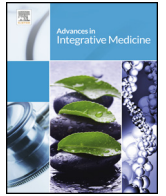




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Guest editorial

Chinese medicine diagnosis and treatment for COVID-2019: Is China ready for implementing a national guideline?



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ABSTRACT

Objectives: COVID-19 sparked a pandemic in December 2019 and is currently posing a huge impact globally. Chinese herbal medicine is incorporated into the Chinese national guideline for COVID-19 management, emphasising the individualisation of herbal treatment guided by *pattern differentiation*, which is an ICD-11-endorsed approach. However, this was not widely implemented with many provincial governments and hospitals developing their own guideline, suggesting the use of *standardised herbal formulae* and *herbal active ingredients* without pattern differentiation.

Methods: Through the case study of COVID-19 guideline implementation, we compared the three approaches of developing Chinese herbal medicine, namely *pattern differentiation-guided prescription*, *standardised herbal formulae*, and *herbal active ingredients*, in terms of their strengths, limitations, and determinants of adoption.

Results: *Pattern differentiation-guided prescription* is the practice style taught in the national syllabus among universities of Traditional Chinese Medicine in China, yet the lack of relevant diagnostic research reduces its reliability and hinders its implementation. Application of *standardised herbal formulae* is straightforward since the majority of clinical evidence on Chinese herbal medicine is generated using this approach. Nevertheless, it is downplayed by regulatory bodies in certain jurisdictions where the use of *pattern differentiation* is required in routine practice. Although *herbal active ingredients* may have clear *in vitro* therapeutic mechanisms, this may not be translated into real world clinical effectiveness.

Conclusions: Multiple COVID-19 clinical trials evaluating the effectiveness and safety of Chinese herbal medicine prescribed using one of the three approaches described above are progressing. These results will demonstrate the comparative effectiveness among these approaches. Forthcoming clinical evidence from these trials should inform the updating process of the national guideline, such that its recognition and compliance may be strengthened. For longer-term development Chinese herbal medicine, serious investment for establishing high-quality clinical research infrastructure is urgently needed.

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1. Introduction

The World Health Organization characterised the coronavirus disease (COVID-19) as a pandemic on 11 March 2020, after the number of new confirmed cases outside China, the former outbreak epicentre, had increased by 13-folds [1]. Traditional Chinese Medicine (TCM), as a formal part of the Chinese healthcare system, has been playing an important role in combating the disease since it received the highest political endorsement at the beginning of the outbreak [2]. After summarising TCM experts' experiences, the Chinese health authority incorporated a section on Chinese herbal medicine (CHM) treatments into the National

COVID-19 Diagnostic and Treatment Guideline published on 22 January 2020 [3]. The guideline recommends the prescription of CHM based on a process called *Bian Zheng Lun Zhi* (pattern differentiation-guided treatment decision). Pattern differentiation is a traditional diagnostic procedure guided by classical TCM theories [4]. The process requires TCM clinicians to examine patients by observation, listening, questioning, and pulse-taking. Subsequently, complex information is analysed in accordance with TCM theories to allow the formulation of a TCM pattern diagnosis. These form the basis for designing individualised treatment strategies.

2. Classical pattern differentiation for individualising Chinese herbal medicine prescriptions

When the pattern differentiation result suggests that a patient is *Yang* deficient, treatment should be directed towards the

Abbreviations: COVID-19, Coronavirus disease; TCM, Traditional Chinese Medicine; CHM, Chinese herbal medicine; ICD-11, The eleventh edition of the International Classification of Diseases.

nourishment of *Yang* using CHM. This diagnostic framework for pattern differentiation has been recognised by the eleventh edition of the International Classification of Diseases (ICD-11) [5]. Drawing upon the successful experience of implementing integrative Chinese–Western Medicine in managing COVID-19 [6], the latest national guideline recommends healthcare professionals in China to offer tailored CHM treatments in accordance with disease trajectory [7]. Patients are stratified into mild, moderate, severe, critical, and recovering stages, and for each respective stage individualised CHM formulae are prescribed based on their TCM pattern diagnosis. Two pattern diagnoses are observed in mild, moderate, severe, and recovering cases respectively. Only one pattern diagnosis is commonly seen among critical cases. Details on the TCM pattern diagnoses and relevant clinical features are illustrated in Table 1.

Unexpectedly, this national guideline is not implemented by all hospitals treating patients with COVID-19 and at least 24 other guidelines were developed by various provincial and regional governments across China [8]. There are multitude of reasons for local healthcare professionals to develop *de novo* guidelines [9]. In the case of COVID-19, these may include uncertainty on quality of national guideline development process; low confidence in the evidence due to lack of clinical research; and finally, possible existence of regional variations in prevalence of different TCM pattern diagnoses [10]. This may also reflect a lack of timely diagnostic research on how pattern differentiation in COVID-19 should be standardised, or stratified, for the country.

