Complementary, alternative and integrative medicine (CAM) for the treatment of Coronavirus disease 2019 (COVID-19): an overview

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This document is not a systematic review. It is based on technical reports, guidelines developed by recognised organisations, systematic reviews and communications by WHO and other health authorities. This report is not a clinical guideline and does not make recommendations for clinical practice. Therefore, this document is not a substitute for medical advice, diagnosis, or treatment.

Executive summary

To our knowledge, no guideline or health authority outside China recommends the use of complementary, alternative and integrative medicine (CAM) for the treatment of COVID-19. On the other hand, the guidelines in China recommend Traditional Chinese Medicine (TCM) and acupuncture as a treatment option for COVID-19. In fact, TCM has been widely used during the outbreak.

There is no current evidence to recommend any specific CAM intervention for the treatment of patients with COVID-19. The Chinese guidelines that recommend the use of TCM or acupuncture for COVID-19 are based only on the consensus of experts.

There is some indirect evidence suggesting that TCM may have a potential role in the treatment of COVID-19, but new clinical research in this area is needed. A high number of clinical trials of TCM, in combination with conventional medicine, for the treatment of COVID-19 are ongoing or will be started soon, mostly in China. However, this research will probably not provide timely clinical evidence to support decision-making in the short term.
1. Introduction
Coronavirus disease 2019 (COVID-19), previously called ‘2019 novel coronavirus’ (2019-nCoV), is an acute respiratory disease. It is caused by the coronavirus called SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus-2). An outbreak of COVID-19 was first reported in Wuhan in December 2019. COVID-19 has rapidly spread to other parts of China and globally, including Switzerland. As declared by the World Health Organization (WHO) on 11 March, COVID-19 is "public health emergency of international concern". The pandemic is overloading healthcare facilities worldwide.

There is currently no effective treatment against COVID-19. The optimal selection of antiviral agents and interventions targeting the virus is unknown. Therefore, evidence from randomised controlled trials (RCTs) to support specific treatment against COVID-19 is urgently needed.

Complementary, alternative and integrative medicine (CAM) might have a role in the treatment and symptomatic management of patients with COVID-19 (1). The Institute for Complementary and Integrative Medicine has prepared this report to summarise the available evidence concerning CAM for the treatment of COVID-19.

2. Aims of the report
This report has two specific objectives.
1. To summarize the effects (benefits and harms) of CAM in patients with COVID-19.
2. To identify the ongoing RCTs of CAM in patients with COVID-19.

3. Methods
a. Criteria for considering studies for this review
Type of studies
We followed a pragmatic approach by first trying to identify rigorous secondary research already published on the topic. We looked for evidence-based clinical guidelines, health technology assessments, and systematic reviews.

If there was no secondary research available, we looked for primary studies, preferably, randomised controlled trials (RCTs). If there were no RCTs, we looked for non-randomised trials, such as quasi-randomised trials (quasi-RCTs), and observational studies. Only if we did not find the previous studies, we included narrative reviews and opinion of experts.

Types of participants: patients with COVID-19 (diagnosis as provided by the study authors).

Types of interventions
Intervention: any CAM therapy (combined or not with conventional medicines for treating respiratory infections).
Comparator: conventional medicines only or no intervention.

Types of outcome measures
We planned to assess the following outcomes measured at the end of treatment or the end of follow-up (adapted from a Cochrane review of Chinese herbs combined with conventional medicine for severe acute respiratory syndrome - SARS) (2).
1. All-cause mortality
2. COVID-19 related mortality
3. Days to loss of fever
4. Symptoms score (symptoms included fever, fatigue, cough, poor appetite, perspiration, constipation, and diarrhoea)
5. Duration of symptoms
6. Duration of absorption of pulmonary infiltration
7. Absorption of pulmonary infiltration (assessed with chest x-ray)
8. The average daily dose of corticosteroid
9. Dosage of corticosteroid at the end of treatment
10. Duration of corticosteroid treatment
11. Quality of life
12. Number of days in the hospital
13. Adverse effects

b. Search methods for identification of studies
We conducted literature searches looking for documents published till 17 March 2020. We applied no language of publication restriction. The search strategies used the next terms (in the fields title, abstract or keywords) combined with the Boolean operator OR: COVID-19, “Coronavirus disease 2019”, “2019 novel coronavirus”, “2019-
nCoV”. We managed the results of the searches with the software Endnote X7 (2).

