

## Review Article

# Principles and treatment strategies for the use of Chinese herbal medicine in patients at different stages of coronavirus infection

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**Abstract:** Coronavirus disease 2019 (COVID-19) is a novel, human-infecting  $\beta$ -coronavirus enveloped, positive-sense single-stranded RNA viruses, similar to the severe acute respiratory syndrome (SARS) infection that emerged in November 2002. In traditional Chinese medicine (TCM), the epidemic disease concepts of “febrile epidemics” (wenyi) or “warm diseases” (wenbing) are based on geographic and cultural aspects, and Chinese herbal medicine (CHM) played an important role in the treatment of epidemic diseases. CHM was widely used to treat patients suffered with SARS almost two decades ago during outbreak of SARS, with proven safety and potential benefits. TCM has also been widely used to treat cancer patients for a long history and much of them associate with immunomodulatory activity and are used to treat coronavirus-related diseases. We propose the use of CHM treatment principles for clinical practice, based on four main stages of COVID-19 infection: early, intermediate, severe, and convalescence. We suggest corresponding decoctions that exhibit antiviral activity and anti-inflammatory effects in the early stage of infection; preventing the disease from progressing from an intermediate to severe stage of infection; restoring normal lung function and improving consciousness in the severe stage; and ameliorating pulmonary and vascular injury in the convalescent stage. We summarize the pharmaceutical mechanisms of CHM for treating coronavirus via antiviral, anti-inflammatory and immunomodulatory effects.

**Keywords:** Coronavirus disease 2019 (COVID-19), severe acute respiratory syndrome (SARS), traditional Chinese medicine (TCM), Chinese herbal medicine (CHM), febrile epidemics (wenyi), warm diseases (wenbing)

## Introduction

After first emerging in Foshan, Guangdong Province, mainland China, in November 2002, severe acute respiratory syndrome (SARS) developed within months into a worldwide epidemic, infecting more than 8,000 patients and causing 774 deaths throughout 26 countries [1]. In December 2019, another infectious disease emerged in Wuhan city, Hubei province, China, which was caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), initially known as the Wuhan pneumonia and then labeled as Coronavirus Disease 2019 (COVID-19) by the World Health Organization (WHO). As of late May 2020, the total number

of confirmed COVID-19 cases is about 5 million, and more than 300,000 deaths have been reported worldwide [2].

## Coronavirus and transmission of COVID-19

COVID-19 is a novel, human-infecting  $\beta$ -coronavirus enveloped, positive-sense single-stranded RNA viruses that shares high similarity with bat coronavirus. Although the genome sequences of COVID-19 are fairly distant from SARS-CoV (with ~79% identity), homology models have revealed that COVID-19 has a similar receptor-binding domain structure of angiotensin-converting enzyme 2 (ACE2) to that of SARS-CoV [3].

Person-to-person transmission of COVID-19 infection was confirmed by infected family members and medical workers [4, 5]. Direct contact occurs due to close exposure to coughing, sneezing, respiratory droplets or aerosols produced by an infected person; indirect contact occurs via environmental or fomite contamination [6]. Symptoms of cough and fever are most common in patients with COVID-19, with other symptoms such as dyspnea and myalgias in mildly infected patients [7], however, predominantly gastrointestinal symptoms (diarrhea, nausea and vomiting) have been reported from hospital patients in New York city [8]. In clinical practice, an epidemiological history and clinical manifestations are the main diagnostic basis of COVID-19 infection, combined with other significant examinations such as chest CT radiography and nucleic acid detection, where real-time quantitative polymerase chain reaction (RT-qPCR) or high-throughput sequencing are commonly used [9]. However, only supportive therapeutic strategies are currently available for treating COVID-19 infection [10]; no specific antiviral drugs or vaccines are available as yet [11].

### *COVID-19 infection in cancer patients*

Patients diagnosed with cancer are more susceptible to COVID-19 infection and have higher risks of developing severe events compared with those without cancer, and those who underwent chemotherapy or surgery in the past months even presented a numerically higher risk [12]. Cancer patients with hematologic cancer, lung cancer, or with metastatic cancer were more vulnerable to SARS-CoV-2 infection and, thus, associated with worse clinical outcomes [13]. The immunocompromised status might be the cause of COVID-19 infection in the patients with cancers [14]. Contact avoidance of hospital visit and admission were proposed for those patients in the French High Council for Public health (HCSP) guideline [15] and the other Chinese study [16] to reduce their risk of infection, which means anticancer treatment might be discontinued or schedule adjustment for cancer patients during the pandemic.

Another very interest link between cancer and COVID-19 is the human TMPRSS2, a key host cell protease for the SARS-CoV-2 virus to enter host cells is known to be activated in prostate cancer through TMPRSS2-ERG fusion gene [17,

18]. Thus, TMPRSS2 inhibitors could be anti-cancer and anti-COVID-19 drugs. In addition, many key enzymes that control SARS-CoV-2 replication including 3-CL protease (also named Mpro), papain-like protease and replicase, etc. have been used as therapeutic targets to develop anti-COVID-19 drugs. The approach and concept are virtually identical to target therapy for cancer precision medicine.

