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State-of-the-art evidence of traditional Chinese medicine for treating coronavirus disease 2019

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1. Introduction

Traditional Chinese medicine (TCM) has a long history of preventing and controlling infectious diseases, and it has widely been used in the treatment of coronavirus disease 2019 (COVID-19) in China. COVID-19 is an acute respiratory disease caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), with typical manifestations, such as fever, cough, fatigue, and dyspnea, as well as a runny nose, sore throat, diarrhea, and a lack of taste and smell. At present, no specific antiviral drug exists for the treatment of COVID-19. Although COVID-19 vaccination has achieved great success in reducing the number of severe cases, the global pandemic is still ongoing, with new variants of the virus emerging (Lamda, Delta, and Omicron), and all countries are vulnerable to imported variants.

Historical classical records on TCM have shown that Chinese medicine was used to prevent and treat infectious disease, and more recently in the past decades it was used against severe acute respiratory syndrome (SARS) and H1N1 influenza. Thus, from the third to the eighth version of the national guidelines of the prevention and control of COVID-19 issued by the National Health Commission in China, Chinese medicines have been recommended for the treatment of COVID-19. A large number of clinical studies on COVID-19 have been registered in trial registries, but the majority of these studies could not be conducted due to the effective control of the virus in China. This review summarizes the current evidence on clinical studies of TCM for COVID-19 and aims to describe the characteristics of TCM therapies in the prevention and treatment of COVID-19 and post–COVID-19 syndrome.
### Table 1
Existing randomized controlled trials on Chinese medicine for the treatment of coronavirus disease 2019.

| Study ID    | Participants (n) | Intervention                                      | Control                        | Outcomes and main findings                                                                 |
|-------------|------------------|---------------------------------------------------|--------------------------------|---------------------------------------------------------------------------------------------|
| Yu P 2020   | Mild and moderate cases (148 + 147)                | Lianhua Qingwen granules + arbidol                | Arbidol                        | Lianhua Qingwen combined with arbidol relieved symptoms, increased the curative effects, reduced the rate of progression to severe disease |
| Duan C 2020 | Mild case (82 + 41)                                | Jinhua Qinggan granules + routine care            | Routine care                   | Jinhua Qinggan significantly improved symptoms of fever, cough, fatigue, and expectoration, and relieved anxiety |
| Sun HM 2020 | Mild and moderate cases (32 + 25)                  | Lianhua Qingke granules + routine care            | Routine care                   | Lianhua Qingke significantly improved symptoms of cough and expectoration; shortened the duration of cough and expectoration; reduced lung inflammation; improved lung function; and relieved symptoms of fever, fatigue, dry pharynx, and sore throat |
| Fu XX 2020  | Mild and moderate cases (32 + 33)                  | Toujie Quwen granules + arbidol                   | Arbidol                        | Clinical symptoms and inflammation were alleviated by early and timely use of Toujie Quwen granules. Symptoms of COVID-19 patients were alleviated by early and timely combined use of Toujie Quwen granules and arbidol. |
| Fu XX 2020  | Mild case (37 + 36)                                | Toujie Quwen granules + arbidol                   | Arbidol                        |                                                                                              |
| Ding XJ 2020| Mild, moderate, severe/critical cases (51 + 49)    | Qingfei Touxiu Fuzheng Fang + routine care        | Routine care based on NHC-China guidelines (5th edition) | Qingfei Touxiu Fuzheng Fang in combination with Western medicines was more effective than Western medicine alone in terms of alleviating fever, coughing, and expectoration; chest tightness and shortness of breath; promoting absorption of pulmonary lesions; and improving oxygenation. The odds of a shift toward death were lower in the CHM plus routine care group than the routine care group. Maxing Xuanfei Jiedu decoction significantly improved symptoms of fever, cough, and chest tightness, and accelerated the absorption of lung inflammation. |
| Ye YA 2020  | Severe case (28 + 14)                              | CHM recommended in NHC-China guidelines (4th edition) + routine care | Routine care                   | The odds of a shift toward death were lower in the CHM plus routine care group than the routine care group. Maxing Xuanfei Jiedu decoction significantly improved symptoms of fever, cough, and chest tightness, and accelerated the absorption of lung inflammation. |
| Qiu M 2020  | Moderate case (25 + 25)                            | Maxing Xuanfei Jiedu decoction + interferon + lopinavir/ritonavir | Interferon + lopinavir/ritonavir | Maxing Xuanfei Jiedu decoction significantly improved symptoms of fever, cough, and chest tightness, and accelerated the absorption of lung inflammation. |
| Zhang CT 2020| Moderate case (22 + 23)                            | Jiawei Dayuan Fang + routine care                 | Routine care                   | Jiawei Dayuan formula significantly improved symptoms for COVID-19 patients with “Yībǐng Bīfei” pattern, increased the percentage of lymphocytes, and accelerated absorption of lung inflammation. |
| Hu K 2021   | COVID-19 cases without classification (142 + 142)  | Lianhua Qingwen capsules + routine care           | Routine care                   | Lianhua Qingwen improved recovery of symptoms, shortened the time to symptom recovery, and improved recovery of chest radiologic abnormalities. |
| Xiao MZ2020 | Suspected and diagnosed cases of COVID-19 (94 + 95 + 94) | Group 1: Lianhua Qingwen granules + Western medicine | Western medicine               | Use of Huoxiang Zhengqi dropping pills and Lianhua Qingwen granules combined with Western medicine may have clinical benefit for COVID-19 patients by improving symptoms, reducing the utilization rate of anti-infective drugs, and improving patient prognosis. |
| Zeng CC2021 | Mild or moderate case (30 + 29)                    | Maxing Shigan–Weijing decoction + routine care     | Routine care                   | Maxing Shigan–Weijing decoction increased the rate of symptom recovery and shortened the time to recovery of symptoms without deterioration to death or needing critical care. |
| Xu XL2021   | COVID-19 cases without classification (77 + 80)    | Reduning injection + routine treatment (NHC-China guidelines, 5th edition) | Routine treatment (NHC-China guidelines, 5th edition) | Compared to routine care, Reduning injection ensured a shorter median time to resolution of symptoms, shorter to negative nucleic acid test results, shorter hospital stay, and shorter time to defervescence. Xyayping injection significantly reduced the time to cough relief, fever resolution, and virus clearance; also, fewer patients receiving Xyayping injection experienced progression to severe disease during the treatment process. |
| Zhang XY2021| Mild or moderate case (65 + 65)                    | Xyayping injection + routine care (NHC-China guidelines, 5th edition) | Routine routine care (NHC-China guidelines, 5th edition) |                                                                                              |

