

Traditional Chinese medicine during the COVID-19 pandemic: recent successes and future perspectives

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The article titled “Three medicines and three formulas in COVID-19: from bench to bedside” introduces the clinical effects and mechanisms of three medicinal products and three prescription formulas (TMTF) from traditional Chinese medicine (TCM) as used during the COVID-19 pandemic^[1]. TMTF includes the Jinhua Qinggan granule, Lianhua Qingwen capsule, Xuanfei Baidu decoction, Huashi Baidu decoction (HSBD), Xuebijing injection, and Qingfei Paidu decoction (QFPD); all formulas are described in Supplementary Table 1^[2] (<http://links.lww.com/AHM/A76>). This present article details the clinical roles and mechanisms of TMTF in China for the treatment of COVID-19 and looks forward to its potential in future epidemics.

The current article summarizes “Three medicines and three formulas in COVID-19: From bench to bedside.” The current article offers an in-depth analysis of TMTF’s application in COVID-19 treatment and direction for the use of these herbs at various stages of the illness while also highlighting the advantages of polypharmacology for the treatment of complex diseases such as COVID-19. Additionally, it demonstrates the increased vitality of and confidence in traditional Chinese culture based on the successful application of TCM. By applying the holistic treatment philosophy of TCM to COVID-19 treatment and integrating TCM theory with modern science and technology, new perspectives and approaches to TCM are offered. Finally, this paper presents directions for future research to further elucidate the clinical applications of these medications, thereby enhancing the effective use of TCM to combat pandemics of the future.

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The clinical roles of TMTF in pandemic prevention

Overall, the practice of TCM owes its success and efficacy to the merit of TCM theory, and, more specifically, the success of Chinese herbal remedies is a testament to the accuracy of TCM principles. According to the principles and theory, disease occurs as a result of disruption to the body’s *yin-yang* balance, and COVID-19 infection is regarded as an invasion of external pathogenic factors leading to a conflict between vital energy (*zheng qi*) and pathogenic energy (*xie qi*). The progression of COVID-19 is categorized into stages with unique symptoms and corresponding treatment approaches. For example, the early stages of the virus that present as cough, fever, or sore throat are perceived in TCM as an invasion of wind-heat or heat-toxin in the lungs. Thus, the therapeutic aim at this stage is typically to disperse the exterior and expel pathogens; that is, to eliminate the virus *via* perspiration. In more severe stages, the virus may lead to an obstruction caused by damp-toxin or blood stasis with symptoms that may include difficulty breathing or shortness of breath and associated symptoms. At this stage, the therapeutic aim is to dissipate dampness and promote blood circulation, or to improve the condition through diuresis, expectoration, and enhancement of blood circulation.

Treatment based on the differentiation of signs and symptoms is a hallmark characteristic of TCM. For example, the primary application of QFPD is to clear a virus from the lungs and eliminate toxins, or in terms of TCM principles, disperse the exterior and clear the lungs. Here, the lungs are expanded, and while the body’s defenses to resist the virus are boosted simultaneously. Another example is the HSBD, a formula that is primarily used to handle the damp-heat symptoms that typically occur during the middle and late stages of a COVID-19 infection. According to TCM theory, damp-heat is formed owing to the body’s inability to properly expel internal dampness and heat; accordingly, HSBD’s function is to dissipate dampness and clear heat, suppressing the growth of the virus by correcting the internal damp-heat environment.

As TCM is integral to traditional Chinese culture, its success in epidemic control serves as a powerful enhancement of confidence in traditional Chinese culture. During the COVID-19 pandemic, TCM demonstrated significant empirical effectiveness in disease prevention, symptom alleviation, disease progression control, and recovery enhancement. These tangible health benefits have bolstered Chinese citizens’ confidence in the wisdom of traditional Chinese culture. The uniqueness of

TCM's medical philosophy lies in its emphasis on the holistic view and principles of prevention before treatment, integrating treatment with prevention, which coincides with the philosophy of modern public health and demonstrates an enduring vitality present in traditional Chinese culture. As TCM is not merely a medical approach but also a significant component of Chinese traditional culture, its success in pandemic control has not only elevated the international status of TCM but has also strengthened the confidence of Chinese people in their traditional culture. Therefore, the positive performance of TCM toward epidemic prevention strongly supports confidence in Chinese traditional culture and is also a vivid example of its endurance in modern society.