We consulted the following sources:

1. **Electronic databases**: Tripdatabase; MEDBOX; Rapid Response Toolbox; The Cochrane Library (2020, Issue 3); Epistemikos; Web of Science (which included MEDLINE and Embase, among other sources); The Cochrane Central Register of Controlled Trials (CENTRAL) 2020, Issue 3 (which contains the Acute Respiratory Infection Group's Specialised Register); and China National Knowledge Infrastructure (CNKI).

2. **Evidence-based collections**: Evidence Aid: Coronavirus (COVID-19) Evidence Collection; UpToDate; and Dynamed: COVID-19 (Novel Coronavirus).

3. **Websites of relevant organisations**: Centers for Disease Control and Prevention (CDC); European Centre for Disease Prevention and Control (ECDC); The National Institute for Health and Care Excellence (NICE); National University of Singapore Saw Swee Hock School of Public Health; US National Center for Complementary and Alternative Medicine; and JAMA resources on COVID-19.

4. **Trial registries (to identify ongoing studies)**: Clinicaltrials.gov; WHO International Clinical Trials Registry Platform (ICTRP); and the Chinese Clinical Trial Registry.

5. **Contact of experts in the field**: we contacted experts in China asking for relevant studies or guidelines.

**4. Results**

See in Appendix 1 the documents that we assessed for this report.

**Objective 1. To summarize the effects (benefits and harms) of CAM in patients with COVID-19**

It has been suggested that TCM may have the potential to alleviate the damage caused in COVID-19 (3). TCM is considered to have a generalized antiviral effect based on the direct inhibition of viruses, and the control of the associated inflammatory response. Previous in vitro studies of Chinese medicinal herbs have suggested their antiviral activity. For instance, Weng JR et al. demonstrated the activity of Sambucus FormosanaNakai ethanol extract against human coronavirus NL63 (4).

The State Administration of TCM of the People's Republic of China, in collaboration with the WHO, initiated clinical research projects on integrated TCM and conventional medicine for the management of SARS (5). A total of 21 projects covering prevention and treatment were started, but firm conclusions on efficacy could not be drawn yet. Experts recommended WHO continue to support the research of TCM in treating SARS and other diseases (5).

**a. Recommendations on the use of CAM for the treatment of COVID-19 in clinical guidelines**

The guidelines developed in Western countries (6-11) and the Korean guidelines (12) did not provide any recommendation on CAM for patients with COVID-19. However, the website of the National Center for Complementary and Integrative Health in the USA stated that “There is no scientific evidence that any of these alternative remedies can prevent or cure the illness caused by this virus” (13). Besides, this site highlights that some alternative treatments may not be safe to consume (13, 14).

In China, the national and provincial guidelines recommend TCM as a treatment option for COVID-19. In fact, TCM has been widely during the COVID-19 outbreak (15). Besides, the two guidelines developed by the World Federation of Acupuncture-Moxibustion Societies (WFAS) (16) and by the Chinese Acupuncture Society (17), respectively, suggest the application of acupuncture and moxibustion in patients with COVID-19.

These five guidelines are exclusively based on the consensus of experts, and the data to support the recommendations is not detailed. We describe below the Chinese guidelines for the management of COVID-19.

1. **Guidance of the National Health Commission (NHC) of the National Administration of Traditional Chinese Medicine, sixth edition (18)**

**Recommendations of TCM:**

Section 8.4 of the guideline claims that “COVID-19 can also be treated with traditional Chinese
Complementary, alternative and integrative medicine (CAM) for the treatment of Coronavirus disease 2019 (COVID-19): an overview by López-Alcalde, Yan, Witt, Barth; Institute for Complementary and Integrative Medicine University Hospital Zurich (2020) is licensed under a Creative Commons Attribution 4.0 International License.

