Current Global Status and Future Development of Traditional Chinese Medicine in the Prevention and Treatment of Coronavirus Disease 2019

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Abstract

Recognizing the potential of globalizing traditional Chinese medicine (TCM) for coronavirus disease 2019 (COVID-19), this review summarizes the current global use of TCM for COVID-19, status of the internationalization of TCM, and strategy on globalizing TCM for COVID-19. COVID-19 is a novel coronavirus disease that has sparked a pandemic in March 2020 affecting over 110 countries. Although researchers have been racing to develop targeted anti-COVID-19 treatment and vaccine, they are still currently unavailable. Thus, in treating patients infected with COVID-19, western medicine mainly recommended symptomatic treatment and monitoring. Existing drugs are used in the context of clinical trials, and the FDA still not yet approved these drugs for COVID-19. On the other hand, TCM proposed herbal treatment for suspected individuals to take within their observation period, as well as for confirmed COVID-19 patients to take during active phase of disease and during recovery. In China, Integrative Chinese-Western Medicine had been used in treating 91.5% of COVID-19 patients and showed its strength in reducing disease severity, shortening recovery time, and lowering the mortality rate. Despite obstacles in globalizing TCM for the treatment of COVID-19, promoting appropriate use of locally registered TCM products may prevent disease in susceptible individuals, improve the quality of life, and assist in the recovery of COVID-19 patients. With increasing global acceptance, TCM may play a more important role in the battle against infectious disease in the future.

Keywords: Coronavirus disease 2019, coronavirus pneumonia, traditional Chinese medicine, traditional Chinese medicine globalization

Introduction

A novel coronavirus disease, coronavirus disease 2019 (COVID-19), was declared as a pandemic by the World Health Organization (WHO) on March 12, 2020, affecting 114 countries with a total of 118,000 reported cases and 4291 fatalities. As of May 17, 2020, the global statistics has mounted up to 4,534,731 confirmed cases and 307,537 deaths, striking 216 countries or territories. The most heavily affected country is the United States of America (USA), with 1,409,452 cases and 85,860 deaths. The symptoms manifested by contracted patients include the common respiratory infection symptoms, such as fever, cough, sputum production, lethargy, and dyspnea, as well as other symptoms such as headache, diarrhea, and myalgia.

While laboratory tests involving real-time reverse-transcription polymerase chain reaction and serological testing are conducted to confirm COVID-19 cases, a minute fraction (1%) of patients had positive results but were asymptomatic yet contagious. Nevertheless, in addressing the COVID-19 outbreak, the WHO treatment guidelines mainly concentrate on symptomatic care as the FDA-approved vaccines and
anti-COVID-19 medications are still lacking.\textsuperscript{[5]} Of 44 vaccine candidates, only mRNA-1273 (NCT04283461) and Ad5-nCOV (ChiCTR2000030906) are undergoing phase I clinical trials, which are only due to be completed in December 2020 and June 2021, respectively.\textsuperscript{[8,9]} The USA’s Centers for Disease Control and Prevention outlined that the current preferred drugs for treating COVID-19 are remdesivir, an experimental intravenous antiviral, as well as hydroxychloroquine and chloroquine, which are oral antimalarial formulations that have been repurposed for COVID-19.\textsuperscript{[10]} In the United Kingdom (UK), however, the latter has been reserved for use in clinical trial contexts by the UK Medicines and Healthcare Products Regulatory Agency.\textsuperscript{[11]} On March 18, 2020, the WHO launched a “Solidarity” clinical study, in attempt to find an effective treatment for COVID-19, drawing participation from over 70 countries. The ongoing global trial investigates four promising drugs, namely remdesivir, lopinavir/ritonavir, interferon-β, hydroxychloroquine, and chloroquine.\textsuperscript{[12]}

Learning from experiences during the severe acute respiratory syndrome (SARS) outbreak, in China’s battle against COVID-19, the Chinese government strongly advocated the integrative use of traditional Chinese medicine (TCM) alongside western medicine in the management of COVID-19.\textsuperscript{[13]} Accordingly, on January 27, 2020, the National Health Commission (NHC) of the People’s Republic of China promoted the vigorous and integrative use of TCM and issued the 4\textsuperscript{th} version of COVID-19 treatment guidelines which included the TCM treatment regimens.\textsuperscript{[14]} The recommended TCM treatments were divided into two categories – suspected COVID-19 cases and confirmed COVID-19 cases. The recommended TCM use in suspected cases aimed to delay progression to confirmed cases. Five patent TCM medicines were recommended for symptom control of suspected cases. On the other hand, TCM treatments for confirmed cases were further stratified into disease severity (mild, moderate, and severe) and according to TCM syndrome differentiation. Furthermore, TCM treatment was recommended for recovering COVID-19 patients.\textsuperscript{[15]} The treatment guidelines have been constantly updated with more corresponding TCM managements as more information regarding the disease comes to light and is currently in its 7\textsuperscript{th} version. Although the disease categories in the 4\textsuperscript{th} and 7\textsuperscript{th} versions were similar, the latest version introduced TCM treatment for critical patients and included more syndrome differentiation. The 7\textsuperscript{th} version also focused more on treating recovering COVID-19 patients, with different TCM herbal formulae being recommended based on the patients’ syndrome differentiation and clinical manifestation.\textsuperscript{[15]}