The use of TMTF in TCM embodies features of polypharmacology, which offer advantages for the treatment of complex diseases such as COVID-19. Infection with this virus involves multiple steps and pathways, including viral entry into host cells, viral replication, and host immune response. Simultaneously, COVID-19 can cause complications such as acute respiratory distress syndrome, which involves numerous biological pathways. Drugs capable of influencing multiple pathways at once may better treat the disease and control its complications. Accordingly, TMTF with polypharmacological actions can concurrently target these different stages, thereby enhancing their therapeutic effects. The descriptions of the efficacy of the drugs in Xiao's article are thorough and encompass the therapeutic effects of the different medications at various stages of the disease. It provides descriptions of key markers such as pneumonia lesions, blood oxygen saturation, and the time required for nucleic acids to turn negative. It also includes descriptions of symptom improvement and provides readers with a clear understanding of the function of each drug. Xiao's article has been well-referenced by clinical studies, enhancing the credibility of this discussion. A summary of the clinical effects of TMTF is shown [Supplementary Table 2, <http://links.lww.com/AHM/A76>].

According to Xiao's article, there are currently few reports on the drug interactions, side effects, and safety of TMTF, which highlights the importance of focusing on these aspects in future clinical research. Further studies are required to gain a comprehensive understanding of the clinical applications of these TMTF.

Mechanisms of TMTF in anti-epidemic action

Elucidating the mechanisms of action of TMTF in the treatment of COVID-19 represents an integration of modern technology and TCM. Most research on the mechanism of action of TMTF summarized in Xiao's article has been conducted using cell models or experimental animals. The main experimental strategies and methods include *in silico* methods (network pharmacology, molecular docking, and chemical bioinformatics analysis), gene expression analysis, pharmacokinetic analysis, microbiome analysis, and systems pharmacology approaches. Based on these techniques, we can gain a deeper understanding of the active ingredients of these drugs, elucidate their anti-viral, anti-inflammatory, and immunomodulatory pharmacological actions, and clarify their mechanisms of action for treating COVID-19.

Based on these results, TCM can provide more specific and detailed interpretations.

Research on the mechanism of action of TMTF reflects the correctness and scientific nature of TCM, the theories and practices of which are based on the accumulation of thousands of years of experience. The results summarized in Xiao's article emphasize the potential regulatory mechanisms of the active ingredients in TMTF on inflammation and immune responses. These constituents play important roles in suppressing IL-6-mediated cytokine storms, inhibiting the release of inflammatory factors, and regulating immune responses, which are major therapeutic targets for severe COVID-19. The results of the mechanistic study also demonstrate the scientific nature of the holistic TCM treatment approach, focusing not only on the disease but also on the balance of the body. In the treatment of COVID-19, TMTF not only targets the virus but also considers the patient's overall health status and comorbidities. TMTF also has potential therapeutic effects in improving lung injury and pulmonary fibrosis (please refer to Supplementary Table 3, <http://links.lww.com/AHM/A76>, for the mechanism of TMTF). Overall, TMTF is promising for the treatment of COVID-19; however, more research is required to fully understand its mechanisms, effectiveness, and safety.

How TCM responds to new viruses and pandemics?

