

## Use of herbal drugs to treat COVID-19 should be with caution

On April 14, 2020, a Chinese official announced at a press conference that indications of three patent herbal drugs were approved to be expanded to include COVID-19 symptoms.<sup>1</sup> This included Lianhuaqingwen capsules and Jinhuaqinggan granules for mild conditions, and Xuebijing (injectable) for severe conditions.

These drugs are widely used to treat COVID-19 in China. The official claimed the patent herbal drugs can effectively relieve symptoms, such as fever, cough, and fatigue, and reduce the probability of patients developing severe conditions, but without giving further details.<sup>1</sup> So far, no high-quality, rigorously peer-reviewed clinical trials of herbal drugs have been reported in internationally recognised journals. The approvals, based on in-vitro investigations and anecdotal clinical data, will probably lead to several worrisome consequences.

First, safety is the top priority. Advocates argue that herbal drugs are widely used and safe, but the truth is that all drugs carry risks. In the 1990s, Vanherweghem and colleagues<sup>2</sup> reported that some women who followed a slimming herbal remedy developed rapidly progressive renal failure and urothelial carcinoma. Further investigations highlighted the role of aristolochic acid, a compound found in many traditional herbs.<sup>2,3</sup> Certain batches of an injectable herbal drug called Xiyanping, which is recommended by the Chinese Diagnosis and Treatment Protocol of COVID-19,<sup>4</sup> have already been recalled after reports of adverse effects.<sup>5</sup> Although these patent herbal drugs have been used clinically for several years, when we apply them to a novel disease like COVID-19, especially in combination with other antivirals, antibiotics, and immune

suppressants, the safety should be cautiously evaluated.

Second, more evidence is required through controlled clinical trials to support the efficacy of these herbal drugs. Many traditional medicine practitioners believe that herbal remedies cannot be tested because they are tailored to each individual's syndromes. This argument is simply not convincing. Because the patent herbal drugs are produced in advance of any treatment and their composition is fixed, clinical endpoints including mortality, time to clinical improvement, and number of days in an intensive care unit can be used to evaluate the efficacy of the herbal drugs for COVID-19. Standardised trials might have methodological challenges, consuming time and effort, but that should not be the reason for lowering safety and efficacy standards. Thousands of years of usage and faith cannot be taken as evidence for efficacy of traditional herbs.

Third, the basic molecular mechanism is obscure. Lianhuaqingwen capsules have been shown to have wide-spectrum antiviral effects and anti-inflammatory activities,<sup>6,7</sup> but the active ingredients and the underlying mechanism of action are unknown. Herbal drugs usually contain many active ingredients, and it is important to better understand which ingredients are functional, and how they work. Limited experimental cell cultures and animal studies cannot guarantee safety and efficacy.

Finally, the public can easily purchase herbal drugs without a doctor's prescription. Driven by the claim that some patent herbal drugs can effectively treat COVID-19, some patients with flu symptoms who fear quarantine measures are likely to self-medicate with herbal remedies and avoid going to hospital, thus delaying the proper diagnosis and treatment of the disease, and hampering the government's testing, tracing, and quarantining efforts. At the end of January, 2020, rumours circulating on

social media suggested that a patent herbal drug called Shuanghuanglian, which contains honeysuckle and forsythia and is used routinely in traditional medicine to treat influenza and the common cold, helps ward off or even cure COVID-19. Millions of people nationwide crowded into drug stores to buy the herbal drug as a just-in-case remedy.

The current COVID-19 pandemic is an unprecedented challenge for the Chinese Government and the general public. Doctors and researchers are desperately seeking a proven cure for it. When the conventional drugs such as lopinavir, ritonavir, chloroquine, and hydroxychloroquine are not as effective as expected,<sup>8,9</sup> screening potential active components from traditional herbal medicine is a viable strategy that should not be dismissed. My colleagues and I have previously called for more attention to testing traditional herbal medicine for the treatment of COVID-19,<sup>10</sup> but a rushed judgment without sufficient scientific evidence should be cautioned against.

Given the formidable morbidity and mortality of COVID-19, it is understandable to see emergency use of unproven drugs, but the approval of a new indication for herbal drugs should still build on evidence. In the past decades, the Chinese Government has invested huge sums of money to promote the modernisation and standardisation of traditional medicine, carrying out sustainable basic and clinical research to get international recognition, but the rushed approval seems to be a backward step. The attempt to develop rigorously tested drugs from traditional herbal medicine should not be given up. It is the only way to protect our vulnerable patients.

I declare no competing interests.

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