TCM has been assimilated into hospitals in China, providing Integrative Chinese-Western Medicine (ICWM) treatment in both outpatient and inpatient settings.\textsuperscript{[16]} Early integration of TCM was evident from the China national guideline that was released in January 2020,\textsuperscript{[14]} which already recommended the usage of TCM for COVID-19. More than 90% of confirmed cases received TCM,\textsuperscript{[17]} which may have contributed to the relatively lower mortality rate (about 4%) in China.\textsuperscript{[18]} Recognizing the potential of TCM in preventing and treating COVID-19, we herein discuss the current global use of TCM, its challenges and strategies in addressing COVID-19, and future directions in this area.

### Current Use of Traditional Chinese Medicine for Coronavirus Disease 2019 in Mainland, China

China’s cumulated evidence and clinical benefits of integrating TCM and western medicine in managing the preceding SARS epidemic outbreak\textsuperscript{[19,20]} served as a foundation in incorporating TCM into its national treatment guidelines for COVID-19 alongside western medicine.\textsuperscript{[15,21]} The extensive use of TCM-western medicine was announced by the NHC of the People’s Republic of China on March 3, 2020, where 91.5% of confirmed COVID-19 cases (equivalent to 74,187 patients) and 90.6% of Hubei COVID-19 patients (equivalent to 61,449 patients) had received TCM treatment, which yielded over 90% of total effective rate.\textsuperscript{[17,22]} Table 1 shows the detailed applications and scientific evidence for the possible beneficial effect of TCM for COVID-19 in China.

### Use and evidence of traditional Chinese medicine in managing coronavirus disease 2019

China’s NHC and State Administration of Traditional Chinese Medicine recommended prescribing TCM as per the disease severity (mild, moderate, severe, and critical), and as per the TCM syndrome differentiation pattern diagnosis classification, and according to the local climate and personal health conditions. The latest version of the treatment guidelines, Version 7 recommended Qing Fei Pai Du (lung-cleansing and toxin-removing) decoction to all suitable mild, moderate, severe, and critical COVID-19 patients.\textsuperscript{[15]} In the latest version, TCM herbal formulae generally include Ma Huang (\textit{Herba Ephedra}), Shi Gao (\textit{Gypsum}), Hou Po (\textit{Cortex Magnolia officinalis}), Ting Li Zi (\textit{Semen Lepidii}), Gan Cao (\textit{Glycyrrhiza Radix Rhizoma}), and Huang Qin (\textit{Radix Scutellaria baicalensis}) among other herbs recommended for confirmed cases.\textsuperscript{[13]} The ethanol extract of Huang Qin (\textit{Radix Scutellaria baicalensis}) was found to impair the activity of SARS coronavirus 2 (SARS-CoV-2) 3CLpro (main protease of SARS-CoV-2) \textit{in vitro} and block the replication of SARS-CoV-2 in the Vero cells at $EC_{50}$ of 0.74 μg/mL.\textsuperscript{[47]} Baiacalein, the primary constituent of \textit{Scutellaria baicalensis}, highly suppressed the activity of SARS-CoV-2 3CLpro at IC$ _{50}$ of 0.39 μM. The study additionally discovered four baikalein analog compounds from other herbs that disrupt the activity of SARS-CoV-2 3CLpro at micromolar concentrations. Taken together, these findings suggest the potent anti-SARS-CoV-2 activity of the extract and compounds from Huang Qin (\textit{Radix Scutellaria baicalensis}), as well as baikalein analogs.\textsuperscript{[47]}

The recommended Chinese patent medicine in severe cases diagnosed with the syndrome of flaring heat in Qi Fen and Ying Fen are Xiyan Ping injection, Xue Bijing injection, Reduning injection, Tan Re Qing injection, and...
Table 1: Current application and evidence of possible beneficial effect of traditional Chinese medicine in China on coronavirus disease 2019

