

REVIEW

Combating COVID-19 with integrated traditional Chinese and Western medicine in China



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Abstract COVID-19, an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread throughout the world. China has achieved rapid containment of this highly infectious disease following the principles of early detection, early quarantine and early treatment with integrated traditional Chinese and Western medicine. The inclusion of traditional Chinese medicine (TCM) in the Chinese protocol is based on its successful historic experience in fighting against pestilence. Current findings have shown that the Chinese medicine can reduce the incidence of severe or critical events, improve clinical recovery and help alleviate symptoms such as cough or fever. To date there are over 133 ongoing registered clinical studies on TCM/integrated traditional Chinese and Western medicine. The three Chinese patent medicines (*Lianhua Qingwen Keli/Jiaonang* (Forsythiae and Honeysuckle Flower Pestilence-Clearing Granules/Capsules), *Jinhua Qinggan Keli* (Honeysuckle Flower Cold-Relieving Granules) and *Xuebijing* (Stasis-Resolving & Toxin-Removing) *Injection*) were officially approved by the National Medical Products Administration to list COVID-19 as an additional indication. The pharmacological studies have suggested that Chinese medicine is effective for COVID-19 probably through its host-directed regulation and certain antiviral effects.

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1. Introduction

Coronavirus disease 2019 (COVID-19) is an emerging infectious disease caused by SARS coronavirus 2 (SARS-CoV-2). People with COVID-19 have had a wide range of symptoms from mild symptoms such as fever, cough and fatigue, to severe illness such as acute respiratory distress syndrome (ARDS) likely precipitated by a cytokine storm^{1,2}. The World Health Organization (WHO) declared the COVID-19 outbreak a public health emergency of international concern (PHEIC) on 30 January 2020 and a pandemic on 11 March 2020^{3,4}. Since the outbreak, China has taken unprecedented public health interventions to contain the spread of the virus within China⁵, and has achieved rapid containment of COVID-19 infection following the principles of early detection, early quarantine and early treatment.

According to WHO, there are no vaccines nor specific antiviral treatments for COVID-19. China's treatment protocol using integrated traditional Chinese and Western medicine attracted increasing attention of the international community. Ever since the COVID-19 outbreak, China's National Health Commission has issued seven versions of *Diagnosis and Treatment Protocol for COVID-19*^{6–10}. Traditional Chinese medicine treatment was included in the third version of integrative treatment protocol officially released on January 22, 2020. A body of evidence from clinical practice and research has shown that integrated traditional Chinese and Western medicine played an important role for China's successful battle with COVID-19¹¹.

2. Chinese protocol for treatment of COVID-19

After the outbreak of COVID-19, the National Health Commission of China issued the diagnosis and treatment protocol, and recommended antiviral drug candidates. The National Administration of traditional Chinese medicine recommended traditional Chinese medicine based on pattern identification from the TCM perspective. So far, the protocol has been updated seven times.

The protocol classifies confirmed cases into mild, moderate, severe and critical, and recommends the use of antiviral drugs that might work to combat COVID-19¹², for example, chloroquine phosphate (500 mg bid for adults), arbidol (200 mg tid for adults), and combination of ribavirin with interferon or lopinavir/ritonavir. There is no specific antiviral medicine yet to prevent or treat this condition. These recommendations (Table 1) are based on the experience in treating the infection of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS).

Right after the COVID-19 outbreak, traditional Chinese medicine doctors rushed to the frontline of the epidemic to work with doctors of modern medicine to control the disease and collect clinical data from the TCM perspective. This firsthand information is essential to pattern identification, treatment recommendations, and national prevention and treatment protocol. Their research paper was published online on January 29, 2020¹³.

As we learn more about COVID-19, the protocol of traditional Chinese medicine treatment is continuously updating.

In Trial Version 3, there were no disease stages; just four patterns and four recommended formulas for clinical reference.

In Trial Version 4, there were two periods: medical observation (for suspected cases) and clinical treatment (for confirmed cases). The clinical treatment was further classified into four stages (early/mild, middle/moderate, severe, and convalescence). The protocol recommended five types of Chinese patent medicine for patients during medical observation. These include *Huoxiang Zhengqi Wan* (Agastache Qi-Correcting Pills), *Lianhua Qingwen Zhiji* (Forsythiae and Honeysuckle Flower Pestilence-Clearing Preparations), *Shufeng Jiedu Keli* (Wind-Expelling and Toxin-Removing Granules), and *Fangfeng Tongsheng Zhiji* (Saposhnikoviae Heat-Clearing Preparations). Besides individualized traditional Chinese medicine decoction, the protocol also recommended four Chinese medicine injections for patients during clinical treatment, including *Xiyanping Injection*, *Xuebijing Injection*, *Shenfu Injection* and *Shengmai Injection*.

In Trial Version 6 and 7, the protocol recommended a specific formula for COVID-19—*Qingfei Paidu Tang* (Lung-Cleansing and Toxins-Removing Decoction), along with modified formulas for different stages (mild, moderate, severe, critical, and convalescence). In addition, *Fangfeng Tongsheng Zhiji* was removed from the recommended lists of Chinese patent medicine and four Chinese medicine injections were added (Table 2), including *Reduning Injection*, *Tanreqing Injection*, *Xingnaojing Injection* (major ingredients: moschus, borneol, Gardeniae Fructus, etc.) and *Shenmai Injection* (ingredients: red ginseng and ophiopogon tuber).

In fighting with COVID-19, three Chinese patent medicines and three herbal formulas have been screened for the effective COVID-19 treatment. The three Chinese patent medicines, i.e., *Lianhua Qingwen Keli/Jiaonang* (Forsythiae and Honeysuckle Flower Pestilence-Clearing Granules/Capsules), *Jinhua Qinggan Keli* (Honeysuckle Flower Cold-Relieving Granules) and *Xuebijing* (Stasis-Resolving & Toxin-Removing) *Injection*, were approved by the National Medical Products Administration to list COVID-19 as an additional indication. Among the three herbal formulas, i.e., *Qingfei Paidu Fang* (Lung-Cleansing & Toxin-Removing Formula), *Huashi Baidu Fang* (Dampness-Transforming & Toxin-Removing Formula) and *Xuanfei Baidu Fang* (Lung-Dispersing and Toxin-Removing Formula), the first two were approved by the National Medical Products Administration to perform clinical trials for the COVID-19 treatment.

3. The successful experience of traditional Chinese medicine in containing pestilence

The understanding of pestilence has been documented throughout the history of traditional Chinese medicine (TCM). These theories have evolved over time and played a significant role in epidemic control. Some examples of great creativity became the inspiration of modern medical breakthroughs, such as variolation for the eradication of smallpox, and the discovery of artemisinin for malaria. From 243 before common era (BCE) to 1949, China suffered at least 500 devastating epidemic diseases. Unlike the

Table 1 Development of treatment protocol for COVID-19.