3. Standardised herbal formulae

Evidence on whether the use of pattern-differentiation would improve treatment outcome is yet to be synthesized. Existing trial comparing individualized CHM treatment based on pattern-differentiation, with standardized CHM treatment showed that the individualized approach is favoured for improving longer term

outcome among patients with irritable bowel syndrome [11]. However, another trial on acupuncture for postmenopausal hot flushes did not observe clinical benefits of pattern-differentiation [12]. Also, slow progress in pattern differentiation research has eroded confidence in its application [13], and increasingly, CHM is prescribed solely based on conventional diagnosis. Indeed, direct application of CHM therapy without considering pattern differentiation was shown to be effective in the treatment of H1N1 influenza in a rigorously designed randomised trial [14]. This successful experience may have encouraged similar approaches in the current outbreak. For instance, the Guangdong provincial government encourages hospitals to prescribe a standardised CHM formula *Pneumonia Prescription 1* to all suspected cases and confirmed cases, regardless of their TCM diagnosis [15]. In Wuhan, TCM clinicians are advised to prescribe three standardised CHM formula to quarantined citizens, suspected cases, and confirmed cases [16]. Consistent with the general trend of low guideline adherence rate among TCM clinicians in China [17], the promulgation of a COVID-19 national guideline backed only by expert opinions has received little recognition, let alone the implementation and adherence at the front line.

4. Herbal active ingredients

In the modern evaluation framework of pharmaceutical science, establishing evidence base of complex TCM diagnosis and treatment is challenging. Development of new drugs based on active ingredients of CHM has been considered a preferred approach for internationalising TCM [18]. This modernisation approach gained momentum since the 1950s when Mao Zedong advocated the use of biomedical technologies in herbal research [19]. Its popularity soared after the award of the Nobel Prize to Youyou Tu in 2015 for the discovery of the antimalarial artemisinin through her research on *Artemisia annua L* [20]. In the treatment of patients with COVID-19, the Chinese Academy of Sciences

Table 1
Traditional Chinese Medicine Diagnostic Patterns of COVID-19 based on the 7th version of the Chinese National Guideline.

TCM pattern diagnosis	Clinical features
<i>Mild cases 1: Cold-dampness obstructing the lung</i>	<ul style="list-style-type: none"> Fever, muscle fatigue, muscle pain, coughing, expectoration of sputum, chest discomfort, shortness of breath, loss of appetite, nausea, vomiting, and ungratifying defecation. Pale tongue with teeth-marked, or pale red tongue. White, thick and curdy tongue fur, or white and slimy tongue fur. Soggy or slippery pulse
<i>Mild cases 2: Dampness-heat in the lung</i>	<ul style="list-style-type: none"> Mild fever or no fever, slight aversion to cold, muscle fatigue, heaviness in the head and body, muscle pain, dry coughing with small amounts of sputum, sore throat, dry mouth without a desire to drink, chest discomfort, absence of sweating or difficulty in sweating, loss of appetite, nausea, vomiting, and watery stool or ungratifying defecation. Pale red tongue. White, thick and slimy tongue fur, or yellow and thin tongue fur. Slippery and rapid pulse, or soggy pulse.
<i>Moderate cases 1: Dampness toxin obstructing the lung</i>	<ul style="list-style-type: none"> Fever, coughing with small amounts of sputum or coughing with yellow sputum, chest discomfort, shortness of breath, abdominal distension, and constipation. Dark red and enlarged tongue. Yellow and slimy tongue fur, or yellow and dry tongue fur. Slippery and rapid pulse, or string-like and soggy pulse.
<i>Moderate cases 2: Cold-dampness obstructing the lung</i>	<ul style="list-style-type: none"> Mild or no fever, feeling of feverishness, dry coughing with small amounts of sputum, fatigue, chest discomfort, stomach discomfort, nausea, and watery stool. Pale or pale red tongue. White tongue fur, or white and slimy tongue fur. Soggy pulse.
<i>Severe cases 1: Epidemic toxin obstructing the lung</i>	<ul style="list-style-type: none"> Fever, flushed face, coughing with small amounts of sticky yellow sputum or with blood, panting, shortness of breath, fatigue, dry mouth with bitter taste and sticky feeling in the mouth, loss of appetite, nausea, ungratifying defecation, reddish urine with reduced amount. Red tongue. Yellow and slimy tongue fur. Slippery and rapid pulse.
<i>Severe cases 2: Blazing of both qi and nutrient</i>	<ul style="list-style-type: none"> High fever, agitation, thirsty, panting, shortness of breath, delirium, loss of consciousness, blurred vision, purpura, hematemesis, nasal bleeding, and convulsion. Crimson tongue. Less or no tongue fur. Sunken and fine pulse, or floating, big and rapid pulse.
<i>Critical cases: Internal block and external collapse</i>	<ul style="list-style-type: none"> Difficulty in breathing, panting after slight movement (may require invasive mechanical ventilation), convulsion, agitation, sweating, and cold extremities. Dark purple tongue. Thick and slimy tongue fur, or dry tongue fur. Floating and big pulse without root.
<i>Recovering cases 1: Lung-spleen qi deficiency</i>	<ul style="list-style-type: none"> Shortness of breath, fatigue, loss of appetite, nausea, vomiting, stomach fullness, difficulty in defecation, and watery stool. Pale and enlarged tongue. White and slimy tongue fur.
<i>Recovering cases 2: Dual deficiency of qi and yin</i>	<ul style="list-style-type: none"> Muscle fatigue, shortness of breath, dry mouth, thirsty, palpitation, profuse sweating, loss of appetite, mild or no fever, and dry coughing with small amounts of sputum. Dry tongue. Fine or vacuous pulse.