<table>
<thead>
<tr>
<th>Severity</th>
<th>Syndrome differentiation</th>
<th>TCM prescription</th>
<th>Beneficial effects</th>
<th>Related clinical studies (registration number)</th>
<th>Sample size</th>
<th>Study design, study period</th>
<th>Scientific evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCM prevention</td>
<td>Suspected Fatigue and gastrointestinal discomfort</td>
<td>Huo Xiang Zheng Qi (Agastache qi-correcting) capsules, pills, liquid, or oral solution</td>
<td>Immunoregulatory, antiviral, and anti-inflammatory effect</td>
<td>Research for TCM technology prevention and control of COVID-19 in the community population (ChiCTR2000029479)</td>
<td>20,000</td>
<td>Interventional, January 30, 2020, till May 1, 2020</td>
<td>[15,23]</td>
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<td>[24-26]</td>
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<td></td>
<td>Fatigue and fever</td>
<td>Jin Hua Qing Gan (honesuckle flower cold-relieving) granules and Lian Hua Qing Wen (Forsythiae and honey flower pestilence-clearing) capsules, granules</td>
<td>Antiviral and anti-inflammatory Alleviate flu symptoms (headache, cough, productive cough, sore throat, fatigue and fever)</td>
<td>A randomized, open-label, blank-controlled trial for Lian Hua Qing Wen capsule/granule in the treatment of COVID-19 (ChiCTR2000029434)</td>
<td>240</td>
<td>Interventional, February 1, 2020, till December 1, 2020</td>
<td>[26-28]</td>
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<td>240</td>
<td>Interventional, February 1, 2020, till December 1, 2020</td>
<td>[26-28]</td>
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<tr>
<td></td>
<td></td>
<td>Shu Feng Jie Du (wind-expelling and toxin-removing) capsules, granules</td>
<td>Antiviral, anti-inflammatory and alleviate acute lung injury</td>
<td>A randomized, open-label, blank-controlled trial for Lian Hua Qing Wen capsule/granule in the treatment of suspected COVID-19 (ChiCTR2000029433)</td>
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<td>[29-33]</td>
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<tr>
<td>TCM treatment</td>
<td>Mild Cold dampness and stagnation lung syndrome</td>
<td>Qing Fei Pai Du (lung-cleansing and toxins-removing) decoction and other prescriptions</td>
<td>Alleviate fever, cough, fatigue, sore throat and shortness of breath; immune-regulatory, anti-inflammatory and suppress the progression to severe cases</td>
<td>The clinical efficacy and safety of “clear lung detoxification soup” in the treatment of COVID-19 at different time points: A retrospective study (ChiCTR2000032767)</td>
<td>782</td>
<td>Interventional, January 27, 2020, till July 27, 2020</td>
<td>[34-36]</td>
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<td>54</td>
<td>Observational, January 27, 2020, till July 27, 2020</td>
<td>[36]</td>
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<tr>
<td></td>
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<td>Integrative Chinese-western medicine (lopinavir/ritonavir, arbidol, and Shu Feng Jie Du capsule) and other prescriptions</td>
<td>Alleviate pneumonia associated symptoms and fever; anti-inflammatory effect</td>
<td>Treatment efficacy analysis of TCM for COVID-19: an empirical study from Wuhan, Hubei Province, China Clinical characteristics and therapeutic procedure for four cases with 2019 novel coronavirus pneumonia receiving combined Chinese and western medicine treatment</td>
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<td>[33,35,37]</td>
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<td>Moderate Dampness and stagnation lung syndrome</td>
<td>Qing Fei Pai Du (Lung-Cleansing and Toxins-Removing) decoction</td>
<td>Alleviate fever, cough, fatigue, sore throat and shortness of breath; immune-regulatory, anti-inflammatory, shorten hospitalization, suppress the progression to severe cases</td>
<td>Clinical study for TCM decoction in the treatment of COVID-19 (ChiCTR2000030864)</td>
<td>50</td>
<td>Interventional, February 1, 2020, till July 31, 2020</td>
<td>[34,35,36]</td>
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<td>98</td>
<td>Interventional, February 1, 2020, till March 3, 2020</td>
<td>[34]</td>
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<td></td>
<td>72</td>
<td>Interventional, January 30, 2020, till March 3, 2020</td>
<td>[34]</td>
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Contd...
Xing Nao Jing injection.\textsuperscript{[15]} For critical cases with the syndrome of inner blocking causing collapse, the Chinese patent medicines Su He Xiang pill (Storax), An Gong Niu Huang (Peaceful Palace Bovine Bezoar) pill, Xue Bi Jing injection, Reduning injection, Tan Re Qing injection, Xiao Nao Jing injection, Shen Fu injection, or Sheng Mai injection are recommended.\textsuperscript{[15]} Based on encouraging clinical evidence of Jin Hua Qing Gan (honeysuckle flower cold-relieving) capsule, Lian Hua Qing Wen (Forsythiae and honey flower pestilence-clearing) granule and capsule, and Xue Bi Jing injection in treating COVID-19 patients in China, the China National Administration of traditional Chinese Medicine approved the indication of COVID-19 to be added to these three TCM patent medicines.\textsuperscript{[49]}

