

WHO Expert Meeting on Evaluation of Traditional Chinese Medicine in the Treatment of COVID-19

(28 February – 2 March 2022)

**Traditional, Complementary and Integrative Medicine
World Health Organization**

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Abbreviations & acronyms

AI	Artificial intelligence
CT	Computerized tomography
GACP	Good agricultural and collection practice
GMP	Good manufacturing practice
HPLC	High-performance liquid chromatography
ICTRP	International Clinical Trials Registry Platform
ICU	Intensive care unit
IRCH	International Regulatory Cooperation for Herbal Medicines
NATCM	National Administration of Traditional Chinese Medicine
PICO	Population, Intervention, Comparison, Outcome
RCT	Randomized controlled trial
RTO	Retrospective treatment outcome
RWD	Real-world data
SDGs	Sustainable Development Goals
SOPs	Standard operating procedures
T&CM	Traditional and complementary medicine
TCI	Traditional, complementary and integrative medicine
TCM	Traditional Chinese Medicine
UHC	Universal health coverage

Background

Following a high-level policy dialogue between the Director-General of WHO and China's National Administration of Traditional Chinese Medicine (NATCM) in Geneva on 17 January 2022, WHO decided to convene a meeting of experts to evaluate the role of Traditional Chinese Medicine (TCM) in the treatment of COVID-19. The subsequent Expert Meeting on Evaluation of Traditional Chinese Medicine in the Treatment of COVID-19 was held virtually from 28 February to 02 March 2022 from 13:00 to 16:00 Central European Time each day.

The 21 international experts from the six WHO regions included five members of the WHO Expert Advisory Panel, representatives of eight WHO collaborating centres, three members of the WHO International Regulatory Cooperation for Herbal Medicines (IRCH), and members of the China Academy of Chinese Medical Sciences. Technical staff from WHO headquarters, regional and country offices also attended the meeting.

The meeting considered three reports on traditional Chinese medicine and COVID-19 – including on clinical service, research and evidence-based evaluation provided by national expert groups in China. The evidence-based evaluation report focused on outcomes from the reports as well from 12 randomized controlled trials (RCTs) which had been registered and published. The objectives of the meeting were:

- to understand the methodology applied in producing the reports;
- to review and analyse the reports and randomized controlled trials of TCM in various phases of the progression of COVID-19 disease;
- to evaluate the contribution of a TCM integrated approach in the treatment of COVID-19; and
- to discuss how effectively to enhance the contribution of traditional medicine in global pandemics.

Opening and welcome

by WHO

The opening of the meeting was moderated by Dr Zhang Qi, Head of the unit of Traditional, Complementary and Integrative (TCI) Medicine in the WHO Department of Integrated Health Services. Dr Zhang welcomed participants to the meeting and introduced Dr Rudi Eggers, Director of the Department of Integrated Health Services, who delivered an opening address. Dr Eggers said that WHO considers traditional and complementary medicine as an essential part of integrated health services. Dr Eggers noted that there is considerable interest worldwide in traditional medicine, pointing out that traditional and complementary medicine was one of the most downloaded topics from the WHO website during the past year. Chinese medicine is officially supported by the Chinese government and it was hoped that the outcome of the meeting would lead to a better understanding of the role of traditional medicine in the response to future pandemics.

by China

Dr Yu Wenming, Commissioner of China's NATCM welcomed WHO's continued support for traditional medicine.¹ He said that the treatment of SARS with traditional Chinese medicine (TCM) had led to satisfactory outcomes, and that the use of TCM in combating COVID-19 disease was an important element in keeping the extent of disease low in China. The Constitution of the People's Republic of China refers to the need to promote both conventional medicine and traditional Chinese medicine, with the latest law to promote TCM (and the improvement of treatment protocols) coming into force in December 2017.

The NATCM, which is a national governmental body of the People's Republic of China for the TCM, sent TCM specialists to Wuhan to investigate and to treat patients as soon as the COVID-19 pandemic was reported. Three TCM medicines were developed for COVID-19, and these treatments are now optimized to treat new variants. The National Administration will continue to optimize TCM diagnosis and treatment protocols, screening formulas and evaluating efficacy, as well as analysing effective formulas to try to explain efficacy mechanisms scientifically. Dr Yu added that China was ready to assist other WHO Member States in strengthening the role of traditional medicine in their health systems.