TCM targets symptoms while Western medicine targets diseases in approaches that are different yet interconnected. Where there is a disease, there will be symptoms, and where there are symptoms, there will be diseases; hence, Western medicine and TCM are not opposing but complement each other with their strengths. TCM's treatment of COVID-19 primarily targets symptoms; that is, clinical manifestations such as fever, cough, and fatigue along with the impact of the disease on overall health. TCM treatment methods include Chinese herbal medicine, acupuncture, and massage, which all aim to restore the natural balance of the human body, boosting immunity, and slowing disease progression. In contrast, Western medicine's treatment of COVID-19 mainly targets the novel coronavirus and the pathological changes it causes, typically using anti-viral drugs, antibiotics (to treat concurrent bacterial infections), and supportive treatments (oxygen therapy and mechanical ventilation) to treat diseases. Therefore, the treatment methods of TCM and Western medicine are not in conflict but can complement each other to provide a more comprehensive and effective epidemic prevention plan.

In the face of possible new pandemics in the future, especially in the early stages when our research and understanding of the disease's cause are still lacking, TCM will have significant potential applications. When the target and mechanisms are not yet clear, phenotypic changes can be observed clinically. At this point, treatment with TCM can be initiated, providing therapeutic effects when medication is urgently required. Subsequent research should focus on elaborating these mechanisms and identifying targets, demonstrating the advantages of TCM treatment.

The Vincent's article highlights the research and development of TCM for future new viruses and pandemics^[3].

Given that viruses possess a certain degree of infectivity and require specific experimental conditions, corresponding drug development also has unique features^[3]. The following aspects should be considered: 1) use of surrogate phenotypes to search for drugs to combat new viruses: changes in gene expression and cell morphology can be used to characterize the therapeutic effects of drugs. This method has been used in cancer and human bone osteosarcoma cell lines and may provide insights into the development of anti-viral drugs. 2) Use of artificial intelligence (AI): commonly used AI concepts in the field of drug development include drug design, protein folding, *in silico* toxicity prediction, and drug repurposing. These machine learning applications of AI are primarily used in two areas: high-throughput analysis of compounds and their structures and analysis of phenotype-associated feature data. For the latter, machine learning is particularly useful when the features of disease mechanisms are unclear. This means that when dealing with a set of complex features or data and the intrinsic structure and relationships within these data are unclear (particularly when a novel virus emerges), machine learning can aid in building models, uncovering potential relationships between these characteristics, and further applying these insights in drug discovery. The strength of machine learning lies in its ability to learn from data and extract useful information. 3) Enhance the research and development system encompassing primary phenotypic assay-animal disease model-patient efficacy. Primary phenotypic assays and animal disease models require substantial support from basic studies. Building and refining phenotypic assays and animal disease models based on the clinical results of medications used during this pandemic can help us respond to future outbreaks; therefore, effective treatment methods may be quickly identified when new viruses emerge.

TCM played a substantial role in combating pandemics as an integral part of traditional Chinese healthcare. Xiao's article systematically synthesizes the clinical effects and mechanisms of action of TMTF in preventing pandemics, offering valuable data support for summarizing the experiences in using Chinese medicine for the prevention of epidemics.

TCM has its unique advantages and potential applications for addressing the challenges posed by future novel viruses and pandemics. In the initial stages of an outbreak, when the disease's causative factors may not yet be well-understood or researched, the symptomatic treatment approach of TCM can rapidly exert effects, alleviate symptoms, and protect human health. In terms of drug development, it may be beneficial to integrate modern technological methods such as AI for high-throughput analysis and complex data processing, to expedite drug research and development, and to allow for market introduction.

Simultaneously, it is necessary to establish a robust clinical trial and drug approval process, intensify international collaborations, and promote information sharing to address the global challenges posed by new viruses. In summary, the uniqueness of TCM lies in its distinct concepts of disease diagnosis and treatment, and its flexibility and practicality when confronted with unknown diseases. These aspects indicate the potential for TCM to play an even more significant role in future epidemic control and prevention, as well as in the development of new drugs.

Conflict of interest statement

Mei Wang is editorial board members of this journal. None of the other authors declare any conflicts of interest.

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Author contributions

Mei Wang and Xiaopeng Chen conceived the idea for this study, Xiaopeng Chen drafted the manuscript, and Mei Wang and Xiaopeng Chen modified the manuscript.

Ethical approval of studies and informed consent

Not applicable.

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Data availability

All data used to support the findings of this study have been included in this article.

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