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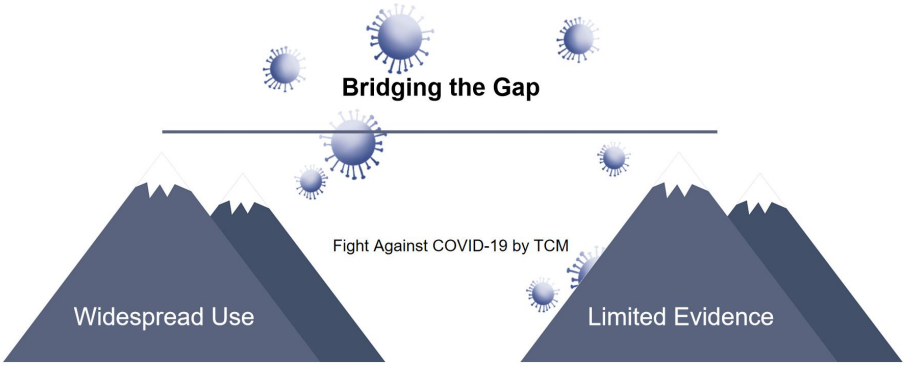
COMMENT

The gap between clinical practice and limited evidence of traditional Chinese medicine for COVID-19

Hui Luo[1*]

[1]Institute for Tibetan Medicine of China Tibetology Research Center, Beijing 100101, China.

*Corresponding to: Institute for Tibetan Medicine of China Tibetology Research Center, No.131 North Fourth Ring Road, Chaoyang District, Beijing 100101, China. E-mail: luohui09@hotmail.com.



***Abbreviations*:**

TCM, traditional Chinese medicine; RCT, randomized controlled trial; CFDA, China Food and Drug Administration.

***Competing interests*:**

The authors declare no conflicts of interest.

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Background

Traditional Chinese medicine (TCM) is the set of knowledge and practices concerning life, health, illness prevention, and treatment that originated in China thousands of years ago. Presently, TCM is still one of the mainstream medical systems, and has been given an equal legal status and place as Western medicine in the healthcare system of China [1]. Whether it was the plague in ancient times or the SARS and influenza A in the past decades, TCM has always played a major role in the prevention and treatment of diseases [2]. As early as the outbreak of COVID-19 in January 2020, the Chinese government established the treatment principle of integrated Chinese and Western medicine, and since then TCM has been fully and deeply involved in the management of the epidemic in China. Till August 18, 2020, the Chinese health authority had issued eight versions of guidelines for the diagnosis and treatment of COVID-19, and starting from the third version, a TCM approach including herbal formulae and drugs has been included. According to the White Paper issued by the Chinese government in June 2020, 92% of all confirmed cases received TCM-based treatment that proved to be effective [3].

Along with the extensive clinical application, a large number of clinical trials have been registered and carried out to evaluate the effectiveness and safety of TCM interventions. According to the data provided by Chinese Clinical Trial Registry, as of August 27, 2020, a total of 165 TCM clinical trials had been registered, accounting for 22.3% (165/741) of all trials on COVID-19 in Chinese Clinical Trial Registry. However, despite the widespread clinical use and so many clinical trial registrations, current high-quality evidence on TCM in the treatment of COVID-19 is still rare. In this comment, TCM clinical trials on COVID-19 were searched in Google Scholar, Web of Science, and PubMed on August 27, 2020. Studies published in journals indexed by Science Citation Index would be identified as influential research and selected for review.

Published clinical trials of TCM in treating COVID-19

Ten studies were obtained through searching and screening [4–13]. Only five studies were randomized controlled trials (RCTs), and one of them was a multicenter study; the rest were either retrospective studies or case reports [4–13]. The sample sizes of the ten studies ranged from 4 to 721, with a median of 51. These studies were heterogeneous in terms of TCM interventions, which included various Chinese patent medicines, decoctions, and comprehensive treatment based on guidelines. Only the Lianhua Qingwen capsule (approval number of CFDA: Z20040063) was evaluated in two RCTs [7, 12]. Guideline-based routine treatment of Western medicine was applied as the basic treatment in both the TCM treatment groups and the control groups of all studies. Placebo control and blinding of participants and personnel were not implemented in any of the studies. One RCT adopted blinding of outcome assessment [10]. In the five RCTs, the details of random sequence generation were reported, while allocation concealment was neither reported nor adopted. The endpoints for outcome measures included symptoms, virus removal, fatality rate, chest CT examinations, length of hospitalization, rate of progression to severe disease, usage of antibiotics and antiviral drugs, etc. All retrospective studies reported positive results, while two out of five RCTs reported negative results on the primary endpoints including the fatality rate of severe cases and symptom improvement of suspected and non-severe cases [8, 12]. The detailed characteristics of clinical trials of TCM in treating COVID-19 are shown in Table 1.