Recent evidence shows that the COVID-19 causative virus, SARS-CoV-2, penetrates the host cells by interacting with hosts’ ACE2 receptor and TMPRSS2 protease.\textsuperscript{[49,50]} Once SARS-CoV-2 resides in host cells, the virus swiftly replicates, causing cytokine storm.\textsuperscript{[51]} During the cytokine storm, surge of cytokines release leads to persistent activation of immune cells by cytokines and piling up of cytokines at the inflammation site. High levels of cytokines are generated, including interferon (IFN), interleukin (IL), chemokines, colony-stimulating factors (CSFs), and tumor necrosis factor (TNF).\textsuperscript{[51]} Consequently, edema, fever, lung tissue injury, and congestion of the upper respiratory tract ensue. Increased activation of T-helper 17 (Th17) and cytotoxic CD8\textsuperscript{+} T-cells which resulted hypoimmunity in certain patients is also observed.\textsuperscript{[51]} Therefore, by inhibiting ACE2 and TMPRSS2, the transmission of SARS-COV-2 can be suppressed.\textsuperscript{[49,50]} On the other hand, attenuating cytokines storm can reduce lung injury and risk of fatality.\textsuperscript{[39]} Chai Hu (Radix Bupleuri), one of the ingredients forming Qing Fei Fei Di Yin (lung-cleansing and toxin-removing) decoction and a recommended herbal formula for clearing damp-heat accumulation in the lung, contains the bioactive compound saikosaponins.\textsuperscript{[15,52,53]} An \textit{in silico} analysis on saikosaponins identified that it disrupts the interaction between the spike protein of SARS-CoV-2 and ACE2 receptor, which then impairs the virus penetration into the host cells and blocks the virus replication.\textsuperscript{[52]} The active constituents in Huo Xiang Zheng Qi (Agastache qi-correcting), Jin Hua Qing Gan (honesuckle flower cold-relieving) granule, Gan Cao (Glycyrrhiza), and Huang Qin (Radix Scutellaria baicalensis) suppress the virus replication by binding to ACE2 and/or targeting 3CLpro.\textsuperscript{[38,54]} Another active compound in Dan Shen (Salviae miltiorrhizae), cryptotanshinone, represses the mRNA level of TMPRSS2\textsuperscript{[55]} Dan Shen (Salviae miltiorrhizae) is one of the constituents in Xue Bi Jing injection and a herbal formula recommended to treat Qi and Yin deficiency syndrome in the COVID-19 convalescent phase.\textsuperscript{[15]} Other recommended herbs
that target cytokines include Ma Huang (Herba Ephedra),\(^{[56]}\) Xue Bi Jing injection,\(^{[38]}\) Reduning injection,\(^{[38]}\) Jin Hua Qing Gan (honesuckle flower cold-relieving),\(^{[38]}\) and Tan Re Qing injection.\(^{[38]}\)

To date, over 90 China-based clinical trials examining the efficacy and safety of TCM for COVID-19 have been registered with the Chinese Clinical Trial Register (www.chictr.org.cn) and ClinicalTrials.gov. Table 1 details the registered clinical studies that are examining the recommended TCM treatment included in the treatment guideline. More than half of the registered studies (\(n = 56\)) evaluate the effects of ICWM, while 19 studies focused solely on the effects of TCM alone. Another 16 studies compared the effects between TCM and western medicine in managing COVID-19 patients. The most frequently examined TCM herbs are Xi Yan Ping injection (ChiCTR2000029756, ChiCTR2000030117, NCT04275388, ChiCTR2000030218, and NCT04295551), Liu Hua Qing Wen granule (Forsythiae and honey flower pestilence-clearing; ChiCTR2000029434, ChiCTR2000029433, and ChiCTR2000030478), Qing Fei Pai Du decoction (lung-cleansing and toxin-removing; ChiCTR2000030864, ChiCTR2000030806), Bao Baodu (pill of eight treasures) capsule (ChiCTR2000029819, ChiCTR2000029769), and Jin Yin Hua (Lonicerae Japonicae Flos) oral liquid (ChiCTR2000029954, ChiCTR2000030545).

One study focused on the prevention of COVID-19 in the community, by analyzing the effect of Qing Hao (Artemisia annua) antipyretic granules and Huo Xiang Zheng Qi oral liquid (Agastache qi-correcting; ChiCTR2000029479).\(^{[57]}\) In a study administering Qing Fei Pai Du (lung-cleansing and toxins-removing) decoction twice daily to 98 newly confirmed cases of COVID-19 in the Sichuan province, laboratory tests returned to normal in over 70% of cases and a total effective rate of 84.2% was reported after 3 days of treatment. The total effective rate increased to 90.2% and 92.1%, after 6 days and 9 days of treatment, respectively. The chest computed tomographic scans of 79 patients showed improvement after treatment. Notably, none of the mild and moderate patients progressed to severe or critical cases, and there were no deaths.\(^{[54]}\)