Introduction

Dr Zhang Qi of WHO proposed two members of the group to serve as co-chairs and two as co-rapporteurs. Consequently, Professor Harry Fong of the College of Pharmacy, University of Illinois at Chicago, USA, and Professor Elaine Elisabetsky of the Institute of Health Basic Sciences, Federal University of Rio Grande do Sul, Brazil, were elected as co-chairs of the meeting. The persons elected as co-rapporteurs were Professor Charlie Xue of RMIT University, Victoria, Australia, and Professor Heather Boon of the University of Toronto, Canada. Meeting participants were informed that Dr Huang Luqi, president of the China Academy of Chinese Medical Sciences, would serve as a temporary advisor for the period of the meeting.

Dr Zhang outlined the purposes of WHO's current traditional medicine strategy, namely: 1) harnessing the potential contribution of traditional and complementary medicine to health, wellness, people-centred health care and universal health coverage (UHC); and 2) promoting safe and effective use of traditional and complementary medicine through the regulation, research and integration of traditional and complementary medicine products, practices and practitioners into the health system, as appropriate. As of 2018, some 170 WHO Member States acknowledged the use of traditional and complementary medicine, and 55% of countries said they had a national office for policy on, and regulation of, traditional, complementary and integrative medicine.

The mission of WHO's TCI team was described as promoting and supporting the effective use of, and equitable access to, quality TCI products and health services that are safe, integrated

¹ For instance, the Beijing Declaration on Traditional Medicine, 2008; the Sixty-second World Health Assembly resolution WHA62.13 on traditional medicine, 2009; the Traditional Medicine Strategy (2014–2023), 2013; and the inclusion of traditional medicine in the International Classification of Diseases, 11th revision (ICD-11), 2019.

and people-centred across the life course, the care continuum and various sectors in order to contribute to UHC and to achievement of the United Nations Sustainable Development Goals (SDGs). WHO's International Clinical Trials Registration Platform (ICTRP) shows 369 trials on traditional medicine, with a further 138 on TCM. In late February 2022, WHO's COVID-19 research database contained 3986 articles on traditional medicine and 1441 on TCM. WHO also organized workshops on traditional medicine and COVID-19 to share the knowledge and practices of traditional and complementary medicine with countries and professional organizations.

Participants in the Expert Meeting included specialists in research, clinical practice, herbal medicines, epidemiology and statistics. Participants were informed that the meeting would reach its conclusions by consensus. The conclusions and recommendations were expected to cover six aspects of TCM, namely: 1) the efficacy/effectiveness of TCM in treating COVID-19; 2) the safety of TCM; 3) whether the benefits of TCM are found throughout the care continuum; 4) whether the integrated approach is a good model; 5) suggestions for future research in China or internationally; and 6) recommendations on experiences to be shared with other countries and on proposals for strengthening international cooperation in the treatment and control of COVID-19, the recovery of health systems from the current pandemic and preparation for future pandemics.

Presentation of reports on traditional Chinese medicine and COVID-19

Dr Huang Luqi, president of the China Academy of Chinese Medical Sciences introduced the three presenters.

Report 1: Clinical use of traditional Chinese medicine in fighting against COVID-19 in China

Dr Li Guangxi

From the first stage of the response to COVID-19 in China (up to 28 April 2020) the treatment model incorporated both TCM and conventional medicine in an integrated approach. TCM was particularly used as an intervention in clusters of infections. In the second stage of response (from 29 April 2020 onwards), TCM was applied in provincial and city hospitals in the early stages of disease, with specialists in both TCM and conventional medicine cooperating closely in ward visiting and consultations, and working together to formulate diagnosis and treatment plans.

The core principles and practices of TCM remain the same, with treatment being adjusted according to different patterns on the basis of the national protocol. Early TCM intervention was important because it helped to reduce progression to serious disease, including in older patients. Significant outcomes have been claimed following treatment – including TCM medicines combined with specific acupuncture, moxibustion, transdermal therapy and Tai Chi exercises – of patients with mild or moderate COVID-19. For patients with severe disease and in a critical condition, TCM intervention was applied as an accompaniment to conventional medicine. It was noted that the proportion of patients progressing to severe disease appeared to be reduced among those receiving TCM. A number of cases of recovery following TCM

intervention were provided as examples, noting interventions designed for specific symptoms such as anorexia and fatigue.