### *The role of Chinese herbal medicine (CHM) in the treatment of coronavirus*

In Traditional Chinese Medicine (TCM), the epidemic disease concepts of “febrile epidemics” (wenyi) and “warm diseases” (wenbing) are based on geographic and cultural aspects, and CHM played an important role in the treatment of epidemic diseases [19]. More recently, TCM was widely used for treating SARS, with proven safety and potential benefits. Patients infected with SARS-CoV who were administered CHM treatment experienced improvements in symptoms, increased lung infiltrate absorption, lower glucocorticoid and antiviral consumption, fewer side effects, and shorter hospital admission durations [20, 21]. As for cancer patients, CHMs also exert antitumor effects by regulating immune response [22] which might be beneficial to reduce the risk of coronavirus infection. In this article, we propose the use of CHM treatment principles for clinical practice, based on four main stages of COVID-19 infection: early, intermediate, severe, and convalescence. The pharmaceutical mechanisms of CHM in the treatment of coronavirus are summarized in **Tables 1** and **2**. And the Chinese characters and pronunciations (pinyin) of syndromes in every stage are listed in [Supplementary Table 1](#).

### **Early-stage febrile disease**

Based on TCM theory, early-stage febrile disease is explained as evil-qi invading lung-wei, presenting as fever, chills, headache, mild sweating and thirst. The symptoms match those of a viral infection in the upper airway. In our experience of coronavirus infection, patients presented with three main syndromes including “heat-toxicity invading lung-wei”, “damp-heat obstructing lung-wei” and “superficial cold and interior heat combining with damp” in the early stage of infection.

## CHM treatment for coronavirus infection

**Table 1.** Pharmaceutical mechanisms of Chinese herbs in treating coronavirus, based on study types conducted during different stages of the disease

| Stages                 | Chinese herbs          | Latin name                      | Clinical trial                        | Animal study   | In vitro study   |
|------------------------|------------------------|---------------------------------|---------------------------------------|--|--|
| Early                  | Jinyinhua              | <i>Flos Lonicerae Japonicae</i> | shorten fever period [24]             | antiviral activity [30]<br>increase nuclear Sp1 binding activity and IL-10 expression of IL-10 [36]<br>decrease nuclear NF-κB binding activities, TNF-α, IL-1β and IL-6 in the lung [36]<br>suppress Toll-Like Receptor 4 signaling [34]<br>inhibit lymphocyte apoptosis [35]<br>anti-inflammatory and antioxidative activities in alveolar macrophages [28] | neuraminidase inhibitory activity [30-32]<br>antiviral activity [33]   |
| Early and intermediate | Lianqiao               | <i>Forsythia suspensa</i>       |                                       | anti-allergic activity by lowering IL-4 and IFN-γ mRNA expression [38]   | antiviral activity [37]<br>antibacterial activity [37]<br>anti-inflammatory activity [37]<br>antioxidant activity [37]<br>neuroprotective activity [37]<br>anti-allergic activity [37] |
| Early                  | Jinyinhua and Lianqiao |                                 | prevent influenza [29]                | anti-Influenza viral activity [25, 26]<br>antibacterial, antiviral, antitumor, anti-inflammatory, and antioxidant effects [27]<br>decrease iNOS, COX-2, NO, prostaglandin E2 (PGE2), TNF-α, IL-1β and IL-6 levels in the lung [28]   | anti-Influenza viral activity [25, 26]   |
| Early and intermediate | Jingjie                | <i>Schizonepeta tenuifolia</i>  |                                       | antiviral activity [40]<br>decrease NF-κB and regulate IFN-γ, IL-4 and IL-2 levels [39]<br>anti-Influenza viral activity [96]  | antiviral activity [40]  |
| Early                  | Danzhuye               | <i>Herba Lophatheri</i>         |                                       |  | antiviral, antibacterial, antioxidant, anticancer activity and suppression of metastasis [41]  |
| Early                  | Mahuang                | <i>Ephedra sinica</i>           |                                       | anti-influenza viral activity [44]<br>anti-influenza viral effects by regulating the TLR7/NF-κB signal pathway [45]<br>inhibit influenza virus replication and mRNA expression via the TLR4 and TLR7 signaling pathways [46]<br>anti-inflammatory effects by decreasing the expression of IL-6, MCP-1 and TNF-α, and increasing expression of IL-10 [47]     |  |
| Early and intermediate | Gancao                 | <i>Glycyrrhiza uralensis</i>    |                                       | antiviral activity [50]<br>SARS-associated viral inhibition [51-53]<br>antibacterial, anti-inflammatory and anticancer effect [49]<br>suppression of platelet responses in acute respiratory distress syndrome [54]<br>suppression of Toll-like receptor 4 (TLR-4) in acute lung injury [55]<br>anti-Influenza virus activity [94]                           | antiviral activity [95]<br>anti-Influenza viral activity [94]  |
| Early                  | Dahuang                | <i>Rheum rhabarbarum</i>        |                                       | anti-fibrosis effect [58, 59]<br>anticancer effect [60]  | blocks S protein and ACE2 interaction [61]   |
| Early                  | Jianghuang             | <i>Curcumae Longae</i>          |                                       | antibacterial, antiviral, antifungal, anticancer, antioxidant, and anti-inflammatory effects [63, 64]  | antibacterial, antiviral, antifungal, anticancer, antioxidant, and anti-inflammatory effects [63, 64]  |
| Early                  | Guanghuoxiang          | <i>Herba Pogostemonis</i>       |                                       |  | antiviral activity [65]  |
| Early                  | Zuling                 | <i>Polyporus Sclerotium</i>     | antiviral activity (hepatitis B) [68] |  | Immunomodulatory activity [66]   |
| Early                  | Zexie                  | <i>Alismatis Rhizoma</i>        |                                       | antiviral activity (hepatitis B) [69]  |  |
| Early                  | Cangzhu                | <i>Rhizoma Atractylodis</i>     |                                       | anti-influenza A virus activity via the TLR7 signaling pathway, decreasing IL-6, TNF-α and IL-1β levels, and increasing IFN-β levels [72]<br>anti-inflammatory effect [70]<br>gastroprotective effects [71]  |  |