(continued on next page)
3. TCM for the prevention of COVID-19

TCM for the prevention of epidemic diseases includes both specific and non-specific procedures. In terms of specific prevention, TCM is used for prevention and control, isolation and avoidance of evil, disinfection and insecticide. Non-specific prevention refers to the enhancement of the healthy qi—that is, immunity—of humans to prevent infection. By improving the self-healing capacity to expel external evil from the body, performing daily exercise and keeping emotions calm are non-specific measures. In the early days of the COVID-19 pandemic in Wuhan, our team published the article “Can Chinese medicine be used for prevention of corona virus disease (COVID-19)? A review of historical classics, research evidence and current prevention programs,” in which we analyzed the potential role of Chinese medicines for the prevention of COVID-19. As of December 27, 2021, the article has obtained a citation count of 238 in the Web of Science, reflecting international attention toward the use of TCM in combatting COVID-19. In this article, we collated and analyzed research evidence from previous SARS and influenza outbreaks. The rate of infection with H1N1 influenza was brought significantly lower by using Chinese medicine than non-Chinese medicine (relative risk, 0.36; 95% confidence interval, 0.24–0.52; n = 4). For the prevention of COVID-19, 23 guidelines from different provinces in China recommend the use of Chinese medicine. The main principles of Chinese medicine use are to tonify qi to protect humans from external pathogens, disperse wind and discharge heat, and resolve dampness.

4. TCM for the treatment of COVID-19

National Health Commission in China officially recommended TCM herbal decoctions (4 patterns, basic formulae) in the third version of the COVID-19 Diagnosis and Treatment Guidance. From the fourth version onward, it was clearly pointed out that COVID-19 patients can be treated by pattern differentiation according to their physical conditions, local climate characteristics, and variable geographical features. Different herbal formulae were recommended according to the different patterns. Also, from the fourth version onward, Chinese patent medicines (e.g., Huoxiang Zhengqi capsule, Jinhua Qinggan granule, Lianhua Qingwen capsule, Shufeng Jiedu capsule, and Fangfeng Tongshen pill) have been recommended, while, beginning with the fifth version, herbal injections began to be recommended. It was not until the eighth version, however, that recommendations of TCM were made for prevention. Chinese experience and guidance on COVID-19 were shared with the international community through publications and webinars.

In an effort to consider clinical research on TCM treatments for COVID-19, our research team previously reviewed published study characteristics and offered guidance for future trials to avoid duplicated efforts. We also reviewed the existing TCM clinical trial registrations and identified potentially promising and available TCM therapies.