### Traditional Chinese medicine in preventing coronavirus disease 2019

Another hallmark of TCM is in the prevention of COVID-19. For suspected COVID-19 patients, five Chinese patent medicines have been recommended to alleviate symptoms during the observation period\(^{[15]}\) and have shown benefits in delaying disease progression.\(^{[17]}\) Huo Xiang Zheng Qi (Agastache qi-correcting) capsule is recommended for individuals with fatigue and gastrointestinal discomfort. However, for individuals experiencing fatigue and fever, Jin Hua Qing Gan (honesuckle flower cold-relieving) granule, Liu Hua Qing Wen (Forsythiae and honeysuckle flower pestilence-clearing) capsule, Shu Feng Jie Du (wind-expelling and toxin-removing) capsule, and/or Fang Feng Tong Sheng (Saposhnikovia powder that sagely unblocks) pill are recommended.\(^{[15]}\) In vitro analysis of Liu Hua Qing Wen (Forsythiae and honey flower pestilence-clearing) showed that it exerts antiviral and anti-inflammatory effect on COVID-19 by blocking the replication of SARS-CoV-2 and downregulating the formation of pro-inflammatory cytokines (TNF-α, IL-6, CCL-2/MCP-1, CXCL-10/IP-10) at the mRNA level.\(^{[27]}\) Local health authorities in 23 provinces in China have recommended herbal medicine for COVID-19 prevention, principally composed of Huang Qi (Radix astragali), Gan Cao (Glycyrrhizae Radix Et Rhizoma), Fang Feng (Radix saposhnikoviae), Bai Zhu (Rhizoma Atractylodis Macrocephalae), and Jin Yin Hua (Lonicerae Japonicae Flos).\(^{[23]}\) External application of TCM, in the form of perfumed bags and feet bath, is also recommended.\(^{[58]}\) Offering preventive means to healthcare workers is vital as about 3.8% of the 44,672 COVID-19 cases were healthcare workers, of which 14.8% were severe or critical and among which were five deaths.\(^{[7]}\)

### Current Global Use of Traditional Chinese Medicine for Coronavirus Disease 2019

The recent WHO-led international joint mission to fight COVID-19 in Italy, Iraq, and other countries provided a platform for Chinese experts to share their experiences in managing COVID-19 and to donate two TCM patent medications: Lian Hua Qing Wen (Forsythiae and honey flower pestilence-clearing) and Jin Hua Qing Gan (honesuckle flower cold-relieving), to the involved countries.\(^{[99]}\) On April 14, 2020, Lian Hua Qing Wen (Forsythiae and honey flower pestilence-clearing) successfully registered in Hong Kong, Macau, Brazil, Indonesia, Romania, Thailand, Canada, and Mozambique under the classification of “Chinese patent medicine,” “drug,” “herbal medicine,” “natural health products,” “food supplements,” and “modern plant medicine,” respectively.\(^{[60]}\)

Outside Mainland, China, other regions and countries have also used and promoted TCM for the prevention and treatment of COVID-19 in various ways. The School of Chinese Medicine of Hong Kong Baptist University offered discounted consultation fees and TCM herbal medicine at its 10 designated affiliated clinics, in efforts to assist in the prevention of COVID-19.\(^{[61]}\) However, the service could not be offered to individuals who had fever, returned from abroad, or with confirmed/suspected COVID-19 cases.\(^{[62]}\) To educate the public, they also promoted TCM methods to prevent COVID-19, such as TCM herbal remedies, Taichi exercises, and dietary advice based on the TCM theories.\(^{[63]}\) Overseas, the American College of Traditional Chinese Medicine at the California Institute of Integral Studies published information on using TCM to fight COVID-19 on their webpage. In view of limited registered TCM herbs in America, the author suggested to take Yu Ping Feng San (jade windscren powder) for prevention and Bu Zhong Yi Qi Tang (tonify the middle and augment the qi decoction) when feeling weak but not sick. As for practitioners with TCM knowledge, San Ren
Tang (three-seed decoction) with Xiao Chai Hu Tang (minor Bupleurum decoction) or Huo Xiang Zheng Qi (Agastache qi-correcting) decoction was suggested for early stages with damp constitution.\[161\] LHSA OMS is a USA-based acupuncture needles and supplies company organized a webinar on the use of TCM to treat COVID-19. Taking into consideration that TCM herbs such as Ma Huang (Herba Ephedrae) and Xi Xin (Herba Asari) are not available in the USA, the webinar also covered information on the substitution for those herbs.\[65\]

In East Asian countries like Japan, the translated version of treatment guideline issued by the NHC of China was adopted. In Korea, both the Association of Korean Medicine and the Korean Association of Traditional Pulmonary Medicine had issued traditional medicine guidelines. The use of Sang Ju Yin (Mulberry leaf and Chrysanthemum decoction) and Yin Qiao San (honesuckle and Forsythia powder) in mild cases and Qing Fei Pai Du (lung-cleansing and toxin-removing) decoction for severe COVID-19 cases was among the recommendations.\[24\] In Malaysia, the Chinese Medicine School of INTI International University gave TCM advice to the public on staying healthy during the outbreak of COVID-19.\[66\] University Tuanku Abdul Rahman joined forces with the TCM Expert Committee of Education Association between Malaysia and China, Beijing University of Chinese Medicine Malaysia Alumni Association, and the School of TCM of Xiamen University Malaysia to establish the Chinese Medicine Task Force of Malaysia (COVID-19). The mission of the task force is to provide TCM-related information on COVID-19, provide safety guidelines for TCM practitioners, and assist healthcare professionals.\[67\] The Malaysian Alumni Association of Shanghai University of TCM had initiated free online TCM consultations and disseminated health information on COVID-19 during Malaysia’s “movement control order.”\[68\] Moreover, one clinical trial was registered in Malaysia (NMRR-20-759-54625) to examine the effects of adding TCM herbs to the standard Western Medicine in treating COVID-19 patients. This study was a collaboration between the Malaysia Ministry of Health, Sunway TCM Centre, and the Alumni Association of Shanghai University of TCM.\[69\]

The global use of TCM to treat COVID-19 is still limited due to legislations, cultural barriers, and other various reasons. Nonetheless, given the experience in the use of TCM for treating SARS and the positive results from the treatment of COVID-10 with ICWM in China, the use of ICWM for COVID-19 can plausibly be expanded and recognized worldwide.