## CHM treatment for coronavirus infection

|                         |                 |  |  |   |
|-------------------------|-----------------|--|--|---|
| Intermediate            | Daqingye        | <i>Folium Isatidis</i>                       | antiviral activity [76, 78]<br>anti-Influenza viral activity [76, 77]  | antiviral activity [76, 78]<br>anti-Influenza viral activity [75, 76]   |
| Intermediate            | Banlangen       | <i>Radix Isatidis</i>                        | anti-Influenza viral activity [84]   | antiviral activity [85-88]<br>anti-Influenza viral activity [79-84]   |
| Intermediate            | Zicao           | <i>Radix Arnebiae</i>                        |  | antiviral activity [89, 90]   |
| Intermediate            | Mianmaguanzhong | <i>Dryopteridis Crassirhizomatis Rhizoma</i> | anti-Influenza viral activity [91]   |   |
| Intermediate            | Yinchen         | <i>Artemisiae Scopariae</i>                  |  | antiviral activity [92, 93]   |
| Intermediate            | Niubangzi       | <i>Arctii Tosum</i>                          | anti-Influenza viral activity [94]   | anti-Influenza viral activity [94]  |
| Intermediate            | Huangqin        | <i>Radix Scutellariae</i>                    | antiviral activity [112-116]<br>anti-Influenza viral activity [98-104]   | antiviral activity [109, 112-115, 117-127]<br>anti-Influenza virus activity [98, 100-102, 105-111]  |
| Intermediate            | Guanghuoxiang   | <i>Herba Pogostemonis</i>                    | anti-Influenza viral activity [128]  | anti-Influenza viral activity [128, 129]  |
| Intermediate            | Qinghao         | <i>Artemisiae Annuae</i>                     |  | antiviral activity [133-135]<br>anti-coronavirus activity [132]   |
| Intermediate            | Fuling          | <i>Poria</i>                                 | antiviral activity [136]<br>and anti-Influenza viral activity [136]  |   |
| Intermediate            | Zhimu           | <i>Anemarrhenae rhizoma</i>                  |  | antiviral activity [65, 141]  |
| Intermediate            | Huanglian       | <i>Rhizoma Coptidis</i>                      | antiviral activity [145]   | antiviral activity [143-145]<br>anti-Influenza viral activity [75]<br>anti-coronavirus activity [142]   |
| Intermediate            | Zhizi           | <i>Fructus Gardeniae</i>                     | antiviral activity [151]<br>anti-Influenza viral activity [147-149]  | antiviral activity [150, 151]<br>anti-Influenza viral activity [75, 146-148]  |
| Intermediate and severe | Dihuang         | <i>Radix Rehmanniae</i>                      | antiviral activity [152]   | antiviral activity [153] and anti-inflammatory activity [163]   |
| Intermediate            | Mudanpi         | <i>Cortex Moutan</i>                         |  | antiviral activity [153, 154]   |
| Severe                  | Danshen         | <i>Salviae Miltiorrhizae</i>                 | attenuates pulmonary fibrosis [163, 164]   |   |
| Severe                  | Niuhuang        | <i>Calculus Bovis</i>                        | antipyretic effect [175]<br>relieves acute lung injury [175]   |   |
| Severe                  | Shigao          | <i>Gypsum Fibrosum</i>                       | antipyretic effect [176]   |   |
| Severe                  | Shuiniujiao     | <i>Cornu Bubali</i>                          | antipyretic activity [165, 166]  |   |
| Severe                  | Jiegeng         | <i>Radix platycodonis</i>                    | anti-inflammatory and immunomodulatory activities [167]<br>attenuates airway inflammation [168]                      |   |
| Severe                  | Renshen         | <i>Rhizoma Ginseng</i>                       | improves influenza vaccination outcomes [170]  |   |
| Convalescent            | Maidong         | <i>Radix Ophiopogonis</i>                    | ameliorates Doxorubicin-Induced Chronic Heart Failure by Inhibiting Oxidative Stress and Inflammatory Response [197] | anti-inflammatory activity [198]<br>antioxidative and cardiovascular protection [199, 200]<br>regulates intestinal flora [199, 200]   |
| Convalescent            | Tianhuafen      | <i>Radix Trichosanthis</i>                   | neuroprotective effects in subarachnoid hemorrhage [185]   | antioxidative effect [184]  |
| Convalescent            | Sangye          | <i>Folium Mori</i>                           |  | promotes macrophagic differentiation [186]<br>activities of immunomodulation, anti-inflammation, antioxidation [201]  |
| Convalescent            | Baizhu          | <i>Atractylodis Macrocephalae</i>            |  | anti-tumor activity, anti-inflammatory activity, anti-aging activity, antioxidative activity, anti-osteoporotic activity, neuroprotective activity, and immunomodulatory activity [202] |