In general, several specific Chinese patent medicines or herbal formulae have been shown to improve symptoms, reduce progression to severe disease in mild and moderate COVID-19 patients. However, the majority of these drugs or formulae were evaluated in a single clinical trial, with a small sample size and moderate to high risk of bias (Figure 1). Therefore, the results should be interpreted with caution.

The gap between clinical practice and limited evidence

Despite the widespread application in clinical practice and recommendation from the national guideline, high-quality clinical research evidence for the treatment of COVID-19 with TCM is still lacking so far. There is limited quality and quantity of evidence from the review of existing studies. The gap between clinical practice and limited evidence could be mainly explained by the following three aspects:

Firstly, there was a paucity of newly-confirmed cases. The majority of trials were simultaneously registered and carried out during the outbreak, resulting in limited sample sizes. The outbreak of COVID-19 in China was brought under control in a short time, which implied that most trials could not attain the predetermined sample size [14]. Secondly, methodological drawbacks weakened the strength of evidence. Due to the small sample size, absence of placebo, absence of blinding, inappropriate outcome endpoints, retrospective design, and other methodological drawbacks, the quality of the current evidence is still limited and not so satisfactory [15]. Lastly, the particularity of TCM interventions inhibited

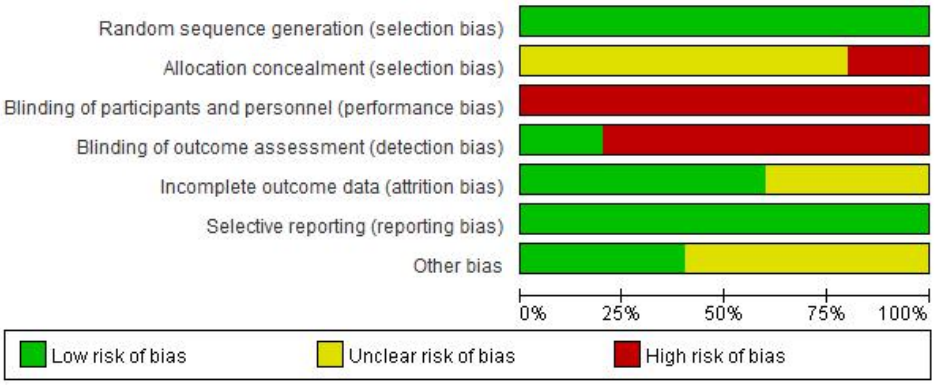

Figure 1 Graphical representation of the risk of bias of randomized controlled trials of traditional Chinese medicine in treating COVID-19

Table 1 The characteristics of clinical trials of traditional Chinese medicine in treating COVID-19

Study ID	Published journal	Online date (d/m/y)	Study design	Sample size	Stage of disease	TCM intervention*	Control	Course	Outcome
Wang ZW 2020 [4]	BioScience Trends	9/2/2020	Case report	4	Mild and severe	Shufeng Jiedu capsule	NA	NR	Symptom, virus removal
Luo ED 2020 [5]	Chinese Medicine	15/4/2020	Retrospective study	54	Mild to critical	TCM treatment in real-world practice	NA	NR	Length of hospitalization
Zhang HT 2020 [6]	American Journal of Chinese Medicine	15/5/2020	Retrospective study	22	Mild or moderate	NHM decoction	Routine treatment	NR	Symptom, virus removal, chest CT examinations
Hu K 2020 [7]	Phytomedicine	16/5/2020	RCT	284	Mild or moderate	Lianhua Qingwen capsule	Routine treatment	15 d	Symptom, chest CT examinations, cure rate, virus removal
Ye YA 2020 [8]	Frontiers in Medicine	27/5/2020	RCT	42	Severe	Guideline-based TCM treatment	Routine treatment	7 d	Change in the disease severity, fatality rate, antibiotic use, virus removal
Xin SY 2020 [9]	Biomedicine & Pharmacotherapy	4/7/2020	Retrospective study	63	No details for severity	Qingfei Paidu decoction	Routine treatment	NR	Symptom, usage of Western drugs, laboratory indices, fatality rate, length of hospitalization, chest CT examinations
Wang JB 2020 [10]	Chinese Journal of Integrative Medicine	16/7/2020	RCT	48	No details for severity	Keguan-1 powder	Routine treatment	14 d	Incidents of ARDS, time to fever resolution, recovery of lung injury
Xiong WZ 2020 [11]	Integrative Medicine Research	25/7/2020	RCT	42	Mild to severe	Xuanfei Baidu decoction	Routine treatment	7 d	Symptom, blood routine examination
Xiao MZ 2020 [12]	Pharmacological Research	8/8/2020	RCT	283	Suspected and non-severe cases	Huoxiang Zhengqi dropping pill, Lianhua Qingwen granule	Routine treatment	14 d	Symptom, use of antibiotics, rate of progression to severe
Tian JX 2020 [13]	Pharmacological Research	10/8/2020	Retrospective study	721	Mild and moderate	Hanshiyi formula	Routine treatment, TCM drugs	> 2 d	Rate of progression to severe

RCT, randomized controlled trial; TCM, traditional Chinese medicine; NA, not applicable; NR, not report; ARDS, acute respiratory distress syndrome.