It was also suggested that TCM could assist in the prevention of COVID-19 illness. During the long lockdown in Wuhan, the public were encouraged not only to maintain a healthy lifestyle and ensure their personal hygiene but also to follow a TCM diet with items such as Chinese yam, Chinese dates and Goji berries. Members of the TCM team took supplies of TCM herbs to communities and delivered TCM items to patients' doors. As people recovered from COVID-19 infection, many who were discharged from hospital still had complaints such as tiredness, anorexia, shortness of breath, insomnia and emotional instability. TCM was therefore also used to ease discomfort and speed recovery.

In summary, the speaker pointed out that TCM had a role to play at all stages of viral infection, as follows:

Prevention – during lockdown many people voluntarily chose to consume plants and herbs with medicinal value. They were encouraged to do so as such foods can help stimulate the immune system and promote health and wellness.

Mild and moderate disease – the RCTs data indicates that TCM was seen to shorten the time to resolution of symptoms, viral clearance and to reduce the proportion of patients progressing to severe disease.

Severe and critical disease – patients were treated with conventional medicine along with TCM. It was felt that this combined approach both shortened the length of stay in intensive care and reduced the duration of mechanical ventilation. It was claimed that TCM reduced mortality among critically ill patients.

Convalescence – TCM serves as the main pillar of care at this stage. TCM interventions were reported to improve clinical symptoms and the quality of life.

The speaker indicated that the advantages of TCM in a pandemic situation include the wide availability of the herbal medicine ingredients and the speed with which TCM can be used to intervene at an early stage of illness. The aim was to boost the immune system before the infection develops and, where severe disease does occur, to assist in recovery by reducing sepsis and emotional disturbance. In conclusion, it was stated that the Chinese approach to COVID-19 was based on the integration of TCM and conventional medicine. Thus TCM played – and continues to play – a key role in reducing the impact of the pandemic.

Report 2: Scientific research on prevention and treatment of COVID-19 with traditional Chinese medicine

Dr Shang Hongcai

When the COVID-19 pandemic began the Government of China allocated funding (equivalent to some US\$ 50 million) through the NATCM for research into this new infection. A dedicated TCM research team was charged with launching anti-pandemic projects in three areas, namely: 1) screening for effective medicines and formulas; 2) clinical and basic research on prevention, treatment and rehabilitation; and 3) the development of TCM and natural medicinal products. The overall aim was to promote the optimization of TCM diagnosis and treatment.

As of March 2022, the Chinese Clinical Trials Registry, which is part of WHO's ICTRP, showed 859 clinical studies of COVID-19 in China, with 70% of the projects registered in January–May 2020. Among these Chinese clinical trials, 213 relate to TCM. The trials include a range of studies which together have addressed six target groups associated with different stages of COVID-19 infection, namely: 1) the general community population; 2) close contacts; 3) suspected cases; 4) patients with mild/moderate disease; 5) patients with severe/critical disease; and 6) convalescent patients. A variety of interventions were implemented – all derived from clinical practice, with existing evidence of their effectiveness, using standard treatment protocols and with controlled quality.

Of the Chinese clinical studies considering mild conditions, 106 looked at TCM's impact on fever, 103 assessed the impact on cough and 94 considered TCM and tiredness. An example was provided of a multicentre RCT with 284 patients from 23 hospitals in nine Chinese provinces who were given TCM in capsule form.² It was reported that, overall, patients in the trial who were given this medicine recovered from their symptoms in a shorter time than patients not given the TCM intervention; the researchers therefore judged that the TCM intervention shortened the period to resolution of clinical symptoms of COVID-19. Twenty-one studies suggest that TCM helps shorten the time of positive-to-negative conversion of COVID-19 nucleic acid and a further 43 indicate that this effect reduces the rate at which non-severe COVID-19 worsens. In line with this finding, another unblinded, cluster-randomized trial that enrolled 408 patients with mild COVID-19 and treated them with another TCM granule formulation reduced the likelihood that COVID-19 would worsen.

A number of studies also looked at TCM's impact on the duration of mechanical ventilation and of stay in an intensive care unit. For instance, a national retrospective registry study of 8939 patients in 15 hospitals found that COVID-19 mortality was 1.2% among patients receiving TCM and 4.8% among those not receiving it, leading the researchers to conclude that TCM was associated with a substantially lower risk of in-hospital mortality.³ More studies – including a multicentre, double-blind RCT which enrolled 131 patients during the rehabilitation period of COVID-19 infection at five hospitals⁴ – showed improvements in exercise tolerance and imaging manifestations on CT. The conclusion of the trial was that TCM may exert strong rehabilitative effects on the physiological activity in patients recovering from COVID-19, which may attenuate symptoms of tiredness and improve exercise tolerance. Throughout the research, no TCM-related serious adverse events were observed. The opportunity was taken to find out more about the pharmacology of certain TCM ingredients, focusing on properties relevant to the treatment of COVID-19, such as those with antiviral and anti-inflammatory effects. Some of the products have been registered in other countries and studies are under way.