## CHM treatment for coronavirus infection

**Table 2.** Pharmaceutical mechanisms of Chinese herbal formulas in treating coronavirus, based on study types conducted during different stages of the disease

| Stages                  | Formula                  | Abbreviation | Clinical trial   | Animal study   | In vitro study   |
|-------------------------|--------------------------|--------------|--|--|--|
| Early                   | Yin Qiao San             | YQS          | Shorten fever period [23]  |  |  |
| Early                   | Ma Xing Gan Shi Tang     | MXGST        |  | inhibited viral entrance via the PI3K/AKT signaling pathway [42]<br>reduced lung inflammation and inhibited virus replication via the TLR3 signaling pathway [43]  |  |
| Intermediate            | Ganlu Xiaodu Dan         | GXD          |  |  | antiviral activity [97]  |
| Intermediate            | Haoqin Qingdan Decoction | HQD          |  | anti-Influenza viral activity [130, 131]   |  |
| Intermediate            | Qingwen Baidu Decotion   | QBD          |  | anti-inflammatory activity [137]<br>promoted immune function [138]<br>prevention and treatment of acute lung injury [139, 140]   |  |
| Severe                  | Qing Ying Tang           | QYT          |  | ameliorate brain tissue edema, attenuate the cytokine increase in brain tissue [161]   |  |
| Severe                  | Jie Geng Tang            | JGT          |  | anti-inflammatory effects [157]  |  |
| Severe and convalescent | Sheng Mai San            | SMS          | Improved exercise tolerance in patients receiving coronary bypass grafting [201] | anti-inflammatory effects [169]<br>preservation of right ventricular dysfunction during chronic intermittent hypoxia in mice [158]<br>improvement of heart failure by regulating ROS generation and the CaMKII signaling pathway [204]<br>protection against doxorubicin-induced cardiotoxicity [205]<br>inhibition of acute lung injury via the TLR4-mTOR-autophagy pathway [179]<br>protection against drug-induced myocardial injury [206, 207] | protected HUVECs from hypoxia/reoxygenation injury, increased cell viability and NO content, decreased LDH leakage, MDA content and ROS generation [178] |
| Severe                  | Shen Fu Tang             | SFT          | rescue in septic shock and resuscitation [170]                                   | reduce TNF- $\alpha$ expression [171]<br>improve systemic microcirculation [171]<br>prolong hypoxia tolerance duration [171]   |  |
| Severe                  | An Gong Niu Huang Wan    | AGNHW        |  | anti-inflammatory effects [173, 174]   |  |
| Convalescent            | Sha Shen Mai Dong Tang   | SSMDT        | Alleviation of radiation-induced xerostomia in cancer patients [181-183]         |  |  |
| Convalescent            | Shen Ling Bai Zhu San    | SLBZS        |  | influence the gut microbiota, protect the gut barrier and regulate gut cytokines [188-190]   |  |

### *Syndrome of heat-toxicity invading lung-wei*

Patients with heat-toxicity invading lung-wei syndrome manifest classical symptoms such as fever, chills, headache, mild sweating, thirst and thin white tongue fur. Appropriate treatments consist of Yin Qiao San (YQS) and Ma Xing Gan Shi Tang (MXGST). YQS is composed of Jinyinhua (*Flos Lonicerae Japonicae*), Lianqiao (*Fructus Forsythiae*), Jingjie (*Schizonepeta tenuifolia Briq*), Dandouchi (*Semen Sojae Praeparatum*), Niubangzi (*Fructus Arctii Tosum*), Bohe (*Herba Menthae*), Gancao (*Radix Et Rhizoma Glycyrrhizae*), Jiegeng (*Radix platycodonis*), Lugen (*Phragmitis Rhizoma*) and Danzhuye (*Herba Lophatheri*). MXGST is composed of Mahuang (*Herba Ephedrae*), Xingren (*Semen Armeniacae Amarum*), Shigao (*Gypsum Fibrosum*) and Gancao. Both formulas are famous for clearing heat and resolving toxin, which are the main mechanisms in early coronavirus infection.

YQS has been used to treat early plague and seasonal influenza for thousands of years. Several randomized controlled clinical trials have demonstrated the antipyretic effect of YQS and its components. Wang et al. found that Oseltamivir and MXGST-YQS, alone and in combination, shortened the time to fever resolution in patients with Hemagglutinin Type 1 and Neuraminidase Type 1 (H1N1) influenza virus infection compared to the CHM untreated control group. The study researchers suggested that MXGST-YQS could be an alternative option for H1N1 infection [23]. During the 2009 H1N1 influenza pandemic, Jinhua Qinggan Granule derived from MXGST and YQS was developed for patients with typical wind-heat affecting lung syndrome [24]. Jinyinhua and Lianqiao as a herbal pair were reported to possess antiviral effects (including against influenza A), antibacterial, antitumor, anti-inflammatory, and antioxidant effects [25-27]. Gao et al. reported that the combination of Jinyinhua and Lianqiao exhibited anti-inflammatory and anti-oxidative effects by reducing inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2), and thus decreasing the production of nitric oxide (NO) and prostaglandin E2 (PGE2), as well as reducing levels of tumor necrosis factor alpha (TNF- $\alpha$ ), Interleukin 1 beta (IL-1 $\beta$ ) and IL-6 expression in the lungs [28]. Liu et al. have shown that compounds including Jinyinhua

