

Feature Article

Chinese Medicine in Fighting against Covid-19: Role and Inspiration

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ABSTRACT Covid-19 pandemic has caused hundreds of thousands deaths and millions of infections and continued spreading violently. Although researchers are racing to find or develop effective drugs or vaccines, no drugs from modern medical system have been proven effective and the high mutant rates of the virus may lead it resistant to whatever drugs or vaccines developed following modern drug development procedure. Current evidence has demonstrated impressive healing effects of several Chinese medicines (CMs) for Covid-19, which urges us to reflect on the role of CM in the era of modern medicine. Undoubtedly, CM could be promising resources for developing drug candidates for the treatment of Covid-19 in a way similar to the development of artemisinin. But the theory that builds CM, like the emphasis of driving away exogenous pathogen (virus, etc.) by restoring self-healing capacity rather than killing the pathogen directly from the inside and the 'black-box' mode of diagnosing and treating patients, is as important, yet often ignored, an treasure as CM herbs and should be incorporated into modern medicine for future advancement and innovation of medical science.

KEYWORDS Chinese medicine, Covid-19, SARS-CoV-2, coronavirus, herbal medicine

Since the outbreak in December, 2019, Covid-19 (SARS-CoV-2) pandemic has caused over 984,000 deaths and over 32 million of infections, dramatically and drastically changing the world.⁽¹⁾ Despite the great efforts the whole world has made, Covid-19 continues spreading, and the second wave of it seems certain and could be even more devastating according to trajectory of the Spanish pandemic. So researchers around the world are racing with Covid-19 to stop its spread or to develop effective treatment strategy. Unfortunately, no drugs have been proven effective although many drugs including those for treatment of malaria and autoimmune diseases or for the treatment of other virus are under investigating. Hydroxychloroquine, a drug deemed promising for treatment of Covid-19, alone or with azithromycin, recently has been found ineffective in improving patients' status.⁽²⁾ On the contrary, more adverse events were reported in patients who receive hydroxychloroquine alone or with azithromycin than standard care.⁽²⁾ Also, lopinavir, a human immunodeficiency virus (HIV) type 1 aspartate protease inhibitor, combined with ritonavir to increase its plasma half-life (lopinavir-ritonavir) brought no benefits to patients with severe Covid-19.⁽³⁾ One

inspiring finding of a study led by Mayo Clinic with 35,322 patients with or at risk of severe Covid-19 is that patients who received convalescent plasma within 3 days of diagnosis had lower mortality risk than patients who received convalescent plasma later in their illness.⁽⁴⁾ But as there was no control group, questions remain as to whether, or the degree to which, convalescent plasma is effective. Besides, the most concerning thing is that viruses are highly adaptive and can mutate so easily, which may lead to its resistance to whatever drugs or vaccines that are developed following modern drug development procedure. Therefore, to fight against this tricky virus, any potentially effective strategies should be considered and tested.

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Chinese medicine (CM) has been widely used in China for thousands of years and constant outbreaks of 'Wen Yi' (infectious diseases) in ancient China have provided CM with a wealth of experience in fighting against such serious infectious diseases.⁽⁵⁾ For example, CM has been found to be able to promote the lung infiltrate absorption in patients infected with SARS-CoV in 2003⁽⁶⁾ and to reduce time to fever resolution in patients with H1N1 infection in 2015.⁽⁷⁾ Also, an extract from CM herbs was found to be effective in inhibiting SARS-CoV *in vitro*.⁽⁸⁾

For Covid-19, at the very beginning of its outbreak in China, the National Health Commission of China had recommended the priority of CM for its treatment and included CM formulae in the Diagnosis and Treatment Protocol of Covid-19 since Version 3. More than 90% of Covid-19 cases in China received CM treatment,⁽⁹⁾ and a retrospective study of 312 patients with severe Covid-19 in Wuhan did show that the use of CM was associated with lower mortality risk.⁽¹⁰⁾