*Details of TCM interventions:

Shufeng Jiedu capsule (Chinese patent medicine), approval number of China Food and Drug Administration (CFDA): Z20090047, ingredients: *Polygoni Cuspidati Rhizoma et Radix* (Huzhang), *Forsythiae Fructus* (Lianqiao), *Isatidis Radix* (Banlangen), *Bupleuri Radix* (Chaihu), *Herba Thlaspis* (Baijiangcao), *Verbenae Herba* (Mabiancao), *Rhizoma Phragmitis* (Lugen), *Radix Glycyrrhizae* (Gancao).

TCM treatment in real-world practice (Experience formula), most frequently used herbs: *Poria* (Fuling), *Coicis Semen* (Yiyiren), *Alismatis Rhizoma* (Zexie), *Armeniacae Semen* (Xingren), *Atractylodis Macrocephalae Rhizoma* (Baizhu), *Scutellariae Radix* (Huangqin).

NHM decoction (Experience formula), ingredients: *Lonicerae Japonicae Flos* (Jinyinhua), *Lablab Semen Album* (Biandou), *Poria* (Fuling), *Rehmanniae Radix* (Shengdi), *Scutellariae Radix* (Huangqin), *Bubali Cornu* (Shuiniujiao), *Eriobotryae Folium* (Pipaye), *Scrophulariae Radix* (Xuanshen), *Forsythiae Fructus* (Lianqiao).

TMR
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Lianhua Qingwen capsule (Chinese patent medicine), approval number of CFDA: Z20040063, ingredients: *Forsythiae Fructus* (Lianqiao), *Lonicerae Japonicae Flos* (Jinyinhua), *Ephedrae Herba* (Mahuang), *Armeniacae Semen Amarum* (Kuxingren), *Gypsum Fibrosum* (Shigao), *Isatidis Radix* (Banlangen), *Dryopteridis Crassirhizomatis Rhizome* (Mianma guanzhong), *Houttuyniae Herba* (Yuxingcao), *Pogostemonis Herba* (Guanghuoxiang), *Rhei Radix Et Rhizome* (Dahuang), *Rhodiolae Crenulatae Radix Et Rhizome* (Hongjingtian), *L-Menthol* (Bohenao), *Glycyrrhizae Radix Et Rhizoma* (Gancao).

Guideline-based TCM treatment, available at: http://www.nhc.gov.cn/xcs/zhengcwj/202001/4294563ed35b43209b31739bd0785e67.shtml.

Qingfei Paidu decoction (Experience formula), ingredients: *Ephedrae Herba* (Mahuang), *Glycyrrhizae Radix et Rhizoma Praeparata Cum Melle* (Zhigancao), *Armeniacae Semen* (Xingren), *Gypsum Fibrosum* (Shengshigao), *Cinnamomi Ramulus* (Guizhi), *Alismatis Rhizoma* (Zexie), *Polyporus* (Zhuling), *Atractylodis Macrocephalae Rhizoma* (Baizhu), *Poria* (Fuling), *Bupleuri Radix* (Chaihu), *Scutellariae Radix* (Huangqin), *Pinellinae Rhizoma Praeparatum* (Jiangbanxia), *Zingiberis Rhizoma recens* (Shengjiang), *Asteris Radix* (Ziwan), Farfarae *Flos* (Kuandonghua), *Belamcandae Rhizoma* (Shegan), *Asari Radix et Rhizoma* (Xixin), *Dioscoreae Rhizoma* (Shanyao), *Aurantii Fructus immaturus* (Zhishi), *Citri reticulatae Pericarpium* (Chenpi), *Pogostemonis Herba* (Huoxiang).

Keguan-1 powder (Experience formula), ingredients: *Lonicerae Japonicae Flos* (Jinyinhua), *Forsythiae Fructus* (Lianqiao), *Mori Folium* (Sangye), *Chrysanthemi Flos* (Juhua), *Coicis Semen* (Yiyiren), *Fritillariae Thunbergii Bulbus* (Zhebeimu), *Armeniacae Semen Amarum* (Kuxingren).

