

Traditional Chinese medicine for treatment of novel infectious diseases: Current status and dilemma

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SUMMARY Traditional Chinese medicine (TCM) is a valuable form of medicine with a long history in China. It has played a significant role in the control and prevention of infectious diseases including SARS and H7N9 flu. After the outbreak of COVID-19, China's National Health Commission included TCM in the Diagnosis and Treatment Protocol for COVID-19. During the COVID-19 pandemic, three traditional Chinese medicines (Jinhua Qinggan granules, Lianhua Qingwen medicine, and a Xuebijing Injection) and three TCM preparations (a Qingfei Paidu decoction, a Huashi Baidu decoction, and a Xuanfei Baidu decoction) have been screened for their efficacy against COVID-19. More than 150 trials involving TCMs are registered in the Chinese Clinical Trial Registry (ChiCTR), and those trials cover prevention, treatment, recovery, and illnesses diagnosed in accordance with TCM principles. TCM can effectively alleviate the symptoms of patients with COVID-19, delay the disease's progression from mild to severe or critical, and reduce severe and critical all-cause mortality. The underlying mechanisms of TCM mainly involve action against SARS-CoV-2, anti-inflammatory and immunomodulatory action, and organ protection. The current work provides a brief description of the current status of and issues with TCM to treat this novel infectious disease. The hope is that TCM can help considerably to control this global epidemic.

Keywords Traditional Chinese Medicine, COVID-19, Chinese protocol, clinical trials, underlying mechanisms

In contrast to other human diseases, infectious diseases may be significant causes of human and animal morbidity and mortality, leading to extensive outbreaks and epidemics. Over the past few decades, several epidemics of new viral respiratory tract infections, such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome coronavirus infection, have emerged and threatened global health security (1). Currently, coronavirus disease 2019 (COVID-19) has been identified as an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and was first reported in 2019 in Wuhan; COVID-19 was declared a pandemic by the World Health Organization (WHO) on March 11, 2020 (2).

Soon after COVID-19 emerged in China at the beginning of 2020, the Chinese Government immediately implemented strong measures to contain the outbreak. Thanks to considerable effort, the number of COVID-19 cases has stabilized in China as a whole, although a small number of imported cases emerge intermittently. A rapid epidemic began to spread around the world starting in April 2020. On June 11, 2021, the total number of confirmed cases reached 175,902,115,

with 3,794,612 deaths reported in 215 countries and territories (3). However, the current management of COVID-19 is based generally on supportive therapy and treatment to prevent respiratory failure. Effective options in the form of antiviral therapy and vaccination are currently being developed and evaluated.

Traditional Chinese medicine (TCM) is a valuable form of medicine with a long history in China. It showcases the wisdom of Chinese people and has played a significant role in the control and prevention of infectious diseases. Based on past experiences with the treatment of infectious diseases in China, TCM has proven effective in treating contagious diseases including SARS and H7N9 flu (4). Therefore, TCM was often used to treat COVID-19 in China from the start. As is well known, TCM has played a positive role in controlling the COVID-19 pandemic. The current work provides a brief description of the current status of and issues with TCM to treat this novel infectious disease.

Chinese protocol for the treatment of COVID-19

Following the outbreak of COVID-19, China's National

Health Commission successively issued eight versions of its Diagnosis and Treatment Protocol for COVID-19, and TCM has been included ever since the third version of the integrative treatment protocol. 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-19 (5). The National Health Commission China declared that 92% of the confirmed COVID-19 cases were treated with TCM in combination with Western medicine, and patients responded well to the treatment by improving substantially or fully recovering in over 90% of cases (6).

As demonstrated by clinical data, three traditional Chinese medicines (Jinhua Qinggan granules, Lianhua Qingwen medicine, and a Xuebijing Injection) and three TCM preparations (a Qingfei Paidu decoction, a Huashi Baidu decoction, and a Xuanfei Baidu decoction) performed well in treating COVID-19 and are recommended in the Diagnosis and Treatment Protocol for COVID-19 (7). Moreover, the three traditional Chinese medicines are now approved for treatment of COVID-19 according to the National Medical Products Administration, and two of the three TCM preparations (Qingfei Paidu Fang and Huashi Baidu Fang) have been approved by the National Medical Products Administration to undergo clinical trials as treatments for COVID-19.

Clinical trials on COVID-19

At the frontline of the fight against the epidemic, TCM personnel have also worked extensively to identify TCM therapies that are effective against the virus. Numerous clinical trials on COVID-19 have been conducted to confirm the efficacy and safety of several traditional Chinese medicines and preparations. As of May 30, 2021, 840 clinical trials addressing various aspects of COVID-19 have been registered in the Chinese Clinical Trial Registry (ChiCTR), including more than 150 studies on TCM (8). Nearly 20% of all trials registered in ChiCTR involved TCM, and those trials covered prevention, treatment, recovery, and illnesses diagnosed in accordance with TCM principles, indicating that the use of TCM has been investigated in the management of COVID-19 in China.