During the fight against Covid-19, 6 prominent traditional Chinese herbal or patent medicine (Lianhua Qingwen Capsule 莲花清瘟胶囊, Jinhua Qinggan Granule 金花清感颗粒, Xuebijing Injection 血必净注射液, Qingfei Paidu Decoction 清肺排毒汤, Huashi Baidu Prescription 化湿败毒方, and Xuanfei Baidu Decoction 宣肺败毒汤) referred to as "Three CM prescriptions and three medicines", were identified and included in Diagnosis and Treatment Protocol of Covid-19. Lianhua Qingwen Capsule, a marketed drug for influenza in China, showed the property of inhibiting SARS-CoV-2 replication *in vitro* study.⁽¹¹⁾ Later, a multicenter randomized clinical trial with 284 patients with Covid-19 demonstrated that the addition of Lianhua Qingwen Capsule to usual treatment led to a higher symptom recovery rate (fever, coughing and fatigue), a higher chest computed tomography (CT) manifestation improvement rate and a higher clinical cure rate.⁽¹²⁾ In addition, meta-analyses of randomized trials⁽¹³⁾ and experimental studies⁽¹⁴⁾ of patients with Covid-19 also showed that Lianhua Qingwen Capsule could improve symptoms and pulmonary imaging manifestation, shorten disease course and generate a higher clinical cure rate. Jinhua Qinggan Granule, also a marketed drug for influenza in China, significantly alleviated fever, cough, fatigue and sputum in a small randomized clinical trial with 129 Covid-19 outpatients.⁽¹⁵⁾ Xuebijing Injection, a

CM injection widely used for systemic inflammatory response syndrome induced by infection,⁽¹⁶⁾ displayed beneficial effects in a case series of 11 patients with severe Covid-19; and further *in vitro* study found that Xuebijing Injection was able to protect cells from SARS-CoV-2 induced cell death in a dose-dependent manner.⁽¹⁷⁾ Xuanfei Baidu Decoction, created by Academician ZHANG Bo-li and Prof. LIU Qing-quan, impressively improved symptoms of Covid-19 and displayed anti-inflammatory effects in a small randomized trial.⁽¹⁸⁾ Huashi Baidu Prescription, a newly developed prescription by CM experts team led by Academician HUANG Lu-qi, exhibited impressive effect on improving symptom and chest CT manifestation, shortening time of full recovery and hospital stay.⁽¹⁹⁾ Qingfei Paidu Decoction, comprising four classic CM prescriptions, was formulated by Prof. GE You-wen and has demonstrated remarkable healing effects in clinical practice.^(20,21) Meta-analysis of 18 small randomized trials of these CM herbal or patent medicine for Covid-19 found that the addition of CM to usual care could improve symptoms and manifestation of chest CT, increase clinical cure rate and decrease C-reactive protein levels.⁽²²⁾ Notably, no serious adverse events related to CM in the treatment of Covid-19 have been reported. Mechanisms of the therapeutic effects of CM are related to alleviation of inflammation and "cytokine storm", immunomodulatory activity, regulation of angiotensin converting enzyme 2 (ACE2), and repair of lung injuries.⁽²³⁻²⁷⁾ Concluded from the evidence above, CM might have played a more important role in the containing and treatment of Covid-19 in China than we have realized. Thus, CM could be promising resources for developing drug candidates for the treatment of Covid-19 in a way similar to the development of artemisinin for malaria by TU You-you who has extracted artemisinin from a CM herb and saved millions of lives suffering from malaria.

Aside from medicinal herbs of CM, the theories that build CM are also an ignored treasure for novel emerging diseases, especially the way that CM understand and treat human body and diseases. According to CM theory, as long as a person is healthy enough or with sufficient and balanced 'Zheng Qi', he will not fall ill even exposed to pathogen. As a result, CM emphasizes strengthening 'Zheng Qi' and balancing yin and yang of human body regarding disease treatment. Different from the 'allopathic'

concept of modern medicine, it focuses on driving away exogenous pathogen (bacteria, virus, etc.) by restoring self-healing capacity rather than killing the pathogen directly from the inside. Such an approach is analogous to immunotherapy of cancer. This notion enables CM to fight against pathogen like virus without hurting human cells it occupies, which is often rather difficult for drugs developed under the notion of modern medicine. In addition, the 'black box' mode of CM by treating a patient based on differentiating manifestations generated by the unknown pathogen gives it a distinct advantage when facing an emerging infectious disease. Like the Covid-19 pandemic, from the very beginning, no one knew anything about this novel new virus and certainly no known effective drug or vaccine exist in modern medical system, leaving patients and physicians in a helpless situation. CM, however, by analyzing fine symptoms and signs, inferred different CM disease syndromes and gave CM herbal formulae by pairing herbs accordingly, which has been demonstrated having reduced mortality risk by a retrospective study of patients with severe Covid-19 in Wuhan.⁽¹⁰⁾ These features make CM a potential and promising choice facing an emerging disease when no effective agents or vaccines are available. Such an approach should be highlighted as opportunities to complement modern medicine, not only at the time when facing an emerging infectious disease, but also for future advancement and innovation of medical science.

Competing Interests

The authors claimed no competing interests.

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