Version	Issued date	Medication	Traditional Chinese medicine treatment
3	1-22-2020	Antiviral therapy: atomization inhalation of α -interferon, and lopinavir/ritonavir tablets. Others: use of glucocorticoids for a short period of time.	Traditional Chinese medicine decoctions Differentiate confirmed cases into four patterns and treat with different traditional Chinese medicine decoctions.
4	1-27-2020	Antiviral therapy: same as version 3. Others: use of glucocorticoids for a short period of time; GI microbiome modulators; and convalescent plasma therapy.	Traditional Chinese medicine decoctions and/or Chinese patent medicine Treat suspected cases with Chinese patent medicine, in particularly for two typical symptoms; differentiate confirmed cases into four stages and treat with traditional Chinese medicine decoctions; and apply traditional Chinese medicine injection to middle stage and severe stage.
5	2-4-2020	Antiviral therapy: atomization inhalation of α -interferon, lopinavir/ritonavir and ribavirin tablets. Others: extracorporeal blood purification for critically ill patients with systemic inflammatory response.	Same as version 4
6	2-18-2020	Antiviral therapy: atomization inhalation of α -interferon, lopinavir/ritonavir tablets, ribavirin (intravenous injection), chloroquine phosphate, and arbidol (using three or more antiviral drugs at the same time is not recommend). Others: same as version 5.	Traditional Chinese medicine decoctions and/or Chinese patent medicine Treat two typical symptoms in suspected cases with Chinese patent medicine ^① ; treat confirmed cases with <i>Qingfei Paidu Decoction</i> ^② and differentiate them into five patterns: mild ^③ , moderate ^④ , severe ^⑤ , critical ^⑥ , and convalescent ^⑦ and treat with different traditional Chinese medicine decoctions. Apply traditional Chinese medicine injection to severe ^⑧ and critical cases ^⑨ .
7	3-3-2020	Antiviral therapy: atomization inhalation of α -interferon, lopinavir/ritonavir tablets, ribavirin (intravenous injection), chloroquine phosphate, and arbidol (using three or more antiviral drugs at the same time is not recommend). Immunotherapy: use tocilizumab for patients with elevated level of IL-6 (contraindicated for patients with active infection such as tuberculosis). Others: intravenous injection of γ -globulin can be used for severe and critically ill children.	Same as version 6

Antonine Plague (165–180 BCE) and Spanish flu pandemic in 1918 that killed millions of lives, epidemic disease in the history of China had been contained soon after the outbreaks. Over time, these successful experiences contributed to an established system to infectious diseases intervention using herbal medicine, non-drug therapies, and numerous single or compound formulas or techniques, such as the well-known *Artemisiae Annuae* for malaria and the use of variolation for smallpox¹⁴. In 2003, TCM and traditional medical physicians made a major contribution to combating SARS in China.

Traditional Chinese medicine shares similar understandings of infectious diseases with modern medicine. It believes that the emergence, outbreak and threat of infectious diseases are closely associated with three interactive factors—epidemic pathogens (pathogenic microorganism), living environment and host (human being, Fig. 1).

Most fundamental theories of traditional Chinese medicine are founded on the *Huang Di Nei Jing* (Yellow Emperor's Inner Classic), an ancient Chinese medical text written in the 2nd

century BCE. This text mentioned the idea of “prevention before disease occurrence”, and the strategies of “prevention of transmission after occurrence” and “prevention of recurrence after recovery”. The measures to “prevent before disease occurrence” include staying away from the source of infection, cutting off the route of transmission, minimizing the environmental impact on susceptible population, and building the body’s self-defending ability against pathogens. After disease occurrence, active measures need to be taken to prevent mild conditions from developing into severe or critical ones. It is also important to take precautions to prevent recurrence upon recovery.

In traditional Chinese medicine, the essential principles for disease prevention and treatment are to “reinforce healthy (anti-pathogenic) qi and remove pathogenic qi” and “treat diseases according to three categories of etiological factors”. To reinforce healthy qi requires regulating the body functions, achieving homeostasis, and maximizing the body’s self-defending ability. In addition to Chinese medicine decoction or patent medicine, nondrug intervention methods include acupuncture, tuina (Chinese

Table 2 Traditional Chinese medicine formulas for COVID-19.