and Lianqiao could prevent influenza A H1N1 infection in a controlled clinical trial [29]. Jinyinhua exhibited antiviral efficacy (including against influenza A), neuraminidase inhibitory activity, antibacterial, anti-inflammatory, and antioxidant effects [28, 30-33]. Kim et al. demonstrated that HS-23, a Jinyinhua extract, harmonized the immune system to attenuate septic injury by suppressing Toll-Like receptor 4 (TLR4) signaling and reversed sepsis-induced immunosuppression status by inhibiting lymphocyte apoptosis in a murine model of infection [34, 35]. Kao et al. reported protective and immunomodulatory effects of Jinyinhua, with increases in nuclear Sp1 binding activity, expression of IL-10 and reductions of nuclear factor kappa-light-chain-enhancer of activated B cells (NF- $\kappa$ B) binding activities, as well as decreased levels of TNF- $\alpha$ , IL-1 $\beta$  and IL-6 in the lung [36]. Furthermore, Lianqiao, which was the candidate for SARS-CoV-2 treatment, demonstrated antiviral, antibacterial, anti-inflammatory, antioxidative, neuroprotective and anti-allergic activity [37, 38]. In TCM, Jingjie is used for expelling wind, accompanied by chills and gastrointestinal symptoms [39]. Jingjie reportedly suppresses NF- $\kappa$ B and regulates levels of Interferon gamma (IFN- $\gamma$ ), IL-4 and IL-2. Chen et al. have demonstrated that Jingjie also has antiviral activities against enterovirus 71 [40]. Danzhuye has exhibited antiviral, anti-bacterial, antioxidative and anticancer activities associated with the suppression of metastasis [41].

MXGST is a common prescription for seasonal flu infection. Scientific research has found that MXGST regulates the phosphatidylinositol 3-kinase and protein kinase B (PI3K/AKT) signaling pathway related to viral entry in influenza virus infection [42]. Chen et al. have demonstrated that a modified MXGST decoction decreases lung inflammation and inhibits viral replication in RSV-infected mice, through the TLR3 signaling pathway [43]. Mahuang (*Ephedra sinica*) is famous for resolving exterior invasion of the influenza virus [44]. The anti-influenza virus effect reportedly occurs through the regulation of the TLR7/NF- $\kappa$ B signaling pathway [45], by inhibiting influenza virus replication and messenger ribonucleic acid (mRNA) expression through the TLR4 and TLR7 signaling pathways [46]. Mahuang has also shown anti-inflammatory effects by decreasing the expression of IL-6, monocyte chemoattractant

protein-1 (MCP-1) and TNF- $\alpha$ , and increasing the expression of IL-10 [47]. Xingren is used in TCM for down-bearing qi and calming panting. Xingren has shown antiasthma activity, inhibiting type 2 helper T cell responses [48]. Antiviral experiments have not yet Xingren. Gancao (*Glycyrrhiza uralensis*) is a famous TCM herb that is used to resolve a toxin. Glycyrrhizin has shown broad antiviral, antibacterial, anti-inflammatory, anticancer and hepatoprotective effects in many studies [49]. Glycyrrhizin inhibits viruses such as hepatitis B, human immunodeficiency virus (HIV) and SARS-coronavirus [50]. Previous studies have reported that glycyrrhizin is effective for inhibiting replication of the SARS-associated virus [51-53]. In cases of acute respiratory distress syndrome, glycyrrhizin suppressed platelet responses and alleviated lung destruction associated with the inhibition of the TLR-4/NF- $\kappa$ B signaling pathway [54, 55].

### *Syndrome of damp-heat obstructed lung-wei*

Patients with damp-heat obstructed lung-wei syndrome manifest typical symptoms such as low-grade fever, headache of heaviness sensation, poor appetite, fatigue and thick slimy tongue fur. We have used San Ren Tang (SRT) and Sheng Jiang San (SJS) to dispel damp-heat. SRT treats triple burner damp heat, which is composed of Xingren, Yiyiren (*Coicis semen*), Douko (*Amomum cardamomum*), Huashi (*Talcum*), Banxia (*Rhizoma pinelliae*) and Houpo (*Magnoliae officinalis*). However, SRT has not been subjected to evidence-based study in coronavirus treatment. SJS has a long history in TCM of specialization for plague diseases, and is composed of Dahuang (*Rheum rhabarbarum*), Jianghuang (*Curcumae longae*), Chantui (*Cicadae periostracum*) and Jiangcan (*Bombyx batryticatus*). Based on TCM theory, Dahuang is mostly used in gastrointestinal symptoms such as constipation and liver-related disease [56, 57]. Dahuang has shown antifibrotic effects, inhibiting stellate cell activation by matrix metalloproteinase (MMP) 1 expression [58, 59] and anti-hepatocellular carcinoma invasion by inhibiting MMP-2 and -9 activities [60]. The major compound extracted from Dahuang, emodin, blocked the S protein and ACE2 interactions in SARS-coronavirus [61]. Thus, emodin might be a potential effective drug for new SARS-coronavirus [62]. Jianghuang has shown antibacterial, antiviral, antifungal, anti-