This section describes in detail (including formulas and compounds) an exhaustive list of TCM options according to the clinical situation of the patient, covering from patients with “fatigue with gastrointestinal upset” to “critical patients”. For example, the guideline recommends administering Xuebijing intravenously 100 mL/day, twice a day for the treatment of severe and critical cases. For patients with “fatigue with gastrointestinal upset” Huoxiangzhengqi Capsule (pill or oral liquid) is recommended. More examples of suggested TCM interventions are qingfei paiyu decoction (QPD), gancaoangjian decoction, sheganmahuang decoction, or qingfei touxie fuzheng recipe (see more details in Ren et al. (19) and the guidelines) (18).

Critical appraisal of the methods of the guideline:
The authors state that “the guidelines were written based on the study, analysis and summary of the treatment of previous COVID-19 cases”. The recommendations are based on the experts’ experience, and no data are provided to support these recommendations. Besides, it is unclear how the guideline team managed the conflict of interests, a rigorous search of the literature searches seems absent, and there was no assessment of the quality of the evidence.

On the other hand, although these recommendations are just based on the experts’ experience, we consider that the document can be of value for healthcare professionals in China and other countries. In a decision-making context characterised by the scarcity of evidence on the management of COVID-19, the experience of healthcare professionals in China can be useful.

2. Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7) (Released by National Health Commission & State Administration of Traditional Chinese Medicine on 3 March 2020)(20)
This guideline is presented as a report (20) and as an article (21). The article states that the guidelines were developed according to the GRADE approach and the WHO guideline development manuals. However, the section dedicated to the treatment of COVID-19 with TCM is based on the guidelines described above (18). Thus, the same conclusions on the strengths and weaknesses apply to these recommendations.

This guidance also has a section dedicated to TCM for the treatment of COVID-19 with the same weakness of the previous two guidelines.

These guidelines recommend using acupuncture and moxibustion in patients with COVID-19. They are also based on the experts’ experience and provide no data to support the recommendations.

b. Systematic reviews and evidence summaries
We found no systematic review or evidence summary of the effects of CAM on the treatment of patients with COVID-19. However, the two reports detailed below suggest that it is plausible to consider that TCM may have a beneficial effect on patients with COVID-19.

We identified one Cochrane review published in 2012 that evaluated the effects of Chinese herbs combined with conventional medicine for severe acute respiratory syndrome (SARS)(23). The review included 12 RCTs and one quasi-RCT. The review concluded that Chinese herbs plus conventional medicine did not reduce mortality in patients with SARS, as compared to conventional medicine alone. Besides, the review suggested that the addition of the Chinese herbs may have a beneficial impact on the following outcomes: symptoms, absorption of pulmonary infiltration, the average daily dose of corticosteroids, the dosage of corticosteroids, days of corticosteroid treatment, quality of life, and length of stay in hospital (24-33). From our perspective, the potential benefits identified in this Cochrane review cannot be transferred to patients with COVID-19 because the results tested in patients with SARS may not apply to COVID-19. In addition, as highlighted in the Cochrane review, the quality of the evidence was low.

Zhang et al. (34) proposed a system to screen TCM compounds that may be candidates against COVID-19. This approach has identified thirteen natural compounds that exist in TCM with potential...
anti-SARS-CoV-2 activity, that is, against the virus that causes COVID-10. In fact, 125 Chinese herbs contain two or more of these thirteen compounds.

c. RCTs
There is no current evidence from RCTs to recommend any specific anti-nCoV treatment for patients with suspected or confirmed COVID-19 (6). Thus, the same conclusion applies to CAM.

d. Observational studies
Following we present five observational studies describing the effects of different preparations of TCM in patients with COVID-19. All these studies are descriptive (without a comparator) with a small samples size. Three studies are case reports (less than five patients in total)(19, 35, 36), and one study is a series of 214 cases (1). Another study did not detail the sample size (37).