Xuanfei Baidu decoction (Experience formula), ingredients: *Ephedrae Herba* (Mahuang), *Armeniacae Semen Amarum* (Xingren), *Gypsum Fibrosum* (Shengshigao), *Atractylodis Rhizoma* (Cangzhu), *Semen Coicis* (Yiyiren), *Pogostemonis Herba* (Huoxiang), *Polygoni Cuspidati Rhizoma et Radix* (Huzhang), *Lepidii seu Descurainiae Semen* (Tinglizi), *Verbenae Herba* (Mabiancao), *Phragmitis Rhizoma* (Lugen), *ArtemisiaeAnnuae Herba* (Qinghao), *Citri Grandis Rubrum Exocarpium* (Juhong), *Glycyrrhizae Radix et Rhizoma* (Shenggancao).

Huoxiang Zhengqi dropping pill (Chinese patent medicine), approval number of CFDA: Z20000048, ingredients: *Atractylodis Rhizoma* (Cangzhu), *Pericarpium Citri Reticulatae* (Chenpi), *Magnoliae Officinalis Cortex* (Houpo), *Radix Angelicae Dahuricae* (Baizhi), *Poria* (Fuling), *Pericarpium Arecae* (Dafupi), *Pinellinae Rhizoma* (Banxia), *Glycyrrhizae Radix et Rhizoma* (Shenggancao), *Pogostemonis Herba* (Huoxiang), *Caulis Perillae* (Zisu).

Hanshiyi formula (Experience formula), ingredients: *Ephedrae Herba* (Mahuang), *Gypsum Fibrosum* (Shigao), *Armeniacae Semen* (Xingren), *Notopterygii Rhizoma et Radix* (Qianghuo), *Lepidii seu Descurainiae Semen* (Tinglizi), *Cyrtomii Rhizoma* (Guanzhong), *Pheretima* (Dilong), *Cynanchi Paniculati Radix et Rhizoma* (Xuchangqing), *Pogostemonis Herba* (Huoxiang), *Eupatorii Herba* (Peilan), *Atractylodis Rhizoma* (Cangzhu), *Poria* (Fuling), *Atractylodis macrocephalae Rhizoma* (Shengbaizhu), *Crataegi Fructus* (Shanzha), *Massa medicate fermentata* (Shenqu), *Hordei Fructus germinates* (Maiya), *Magnoliae Officinalis Cortex* (Houpo), *Arecae Semen* (Binglang), *Tsaoko Fructus* (Caoguo), *Zingiberis Rhizoma Recens* (Shengjiang).

the publication of the study in high-impact journals. Since the preparation of placebos of Chinese medicine, especially decoctions were difficult [16], and due to the urgency of the epidemic, all studies adopted an open-label design instead of placebo-control and blinding. Besides, the composition of TCM formulae was complex, and there was a lack of basic data on chemical composition and pharmacological research, making it difficult to be accepted outside China.

Bridging the gap between clinical practice and limited evidence

Presently, the public's knowledge of the efficacy of TCM in the treatment of COVID-19 is mainly based on the introduction of official press conferences and media publicity, supplemented by published clinical trials. However, we should realize that in the long run, only high-quality published clinical trials will be the most convincing and lasting pieces of evidence to prove the effectiveness of TCM and support its use worldwide.

Strategies could be adopted to bridge the gap between clinical practice and limited evidence of TCM for COVID-19 and other infectious diseases in the future. For the TCM authorities at all levels of China, the management and coordination of registered clinical trials should be strengthened during the outbreak. The limited medical, scientific, and case resources should be prioritized for evaluating TCM interventions that have potential advantages and/or historical evidence of use in similar diseases. For TCM researchers and physicians, the study design should be given high priority before the start of clinical trials. Only a trial with a rigorous design and standardized procedure can generate high-quality evidence.

As for clinical trials on TCM in COVID-19, multicenter RCTs with large samples are warranted. On the basis of providing all participants with guideline-based Western medicine treatment, the use of placebo in the control group is in line with medical ethics and can be accepted by patients. Blinding should be adopted to evaluate symptoms and other subjective outcomes. Core outcome of COVID-19 including the rate of recovery and time taken for recovery/improvement/progression/death to occur, SARS-CoV-2 nucleic-acid tests, rate of prevention of the progression mild-to-moderate cases to severe disease, and symptoms should be adopted for the assessment of efficacy [17]. Currently, the global epidemic is still far from being controlled; imported and indigenous cases in China occur from time to time. Therefore, there are still opportunities to perform or continue those promising TCM trials in China or through international cooperation, so as to generate more high-quality evidence of the efficacy of TCM in the treatment of COVID-19.

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