Number	TCM pattern	Ingredient
①	Fatigue and gastrointestinal discomfort	<i>Huoxiang Zhengqi Jiaonang/Wan/Shui/Kou Fu Ye</i> (<i>Agastache</i> Qi-Correcting Capsules/Pills/Oral Liquid)
	Fatigue and fever	<i>Jinhua Qinggan Keli</i> (Honeysuckle Flower Cold-Relieving Granules), <i>Lianhua Qingwen Jiaonang/Keli</i> (<i>Forsythiae</i> and Honeysuckle Flower Pestilence-Clearing Capsules/Granules), <i>Shufeng Jiedu Jiaonang/Keli</i> (Wind-Expelling and Toxin-Removing Capsules/Granules), and <i>Fangfeng Tongsheng Wan/Keli</i> (<i>Saposhnikoviae</i> Heat-Clearing Pills/Granules)
②	Lung-cleansing and toxin-removing decoction	Ma Huang (Ephedrae Herba) 9 g, Zhi Gan Cao (Glycyrrhizae Radix et Rhizoma Praeparata cum Melle) 6 g, Xing Ren (Armeniacae Semen Amarum) 9 g, Shi Gao (Gypsum Fibrosum) 15–30 g, Gui Zhi (Cinnamomi Ramulus) 9 g, Ze Xie (Alismatis Rhizoma) 9 g, Zhu Ling (Polyporus) 9 g, Bai Zhu (Atractylodis Macrocephalae Rhizoma) 9 g, Fu Ling (Poria) 15 g, Chai Hu (Bupleuri Radix) 16 g, Huang Qin (Scutellariae Radix) 6 g, Zi Wan (Asteris Radix et Rhizoma) 9 g, Kuan Dong Hua (Farfarae Flos) 9 g, She Gan (Belamcandae Rhizoma) 9 g, Xi Xin (Asari Radix et Rhizoma) 6 g, Shan Yao (Dioscoreae Rhizoma) 12 g, Zhi Shi (Aurantii Fructus Immaturus) 6 g, Chen Pi (Citri Reticulatae Pericarpium) 6 g, and Huo Xiang (Pogostemonis Herba) 9 g
③	Cold-dampness stagnating in the lung	Ma Huang (Ephedrae Herba) 6 g, Shi Gao (Gypsum Fibrosum) 15 g, Xing Ren (Armeniacae Semen Amarum) 9 g, Qiang Huo (Notopterygii Rhizoma et Radix) 15 g, Ting Li Zi (Descurainiae Semen Lepidii Semen) 15 g, Guan Zhong (Dryopteridis Crassirhizomatis Rhizoma) 9 g, Di Long (Pheretima) 15 g, Xu Chang Qing (Cynanchi Paniculati Radix et Rhizoma) 15 g, Huo Xiang (Pogostemonis Herba) 15 g, Pei Lan (Eupatorium Herba) 9 g, Cang Zhu (Atractylodis Rhizoma) 15 g, Yun Ling (Poria) 45 g, Bai Zhu (Atractylodis Macrocephalae Rhizoma) 30 g, Jiao Mai Ya (Hordei Fructus Germinatus) 9 g, Jiao Shan Zha (Crataegi Fructus) 9 g, Jiao Shen Qu (Massa Medicata Fermentata) 9 g, Hou Po (Magnoliae Officinalis Cortex) 15 g, Jiao Bing Lang (Arecaesementostum) 9 g, Wei Cao Guo (Tsaoko Fructus) 9 g, and Sheng Jiang (Zingiberis Rhizoma Recens) 15 g
	Damp-heat accumulating in the lung	Bing Lang (Arecaesementostum) 10 g, Cao Guo (Tsaoko Fructus) 10 g, Hou Po (Magnoliae Officinalis Cortex) 10 g, Zhi Mu (Anemarrhenae Rhizoma) 10 g, Huang Qin (Scutellariae Radix) 10 g, Chai Hu (Bupleuri Radix) 10 g, Chi Shao (Paeoniaeradix Rubra) 10 g, Lian Qiao (Forsythiae Fructus) 15 g, Qing Hao (Artemisiae Annuae Herba) 10 g, Cang Zhu (Atractylodis Rhizoma) 10 g, Da Qing ye (Isatidis Folium) 10 g, and Gan Cao (Glycyrrhizae Radix et Rhizoma) 5 g
④	Damp toxin stagnating in the lung	Ma Huang (Ephedrae Herba) 6 g, Xing Ren (Armeniacae Semen Amarum) 15 g, Shi Gao (Gypsum Fibrosum) 30 g, Yi Yi Ren (Coicis Semen) 30 g, Cang Zhu (Atractylodis Rhizoma) 10 g, Huo Xiang (Pogostemonis Herba) 15 g, Qing Hao (Artemisiae Annuae Herba) 12 g, Hu Zhang (Polygoni Cuspidati Rhizoma et Radix) 20 g, Ma Bian Cao (Verbenae Herba) 30 g, Gan Lu Gen (Phragmitis Rhizoma) 30 g, Ting Li Zi (Descurainiae Semen Lepidii Semen) 15 g, Ju Hong (Citri Exocarpium Rubrum) 15 g, and Sheng Gan Cao (Glycyrrhizae Radix et Rhizoma) 10 g
	Cold-dampness obstructing the lung	Cang Zhu (Atractylodis Rhizoma) 15 g, Chen Pi (Citri Reticulatae Pericarpium) 10 g, Hou Po (Magnoliae Officinalis Cortex) 10 g, Huo Xiang (Pogostemonis Herba) 10 g, Cao Guo (Tsaoko Fructus) 6 g, Sheng Ma Huang (Ephedrae Herba) 6 g, Qiang Huo (Notopterygii Rhizoma et Radix) 10 g, Sheng Jiang (Zingiberis Rhizoma Recens) 10 g, and Bing Lang (Arecaesementostum) 10 g
⑤	Epidemic toxin blocking the lung	Ma Huang (Ephedrae Herba) 6 g, Xing Ren (Armeniacae Semen Amarum) 9 g, Shi Gao (Gypsum Fibrosum) 15 g, Gan Cao (Glycyrrhizae Radix et Rhizoma) 3 g, Huo Xiang (Pogostemonis Herba) 10 g, Hou Po (Magnoliae Officinalis Cortex) 10 g, Cang Zhu (Atractylodis Rhizoma) 15 g, Cao Guo (Tsaoko Fructus) 10 g, Fa Ban Xia (Pinelliae Rhizoma Praeparatum) 9 g, Fu Ling (Poria) 15 g, Da Huang (Rhei Radix et Rhizoma) 5 g, Huang Qi (Astragali Radix) 10 g, Ting Li Zi (Descurainiae Semen Lepidii Semen) 10 g, and Chi Shao (Paeoniaeradix Rubra) 10 g
	Flaring heat in both qi and ying phases	Shi Gao (Gypsum Fibrosum) 30–60 g, Zhi Mu (Anemarrhenae Rhizoma) 30 g, Sheng Di (Rehmanniae Radix) 30–60 g, Shui Niu Jiao (Bubali Cornu) 30 g, Chi Shao (Paeoniaeradix Rubra) 30 g, Xuan Shen (Scrophulariae Radix) 30 g, Lian Qiao (Forsythiae Fructus) 15 g, Dan Pi (Moutan Cortex) 15 g, Huang Lian (Coptidis Rhizoma) 6 g, Zhu Ye (Lophatheri Herba) 12 g, Ting Li Zi (Descurainiae Semen Lepidii Semen) 15 g, and Gan Cao (Glycyrrhizae Radix et Rhizoma) 6 g
⑥	Internal blocking causing external collapse	Take <i>Suhexiang Wan</i> (Storax Pill) or <i>Angong Niuhuang Wan</i> (Peaceful Palace Bovine Bezoar Pill) with the decoction of Ren Shen (Ginseng Radix et Rhizoma) 15 g, Hei Fu Zi (Aconiti Lateralis Radix Praeparaia) 10 g, and Shan Zhu Yu (Corni Fructus) 15 g
⑦	Qi deficiency of the lung and spleen	Fa Ban Xia (Pinelliae Rhizoma Praeparatum) 9 g, Chen Pi (Citri Reticulatae Pericarpium) 10 g, Dang Shen (Codonopsis Radix) 15 g, Zhi Huang Qi (Astragali Radix Praepara cum Melle) 30 g, Chao Bai Zhu (Atractylodis Macrocephalae Rhizoma) 10 g, Fu Ling (Poria)

Table 2 (continued)

Number	TCM pattern	Ingredient
	Deficiency of qi and yin	15 g, Huo Xiang (Pogostemonis Herba) 10 g, Sha Ren (Amomi Fructus) 6 g, and Gan Cao (Glycyrrhizae Radix et Rhizoma) 6 g
⑧	Severe	Nan Sha Shen (Adenophorae Radix) 10 g, Bei Sha Shen (Glehniae Radix) 10 g, Mai Dong (Ophiopogonis Radix) 15 g, Xi Yang Shen (Panacis Quinquefolii Radix) 6 g, Wu Wei Zi (Schisandrae Chinensis Fructus) 6 g, Shi Gao (Gypsum Fibrosum) 15 g, Dan Zhu Ye (Lophatheri Herba) 10 g, San Ye (Mori Folium) 10 g, Lu Gen (Phragmitis Rhizoma) 15 g, Dan Shen (Codonopsis Radix) 15 g, and Gan Cao (Glycyrrhizae Radix et Rhizoma) 6 g <i>Xiyanping Injection, Xuebijing Injection, Reduning Injection, Tanreqing Injection, and Xingnaojing Injection.</i> (These injections can be used in combination with traditional Chinese medicine decoction)
⑨	Critical	<i>Xuebijing Injection, Reduning Injection, Tanreqing Injection, Xingnaojing Injection, Shenfu Injection, Shengmai Injection, and Shenmai Injection</i> (One or two injections can be used together, in combination with traditional Chinese medicine decoction)

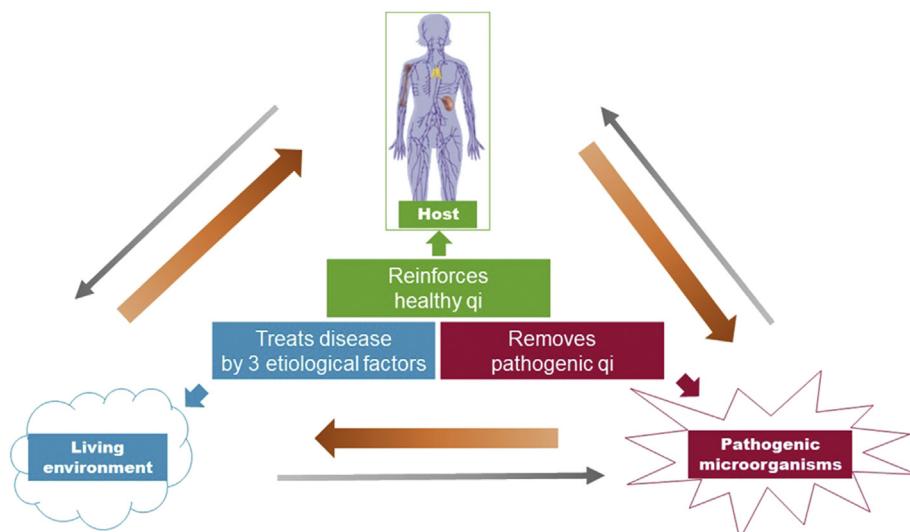


Figure 1 A diagrammatic illustration: essential TCM theory on pestilence prevention and treatment. This includes prevention and treatment strategies. Prevention strategy: to stop pathogens from attacking the host, change the existing environment of pathogens, and make the host stay away from pathogens. Treatment strategy: to reinforce healthy qi to boost the host's ability to defend against diseases, and to remove pathogenic factors, i.e., to fight off pathogens.

therapeutic massage), qigong, mental adjustment and nutrition. To treat disease by three categories of three etiological factors requires the physician to conduct individualized precision intervention according to different timing, geographic region and population groups.