All these studies share common pitfalls of uncontrolled designs, which do not allow determining the effectiveness of TCM; they can only suggest that there may be an effect. In addition to that, the TCM compounds and the conventional treatment received are vaguely described in the reports.

1. Ren JL et al. (19, 38)
According to this one-case report, an early intervention with TCM based on a plant-based mixture called Qingfei Paiyu decoction (QPD) (Lung-Clearing and Detoxification Soup) showed effects to prevent the severe and critical disease in one patient with suspected COVID-19. This case is described in two articles (19, 38). As Dr Elisabeth M highlights (39, 40), this case report raises serious concerns. First, the report describes the success of just one patient. Second, the patient was not confirmed as suffering from COVID-19.

2. Yang Q, et al. (1)
According to this report, the State Administration of Traditional Chinese Medicine has recently recommended combining TCM and conventional medicine for the treatment of COVID-19 pneumonia. As an example, QPD has been devised to be used in viral infections. According to Yang et al., in the 214 cases that received this treatment, the symptoms disappeared quickly, and there was a rapid disease recovery.

3. Wang et al. (36)
Wang Z et al. described the care provided to four patients with mild to severe COVID-19. The patients received antiviral treatment (including lopinavir/ritonavir, and arbidol), Shufeng Jiedu Capsule (SFJDC), that is, a TCM herbal formula, and other necessary supportive care. The authors state that “Shufeng Jiedu Capsule” may alleviate acute lung injury in patients with COVID-19 and warrants further study (36).

4. Kaijin Xu et al.
This report describes the experience of treating patients with COVID-19 at the main hospital in Zhejiang (the number of patients treated is not reported). The authors state that they “[...] also integrated Chinese medicine in treatment to promote disease rehabilitation through classification methods of traditional Chinese medicine”. However, we only could access the abstract, which describes the intervention vaguely and does not provide any outcome measure to prove treatment effects.

5. Ni L, et al. (35)
This report describes the first family case of COVID-19 confirmed in Wuhan. The three family members (parents and daughter) responded poorly to routine conventional treatments, so they also received Shuanghuanglian oral liquid (SHL), a Chinese traditional patent medicine. SHL contains extracts of three Chinese herbs, namely, honeysuckle, forsythia, and Scutellaria baicalensis, and is used to treat sore throat, cold, and cough with fever.

The report highlights that “the three cases [...] achieved rapid recovery” and suggests that SHL treatment might be effective. Thus, the authors have started a clinical trial (ChiCTR2000029605) to assess the effects of SHL for the treatment of COVID-19. This multicentre not-blinded RCT will include 100 patients per study arm. It seems to have started in February.

Objective 2. To identify the ongoing RCTs of CAM therapy in patients with COVID-19
To identify treatment options as soon as possible is critical to alleviating the impact of the COVID-19 outbreak. The WHO has published a list of candidate therapeutics (41), which does not include any CAM intervention. However, TCM for the treatment of COVID-19 is considered in China as an area that requires further clinical research (42). We found three reviews (not peer-reviewed)
describing the COVID-19 trials that had been registered so far (43-45).

One review (45) identified a total of 382 COVID-19 trials registered on the WHO’s International Clinical Trials Registry Platform (ICTRP) till 8 March. Two of these trials have been stopped and 379 trials were registered in China. 98 (26%) of the registered trials on the ICTRP evaluate TCM interventions. From these, 48 (49%) trials defined the TCM evaluated. However, 18 trials (18%) used defined TCM compounds in combination with unspecified conventional therapies. Twenty-seven trials (28%) used unspecified TCM interventions. Five trials evaluated other interventions, such as acupuncture.

