C.E.) and recorded that plague, with symptoms familiar to modern times, could be transmitted from human-to-human. *Shang Han Za Bing Lun* (*Treatise on Cold Damage Diseases*) written by Zhang Zhongjing (200 C.E.–210 C.E.), *Wen Yi Lun* (*Theory of Plague*) and *Wen Re Lun* (*Theory of Warm*) written by Wu Youke (1642 C.E.) recorded therapies and formulae used to treat plague, including Da Yuan Yin and the use of human variolation to prevent smallpox [34, 35]. Dr. Tu Yoyo credited the discovery of artemisinin for the treatment of malaria according to the early records of *Zhou Hou Fang* (*Handbook of Prescriptions for Emergencies*) written by Ge Hong (284 C.E.–364 C.E.) [36]. TCM has provided significant and important therapies for SARS-CoV, influenza A H1N1, influenza A H7N9 and Ebola virus [37–40]. Consequently, TCM is becoming an important means for developing therapies to treat COVID-19.

Pathogenesis of COVID-19 in TCM theory

Ancient Chinese people believed that man is an integral part of nature. According to this theory, environmental factors are critical elements in the pathogenesis of plague. For example, TCM considers that the characteristics of COVID-19 may largely depend on the environment in Wuhan. During the winter of 2019, a large amount of precipitation fell in Wuhan, which resulted in a moist environment and increased the risk of virus infection. This observation implies that a Chinese herb that promotes the elimination of dampness (a kind of pathological product of disease in TCM theory) can be used in the treatment of COVID-19.

TCM treatments for COVID-19

Classical prescription. The fifth edition of “Standard Therapy of COVID-19” (abbreviated Standard Therapy) published on February 9, 2020, recommended that a modification of the integrated Ma Xin Gan Shi decoction with Da Yuan Yin could be used to improve the chest distress, cough and asthmatic symptoms that develop in COVID-19 [12].

The Ma Xin Gan Shi decoction that includes Mahuang (*Ephedrae herba*), Xingren (*Armeniacae semen amarum*), Gancao (*Glycyrrhizae radix et rhizoma*), Shigao (*Gypsum fibrosum*) together with Da Yuan Yin had significant impact on SARS in 2003 [41, 42]. The use of Da Yuan Yin, composed of Binlang (*Arecae semen*), Houpo (*Magnoliae officinalis cortex*), Caoguo (*Tsaoko fructus*), Zhimu (*Anemarrhenae rhizoma*), Shaoyao (*Dioscoreae rhizoma*), Huangqin (*Scutellariae radix*), Gancao (*Glycyrrhizae raadix et rhizoma*), was first recorded in *Wen Yi Lun* (*Theory of Plague*) (1642 C.E.); this decoction has been used to treat plague for thousands of years. The effectiveness of this decoction for the treatment of SARS was evaluated using a molecular docking method; quercetin, kaempferol, 7-methoxy-2-methyl isoflavone, formononetin and baicalein were identified as the five compounds with highest connectivity to the SARS-CoV 3CL protease [43]. A report dated February 6, 2020 from the State Administration of Traditional Chinese Medicine recommended the use of Qing Fei Pai Du decoction that includes Mahuang (*Ephedrae herba*), Shigao (*Gypsum fibrosum*), Banxia (*Pinelliae rhizoma*), Zhishi (*Aurantii fructus immaturus*), Shengjiang (*Zingiberis rhizoma recens*), that was derived from a modification of the integration of Ma Xing Gan Shi, She Gan Ma Huang, Xiao Chai Hu, and Wu Ling San decoctions in *Shang Han Za Bing Lun* (*Treatise on Cold Damage Diseases*) (200 C.E.–210 C.E.); this recommendation was based on previous experience with SARS and the cold and wet weather in Wuhan. The Qing Fei Pai Du decoction has been demonstrated to be 90% effective in treating COVID-19 [44].