cancer, antioxygenic, and anti-inflammatory effects in both in vitro and in vivo studies [63, 64]. In addition to SRT and SJS, we sometimes use the combination of Huo Pu Xia Ling Tang (HPXLT) to enhance the effect of damp clearance. The components of HPXLT are Hohsiang (*Agastachis herba*), Houpo, Banxia, Chifuling (*Poria cocos*), Zhuling (*Polyporus umbellatus*), Zexie (*Alismatis rhizoma*), Xingren, Yiyiren and Douko (*Amomum cardamomum*). Hohsiang, the principal drug of HPXLT, elevated immunoglobulin titers and reduced morbidity in an animal study, indicating antiviral activity [65]. In recent studies, Zhuling has demonstrated immunomodulatory [66], anticancer [67] and anti-hepatitis B activities [68]. Zexie has been associated with a wide spectrum of pharmacological effects such as diuretic, antiviral, antibacterial, antitumor, anti-inflammatory and immunomodulatory effects [69].

### *Syndrome of superficial cold and interior heat with damp*

Patients with superficial cold and interior heat with damp syndrome manifest symptoms such as fever, sweating, severe thirst and yellowish slimy tongue fur. We prescribe MXGST and SJS to resolve the exterior cold, clear interior heat and transform dampness. For patients with heavy damp, we add Cangzhu (*Rhizoma atractylodis*) to dry the dampness. Cangzhu has exhibited anti-inflammatory [70] and gastroprotective effects [71]. Furthermore, atractylon, a derivative from cangzhu, has shown significant anti-influenza A virus effects. By regulating the TLR7 signaling pathway, atractylon is capable of reducing risk of virus-induced lung injury by decreasing levels of IL-6, TNF- $\alpha$  and IL-1 $\beta$  expression and increasing IFN- $\beta$  expression [72].

### **Intermediate-stage febrile disease**

In the intermediate stage of disease, the patient will have repeated high fevers, cough, limb weakness or fatigue, and may have begun to have dyspnea. The time taken to develop from the early stage to the intermediate stage is about 8 days, by which time the patient may already require hospitalization, and the majority will have bilateral lung involvement on imaging [73]. According to TCM theory, the hyperthermic reaction of patients can be divided into four types of syndromes, as follows: “syndrome of dual exterior and interior heat”; “syndrome of

retained dampness-heat toxin”; “syndrome of dampness-heat obstructing the Shaoyang”; and “syndrome of intense heat toxin”.

### *Syndrome of dual exterior and interior heat*

The “Syndrome of dual exterior and interior heat” is a heat syndrome involving both exterior and interior, caused either by a heat pathogen entering the interior before the exterior syndrome is resolved, or by superimposition of a new exterior syndrome on a preexisting illness. It usually manifests with fever, an aversion to wind, headache, flushed face, thirst, irritation or even delirium, constipation, dark-colored urine, reddened tongue with dry yellow coating and rapid forceful floating pulse [74]. For patients suffering from this type of syndrome, modified Qing Fei Jie Du Tang (QFJDT) can be used to clear heat and down-bear fire, enrich yin and moisten dryness of lung.

QFJDF is composed of Daqingye (*Folium isatidis*), Banlangen (*Radix isatidis*), Zicao (*Radix arnebiae*), Chonglou (*Paridis rhizoma*), Yinchen (*Artemisiae scopariae*), Mianmaguanzhong (*Dryopteridis crassirhizomatis rhizoma*), Baibu (*Stemonae radix*), Gancao and Jiegeng. Daqingye, Banlangen, Zicao, Chonglou, and Mianmaguanzhong all have strong heat-clearing and detoxifying effects and are particularly effective for viral infection. Daqingye has antiviral effects in herpes simplex virus type I, influenza A virus (IAV), coxsackievirus B3 (CVB3), respiratory syncytial virus (RSV), and adenovirus type 7 (Ad-7) [75-78]. Banlangen has anti-influenza viral activities in H1N1, H3N2, H6N2 and H9N2 [79-84]. It also has other antiviral activities in cases of pseudorabies virus, hepatitis B virus and porcine reproductive and respiratory syndrome virus [85-88]. Zicao has antiviral activities in adenovirus type 3 and HIV1 [89, 90]. Mianmaguanzhong has anti-influenza virus activity in H5N1 [91]. Yinchen, Baibu and Gancao also exhibit detoxifying effects. Yinchen has antiviral activities in hepatitis B virus [92, 93]. Gancao has anti-influenza virus activity in H2N2 [94] and antiviral activity in Ebola virus [95]. Finally, Jiegeng is added to diffuse lung qi and expel the pathogen, giving the whole formula the effects of clearing and detoxifying the lung.