As of May 14, 2020, a total of 161 TCM clinical trials for COVID-19 were registered (https://clinicaltrials.gov) and http://www.chictr.org.cn/enindex.aspx, including 94 (59.4%) RCTs, 25 non-randomized studies, and 18 case series. Of these, 70.8% evaluated therapeutic effects, focusing on Chinese medicine decoctions, Chinese patent medicine, and herbal injections. However, most of the TCM therapies recommended in the national guidelines are not supported by clinical evidence, and a persistent gap has remained between their wide use and research evidence.

For the prevention, control, and treatment of COVID-19 cases, China has been adhering to the combined use of Chinese and Western medicines. In the process of epidemic prevention and control, three medications (Jinhua Qingwen capsules, Jinhua Qinggan granules, and Xuebijing injection) and three prescriptions (Lung Clearing and Detoxifying decoction, Huashi Baidu Fang, and Xuanfei Baidu Fang) have been selected as the recommended Chinese medicines for the treatment of COVID-19. These three medications are all herbal drugs approved for sale, and all three play an important role in the treatment of COVID-19 and have significant clinical effects in patients with COVID-19.

The National Medical Products Administration in China gave fast-track approval for the treatment of COVID-19 to be included in the treatment indications of the aforementioned three prescriptions. Among the three medications and three prescriptions listed above, Jinhua Qinggan granules and Lianhua Qingwen capsules are recommended for use by contacts of COVID-19 cases during the medical quarantine period, the Lung Clearing and Detoxifying decoction is recommended for all types of COVID-19 patients, Xuanfei Baidu Fang is used to treat moderate cases, and Huashi Baidu Fang and Xuebijing injection are prescribed for severe and critical cases. The potential molecular mechanisms of the active components in the six TCM formulations targeting ACE2,3CL (pro) and inteleukin-6 have been fully revealed by molecular biological studies and/or network pharmacology prediction/molecular docking analysis/visualization analysis.

As of December 26, 2021, 15 RCTs on TCM treatment in the Clinical Guidelines for the Management of COVID-19 developed by National Health Commission in China have been published (Table 1).

In our previous systematic review,23 we analyzed the use of Chinese herbal medicine (CHM) and estimated the effectiveness and safety of CHM in the treatment of COVID-19. Considering the updated RCTs included in Table 1, we found that TCM in combination with conventional therapy has more potential benefits compared to conventional therapy alone, such as a reduced rate of progression to severe COVID-19; increased resolution rate, shortened duration of fever, cough, and fatigue; negative conversion rate of nucleic acid test results; and an increased number of patients.
with inflammatory disappearance or shortening of the time between receiving treatment and inflammation absorption. The evidence of TCM was mainly for COVID-19 patients with mild and moderate cases. From the reporting of adverse events in three systematic reviews, it was suggested that the use of TCM appears to be safe.

5. TCM clinical trials for long COVID-19

Several clinical studies reported that more than half of COVID-19 patients experience persistent symptoms, such as fatigue and chest pain after viral clearance; these symptoms have come to be known as long COVID or post-COVID syndrome (Box 1).

A systematic review of current data on post–COVID-19 syndrome showed that, by February 15, 2021, a total of 145 studies had reported long-term COVID-19 symptoms, including abnormal lung function (20.70%), neurologic complaints and olfactory dysfunction (24.13%), and systemic symptoms such as fatigue and pain (55.17%). TCM has many approaches to deal with long-term symptoms, including CHM, acupuncture, moxibustion, Taichi, Qigong (i.e., six-character formula, Baduanjin), Tuina, and mental therapy. As of December 27, 2021, there were four clinical trial protocols testing Chinese medicine therapies for long COVID that were registered with ClinicalTrials.gov (Table 2).

As of December 22, 2021, 30 protocols of clinical trials testing CHM or Chinese patent herbal drugs (26, 86.7%), Taichi (1, 3.3%), and Qigong (3, 10.0%) were registered for COVID-19 convalescent patients. Here, study designs include RCTs (25, 83.3%), pilot non-randomized controlled studies (1, 3.3%), and prospective case series (4, 13.3%).

The lack of COVID-19 patients and international cooperation are the main current limitations placed on TCM research for long COVID-19. We encourage future international collaborative trials on the most potential patent herbal drugs.

6. Conclusion

TCM therapies have widely been used in the treatment of COVID-19, either alone or in combination with conventional therapy in China, and they have achieved significant achievements. There have been some randomized clinical trials completed and published demonstrating benefits of CHMs in the areas of symptom relief and lung inflammation. However, due to the lack of double-blind, placebo-controlled trials and endpoint outcomes such as mortality, the beneficial effects still need to be verified in rigorous trials. There might be great value to explore the potential of TCM for long persistent symptoms after COVID-19.