The *Shang Han Lun* (Treatise on Cold Damage) written in the 2nd century is another classic text of traditional Chinese medicine, which preliminarily established the system of Chinese herbal medicine. This text recorded a total of 113 compound formulas and usage for infectious diseases. Like precision medicine, these formulas are modified according to individual conditions. As most of these formulas are directed at regulating the body functions, they have also been widely used for non-communicable diseases in China and Japan. They have survived the passage of time and are still regarded as having great relevance in today's environment. The recommended formulas (Fig. 2) in the Chinese protocol for the diagnosis and treatment

of COVID-19 have all been proven effective in the long history of combating infectious diseases. The safety and efficacy of some formulas have been proven by evidence-based clinical trials, for example, *Ma Xing Shi Gan Tang* (Ephedra, Apricot Kernel, Gypsum and Licorice Decoction)—*Yin Qiao San* (Lonicera and Forsythia Powder) for H1N1¹⁵.

4. Current status of clinical studies on integrated traditional Chinese and Western medicine for COVID-19

Unlike evidence-based modern medicine, traditional Chinese medicine is an empirical medicine developed on accumulated clinical observations gathered over centuries of practice. It not only deals with the etiological factor to eradicate the pathogenic microbial, but also supports the body's immune function to help fight the disease and ameliorate its consequences. In ancient times, when facing infectious disease, specific pathogens could not be

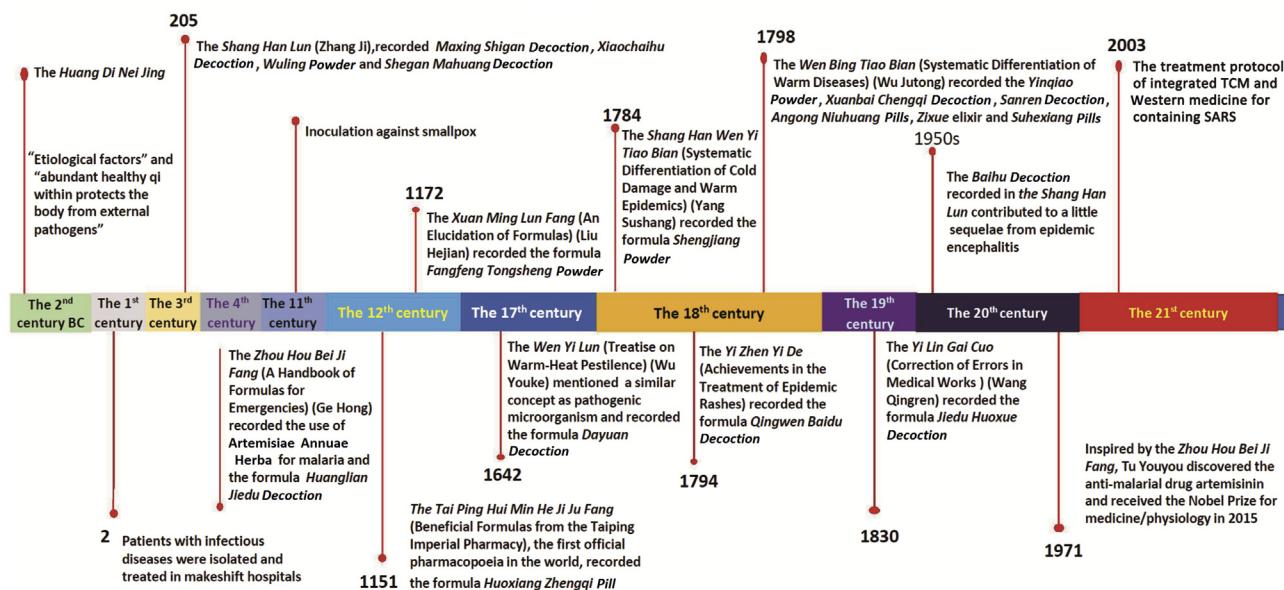


Figure 2 A brief history timeline: traditional Chinese medicine for pestilence prevention and treatment of infectious diseases.

identified; however, doctors could observe the patient's sign and symptoms, assess the condition and develop strategies and formulas for the different stages of the illness.

So far there are over 133 ongoing registered clinical studies on TCM/integrated traditional Chinese and Western medicine. The results of 16 published papers on this topic (not including case reports) and a systematic review on 8 clinical trials (804 cases) have suggested that integrated traditional Chinese and Western medicine can reduce the incidence of severe or critical events, improve clinical recovery and help alleviate symptoms such as cough or fever¹⁶. Two papers^{17,18} reported the detailed information of its adverse reactions during the treatment for COVID-19.

4.1. Overview of registered clinical studies

A search was performed on clinical trial registries of privately and publicly funded clinical trials worldwide. We selected Chinese clinical trial registries (www.chictr.org.cn/) and U.S. (<https://clinicaltrials.gov/>). Our search strategy was designed to identify all the clinical trials that were registered for COVID-19. The following search terms were used for our search to capture relevant studies: “2019 novel coronavirus”, “2019-nCoV”, “COVID-19”, “SARS-CoV-2”, and “novel coronavirus pneumonia (in Chinese)”. The eligibility criteria were developed using the Patient Intervention Comparison Outcomes Study type (PICOS) framework¹⁹.

Up until March 25, 2020, 642 registered clinical trials on COVID-19-related were retrieved from Chinese Clinical Trial Registry (ChinCTR) and ClinicalTrials.org, among which 514 were registered in ChinCTR, and 133 were about traditional Chinese medicine/integrated traditional Chinese and Western medicine. The research subjects of the 133 trials include confirmed cases (mild, moderate, and convalescent), suspected cases and those who had been in close contact with a confirmed case. The planned sample size was 52,744 cases. The smallest sample size was 16 cases (case-control study, Guangzhou). The largest sample size was 20,000 cases (Health Service Research, Chengdu). 103 of the 133 trials were related to interventions (including 13 nondrug therapies such as exercise and

acupuncture), among which 77 were randomized controlled clinical trials (74.76%) and only 6 were double-blind design. Conventional Western medicine was used as control (symptomatic treatment or standard treatment). These trials measured 416 outcomes, including 220 primary outcomes such as time to defervescence, routine blood test, pulmonary functions, chest CT scan, St. George’s Respiratory Questionnaire (SGRQ), TCM patterns, length of hospital stay and the viral negative-transforming time. The top 3 research organizations for registered clinical trials on COVID-19 were Hubei University of Traditional Chinese Medicine (Wuhan, 13 trials), Shanghai University of Traditional Chinese Medicine (Shanghai, 12 trials) and Chengdu University of Traditional Chinese Medicine (Chengdu, 9 trials, Table 3).