**Progress of Globalization of Traditional Chinese Medicine**

Since the establishment of the People’s Republic of China in 1949, TCM has been inseparable from the national healthcare system, TCM hospitals have flourished, and the government has been continuously emphasizing the integration of TCM-western medicine.\[162\] By 2016, China had TCM cooperation agreements with 86 countries and international organizations, backing the establishment of 10 TCM centers abroad. TCM has been gaining acceptance worldwide so much so that the export value of TCM added up to $3.72 billion in 2015,\[70\] and the global value of the TCM market (including service and medicines) has been estimated to be worth over $50 billion.\[71\] Under the Belt and Road Initiative, TCM was introduced to the involved countries through education, cultural exchanges, scientific research, and medical services.\[71\] The WHO incorporated TCM in the International Statistical Classification of Diseases and Related Health Problems in 2019, thus acknowledging the contribution of TCM in healthcare and supporting the integration of TCM-western medicine.\[72\] On a global scale, TCM is an integral part of complementary and alternative medicine (CAM), which comprehensively refers to nonmainstream medical treatment. CAM also includes other medicinal practices such as acupuncture, herbal medicine, Ayurveda, and Unani medicine.\[73\] However, the acceptance of TCM and CAM outside China varies [Figure 1].

**Frequency of traditional Chinese medicine use**

A review on the use of CAM in the general population among 15 countries reported a range from 5.8% (in Israel) to 76% (in Japan). The use of CAM was relatively higher in the general population in Asian countries, such as South Korea (75%),\[74\] Malaysia (55.6%),\[74\] and Singapore (44.6%).\[74\] Outside Asia, the use of TCM was highest in Australia (68.9%).\[74\] In a more focused study on 10,287 Australian elderly women, the authors revealed that 8.5% had used TCM, primarily for allergies, hay fever, sinusitis, severe fatigue, joint problem, digestion problem, and depression. Their countries of birth, visits to CAM practitioners, and use of self-prescribed CAM predominantly affected their use of TCM.\[75\] In the Singapore National Health Surveillance Survey 2013, 26.5% had visited TCM practitioners at least once.\[73\] More than half of the Taiwanese population (62.5%) used TCM including nearly one quarter of its children population (22.5%), primarily for allergic rhinitis, dyspepsia, and musculoskeletal disease.\[77\] Another systematic review on the use of CAM among 19 countries described a range from 0.8% to 85.5% of children, and adolescents populations had a history of taking herbal medicines; high CAM usage in Germany (85.5%), Brazil (63.8%), Turkey (58.6%) and very low in countries such as North America (12.1%), Ireland (8.7%) and UK (4.1%). Parental education and parental usage were related to high usage in children and adolescents.\[78\]

**Regulation of traditional Chinese medicine**

The legislation of TCM differs across the countries. In the UK, over-the-counter (OTC) herbal medicines are regulated under the Traditional Herbal Medicines Regulation scheme, with similar requirements as that of conventional pharmaceutics, except the evidence of traditional use being submitted for verification of efficacy. Herbal medicines are available as unlicensed herbal remedies, registered herbal remedies, and licensed herbal medicines.\[73\] As for Canada, herbal medicines are categorized as natural health products, governed by the
Natural Health Products Regulations. As of 2012, over 56,000 natural health products have been registered in the Licensed Natural Health Products Database.[73] In Europe, there are no specific regulations to register TCM, and herbal products can be marketed as food, cosmetics, traditional herbal medical products, medicines for human use or veterinary products. Conversely, in the United States, TCM is regulated as biological products, cosmetics, devices, or food under the Federal Food, Drug, and Cosmetic Act or Public Health Service Act. For TCM remedy to be registered as a new drug for disease treatment, well-designed clinical studies are required to provide evidence on its safety and efficacy and must comply with all regulatory requirements for new drugs. Other challenge when registering TCM as a new drug for disease treatment is the necessity to provide evidence on quality and therapeutic consistency, despite the complex composition of TCM herbs.[79]