² Hu K, Guan W-J, Bi Y, Zhang W, Li L, Zhang B et al. Efficacy and safety of Lianhuaqingwen capsules, a repurposed Chinese herb, in patients with coronavirus disease 2019: a multicenter, prospective, randomized controlled trial. *Phytomedicine*. 2021;85:153242. doi: 10.1016/j.phymed.2020.153242.

³ Zhang L, Zheng X, Bai X, Wang Q, Chen B, Wang H et al. Association between use of Qingfei Paidu Tang and mortality in hospitalized patients with COVID-19: a national retrospective registry study. *Phytomedicine*. 2021;85:153531. doi: 10.1016/j.phymed.2021.153531.

⁴ Chen Y, Liu C, Wang T, Qi J, Jia X, Zeng X et al. Efficacy and safety of Bufei Huoxue capsules in the management of convalescent patients with COVID-19 infection: a multicentre, double-blind, and randomised controlled trial. *J Ethnopharmacol*, 2022;284:114830. doi: 10.1016/j.jep.2021.114830.

Report 3: Methodology applied in selection of the randomized controlled trials

Dr Sun Xin

As of late February 2022 there were no conventional medications for COVID-19. TCM products had played an important role by lowering progression to severe disease, shortening the time to viral clearance and speeding up recovery. However, there were no efficacy studies of this so a team was established to carry out an evidence-based investigation. The team reviewed the type of evidence (RCTs), type of TCM (fixed process, national standards), type of publication (peer-reviewed), quality (design, implementation, reporting), registration (ethical approval, registration platform) and outcomes. The PICO eligibility criteria were used, and eight databases were searched as well as the COVID-19 repository.

Some 150 522 reports were searched and 12 RCTs were selected (see Annex 3). These included 2066 inpatients in China in 2020. All 12 trials – 11 on non-severe COVID-19 and one on severe disease – were published in peer-reviewed journals. Sample sizes ranged from 40 to over 400, and all trials used diagnoses based on National Health Commission guidelines. Overall, it appeared that TCM shortened the time to symptom resolution of fever, cough and tiredness. A cohort study of 780 patients showed that TCM shortened several parameters of COVID-19 recovery – such as nucleic acid conversion and time to resolution of symptoms – and that it reduced the rate of conversion to severe disease.⁵ However, the assessment noted the paucity of evidence of the effect of TCM on severe disease. It was reported that there was sufficient evidence of efficacy on mild and moderate COVID-19 but only preliminary evidence on severe or critical patients. A number of suggestions were made for future research, and it was felt that greater international collaboration and multicentre research could lead to better evidence in future.

Questions and answers (begun on Day 1 and continued on Day 2)

Members of the Expert Panel thanked the three speakers for their reports and acknowledged the emergency context in which the trials had been conducted. Members of the panel asked a series of questions about the presentations and the accompanying printed reports.

Regulatory challenges: selection criteria and quality control

Members of the Expert Panel raised questions about the selection criteria used in choosing the TCM formulas. It was pointed out that selection should be based on quality, efficacy and safety but it was unclear what criteria were used in the Chinese studies as these formulas can be made up of numerous plant species and therefore a diversity of chemical ingredients. In response it was stated that there are different prescriptions according to the grading and severity of the patient and there is a quality standard within the Chinese Pharmacopeia for the medicines that were used in the studies. As for the raw materials, the plants and herbs are grown and collected in accordance with Good Agricultural Collection Practices (GACP), processed in accordance with Standard Operating Procedures (SOPs) and produced in

⁵ Shi N, Liu B, Liang N, Ma Y, Ge Y, Yi H et al. Association between early treatment with Qingfei Paidu decoction and favorable clinical outcomes in patients with COVID-19: a retrospective multicenter cohort study. *Pharmacol Res.* 2020;161:105290. doi: 10.1016/j.phrs.2020.105290.

accordance with Good Manufacturing Practice (GMP). The Chair reminded participants that WHO has guidelines for the collection and processing of medicinal plants. In response to a subsequent question on quality control and the consistency of the ingredients, it was noted that the amount and profiles of chemical constituents may vary according to geographical and seasonal variations, but that all variations are controlled to ensure that they comply with official standards. With regard to any possible adverse effects from the TCM, it was pointed out that, even when some persons who were living with HIV or had autoimmune disorders were among the patients who received the medicine, no adverse effects were reported.