4.2. Ethical review process

Ever since the outbreak of COVID-19 epidemic, ethical reviews have been performed on all related clinical studies to protect research participants. On January 30, 2020, the consensus on Clinical Trial Management under the First-Level Response to Major Public Health Emergency was issued during the China Forums of Clinical Research Capacity Building and Human Research Participants Protection (CCHRPD, Version1.0)²⁰. This was followed by the consensus on Clinical Trial Management under the First-Level Response to Major Public Health Emergency (Infectious Diseases) (Version 2.0) on February 2, 2020²¹. On February 13, 2020, the operation instructions on using teleconference for ethical review were published on Chinese Medical Ethics online²². On February 19, 2020, the Chinese version of Guidance for Managing Ethical Issues in Infectious Disease Outbreaks was officially released by the Institutional Review Board, World Federation of Chinese Medicine Societies²³. On February 25, the Guideline on Regulating Clinical Trials of COVID-19 Drugs among Medical Organizations was issued by the National Ministry of Science and Technology²⁴. On March 23, 2020, Chinese scholars published a paper on ethical review online in *JAMA*²⁵, which summarized ethical committee reviews and

Table 3 Registered TCM clinical studies on COVID-19.

Category	Traditional Chinese medicine/interventional measure
Chinese patent medicine	<i>Tanreqing Injection/Capsules, Babao Elixir, Reduning Injection, Xiyaping Injection, Shenfu Injection, Jingyin Granules, Xuebijing Injection, Kesouting Syrup, Keqing Capsule, Jinyinhua Oral Liquid, Xiangxue Kangbingdu Oral Liquid, Lianhua Qingwen Capsules/Granules, Shuanghuanglian Oral Liquid, Shenqi Fuzheng Oral Liquid, Jinye Baidu Granules, Liushen Pills/Capsules, Fufang Yuxingcao Mixture, Zedoray Turmeric Oil Injection, Qingqiao Kangbingdu Granules, Fufang Yinchai Granules, Shufeng Jiedu Capsules, Qingwen Baiduyin Peifang Granules, Ganke Shuangqing Capsules, Hamma Capsules, Chansu Injection, Huajuhong Tanke Liquid, Gushen Dingchuan Pills and Huashi Baidu Granules</i> (45 studies)
Exercise	Traditional qigong exercise, breathing of six healing sounds, turtle breathing qigong (to benefit the lung), healthy qigong, daoyin, eight-step lung-benefiting exercise, baduanjin, meditation (10 studies)
Classical formula	<i>Maxing Shigan Decoction, Shengjiang Powder, and Shenling Baizhu Powder</i> (3 studies)
Acupuncture	Point pressure, needling, applying magnetic seeds to auricular points (3 studies)
Tuina	Chest-soothing and qi-regulating manipulation, tuina (2 studies).

found that the ethical approval during an epidemic outbreak was more quickly; however, the review standards were not lowered.

4.3. Role of current research findings in clinical practice

According to a retrospective study on 1305 COVID-19 cases treated in Wuhan University Tongren Hospital, patients who took Chinese medicine preparations had a smaller death risk than those who did not ($0.273, P < 0.05$); severe/critically ill patients had 74.364 times increased death risk than patients with moderate conditions ($P < 0.05$); and patients with pre-existing medical conditions had 29.420 times increased death risk ($P < 0.05$)²⁶. In addition, we searched MEDLINE, EMBASE, WANFANG DATA and CNKI, manually removed papers irrelevant to traditional Chinese medicine or clinical trials, and retrieved 16 clinical trial papers on traditional Chinese medicine/integrated traditional Chinese and Western medicine for COVID-19^{27–41}, involving a total of 1529 cases (shown in Table 4). Preliminary study findings have shown that integrated traditional Chinese and Western medicine had a shorter time to defervescence than standard Western medicine treatment alone.

A multicenter, prospective, and randomized controlled trial ($n = 284$) showed *Lianhuaqingwen Capsule*, a repurposed marketed Chinese herb product, could be considered to ameliorate clinical symptoms of COVID-19. Compared with control group, the recovery rate (91.5% vs. 82.4%, $P = 0.022$), the rate of improvement in chest computed tomographic manifestations (83.8% vs. 64.1%, $P < 0.001$) and clinical cure (78.9% vs. 66.2%, $P = 0.017$) were significantly higher, the median time to symptom recovery (median: 7 vs. 10 days, $P < 0.001$), time to recovery of fever (2 vs. 3 days), fatigue (3 vs. 6 days) and coughing (7 vs. 10 days) were significantly shorter in treatment group⁴². Another retrospective analysis on 308 cases³⁴ have suggested that, after receiving traditional Chinese medicine treatment, all mild and moderate COVID-19 cases recovered and none became severe/critical.

In terms of adverse reactions, *Jinhua Qinggan Granules* caused diarrhea in 32.93% (27/82) of the patients¹⁷; Zhang et al.¹⁸ reported *Qingfei Paidu Decoction* caused excessive sweating in 2 cases, gastric pain in 20 causes, nausea and vomiting in 8 cases, diarrhea in 16 cases, elevated serum transaminase in 11 cases, palpitations in 4 cases, elevated blood pressure in 2 cases, elevated blood sugar in 3 cases, insomnia in 7 cases, and skin allergy in 1 case. The author advised modification for individual patients, for example, *Qingfei Paidu Decoction* is not indicated for patients with a red tongue with scanty coating (due to stomach yin deficiency). It is also worth noting some adverse reactions are associated with the combination

of Western medication, for example, the serum transaminase can be restored normal after discontinuation of arbidol alone or discontinuation of both arbidol and *Qingfei Paidu Decoction*.

4.4. Limitations of clinical studies

On March 18, Drifa et al.⁴³ published a brief review of antiviral drugs evaluated in registered clinical trials for COVID-19 in medRxiv. Their study underlines the need to register as much details as possible on clinical trials registries during outbreaks in order to inform the development of future trials. And they believe reporting as much details as possible is key to have consistent clinical trials and to enhance the reproducibility of the results, especially as studies are more often associated with a low number of planned inclusions and composite or weak outcomes that can limit the efficacy assessment of the treatments. Our study data found similar limitations in registered TCM clinical trials.

As shown in Table 4, except for three randomized controlled trials, the rest of the published clinical studies are observational, whose overall evidence is relatively low. Due to insufficient studies and a large heterogeneity in outcome measures, it is too soon to conduct a systematic review. Higher levels of evidence are further needed to justify the efficacy of traditional Chinese medicine treatment for COVID-19. It is worth noting that it is challenging to conduct large-scale randomized controlled trials (RCT) during an ongoing pandemic, especially the ethical issue of RCTS with a double-blind design. However, it is a unique setting to prioritize the patients' safety, deliver precision treatment and, at the same time, conduct pilot studies in clinical research.

4.5. Pharmacological studies

Chinese medicine formulas recommended in the Chinese protocol are composed of multiple ingredients. The roles of these ingredients are categorized into monarch, minister, assistant and guide according to their roles. This categorization is based on the two characteristics of traditional Chinese medicine: a holistic concept and treatment based on pattern identification. The sequences of R&D strategy in Chinese medicine are safety and efficacy in patients (clinical experience), then safety and efficacy in animals, and finally clinical trials. The "clinical experience-clinical trial" model works for epidemic control and saving lives.

Application of TCM in the treatment of the patients with COVID-19 is largely inspired by the treatment of SARS in the late of 2002⁴⁴. Different from Western medicine, TCM exerted broad-spectrum antiviral and immune regulatory effects to treat COVID-

Table 4 Characteristics of clinical trials (16 published clinical trial papers on traditional Chinese medicine/integrated traditional Chinese and Western medicine for COVID-19).