**Treatment setting of traditional Chinese medicine**

In China, TCM is widely provided in clinics, hospitals, and community health centers. The number of TCM hospitals across China summed up to 3966 at the end of 2015, with 446 ICWM hospitals. Of the 42,528 total TCM clinics in Mainland China, 7706 clinics provided integrated TCM-western medicine.[73] TCM expanded outside China, and there are currently about 100,000 TCM clinics globally.[80] TCM in Hong Kong is commonly provided by private sector clinics, with only a few being under the tax-funded healthcare system, although a pilot TCM inpatient program is underway.[81] Comparatively, TCM treatment has wider coverage in Taiwan, with 2 public TCM hospitals, 42 private TCM hospitals, and 2544 private TCM clinics.[76] In Malaysia, TCM was initially provided by a charitable hospital in 1894.[82] The Malaysia government hospitals later established four Traditional and Complementary Medicine Units offering TCM herbs to cancer patients, as supplementary to conventional cancer treatment.[83] In Singapore[73] and Australia,[81] TCM treatment is predominantly provided in charitable clinics,[73] private clinics,[73,81] or university teaching clinics.[81] In Germany, a 76-bed TCM hospital was first founded in Kotzling,[84] and later, TCM treatment was integrated in the outpatient clinic and wards of three pediatric hospitals.[85]

**Challenges and Strategies in Extending Traditional Chinese Medicine Use to Coronavirus Disease 2019 and Other Infectious Disease**

Despite the evidence showing the benefits of TCM in the management of COVID-19, there are still many obstacles in expanding its global usage, which involve the legislation of TCM herbs, TCM distinct features, complexity of TCM herbs, integration of TCM-western medicine, as well as evidence-based usage of TCM [Figure 2]. Thus, in the quest of globalizing TCM usage, a multifaceted approach is warranted, particularly in addressing the registration and formulation of TCM herbs, as well as refining the quality of TCM herbs and clinical studies.

**Legislation issue of traditional Chinese medicine herbs**

One of the biggest obstacles in globalizing TCM is that TCM herbs are not considered as medicines outside China. TCM herbs are largely marketed as natural health products or food supplements in countries such as Canada,[73] Europe, and the USA,[79] whereby the safety of TCM herbs is regulated in accordance with food standards. Clinical evidence of their effectiveness is not required, and these TCM herbs cannot be labeled and used for treatment. Furthermore, medical doctors are liable for malpractice when using non-FDA-approved drugs. In special cases, for example, in the current lack of targeted anti-COVID-19 treatment, medical doctors may cautiously use nonconventional treatments in the context of clinical trials, including the off-label use of registered

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**Figure 1:** Global prevalence of traditional Chinese medicine/complementary and alternative medicine usage. Schematic depiction with estimated general prevalence (red histogram), prevalence among children and adolescents (blue histogram) and selected information on traditional Chinese medicine/complementary and alternative medicine in some countries and regions worldwide (black box)
drugs, such as antimalarial hydroxychloroquine and chloroquine.\(^{[11,12]}\) Among the TCM herbs outlined in the China national COVID-19 treatment guidelines,\(^{[13]}\) the principal herbs Ma Huang (Ephedra) is prohibited by the FDA due to safety concern\(^{[86]}\) while TCM injection is considered beyond the scope of food supplements.

Ideally, by harmonizing or narrowing down the disparities of regulations and standards among countries shall safeguard the public and allow worldwide usage of TCM herbs. However, matters such as standardizing the definition and categorizing TCM products (whether it is dietary supplement, OTC drug, traditional drug, or prescription drug) may first need to be ironed out.\(^{[79]}\) Although the unfavorable regulations for TCM herbs may not be changed anytime soon, TCM practitioners can legally provide TCM consultations and recommend TCM herbs to improve their patients’ health.

### Evidence-based of traditional Chinese medicine use

A search on PubMed found over 5000 TCM studies (as of April 24, 2020) on a wide range of topics. However, disparities between quantity and quality of TCM clinical studies exist, which necessitate improvement on quality of TCM clinical studies. Two systematic reviews on TCM randomized controlled trials (RCTs) published in China outlined the challenges that needed to be overcome for TCM clinical studies to gain credibility.\(^{[87]}\) The necessary improvement on methodology included improving methodology of RCT, providing sufficient details on intervention, well-defined method of randomization, adequate reporting, well-designed and performed trials with enough participants for subgroup analyses.\(^{[87]}\) Adopting Consolidated Standards for Reporting Trials (CONSORT) can improve the quality of RCT’s reporting and providing sufficient and credible data for audience to appraise the RCTs.\(^{[88]}\) CONSORT checklist entails clear description on intervention, eligibility criteria for participants, allocation of participants, method of randomization, outcome measurement, sample size calculation, and other critical methodology. With clearly defined eligibility criteria of participants, selection bias is avoidable. While adequate data on methodology are required for reproducibility of the study, clarifying occurrence of adverse events shall provide a proper estimate on safety of TCM herbs.\(^{[89]}\) Good-quality clinical studies that prove the effectiveness and safety of TCM herbs are firm foundation for the globalization of TCM.