Efficacy: preventative effects of TCM

One issue raised was the suggestion that some TCM formulations may inhibit the virus. Meeting participants asked what evidence exists to support this antiviral potential. In response it was stated that there had been a study which showed antiviral potential.⁶

There was a discussion about how one could determine the possibility of prevention from a few hundred people when the medicine might be given to hundreds of thousands. In particular, owing to limited safety information on pregnant women and children using TCM against COVID-19, what criteria have been taken to conduct a large-scale clinical trial? In response it was stressed that, so far, pregnant women and children have been treated with certain TCM with no serious adverse reactions. It was stated that one study that was not included among the 12 submitted to the meeting, and that had not yet been published, had looked at 202 children who were treated with TCM in six provinces at different times during the past two years and found that no adverse reactions had been reported. It was also pointed out that, as in conventional medicine, TCM has certain contraindications for pregnant women and doses are adjusted according to age and weight. (However, one participant noted that, according to a WHO publication on medicinal plants, these substances should not be used in women and children without prior data). It was also noted that pregnant women were excluded from the 12 selected RCTs.

Safety of TCM and liver functions

A comment had been made about a study which reported problems of liver function in some 20% of patients.⁷ In fact, in the study in question, it was found that both the treated group and the control group had elevated liver enzymes. It was suggested that this might be due to the use of conventional medication to lower the temperature of the patients since some medicines that lower temperature may have an effect on the liver. Nevertheless, it was pointed out that conventional medicine can also be linked to problems of liver function, and COVID-19 is not only a disease of the lungs but may have some impact on the liver too.

⁶ Zhao C, Li L, Yang W, Lv W, Wang J, Guo J et al. Chinese medicine formula Huashibaidu granule early treatment for mild COVID-19 patients: an unblinded, cluster-randomized clinical trial. *Front Med.* 2021;16 Sept. doi.org/10.3389/fmed.2021.696976.

⁷ Hu K, Guan WJ, Bi Y, Zhang W, Li L, Zhang B et al. Efficacy and safety of Lianhuaqingwen capsules, a repurposed Chinese herb, in patients with coronavirus disease 2019: a multicenter, prospective, randomized controlled trial. *Phytomedicine.* 2021;85:153242. doi:10.1016/j.phymed.2020.153242.

Blinding of studies

Another question was raised about how TCM interventions were blinded and, in the case of one study in particular, what placebo was used.⁸ It was explained that the TCM (Xuebijing, or XBJ) intervention was delivered by injection diluted with saline, and that saline was also used as the placebo in the control group. Both the XBJ-saline and the placebo saline were delivered in brown infusion bags and via brown infusion sets to ensure that they looked the same.

Mechanistic study: symptom differentiation

A question was asked about symptom differentiation in the studies. The response was that the pandemic presented common symptoms so it was possible to come up with a standard prescription which could be adjusted, if necessary, for variations such as different patient conditions or regions. There were comments with regard to the need to evolve these ideas in view of the growing interest in customized medicine.

A mechanistic study was proposed to investigate the antiviral effects of specific formulas.

Summary

At the end of the first day's discussion, the Chair (Dr Elisabetsky) reminded participants of the stated purposes of the meeting. Because the experts were presented with a body of data that showed marked heterogeneity of study designs, cohort size, primary and secondary endpoints used to evaluate the effects of diverse patent (branded) TCM, each formulated with different and complex compositions, and because the experts received a large and complex volume of data based on different groups of patients at different times and different places, a deep analysis of the 12 studies would not be a useful approach. Rather, on the basis of what had been presented, the question to answer would be: "How can we improve the study of TCM for the future?" Participants noted the need for ideas on how to optimize analysis of the database and potentially how to promote and cooperate in international trials on these medicines. She asked for an open-minded discussion the following day.