Author	Design	n		Treatment (T)	Control (C)	Outcome
		C	T			
Ding ²⁷	RCT	49	51	<i>Qingfei Touxie Fuzheng Formula + C</i>	Antibiotics, antiviral drugs and mechanical ventilation	①②③④⑤⑥
Yao ²⁸	RCS	21	21	<i>Lianhua Qingwen Capsules + C</i>	Standard treatment (unknown details)	①②⑦
Xia ²⁹	RCS	18	34	TCM decoction + Chinese patent medicine + TCM injection + C	Antibiotics, antiviral drugs, immunologic agents, and glucocorticoids	①②④⑤⑦⑧⑨
Qu ³⁰	RCS	30	40	<i>Shufeng Jiedu Granules + C</i>	Standard treatment (unknown details)	①②⑧⑩⑪
Shi ³¹	RCS	18	49	TCM decoction + Chinese patent medicine + C	Oxygen therapy, antiviral drugs, anti-inflammatory drugs, and immunologic agents	①②⑤⑦⑧
Cheng ³²	BA	0	54	<i>Lianhua Qingwen Capsules + C</i>	Antiviral drugs, immunologic agents, and glucocorticoids	①②⑦
Huang ³³	CS	0	111	TCM decoction + Chinese patent medicine + TCM injection + Standard treatment (unknown details)	N	①②⑦⑧⑨⑩
Fang ³⁴	RCS	0	308	TCM decoction + Chinese patent medicine + TCM injection + antiviral drugs, immunologic agents, and glucocorticoids	N	①②⑤⑦⑨
Yang ³⁵	MCT	26	28	<i>Reyanning Mixture + C</i>	Antiviral drugs, interferon	①②③④⑤⑥⑧⑨⑩⑪
Wang ³⁶	BA	0	98	<i>Qingfei Paidu Decoction</i>	N	①②④⑨⑪
Xiao ³⁷	CT	100	100	<i>Shufeng Jiedu Capsule + C</i>	Arbidol	①②④⑤⑧⑪
Duan ¹⁷	RCT	41	82	<i>Jinhua Qinggan Granules + C</i>	Antibiotics, antiviral drugs and mechanical ventilation	②④⑥⑨⑪⑫
Chen ³⁸	BA	0	131	<i>Ganlu Xiaodu Decoction + oxygen therapy, antiviral drugs, anti-inflammatory drugs, Chinese patent medicine + TCM injection and immunologic agents</i>	N	②③④⑤⑥⑦⑧⑨⑩⑪
Yang ³⁹	BA	0	40	Matrine and Sodium Chloride Injection + oxygen therapy, antiviral drugs, anti-inflammatory drugs, and immunologic agents	N	②③④⑤⑥⑨⑩⑪
Li ⁴⁰	BA	0	6	Lung-toxin dispelling formula No. 1 + oxygen therapy, antiviral drugs, antibiotics, Chinese patent medicine, TCM injection	N	①②③④⑤⑥⑨⑩
Fu ⁴¹	RCT	36	37	<i>Toujie Quwen Granules + C</i>	Arbidol	①②④⑤⑥⑨⑩⑪

RCT, randomized controlled trial; RCS, retrospective cohort study; BA, before-and-after comparison; CS, case-control study; MCT, multicenter controlled trial; N, No; C, control; T, treatment.

① defervescence; ② improvement of main symptoms (cough, fatigue, a poor appetite and diarrhea); ③ inflammatory factors; ④ blood test results; ⑤ improvement by CT (scan inflammatory absorption shown in chest X-ray); ⑥ oxygenation index; ⑦ death rate; ⑧ clinical recovery; ⑨ numbers and ratios from moderate to severe or fatal; ⑩ negative of novel coronavirus nucleic acid; ⑪ numbers and ratios of adverse reactions; ⑫ Hamilton Anxiety Scale.

19. For example, *Lianhua Qingwen Capsules* exerted its anti-coronavirus activity by inhibiting the SARS-CoV-2 replication and reducing the cytokine release from host cells, thus supporting the clinical application for COVID-19⁴⁵. In addition, *Liu Shen*

Capsule significantly inhibited SARS-CoV-2 replication in Vero E6 cells, greatly reduced the production of pro-inflammatory cytokines (TNF- α , IL-6, IL-1 β , IL-8, CCL-2/MCP-1 and CXCL-10/IP-10), and regulated the activity of NF- κ B/MAPK signaling

pathway *in vitro*⁴⁶. With multiple components, multiple targets and multiple links, compound Chinese medicine formulas produce an overall regulation of the body. Studies have shown that some Chinese medicine indirectly inhibit virus growth via host-directed regulation to boost the immune function of the host or inhibit virus-mediated inflammatory response, and some Chinese medicine can directly exhibit broad-spectrum antiviral effects, such as Jin Yin Hua (Flos Lonicerae Japonicae), Huang Qin (Radix Scutellariae) and Da Qing Ye (Folium Isatidis)⁴⁷. In the past decade, scientists have confirmed multiple components in TCM with immune regulatory and antiviral activity. Due to the similarity of SARS-CoV-2 and other RNA viruses, these naturally occurring compounds from TCM in previous studies may have the capacity to inhibit SARS-CoV-2⁴⁴. Yang et al.⁴⁴ have summarized TCM herb formulae against SARS-CoV and ongoing TCM clinical trials for the treatment of SARS-CoV-2 infection. Moreover, through analysis of historical records on prevention and treatment of SARS and H1N1 influenza infections and the frequency of TCM used in 23 provinces, Luo et al.⁴⁸ concluded that the most frequently used herbs contained Astragalus Radix (Huang Qi), Radix glycyrrhizae (Gan Cao), Saposhnikoviae Radix (Fang Feng), Atractylodis Macrocephalae Rhizoma (Bai Zhu), Lonicerae Japonicae Flos (Jin Yin Hua), and Forsythia Fructus (Lian Qiao).

4.5.1. Host-directed regulation

COVID-19 caused by SARS-CoV-2 is mainly associated with rapid virus replication, massive inflammatory cell infiltration and elevated pro-inflammatory cytokine responses^{45,49}. TCM works not only to inhibit the virus, but to block the infection, regulate the immune response, cut off the inflammatory storm, and promote the repair of the body⁵⁰, such as *Lianhua Qingwen Capsules*, which suppressed the increased cytokine (TNF- α , IL-6, CCL-2/MCP-1, and CXCL-10/IP-10) release in a dose-dependent manner, when host cells were infected with HCoV-229E and SARS-CoV-2⁴⁵. Since viral pneumonia involves infection, inflammation, immune response, blood coagulation, tissue injury, and genetic polymorphism, Ye et al.⁵¹ constructed a component-target-pathway to analyze the components in *Lianhua Qingwen Capsules* and pathways to boost immunity, such as T cells, B-cell receptor signaling, natural killer (NK) cell-mediated cytotoxicity, and anti-inflammatory Fc epsilon RI, ErbB, and MAPK signaling pathways. Of ten inflammatory and immune signals, formononetin, rutin, emodin 8-O- β -D-glucoside, hyperoside, loganic acid, and salidroside are more important than the other components. Consequently, *Lianhua Qingwen Capsules* have antiviral effect as well as anti-inflammatory and immune mechanism of action.