Table 2
Three approaches for developing Chinese herbal medicine: A comparison.

	Pattern differentiation to guide individualization of CHM treatment	Using standardized CHM formulae based on conventional diagnosis	Using CHM active ingredient extracts
<i>Strengths</i>	Adherence to the wealth of clinical experience in TCM. Practice style taught in the national syllabus among TCM universities [30]	CHM could be prescribed more widely by clinicians without training in TCM and pattern differentiation.	Clear understanding on the <i>in vitro</i> therapeutic mechanism of CHM.
<i>Limitation</i>	Evidence supporting the comparative advantage of pattern differentiation, versus the absence of it, for guiding CHM prescription, is yet to be established.		<i>In vitro</i> discovery of herbal active ingredient may not translate to clinically effective CHM medications [31]
<i>Facilitators to adopt this approach</i>	Addition of diagnostic framework for pattern differentiation in ICD-11, allowing the incorporation of pattern differentiation process in randomized trials [32]	Majority of current clinical evidence on CHM is generated using this approach, making their clinical application straightforward [33]	Opportunities for promoting overseas registration and trade of CHM products [34]
<i>Barriers to adopt this approach</i>	Lack of diagnostic research results which would guide the reliable use of ICD-11 pattern differentiation codes [35]	In certain jurisdictions, the use of classical theories and pattern differentiation in daily practice is required by regulatory bodies [36]	Substantial upfront investment on time and resources for <i>in vitro</i> and <i>in vivo</i> research prior to clinical application.
<i>Example of success</i>	Individualized CHM is superior to standardized CHM for reducing longer term symptoms among irritable bowel syndrome patients [11]	Maxingshigan-Yinqiaosan is effective for reducing time to fever resolution among patients with H1N1 influenza [14]	Discovery of the antimalarial artemisinin [20]

Chinese herbal medicine (CHM); Traditional Chinese medicine (TCM).

endorsed this active ingredient approach and, wittingly or unwittingly, promoted the use of *Shuanghuanglian oral liquid* via the state media. [21]. This remedy consists of extracts from three herbs, and preliminary laboratory investigations conducted by the Shanghai Institute of Materia Medica and the Wuhan Institute of Virology have demonstrated its capability in inhibiting the SARS-CoV-2 *in vitro* [21].

From Chinese government and business perspectives, understanding CHM bioactivities does not only generate new leads for drug development. It is also crucial for potential international exports of CHM products, as the discovery of therapeutic mechanisms is important for satisfying registration requirements from overseas regulatory authorities [22]. For example, the United States Food and Drug Administration botanical drug registration requires proofs of mechanism using clinical relevant bioassays [18]. For TCM clinicians and guideline developers, mechanistic investigations help with clarifying dosage for achieving beneficial outcomes with minimal side effects [23]. However, without clinical research providing effectiveness and safety evidence *in vivo*, the current trend of investing heavily on *in vitro* investigation will contribute little for improving quality of TCM practice [24].

5. Conclusion: research recommendations

Developing a national consensus on what constitutes the best strategy based on current observations and, subsequently, revising the national guideline to attain wider recognition and higher compliance are urgently needed. With such a guideline, national clinical research programmes can be initiated to facilitate in-depth investigations on the three aforementioned approaches, namely classical pattern differentiation for individualising CHM prescriptions, standardised herbal formula, and herbal active ingredients, in a coordinated manner across hospitals. A comparison on the relative strengths and weaknesses of the three approaches is illustrated in Table 2.

For the first approach, standards for operationalising TCM pattern differentiation process for COVID-19 under the ICD-11 framework should be established using innovative diagnostic research methods. [25]. For the second and third approaches, focused investment should be channelled to support the conduct of rigorous phase II or III randomised trials on the most promising CHM treatment strategy, instead of spreading scare resources across numerous different trials [26]. Moreover,

complex trials evaluating the effect of ICD-11-based pattern differentiation on patients' response to CHM should subsequently be performed, with all details reported in accordance to the CONSORT (CONSOLIDATED STANDARDS OF REPORTING TRIALS) reporting guideline for CHM trials [27]. The results of such trial will reveal how different ICD-11 based TCM diagnosis across different regions may impact treatment outcomes [25]. With such evidence, regional guideline could be developed based on how individualised treatment may yield different outcomes among different types of patients, with different TCM pattern diagnoses. Without serious investment in building clinical research capacity, CHM will remain a "pseudoscience" among sceptics [28]. It is now prime time for policymakers to work towards the World Health Organization's goal of promoting evidence-informed decision-making in traditional medicine [29].

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