Day 2

At the invitation of the chair, the rapporteur (Dr Heather Boon) summarized Day 1 proceedings, and reminded the panel participants of the objectives and anticipated outcomes of the meeting, specifically the conclusions and recommendations expected to cover six aspects of TCM, namely: 1) the efficacy of TCM in treating COVID-19; 2) the safety of TCM; 3) whether the benefits of TCM are found throughout the care continuum; 4) whether the integrated approach is a good model; 5) suggestions for future research in China or internationally; and 6) recommendations on experiences to be shared with other countries and on proposals for strengthening international cooperation in the treatment and control of COVID-19, the recovery of health systems from the current pandemic and preparation for future pandemics.

⁸ Luo Z, Chen W, Xiang M, Wang H, Xiao W, Xu C et al. The preventive effect of Xuebijing injection against cytokine storm for severe patients with COVID-19: a prospective randomized controlled trial. *Eur J Integr Med.* 2021;42:101305. doi: 10.1016/j.eujim.2021.101305.

Discussion

Members of the Expert Panel acknowledged that the study results showed that TCM resulted in a shorter time for resolution of the illness among the study participants, but also asked how long patients were followed up. Panel members proposed that a retrospective study of treatment outcomes should be carried out by looking at the patients in these studies over longer periods to see if TCM might have any effects with respect to Long COVID-19.

Members of the panel also asked for a fuller analysis of results, such as: 1) a pooled analysis with either: (a) all available RCTs or (b) a focus on subcategories (herbal combinations or single herbs); 2) review of real-world data (RWD) for safety outcomes, particularly when RWD has a longer follow-up period; and/or 3) for symptoms resolution: (a) time in days for symptoms resolution (overall and for each study) and (b) rate/proportion of symptoms resolution in order to provide a meaningful interpretation for clinical practice and research. Trial design would need to evolve to enable rigorous studies of individualized interventions, and it would also be helpful to identify any factors that contribute to the heterogeneity of the findings. Members proposed that Artificial Intelligence (AI) could be used for the analysis of pooled data (e.g. safety and clinical outcomes and correlations with laboratory data).

Participants were informed that the data from the studies had already been pooled and the researchers also looked at trials with similar approaches.

The chair raised the issue of “lack of appetite” which had been mentioned in the reports by the Chinese delegation as part of the impact of TCM on COVID-19. This is often ignored in the West but could be an important issue, especially in the context of Long COVID which can last for months or even a year. There is a growing understanding of the impact of COVID-19 on the brain and it could be of interest to see if the TCMS used have anti-neuroinflammatory properties and/or impact on blood flow to the brain. Additionally, if there are interactions between some TCM treatments and conventional medicines, this would also be an important issue to address in international trials where standard treatments may differ from those used in the selected RCTs. The experts were reminded that the national policy of China is to use both TCM and conventional medicine.

Dr Huang informed the meeting that the first TCM team that went to Wuhan tried to reduce the use of conventional medicine alone. The research suggested that combined use of TCM and conventional medicine can work against COVID-19 and can reduce the adverse effects of conventional medicine. It was pointed out that conventional medicine focuses on the standardization of medicines, and no components are increased or decreased. TCM products also have fixed standards but, when giving treatment, clinicians may vary the dose or adjust the balance of contents to suit a particular patient. However, the meeting was informed that fixed standards were maintained in the RCTs. The meeting noted that experience indicated the inflexibility of conventional medicine and the flexibility of TCM.

In order to emphasize the safety and efficacy of TCM in treating patients with COVID-19, Dr Zhang Weidong outlined the evidence that is readily available. He presented existing pooled data showing the following:

- 12 reliable RCTs were selected from a list of 71 for consideration by the Expert Panel, and there are reliable examples of real-world evidence among 79 cohort studies.
- For evidence on shortening the time to symptom resolution in patients with non-severe disease, there are seven RCTs with over 1000 patients.
- Evidence for slowing the rate of progress from non-severe to severe disease is supported by five RCTs and two real-world evidence studies with a total of 2179 patients.
- The time taken for nucleic acid conversion in patients with non-severe disease is reported in five RCTs with 826 patients.
- There are three RCTs and one real-world study with evidence of reduced hospital stays for non-severe patients, and one RCT and five real-world evidence studies (11 676 patients) to support the argument for reduced mortality in patients with severe disease.
- One RCT with 58 patients showed that a TCM product significantly reduces the rate of conversion of critical cases, the rate of mechanical ventilation and the length of ICU stay, as well as shortening the time to symptom resolution.
- TCM can reduce the use of resources and there is also evidence to suggest that TCM may help to prevent communicating the disease to close contacts. A study conducted in Yangzhou among 5686 persons in quarantine facilities found that the 3438 persons in the TCM treatment group had a positive infection rate of 0.29%, while the 2248 persons in the untreated group had a positive rate of 1.73%.