Network pharmacological study⁵² has suggested that the compound formula *Qingfei Paidu Decoction* contains 948 chemical components, which act via modulation of 790 potential target proteins. The protein–protein interactions may form a molecular network. As modulations of these targets may regulate immunity- and cytokine-related pathways, inhibit the activation of cytokines, and thus mediate overactive immune response and reduce inflammation, multiple active components of Chinese medicine have been found to protect organ damage from virus infection, virus replication and secondary inflammatory factors. Liu et al.⁵³ studied major chemical components in *Qingfei Paidu Decoction* and tissue distribution in mice using UHPLC–Q-Orbitrap HRMS technology. They identified 39 chemical components, among which 9 can be rapidly absorbed and distributed over multiple tissues. Except for baicalin (exhibited a peak value at 2 or 4 h), the

serum and tissue concentrations of the other eight components exhibited a peak value within 0.5 h. At 0.5 h, the exposed components in the lung tissues (in sequence) are ephedrine, prunasin, pseudoephedrine, amygdalin, hesperidin, irisflorentin, baicalin, hyperin, and liquiritin; and the concentrations of ephedrine, prunasin, pseudoephedrine and baicalin remained high at 2 and 4 h. These findings provided pharmacokinetic information for its further efficacy study and clinical use. Previous studies have suggested that ephedrine, pseudoephedrine and amygdalin have notable anti-inflammatory⁵⁴ and immunomodulatory actions⁵⁵, and therefore, are main components in therapeutic drugs for respiratory disorders. Zhang et al.⁵⁶ found that amygdalin could protect acute lipopolysaccharide (LPS)-induced lung damage through inhibiting nuclear factor kappa-B (NF- κ B) and LRR and PYD domains-containing protein 3 (NLRP3) signaling pathways.

Network pharmacology and molecular docking have also been used in potential targets and action mechanism of recommended formulas in the *Diagnosis and Treatment Protocol for COVID-19*^{57–71}. In traditional Chinese medicine treatment protocol for COVID-19, *Xuanfei Paidu Keli* (Lung-Dispelling and Toxins-Removing Granules), *Shengjiang San*, *Sangju Yin* (Mulberry Leaf and *Chrysanthemum* Beverage), *Yinqiao San* (*Lonicera* and *Forsythia* Powder), *Lianhua Qingwen Jiaonang* (*Forsythiae* and *Honeysuckle Flower Pestilence-Clearing Capsules*), *Maxing Shigan Tang* (*Ephedra*, Apricot Kernel, Gypsum and Licorice Decoction), *Maxing Yigan Tang* (*Ephedra*, Apricot Kernel, Coicis and Licorice Decoction), *Haoqin Qingdan Tang* (Sweet Wormwood and *Scutellaria* Gallbladder-Clearing Decoction), *Xueshi Wuye Lugen Tang* (Xue's Five Leaves Reed Rhizome decoction) and *Kangbingdu Keli* (anti-viral granules) work for both the virus and human body; *Huoxiang Zhengqi Formula*, *Jinhua Qinggan Granules*, *Lianhua Qingwen Capsules*, *Maxing Shigan Tang*, *Xuebijing Injection*, *Qingfei Paidu Tang*, *Dayuan Yin* (*Arecae* and *Magnoliae Officinalis* Liquid), *Xiaochaihu Tang* (Minor *Bupleurum* Decoction), *Shashen Maidong Tang* (*Glehniae* and *Ophiopogon* Decoction), *Qingwen Baidu San* (Epidemic-Clearing Toxin-Resolving Powder), *Shenzhu San* (Atractylodis and *Angelicae Dahuricae* Powder), *Huanglian Jiedu Tang* (Coptis Toxin-Resolving Decoction), *Shengmai Injection* and *Xuebijing Injection* can help with COVID-19 cases by reducing expression of inflammatory factors, inhibiting cytokine storm, decreasing oxidative stress and apoptosis, boosting immune functions, regulating energy metabolism, promoting nutrient absorption and metabolism, improving cardiopulmonary function, and modulating nervous system.

4.5.2. Anti-coronavirus effects

Some Chinese medicine directly exhibit broad-spectrum antiviral effects, some were found to possess their anti-coronaviruses effects via potential targets such as SARS-CoV-2 3CL protease, RNA dependent RNA polymerase (RdRp), papain-like protease (PL^{pro}), helicase, and spike glycoprotein (Spike). Ye et al.⁵¹ studied the molecular mechanism of *Lianhua Qingwen Capsules* for COVID-19 via molecular docking. By docking and scoring of 21 compounds and SARS-CoV-2 3CL protease, they found that the scores of rutin, forsythoside B and hyperoside are higher than lopinavir; and hyperoside might be the most potential SARS-CoV-2 3CL protease inhibitor. Wu et al.⁵⁷ systematically analyzed all the proteins encoded by SARS-CoV-2 genes, selected a total of 21 targets, including two human targets (ACE2 and TMPRSS2) and screened a ZINC drug database (2924 compounds) and natural products database of their own (containing 1066 chemicals), and a

database of 78 anti-viral drugs using target-based computer virtue screening. They found that some natural flavanoids, licoflavonol from *Glycyrrhiza uralensis*, cosmosin from *Scutellaria baicalensis*, neohesperidin from *Citrus aurantium*, mangostin from *Garcinia mangostana*, kouitchenside D from *Swertia kouitchensis*, excoecariatoxin from *Excoecaria agallocha*, phyllaemblicin G7 from *Phyllanthus emblica*, and piceatannol from *Vitis vinifera*, exhibited high binding affinity. The only compound that could target the binding interface between Spike and ACE2 was hesperidin. This study provided new lead compounds, targets and research strategy for further *in vivo* and *in vitro* anti-SARS-CoV-2 research. Chinese medicinal plant Jin Yin Hua (Flos Lonicerae Japonicae) can remarkably inhibit influenza virus⁷², EV71⁷³, and Dengue virus type 2⁷⁴. Its active antiviral components include chlorogenic acid⁷⁵, flavonoids and triterpene saponins⁷⁶. It is a major component of *Yinhuang Injection*, *Shuanghuanglian Injection*, *Yinhuang Tablets*, *Vitamin C Honeysuckle Pills* and *Yinhuang Tablets*, which are commonly used for fever and respiratory tract infections⁷⁷. Huang Qin (Radix Scutellariae) can inhibit respiratory syncytial virus, influenza virus and Coxsackie virus^{78–80}. Its chemical components include flavonoids, flavonols (baicalin, baicalein, wogonoside, wogonin, dihydrobaicalin, etc.), terpenoids, volatile oil, trace elements and polysaccharide⁸¹. Rao and his team⁸² screened baicalein, a SARS-CoV 3CL protease inhibitor, and assumed that flavonoids have the similar activity as they share the similar structure. Enzyme inhibitory assays have found that scutellarein, quercetagetin, myricetin and robinetin can inhibit SARS-CoV 3CL protease. During the study on active anti-SARS-CoV compounds, we screened a natural product quercetin-3-β-galactoside, a potential SARS-CoV 3CL protease inhibitor, from MDL-ACD database. Its inhibition mechanism has been confirmed by molecular simulation, point mutation experiment, FRET method and SPR technology⁸³. The components of *Shuanghuanglian Oral Liquid* are Jin Yin Hua (Flos Lonicerae Japonicae), Huang Qin (Radix Scutellariae) and Lian Qiao (Fructus Forsythiae). Recent studies reported the first family case of COVID-19 achieved rapid recovery to combined Western medicine and *Shuanghuanglian Oral Liquid* without obvious adverse reactions; however, sufficient evidence is needed for recommended clinical use⁸⁴. Recently, shikonin as an active ingredient derived from *Lithospermum erythrorhizon* Sieb. et Zucc was reported to have the inhibitory activity against SARS-CoV-2 3CL protease with IC₅₀ of 15.75±8.22 μmol/L⁸⁵. The main components of *Lianhua Qingwen Capsules* include Lian Qiao (Fructus Forsythiae), Jin Yin Hua (Flos Lonicerae Japonicae) and Zhi Ma Huang (Herba Ephedra Praeparata cum Melle). It has been proven to have broad-spectrum activities (IC₅₀ = 0.35–2 mg/mL) against influenza virus, including H7N9. It can effectively damage the nuclear export signals of nucleocapsid protein (RNP) and at the same time, regulate viral infection-induced immune response, and reduce levels of inflammatory cytokines during early infection⁸⁶. What's more, it can significantly inhibit the SARS-CoV-2 replication, affect virus morphology and exert anti-inflammatory activity *in vitro*. These findings indicate that it protects against the virus attack and thus, can be used as a novel strategy for controlling the COVID-19⁸⁷. In addition, *Lianqiao Baidu Pian* (Forsythia Toxin-Resolving Tablets), *Xiongju Shangqing Wan* (Chuanxiong and Chrysanthemum Pills) and *Qingwen Baidu Pian* (Epidemic-Clearing Toxin-Resolving Tablets) have better anti-coronavirus effects. Compound *Qinlan* (Scutellariae and Isatisidis) *Oral Liquid* and *Reyanning Mixture* have shown a good anti-