Chinese patent medicine. According to the standard therapy, the patent medicine of Huo Xiang Zheng Qi capsule can be used to treat the gastrointestinal symptoms of COVID-19. Huo Xiang Zheng Qi capsule, derived from *Tai Ping Hui Min He Ji Ju Fang* (*Prescriptions People's Welfare Pharmacy*) written by Chen Shiwen and others (1151 C.E.), has the effects of resolving dampness and is used to treat diarrhea associated with virus infection [45]. The usage of Huo Xiang Zheng Qi capsule for COVID-19 was closely related to the cold and wet weather in Wuhan. Likewise, Lian Hua Qing Wen capsules and Fang Feng Tong Sheng pills can be used to treat fever, fatigue and cough associated with COVID-19 [12]. Lian Hua Qing Wen capsule has broad-spectrum antiviral and antibacterial effects, most notably used for respiratory virus infections including influenza, SARS and MERS [46]. According to a recent retrospective analysis, use of Lian Hua Qing Wen capsule might reduce fever, cough, expectoration, fatigue and difficulty with breathing in COVID-19 patients. Among the findings, the fraction of severe cases was decreased after the treatment of Lian Hua Qing Wen capsule [47, 48].

Other treatments. Other therapies associated with TCM such as acupuncture, moxibustion, and Tai Chi promote health by enhancing the immune system and improving pulmonary function. Although there is no current evidence relating any of these therapies with COVID-19, they may have crucial roles in disease prevention and likewise in promoting recovery of pulmonary function during recuperation from COVID-19. Acupuncture has been shown to relieve the side-effects of hormonal therapy and to alleviate pulmonary injury [49]. *Ben Cao Gang Mu* (*Materia Medica with Commentaries*) written by Li Shizhen (1578 C.E.) recorded that moxibustion could improve digestion, relieve asthma and prevent plague; modern studies reveal that moxibustion can limit the acute inflammatory response in respiratory tract [50]. Tai Chi is a traditional sport in TCM and can enhance recovery of pulmonary function through respiratory training [51]. In addition, Jin Zhi (Gold Juice), first recorded in *Ben Cao Qiu Zhen* (*Truth-Seeking Herbal Foundation*) written by Huang Gongxiu (1769 C.E.), was made from the fermentation of feces from young men. During the Qing dynasty, Jin Zhi was used to reduce fever in patients with plague [52].

Summary and future perspectives

Since the emergence of COVID-19, clinicians and researchers have made great efforts to understand the pathogenesis and clinical characteristics of this infection and to develop effective drugs for its treatment. Currently, there are no effective antiviral available to treat SARS-CoV-2. On February 6, 2020, a clinical trial of remdesivir, a newly-discovered antiviral drug with potential impact on SARS-CoV-2, was initiated in Wuhan. However, given issues related to both safety and efficacy, it will take some time to develop both antiviral drugs and a vaccine to prevent SARS-CoV-2 infection. Western-type antiviral therapies including α-interferon and lopinavir, treatment with antibiotics, and support therapies including oxygen and mechanical ventilation have been used as the treatment of COVID-19. Therapies based on principles of TCM have improved symptoms and enhanced immunity against virus in COVID-19 patients. Positive responses from patients have been noted when efforts are made to combine approaches from TCM and Western medicine on COVID-19. In the future, TCM may also have a role in decreasing the some of the side-effects of Western medicine, notably with respect to recovery of pulmonary function. Finally, we would like to note that many herbs used in these decoctions, including Mahuang *(Ephedrae herba),* Xingren *(Armeniacae semen amarum),* and Chaihu (*Bupleuri radix*) have a bitter taste. Many of the bitter contents of these herbs such as ephedrine and amygdalin are aromatic substances; the hydrophobic properties of these aromatic substances may inhibit the interaction of the virus S protein with ACE2. However,

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due to the complex targets and multiple contents that are characteristics of TCM decoctions, further studies would be needed to elucidate the detailed mechanisms involved in their impact on COVID-19 using network pharmacology analysis, experimental validation and multi-omics.

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