The effect of QFJDF formula for dispersing exterior heat is slightly insufficient. CHM of Jingjie

(*Schizonepeta tenuifolia*), Bohe (*Mentha canadensis*), Niubangzi (*Arctii fructus*) and other medicines can be added to disperse exterior heat, and increase the efficiency. After mixing these medicines together, the effects of heat-clearing, detoxifying and purging the lung to down-bear the counterflow will be more powerful. Jingjie has shown anti-influenza virus activity in H1N1 [96], while Niubangzi has shown anti-influenza virus activity in H2N2 [94].

### *Syndrome of retained dampness-heat toxin*

The “syndrome of retained dampness-heat toxin” is marked by redness, swelling, ulceration and exudation of the hand, foot, ear, nose, head, face or genital region, or by fever, jaundice, impaired consciousness, eruptions, reddened tongue and a rapid soggy pulse [74]. When facing this syndrome, physicians can choose modified Gan Lu Xiao Du Dan (GLXDD) to resolve dampness, dispel filth, clear heat and detoxify. GLXDD can significantly inhibit the proliferation of coxsackievirus B2, B3 and B4 strains at a concentration of 25 g/L [97]. GLXDD is composed of Huashi, Yinchen, Huangqin (*Radix scutellariae*), Shichangpu (*Acori tatarinowii*), Chuanbeimu (*Fritillariae cirrhosae*), Chuanmutong (*Clematidis armandii*), Guanguhuoxiang (*Herba pogostemonis*), Shegan (*Belamcandae rhizoma*), Lianqiao, Bohe and Amomi fructus rotundus.

Huashi, Yinchen, and Huangqin in GLXDD are greatly used. Huashi can drain dampness and clear heat to release summerheat; Yinchen can drain dampness and clear heat to anti-icteric; Huangqin can drain dampness and clear heat to dry dampness. Huangqin has anti-influenza virus activities in H1N1 and H3N2 infections [98-111]. It also has antiviral activities in coxsackievirus B3, respiratory syncytial virus, hepatitis B virus, HIV1, duck hepatitis A virus type 1, Sendai virus, Newcastle disease virus, vesicular stomatitis virus, dengue virus, Enterovirus 71, tick-borne encephalitis virus, and human T cell leukemia virus type I [109, 112-127].

The other herbs, including Shichangpu, Doukou, Guanguhuoxiang and Bohe, are applied to resolve turbidity and move qi to regulate the spleen. Guanguhuoxiang has anti-influenza virus activity in H1N1 infection [128, 129]. Shegan, Chuanbeimu can direct lung qi downward and soothe the throat. Chuanmutong can assist



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Huashi and Yincheng to clear heat and drain dampness. Lianqiao can assist Huangqin to clear heat and detoxify. Lianqiao also has anti-influenza virus activity in H1N1 infection [25]. After being combined together, this formula can resolve dampness to dispel filth, clear heat and detoxify.

### *Syndrome of dampness-heat obstructing the Shaoyang*

When the dampness-heat pathogen obstructs qi movements of Shaoyang, the “syndrome of dampness-heat obstructing the Shaoyang” develops, in which the pathogen products exist between the exterior and interior of the body, marked by clinical manifestations of alternate fever and chills, fullness and choking feelings in the chest and hypochondriac regions, a dry throat and string-like pulses [74]. For this syndrome, the patients can be prescribed a modified Hao Qin Qing Dan Decoction (HQQDD) to purge Shaoyang and separate dampness-heat. HQQDD in combination with ribavirin inhibited the expression of CD14 and TLR4 and prevented influenza virus A1/FM1 from inducing febrile disease dampness-heat syndrome in mice [130]. HQQDD treats the damp-heat syndrome of pneumonia infection of influenza virus by reducing TLR2 expression, decreasing the levels of NF- $\kappa$ B mRNA and the proportionality of Th1/Th2 [131]. HQQDD is composed of Qinghao (*Artemisiae annuae*), Zhuru (*Bambusae caulis*), Banxia, Fuling, Huangqin, Zhiqiao, Chenpi (*Citri reticulatae*), Huashi, Gancao and Qingdai (*Indigo naturalis*).

Qinghao and Huangqin are bitter-cold, aromatic herbs that expel the pathogen and purge heat in Shaoyang. Both herbs act as sovereign medicines in this formula. Qinghao has demonstrated anti-coronavirus activity in SARS-associated coronavirus [132] and also antiviral activities in hepatitis C virus, HIV1, and bovine viral diarrhea virus [133-135]. In addition, both Zhuru and Banxia can clear and resolve phlegm-heat, while the combination of Chenpi and Zhiqiao can soothe the chest and harmonize the stomach to down-bear counterflow. The four above-mentioned herbs are minister medicines in this formula, while Fuling, Huashi and Qingdai act as assistants. These assistant herbs can clear heat, drain dampness, and guide pathogens to urine. Fuling has anti-Influenza virus activity in

H1N1 [136] as well as anti-hepatitis B virus activity [134]. Such compatibility can clear Shaoyang's pathogenic heat, resolve phlegm-dampness and soothe qi movement.