### Integration of traditional Chinese medicine-western medicine

Integrating the treatments of TCM and western medicine is a challenging task. TCM and western medicine have been developed through different social and cultural backgrounds and have their respective advantages and limitations. However, they may be able to complement each other through integration. For instance, in managing COVID-19, targeted anti-COVID-19 western medical treatment is not yet available and the underlying mechanism of the virus has not yet been fully understood; however, the syndrome differentiation and holistic approach of TCM may provide management options or assistance.\(^{[15]}\) The use of Lian Hua Qing Wen (Forsythiae and honey flower pestilence-clearing) is supported by an \textit{in vitro} study, showing that it has both antiviral and anti-inflammatory effects against SARS-CoV-2. Its anti-inflammatory activity of lowering the formation of proinflammatory cytokines is vital to downplay the cytokine storm\(^{[27]}\) that is responsible for causing critical conditions in COVID-19 patients.\(^{[89]}\) However, as TCM herbs may require time to exert effects, therapy plans combining western medicine could be adopted for faster clinical improvement. To promote communication and cooperation between TCM practitioners and western medicine clinicians, the ability of TCM practitioners to communicate using western medicine medical terms may be helpful.

As western medicine is the mainstay treatment for COVID-19 outside Mainland, China, the issue of herb–drug interaction may potentially arise from ICWM. Interactions may develop at the pharmacodynamic level where drug action is affected or at the pharmacokinetic level, whereby drug absorption, distribution, metabolism, and excretion are affected. A life-threatening example is when there is concurrent consumption of a Dan Shen (Salviae miltiorrhizae)-containing formula with warfarin, which can aggravate the international normalized ratio and cause severe bleeding. However, it should be noted that beneficial herb–drug interaction has also been documented. For example, the antiviral activity of oseltamivir was increased when taken together with Yin Qiao San (honeysuckle and Forsythiae powder) or Sang Ju Yin (Mulberry leaf and Chrysanthemum decoction) formula, resulting in increased therapeutic effect without any untoward consequences.\(^{[87]}\)

Convincing western medicine healthcare professionals, policymakers, and stakeholders with rigorous scientific evidence is essential. The current situation compels TCM to engage in scientific experimental methods to explain the basis of TCM therapeutic effects, as well as to describe the active components, effective dose, onset of action, half-life, toxicity, adverse event, and mechanism of action of TCM herbs. These scientific data are necessary to mold the theoretical framework in guiding more scientific integration.
of TCM-western medicine. When conducting clinical studies, the aspects of herb–drug interactions need to be examined as well. By transparently reporting the results on treatment effectiveness and safety, the findings will guide both TCM and western medicine clinicians in providing herbal treatment with other drugs to attain therapeutic effect without affecting patients’ safety.\[87\]

**Dosage forms, smell, and taste of traditional Chinese medicine herbs**

The recommended TCM herbal formulae for COVID-19 consist up to 15 single herbs and are in the decoction form. Some patients may not be able to tolerate the smell, taste, and dosage form of TCM herbs. An Australian study indicated that patients were reluctant to take herbal preparations due to the inconvenient dosage form and unappealing smell and taste, which then lowered their adherence to herbal treatment.\[90\] Recent development of TCM also emphasized on palatability issues of TCM herbs, as they affect patients’ compliance and treatment effectiveness. Taste-masking technique applicable to oral formulation of TCM herbs is generally grouped into three categories: (i) excipient such as sweeteners, flavors, and bitter blockers in the formulation; (ii) polymer film-coating and lipid barrier systems to avoid bitter ingredients to come into contact with taste receptors; and (iii) binding charged polymers and ion-exchange resins to TCM drug molecules.\[91\] TCM herb production sectors that are targeting the international market need to consider research and development for convenient dosage forms, favorable smell, and palatability.

**Conclusions**

COVID-19 is a new infection caused by coronavirus, with its pathophysiology and virology yet to be fully understood. Targeted anti-COVID-19 drugs and vaccines are still under development. Turning crisis into chance, this is an advantageous situation for TCM that applies syndrome differentiation treatment principles. Clinical studies involving large numbers of patients have shown that ICWM shortened recovery time and reduced mortality rate. In line with China’s national treatment guidelines, TCM treatment was provided to 91.5% of COVID-19 patients and is one of the contributing factors to clinical improvement in more than 90% of COVID-19 patients\[17\] and a considerably low fatality rate of about 4%.\[18\] The global use of TCM for COVID-19 differs across countries due to various inherent constraints. To date, more TCM practitioners and institutions in countries outside China have offered TCM consultations, provided COVID-19 health-related information to the public, and promoted the use of locally registered TCM herbs. Although there is a clinical study outside China using combined TCM herbs with western medicine for COVID-19, the opportunities for TCM to be directly involved in treating COVID-19 patients are still limited outside China. To share and extend China’s TCM experience in combating COVID-19, the situations and barriers in other countries need to be thoroughly understood and addressed accordingly. The recommended strategies to overcome the barriers include conducting quality scientific studies to provide robust scientific evidence, aligning China’s regulations and standards on TCM herbs with international requirements, encouraging TCM practitioners to adopt appropriate language to communicate with western medicine healthcare professionals, and improving the formulation of TCM herbs.

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**Conflicts of interest**

There are no conflicts of interest.

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