The Chair proposed that these data should be published in an international journal to generate further discussion and analysis

Participants felt that there were sufficient data for the meeting to make a “cautiously optimistic” judgement that TCM could be helpful in the treatment of COVID-19. A meta-analysis of studies had been proposed as being necessary to get the topic into a high-impact journal, but publication would be unlikely since herbal studies in such journals are rare.

TCM practitioners base their understanding of active compounds on animal data extrapolated to humans. A pharmacology study on this was recommended as it would be important to understand why these treatments work. By learning more about the medicines that work one learns more about the disease. Dr Huang commented that TCM can teach us more about disease and more about human physiology.

As the discussion of Day 2 came to an end, the Chair reminded participants that Day 3 would be focused on finalizing recommendations.

Day 3

The rapporteur summarized the key points of the discussions of the previous day, and reiterated again the objectives of the meeting and the five expected outcomes on: efficacy in treating COVID-19, safety, whether there are benefits throughout the care continuum, the value of the integrated model, international research and experiences to be shared with other countries, recommendations on experiences and lessons, and strengthened international collaboration and health systems.

Discussion

The experts agreed that the studies presented had applied appropriate and rigorous methodology given the context in which they were being conducted. Although the trials involved different settings, the data suggested that TCM was both safe and beneficial when combined with conventional antiviral medicine. It was agreed that there are promising data on the benefits of TCM in reducing the disease exacerbation rate for mild and moderate cases of COVID-19. However, evidence on the benefit of TCM injection for severe cases is limited and further evaluation is critically needed. It was noted that more data are available on this issue but the meeting needs to address only the material as presented.

A set of draft findings, suggestions and recommendations – to WHO and to its Member States – were presented by the Chair (Dr Elisabetsky). These were then the subject of discussion by participants who, while recognizing that the studies suggested the benefits of TCM, called for further investigation into the effectiveness of these products in other populations. It was noted that most of the trials presented had been done with branded TCM that are produced in a consistent manner in accordance with NATCM safety requirements. In this regard it was agreed to make clear that the consultation's findings and recommendations are based on the materials presented to the meeting.

It was agreed that international cooperation and trials should be promoted, with reports in line with international reporting standards in order to make the results more widely accessible. This could be done together with TCM hospitals outside China, and in partnership with WHO TCI collaborating centres – identifying potential partners to replicate the most promising studies and producing a comprehensive analysis. Quality control would have to be assured at all stages and there must be adherence to WHO's guidelines on good practices. There would need to be a clearer focus on the study design, general guidelines would need to be prepared and adequate placebos provided. WHO was asked to consider producing a technical document for this purpose.

Expert Meeting participants then adopted the findings, suggestions and recommendations, as amended.

Key findings of the Expert Meeting

- The experts agreed that the evidence evaluation reports applied appropriate and rigorous methodology to determine the current level of clinical evidence and safety of the studied TCM interventions used in the trials.
- The experts acknowledged that the included trials involved heterogeneous settings and various types of patients and outcome measures.
- In addition to routine treatment, the results from the studied TCMs suggest that, on the basis of clinically relevant outcome measures, the studied TCMs are beneficial in the treatment of COVID-19, particularly in mild-to-moderate cases.
- There are promising data to suggest that TCM is beneficial in reducing the risk of progression from mild-to-moderate cases to severe COVID-19.
- The evidence on the benefit of TCM injection for severe cases is limited, and further evaluation is critically needed.
- For mild-to-moderate cases, there is encouraging evidence that the studied TCMs, when administered as add-on interventions to conventional treatment, may shorten the time for viral clearance, resolution of clinical symptoms and length of hospital stay when compared to conventional treatment alone.
- The results of the TCM trials do not substantiate the use of any specific plant species outside the general TCM framework in the context of COVID-19.
- The studied TCM interventions given in addition to conventional treatment were well tolerated and have a safety profile that is comparable to that of conventional treatment alone.
- There is encouraging evidence that early application of TCM may result in better clinical outcomes for patients with mild-to-moderate COVID-19.
- Despite inherent limitations, the results from the selected RCTs justify further investments in clinical trials to evaluate the potential benefits of selected TCMs in the management of COVID-19.