HCoV-229E efficacy, probably by inhibiting viral replication within the lung, improving gastrointestinal function, boosting the immune function and reducing the expression of inflammatory cytokines within pulmonary cells^{88,89}. These Chinese medicines and their components provided reference for anti-SARS-CoV-2 drug screening and clinical treatment as well as the R&D of anti-coronavirus drugs.

5. Discussion

To date, there is no specific therapeutics and vaccines for COVID-19, a new emerging infectious disease. During the fight against the outbreak of COVID-19 in China, traditional Chinese medicine showed some significant benefit in alleviating symptoms and preventing disease deterioration. It must be pointed out that the updated versions of traditional Chinese medicine treatment in the protocol are based more on essential theories and clinical experience rather than high-quality clinical evidences. Most published TCM clinical studies are observational, but the epidemic context is not an ideal setting to conduct large-scale randomized controlled trials. Historically, traditional Chinese medicine has been proven effective in combating epidemics of infectious disease. Despite its often-unknown mechanism of action and low level of evidence, the TCM concepts and methods deserve attention for the management of sudden unexpected outbreaks of infectious diseases, especially when there is no specific medicine to help cure the illness.

The COVID-19 is a stark reminder of the ongoing challenge presented by emerging and re-emerging infectious pathogens. The outbreak of this infection was not the first threat and will not be the last. We need to be better prepared to cope with these infection outbreaks especially when there are no specific medicine/approaches for management. According to traditional Chinese medicine, SARS-CoV-2 is the external cause of COVID-19; however, its contagion and severity are also associated with climate, geographic regions and body functions. As a result, the TCM treatment strategy for infectious disease is to reinforce the anti-pathogenic qi and remove pathogenic factors. This is similar to the concept of combining antiviral therapy with HDT. The clinical value of TCM is necessary to be evaluated on base of the TCM theory-based method.

In addition, TCM doctors, with their experience and understanding on infectious diseases, can often notice special manifestations during an early stage that may not be considered by conventional medicine. For example, the traditional Chinese medicine treatment in the Trial Version 3 protocol clearly stated that COVID-19 cases do not necessarily develop a fever⁶, whereas conventional medicine lists fever as one initial symptom necessary to identify patients. Modern medicine also confirmed the predictive analytics of TCM for this infectious disease, such as “dampness tends to affect the spleen and stomach” (indicating the nature of virus and its effects on gastrointestinal tract), and “over time, pathogens may also affect the heart” in severe stage. All these analyses are consistent to the autopsy report on the first patient who died of COVID-19⁹⁰: the diffuse alveolar damage and pulmonary hyaline membrane formation as in ARDS, pathologic pulmonary changes as in SARS and MERS, mild liver fatty degeneration and abnormal hepatic lobules and portal vein by liver biopsy (indicating liver damage might be induced by virus or drugs), and presence of a small

amount of inflammatory monocyte infiltration without substantial damage (indicating the heart tissue is also affected by the virus). Another example is the association with gastrointestinal symptoms: some COVID-19 cases experienced diarrhea during an early stage, which has later been confirmed by stool samples (nucleic acid positive in fecal specimens or virus isolation (indicating viral multiplication in the gastrointestinal tract upon infection of COVID-19)⁹¹. Timely and effective communication between TCM and Western medical doctors is helpful in managing infectious diseases like COVID-19. Furthermore, TCM concepts may be beneficial to the identification of herbal active components useful as antiviral drugs. TCM can thus help to improve the clinical diagnosis and treatment of infectious diseases.

Despite the large number of registered clinical trials, there are still many limitations. We believe that it is necessary to avoid duplicate studies and conduct appropriate clinical trials to satisfy the TCM features and epidemic control. A rational design of clinical trials for COVID-19 should put the patients' interests first. An emergency censorship policy should be set up during major public health events to mobilize and integrate resources to ensure reliable research findings⁹². There are great uncertainties in the clinical research of TCM in emerging infectious diseases, and it is very difficult to fully carry out randomized double blind controlled multicenter clinical trial and provide high-quality evidence-based medical evidence for COVID-19 treated by TCM.

We also believe that the future advancement in TCM lies in getting high-quality evidence using modern scientific approaches. To explore the scientific value in TCM therapies, it is important to discover specific active herbal ingredients like artemisinin, but it is equally important to highlight the synergistic effect of TCM via multidisciplinary approaches. A Chinese medicine formula, no matter it contains a single ingredient or multiple ingredients, is a complex system involving multiple ingredients, targets and pathways. Despite its advantage in overall regulation, it is inevitably challenging to study its effective components and assess its clinical safety and efficacy using the method to study a single chemical substance, either in laboratories or a clinical setting. However, the particular TCM value cannot be overlooked simply because it is hard to be assessed scientifically.

The ongoing studies of TCM on mechanism of action for COVID-19 represent the future research orientations in Chinese medicine. These include the conservation and sustainable use of Chinese medicine resource and studies on their active components and mechanism of action, standardization and quality control techniques, new compound Chinese medicine, efficacy evaluation and clinical studies, and modern industrial technologies. The essential theories and clinical experiences are worthy of further studies using modern concepts and approaches. Today, with the help of big data technology, systems biology, integrative pharmacology, network pharmacology, and progress in information & computing science, chemistry and the life sciences, we can now develop multidisciplinary and multi-tiered screening and evaluation to better understand the effective components, action mechanism and pattern of prescriptions against COVID-19. From the ongoing global fight against COVID-19, the integration of traditional Chinese and modern medicine may be may offer valuable experience since it can contribute to an all-around progress in human medicine.

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Author contributions

Hongzhan Chen, Liqiang Ni, Weian Yuan, Lili Chen and Xia Huang did the literature search, selected relevant articles, interpreted data, and wrote the report. Lili Chen and Xia Huang as the co-first authors, Weian Yuan as the co-corresponding author. Chouping Han contributed to writing of report. Jianguang Xu, Yongfang Zhao, Jianrong Xu, Hong Zhang and Luan Xin contributed to interpreted data.

Conflicts of interest

All authors declare that they have no conflicts of interests.

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