Another review (43), which has been published as non-reviewed preprint¹, describes the COVID-19 clinical trials that were registered before 10 February 2020 in two databases: the Chinese Clinical Registration Center (CCRC) and ClinicalTrials.gov. The review has identified a total of 75 COVID-19 trials (57 trials of the Chinese register and 18 clinical trials from Clinicaltrials.gov). 97% of the trials were initiated by Chinese organisations. According to search results, the current studies are concentrated in China. Twenty-two trials registered in CCRC or Clinicaltrials.gov evaluate TCM interventions for COVID-19. The interventions evaluated are mostly Chinese herbal medicines (decocition, capsule, granule, etc.), including Feiyanthihao, Qingfeijiedutang, Xinguanyihao, Lianhuaqingwen capsule, etc. Besides, TCM treatment also involves some injections of herbal extracts, such as Shuanghuanglian Injection, Xue-Bi-Jing Injection and Tanreqing Injection. The review authors highlight the poor methodological quality of the TCM registered trials. For example, 17 trials (77%) did not mention if they were randomised, and six trials (23%) were not randomised. Moreover, only nine trials (40%) will be fully blinded (participants, personnel, and outcome assessment). Besides, most of the trials are still exploratory research with small samples, and a mean duration longer than five months. Therefore, the results will not be fast enough available.

The third review, also published as a non-reviewed preprint (44), concluded that the outcome reporting in the protocols of COVID-19 clinical trials is inconsistent. The review concludes that developing a core outcome set for clinical trials in this field is necessary.

5. Conclusions

To our knowledge, no medical guideline or health authority outside China recommends the use of CAM for the treatment of COVID-19. The national guidelines in China recommend TCM and acupuncture as a treatment option for COVID-19. In this line, TCM has been widely used during the outbreak in China.

To date, based on the scarce data available, no recommendation for any specific CAM intervention for the treatment of patients with COVID-19 can be made. The Chinese guidelines that recommend the use of TCM for COVID-19 are based exclusively on the consensus of experts.

We have not found solid evidence to recommend the use of TCM for the treatment of COVID-19. However, there is some indirect evidence suggesting that TCM may have a potential role in the treatment of COVID-19 (case reports of patients with COVID-19 and RCTs of TCM for the treatment of SARS). Clinical research on the effects of TCM in patients with COVID-19 is needed.

A high number of clinical trials of TCM, in combination with conventional medicine, for the treatment of COVID-19 are ongoing or will be started soon in China. However, we consider that the results will not be timely to support decision-making in the short term.

¹ Due to the peer-review process can be lengthy, the authors of this systematic review used medRxiv (www.medrxiv.org/content/what-unreviewed-preprint) to make their manuscripts available as “preprints” before peer review.
Appendix 1: Documents that were assessed for this report

a. Clinical guidelines

1. WHO Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected. Interim guidance. 13 March 2020 (6)
2. Guidance for Corona Virus Disease 2019: Prevention, Control, Diagnosis and Management (National Health Commission (NHC) of the National Administration of Traditional Chinese Medicine, 2020(18).
4. Handbook of COVID-19 Prevention and Treatment, he First Affiliated Hospital, Zhejiang University School of Medicine
5. South Korean physicians treatment guidelines(12)
6. CDC. Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19)(11)
7. ECDC. COVID-19(7)

b. Systematic reviews

Although several narrative reviews were found (see section f. Narrative reviews), to our knowledge there is no systematic review assessing the effects of CAM in patients with COVID-19.

We found a Cochrane review (23) published in 2012 assessing the effectiveness and safety of Chinese herbs combined with conventional medicines versus conventional medicines alone for patients with ‘severe acute respiratory syndrome’ (SARS). SARS was recognised in 2003 caused by another coronavirus, known as SARS CoV. Another systematic review has proposed a system to identify herbal components of TCM that may have an effect on COVID-19 (34)

c. Evidence summaries

We found the following evidence synopses:


d. Randomised controlled trials (RCTs)

We found no finished RCTs to support specific CAM treatments in suspected or confirmed cases of COVID-19.
e. Narrative reviews

1. National University of Singapore, Saw Swee Hock School of Public Health. COVID-19 Science Report: Therapeutics 2020 (49)
5. Lu. Drug treatment options for the 2019-new coronavirus (42)
8. Denis M. Overview of information available to support the development of medical countermeasures and interventions against COVID-19 (3).

f. Case reports

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Bibliography