Suggested measures

- 1. To optimize the analysis of the current database**
 - Conduct pooled analyses based on subcategories (e.g. shared herbal combinations, single herb if available, individual symptom resolution, rate/proportion of symptom resolution, length of stay in hospital, days in intensive care unit, conversion rates, viral clearance).
 - Conduct retrospective treatment outcome (RTO) studies regarding Long COVID.
 - Use artificial intelligence (AI) to scrutinize the data for meaningful correlations.
 - Explore the potential of AI for data/sample/cohort analysis.
- 2. To facilitate and improve new trials**
 - Focus from the beginning on the study design, and especially on key details such as the sample size, randomization method, blinding and follow-up.

- Prepare general guidelines for formatting new trials, including statistics and research design.
- Provide adequate placebos for enteral TCM to allow for double-blind trials.
- Incorporate the TCM theoretical framework in the process of trial design to facilitate translation of findings into practice.
- Share all raw data from clinical trials in order to ensure openness, transparency and sharing as a means towards the recognition of TCM worldwide.
- Consolidate safety data.
- Employ a holistic approach in order to ensure batch-to-batch consistency of trial medications (i.e. products quality control).
- Incorporate qualitative measurement in trial design in order to gain insight into the overall benefit of TCM for COVID-19 patients.

3. To promote international trials and cooperation

- Report studies in accordance with international reporting standards for clinical research (CONSORT and/or CONSORT Extension for Chinese Herbal Medicine Formulas) so that quality can be evaluated comprehensively and accurately and to allow for transparency.
- Partner with existing TCM hospitals outside China.
- Work with WHO collaborating centres for traditional medicine.
- Identify potential partners to replicate the most promising studies with specific branded TCMs.
- Produce a comprehensive analysis of biological data relevant to COVID-19 for the species that comprise the studied TCM.
- Encourage the quantification of potentially toxic compounds (such as ephedrine and others) in the actual TCM dose given to patients.

Recommendations to WHO

The Expert Meeting recommended to WHO:

- to share the outcomes of this consultation with Member States in a timely manner given the evolving nature of COVID-19 globally;
- to encourage Member States to consider the integration of traditional medicine interventions such as TCM in planning for the clinical management of COVID-19 in the context of their health-care systems and regulatory frameworks;
- to provide technical support to Member States for the application of TCM in practice and in further research;
- to facilitate international clinical trials to further evaluate the potential benefits and safety of TCM for treatment of persons with COVID-19 across the care continuum;
- to encourage Member States to consider the integrative care model that has been developed and applied in China.

Recommendations to Member States

The Expert Meeting recommended to Member States:

- to consider the potential use of TCM for the management of COVID-19 in the context of their health-care systems and regulatory frameworks;

- to share experiences and lessons, particularly those actively acquired through this organized research programme in TCM and clinical experience from China;
- to collaborate actively in clinical and mechanistic research to further evaluate and elucidate the clinical benefits and safety of TCM in the management of COVID-19;
- to collaborate in developing consistent approaches, where practicable, and to improve health-care systems for the management of the current pandemic and preparedness for future pandemics.

Commendations

The participants in the Expert Meeting:

- commended the experts from China for sharing research data and clinical experience in using TCM in conjunction with conventional medicine in the management of COVID-19;
- expressed their appreciation for the significant investment and effort made by the Chinese government and its researchers to advance knowledge and to develop therapeutics for the management of COVID-19 from the outset of the current pandemic;
- stated that further research is warranted on TCM for the treatment of COVID-19 since the progress to date lays a strong foundation for international collaboration and cooperation that will potentially benefit human health globally through more effective and appropriate application of TCM for COVID-19;
- expressed appreciation to the leadership provided by WHO in the organization and conduct of this consultation.

Closing

The co-chairs of the meeting thanked all the participants for their contributions and expressed their deep appreciation to the Chinese group of experts and the interpreters. All involved in the meeting had made very worthwhile contributions.

Dr Huang expressed his appreciation for the opportunity to present to WHO the efforts of TCM practitioners and producers in China. He thanked the experts for their valuable suggestions to improve studies of TCM and stressed that the NATCM of China stands ready to assist other countries in promoting the use of traditional medicine.

Dr Zhang Qi thanked the participants on behalf of WHO, noting that the key findings and recommendations covered a variety of important matters. He informed the experts that the traditional, complementary and integrative medicine team in WHO also has a project for the development of a WHO international herbal medicines pharmacopoeia, and that the provision of further documentation and guidance is planned.

The meeting closed at 16:20 Central European time.