Commentary

Integrative Medicine Demonstrates Advantage in COVID-19 Treatment

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In December 2019, a cluster of patients in Wuhan, China with a new type of pneumonia with unknown etiology were found. The origin was subsequently discovered to be an infectious disease caused by a new coronavirus, SARS-CoV-2, and named COVID-19 by the World Health Organization (WHO).

In China, the disease progression of COVID-19 is divided into 4 phases—mild, moderate, severe and critical. And in terms of pathogenesis, there are 3 phases—early infection, pulmonary and hyper inflammation. In addition to conventional and reductionist approaches to finding antiviral and anti-inflammatory drugs, Chinese researchers have also investigated experienced-based Chinese medicine (CM) to look for formulae or formula-based drugs used to treat respiratory-related diseases to deal with the complexities of COVID-19's disease, symptoms and complications.

Learning through front-line experiences battling COVID-19, the Chinese government began recommending "3-Drugs-3-Formulations" for treating different phases of COVID-19, including Jinhua Qinggan Granule (金花清感颗粒), Lianhua Qingwen Capsule (连花清瘟胶囊), Xuebingjing Injection (血必净注射液), Qingfei Paidu Decoction (清肺排毒汤), Huashi Baidu Formula (化湿败毒方), and Xuanfei Baidu Formula (宣肺败毒方). With the exception of one injectable formula, the other 5 formulae are orally administered and are all evolved from CM with a long history of usage and still in use today. Each of the recommended formulae uses more than 12 herbs. With more herbs, there can be more complexities, resulting in greater challenges for quality control. Among the many herbs used, at least one of the herbs, *Ephedrae herba*, is also heavily regulated. The clinical evidence to support each formula's efficacy claims is not well described in most incidences. Well-designed clinical studies using well-documented quality control of CM formulae [with or without Western medicine (WM)] are rare.

The manuscript by Wang, Xiao and colleagues (Exploring an integrative therapy for treating COVID-19: a randomized controlled trial. *Chin J Integr Med* 2020;26:648-655.) is an exceptional case. It describes a new 7-herb formula, Keguan-1, deduced from 3 CM formulae—Yinqiao Powder (银翘散), Sangju Drink (桑菊饮) and Sanren Decoction (三仁汤), which were used for treating respiratory-related disease for more than a thousand years. And Keguan-1 does not include the regulated herb *Ephedrae herba*, simplifying its regulatory hurdles. Chemical analysis of the final product for Keguan-1 using chemical markers was well-defined and presented to describe the quality control. The phase I/II study was designed as a 2-arm trial, using a combination of a conventional WM drugs (antiviral, antibacterial and glucocorticoid) with or without Keguan-1. The study recruited 47 evaluable patients with early or mild phase of COVID-19. The treatment for each patient was well-described, which has not been done in most COVID-19 clinical trials reported. Patients were well-matched between the 2 arms and the clinical endpoint was well-defined. The results with statistical significance suggested that Keguan-1 shortened the time to fever resolution and decreased disease progression to acute respiratory disease syndrome. It also demonstrated the potential of the treatment to reduce the time required to get a negative result for an active COVID-19 virus, secondary infection, acute kidney injury, usage and days needed for mechanical ventilation. It can be concluded from the encouraging results that there is potential usage of the combination with Keguan-1 and WM for mild and even moderate phase of COVID-19 patients. In addition, it would be interesting to compare this 7-herb formula with the "3-Drugs-3-Formulations" treatments: Lianhua Qingwen Capsule and Jinhua Qinggan Granule.

It will be worthwhile to further study this treatment in an international, multi-center clinical trial. This study and its clinical results are a good demonstration of synergies of integrating WM (exemplified by conventional medicine) and Eastern medicine (exemplified by CM). The concept of integrative medicine should be further explored to treat current and future unmet medical needs, including COVID-19.

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