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CRediT authorship contribution statement

Jianping Liu: Conceptualization, methodology, funding acquisition, and writing—review & editing. Fei Dong: Data curation, investigation, and writing—original draft, and writing-review & editing. Nicola Robinson: Funding acquisition and writing—review & editing.

Declaration of competing interest

Professor Jianping Liu is an outstanding evidence-based medicine expert and acts as an executive deputy editor-in-chief of the Journal of Traditional Chinese Medical Sciences. He was excluded from the review process of this paper.

References

1. WHO Director-General’s remarks at the media briefing on 2019-nCoV on 11 February 2020. World Health Organization Web site. https://www.who.int/dg/speeches/detail/who-director-general-s-remarks-at-the-media-briefing-on-2019-ncov-on-11-february-2020. Accessed June 12, 2020.
2. Luo H, Tang QL, Shang YX, et al. Can Chinese medicine be used for prevention of coronavirus disease 2019 (COVID-19)? A review of historical classics, research
13. Ding XJ, Zhang Y, He DC, Zhang MY, Tan YJ, Yu AR. Clinical effect and mechanism of ancient Chinese medicine in the treatment of COVID-19: a systematic review. Chin J Exp Tradit Med. 2020;9(5):1583.

14. Ye Y, G-Champs Collaborative Group. Guideline-based Chinese herbal medicine treatment plus standard care for severe coronavirus disease 2019 (G-CHAMPS): evidence from China. Front Med. 2020;7:256.

15. Qu M, Li QF, Zhu DP, et al. Efficacy observation of Maxing Xuanfei Jiedu decoction on moderate COVID-19 patients. J Emerg Tradit Chin Med. 2020;29(7):1129–1130, 1132 [Chinese].

16. Zhang CT, Yang Y, You FM, et al. Clinical study on COVID-19 from the perspective of “Yidujishi” theory. Pharmacol Clin Chin Mater Clin Med. 2020;36(2):43–45 [Chinese].

17. Hu K, Guan WJ, Bi Y, et al. Efficacy and safety of Lianhuaxingwen capsules, a repurposed Chinese herb, in patients with coronavirus disease 2019: a multicenter, prospective, randomized controlled trial. Phytomedicine. 2021;85:153242.

18. Xiao MZ, Tian JX, Zhou YN, et al. Efficacy of Huoxiang Zhengqi dropping pills and Lianhua Qinqqen granules in treatment of COVID-19: a randomized controlled trial. Pharmacol Res. 2020;161:105126.

19. Zeng C, Yuan ZZ, Zhu JH, et al. Therapeutic effects of traditional Chinese medicine (Maxingshigan-Weijing decoction) on COVID-19: an open-label randomized controlled trial. Integ Med Res. 2021;10(suppl 1):100782.

20. Xu XL, Zhang JH, Zheng WK, et al. Efficacy and safety of Reduning injection in the treatment of COVID-19: a randomized, multicenter clinical study. Ann Palliat Med. 2021;10(5):5146–5155.

21. Zhang XY, Lv L, Zhou YL, et al. Efficacy and safety of Xiyangping injection in the treatment of COVID-19: a multicenter, prospective, open-label and randomized controlled trial. Phytother Res. 2021;35(8):4401–4410.

22. Wen L, Zhou Z, Jiang D, Huang K. Effect of Xuebijing injection on inflammatory markers and disease outcome of coronavirus disease 2019. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue. 2020;32(4):426–429 [Chinese].

23. Liang SB, Zhang YY, Shen C, et al. Chinese herbal medicine used with or without conventional Western therapy for COVID-19: an evidence review of clinical studies. Front Pharmacol. 2021;11:583450.

24. Ang L, Song E, Lee HW, Lee MS. Herbal medicine for the treatment of coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis of randomized controlled trials. J Clin Exp Tradit Chin Med. 2020;9(5):1383.

25. Fan AY, Gu S, Alemi SF, Research Group for Evidence-based Chinese Medicine. Traditional Chinese medicine for COVID-19: current evidence with systematic review and meta-analysis. J Integr Med. 2020;18(5):385–394.

26. Huang CL, Huang LX, Wang YM, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet. 2021;397(10270):220–232.

27. Xiong QT, Xu M, Li J, et al. Clinical sequelae of COVID-19 survivors in Wuhan, China: a single-center longitudinal study. Clin Microbiol Infect. 2021;27(1):89–95.

28. Liang LM, Yang BH, Jiang NC, et al. Three-month follow-up study of survivors of coronavirus disease-2019 after discharge. J Kor Med Sci. 2020;35(47):e418.

29. De Lorenzo R, Conte C, Lanzani C, et al. Residual clinical damage after COVID-19 pneumonia: the persistent symptoms at the post-viral stage of the disease. A systematic review of the current data. Front Med. 2021;8:653516.