To date, randomized controlled clinical trials on several traditional Chinese medicines and preparations to treat COVID-19 have been published. These TCMS include Lianhua Qingwen capsules, Jinhua Qinggan capsules, and Shufeng Jiedu capsules. Three trials including 245 patients with COVID-19 indicated that Lianhua Qingwen capsules had significant efficacy in improving clinical symptoms such as fever, cough, and fatigue and in curbing progression to severe or critical disease (9). Shufeng Jiedu capsules have also been recommended for treatment of COVID-19 since the fifth

version of the Diagnosis and Treatment Protocol; some clinical cases have been reported and some clinical trials have been registered and are underway (10,11). A retrospective cohort study including 200 patients with COVID-19 at Wuhan Hospital indicated that Shufeng Jiedu capsules combined with Arbidol reduces the duration of symptoms and increases the likelihood of clinical efficacy without causing significant adverse reactions (12).

Although some randomized and controlled clinical trials on TCM for the treatment of COVID-19 have been published, most might not be able to continue or may have little significance to the use of TCM in the global management of COVID-19 based on an analysis of the details of the registered trials and the current status of the epidemic in China. This situation might be explained by the following three factors: (i) the generally low methodological quality and limited sample size mean that many trials are unlikely to generate strong evidence regarding the efficacy of TCM in China; (ii) the COVID-19 epidemic has been controlled in China, so many studies may not be completed due to a lack of patients and will have to be terminated; (iii) interventions in these trials lacked sufficient evidence in previous clinical practice or were not available outside of China, such as personalized treatment based on identification of an illness according to TCM principles (13,14). Hence, due to the limited quantity and quality of the current studies, better quality, rigorously designed, and multi-center randomized controlled trials with large samples need to be conducted in order to provide more clinical evidence of the clinical efficacy of TCM.

Underlying mechanisms of TCM in treating COVID-19

To the extent know, COVID-19 can cause fatal systemic complications due to a strong immune response or cytokine storm and also cause multiple organ dysfunction syndrome (MODS), which is the main cause for a transition from mild to severe disease or even death in patients with COVID-19 (15). Mounting evidence supports the therapeutic efficacy of TCM in alleviating the clinical symptoms of COVID-19; the underlying mechanisms of TCM mainly involve antiviral, anti-inflammatory, and immunomodulatory actions and organ protection (16). TCM can inhibit the replication and transcription of SARS-CoV-2, prevent the entry of SARS-CoV-2 into host cells, and attenuate the cytokine storm, immune deficiency, and coagulation abnormalities caused by the virus infecting the human body.

One network pharmacology analysis indicated that Lianhua Qingwen capsules modulated the inflammatory process, had antiviral action, and repaired lung injury caused by COVID-19 (17). Moreover, they were also

able to alleviate the cytokine storm and symptoms caused by abnormal ACE2 expression. Another network pharmacology analysis indicated that a Qingfei Paidu decoction had immunoregulatory, anti-infection, and anti-inflammatory action and provided protection from SARS-CoV-2 in multiple organs (18). Four compounds (baicalin, glycyrrhizic acid, hesperidin, and hyperoside) and 7 targets (AKT1, TNF- α , IL-6, PTGS2, HMOX1, IL-10, and TP53) were identified as key molecules involved in the effects of a Qingfei Paidu decoction.

Although the underlying mechanisms of TCM have been briefly evaluated using network pharmacology analysis, the in-depth mechanisms remain unclear, such as antiviral action in a model of viral infection, the immune regulatory response, and the cytokine storm induced in host cells (19). Therefore, the exact mechanism and efficacy of TCM still need to be studied using molecular biological techniques, including genomics, proteomics, and metabolomics, and in vitro and in vivo models.

Conclusion

Efforts to control COVID-19 outbreaks in China have demonstrated the superiority of TCM. TCM can effectively alleviate the symptoms of patients with COVID-19, delay the disease's progression from mild to severe and critical, and reduce severe and critical all-cause mortality. The underlying mechanisms of TCM mainly involve action against SARS-CoV-2, anti-inflammatory and immunomodulatory action, and organ protection. Given that the global epidemic is still raging, better quality, rigorously designed, and multi-center randomized controlled trials with large samples need to be conducted in order for TCM to serve patients around the world. The myriad components, targets, and pathways of TCMs also need to be studied using molecular biological techniques in order to determine their exact mechanism and efficacy. In short, the hope is that TCM can help to control this global epidemic.

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