### *Syndrome of intense heat toxin*

The “Intense heat toxin syndrome” arises when accumulated exuberant pathogenic fire-heat transforms into a toxin and manifests as sores and eruptive diseases, marked by fever, thirst, cough, dyspnea or chest pain, constipation, dark urine, and a reddened tongue with a yellow coating [74]. For this condition, the physician can choose the modified Qing Wen Bai Du Decoction (QWBDD) to clear heat, cool blood, purge fire and detoxify. By changing the level of inflammatory mediators, QWBDD has anti-inflammatory effects in sepsis [137]. It has also shown significant effects in cytoimmunity and humoral immunity, and the potentiation of immune function [138]. Verbascoside and angoroside C in QWBDD play a key role in reducing pulmonary edema. Ethyl gallate, pentagalloylglucose, galloyl paeoniflorin, mudanpioside C and harpagoside in QWBDD can treat lipopolysaccharide-induced acute lung injury, mainly by reducing the infiltration of activated polymorphonuclear leukocytes [139, 140]. QWBDD is composed of Shigao, Dihuang (*Radix rehmanniae*), Huanglian (*Rhizoma coptidis*), Zhizi (*Fructus gardeniae*), Jiegeng, Huangqin, Zhimu (*Anemarrhenae rhizoma*), Chishao (*Paeoniae radix Rubra*), Xuanshen (*Scrophulariae radix*), Lianqiao, Danzhuye, Mudanpi (*Cortex moutan*), and Gancao. This formula consists of three major formulas. It includes mainly Bai Hu Tang (BHT) with a clearing heat toxin in qi aspect, Huang Lien Jie Du Decoction (HLJDD) with a fire purging effect and Xi Jiao Di Huang Decoction (XJDHD) with a blood cooling effect.

QWBDD can treat pestilence and heat toxin both on interior and exterior blazing of both qi and blood. This formula focuses on massively clearing heat toxin in the qi aspect of yang brightness, so it uses a lot of Shigao with Zhimu and Gancao. This idea originates from another formula, Bai Hu Tang (BHT) which can clear heat and engender fluid. Zhimu has antiviral activity in respiratory syncytial virus and Newcastle disease virus infection [65, 141].

Huanglian, Huangqin and Zhizi are often used together. This prescription is similar to another

formula, Huang Lien Jie Du Decoction (HLJDD), which can purge fire of triple energizers. Huanglian has anti-influenza virus activity [75]. Huanglian has also demonstrated anti-coronavirus activity in the porcine epidemic diarrhoea virus [142], and antiviral activity in herpes simplex virus type I, respiratory syncytial virus and hepatitis C virus [143-145]. Zhizi has shown anti-influenza virus activity in H1N1 infection [75, 146-149], and demonstrated antiviral activity in Enterovirus 71 and white spot syndrome virus [150, 151].

Shuiniujiao (*Cornu Bubali*), Dihuang, Chishao and Mudanpi in combination is similar to Xi Jiao Di Huang Decoction (XJDHD), which can clear heat, detoxify, cool the blood and dissipate stasis. This prescription effectively treats the syndrome of blazing both qi and blood. Dihuang has demonstrated antiviral activity in duck hepatitis A virus type 1 infection [150]. Mudanpi has also shown antiviral activity in hepatitis B and C viruses [153, 154]. Lianqiao and Xuanshen are applied to dissolve floating fire.

In the composition of these four formulas, 18 single herbs have been proven to have antiviral activities, two of which are specifically effective at fighting coronavirus - Qinghao and Huanglian [142].

### Severe-stage febrile disease

In the severe stage, the disease is further aggravated if not treated properly. Patients may present with severe dyspnea, hypoxemia, and respiratory failure due to acute lung injury. The heavy load of inflammation may lead to pulmonary fibrosis, which affects lung function in the long-term [155]. In this stage, patients may also present with impaired consciousness due to direct viral invasion of the central nervous system (CNS) or induction of CNS inflammatory mediators [156]. Patients in this stage are at risk of septic shock with multiple organ dysfunction syndrome (MODS) due to a cytokine storm immune response [73].

#### *Syndrome of phlegm and blood stasis obstructing the lung*

Based on TCM theory, retention of pathological products such as phlegm and blood stasis can block qi circulation and therefore impair lung function. Qi stagnation resulting from retention of the pathological products may transform into fire, which causes damage to qi and yin. The

excessive pathogenic qi may lead to expulsion of the original qi, resulting in abrupt failure of body function. The exuberant heat may disturb the heart spirit and cause impaired consciousness. Qing Ying Tang (QYT) is a classic CHM formula for febrile disease entering the ying level, which presents with night fever, delirium, and insomnia. QYT is composed of Shuiniujiao, Dihuang, Xuanshen, Danzhu, Maidong (*Radix ophiopogonis*), Danshen (*Salviae miltiorrhizae*), Huanglian, Jinyinhua and Jianqiao. Jie Geng Tang (JGT) is composed of Jiegeng and Gancao and is well recognized for its efficacy in clearing heat, relieving toxicity, and diffusing the lung to dispel phlegm [157].

#### *Syndrome of dual deficiency of qi and yin*

As excessive heat-toxin leads to deficiency of both qi and yin, Sheng Mai San (SMS) is widely used to tonify qi and nourish yin [158]. SMS is composed of renshen (*Radix et Rhizoma Ginseng*), maidong and wuweizi (*Fructus Schisandrae Chinensis*).

#### *Syndrome of internal block and external collapse*

Shen Fu Tang (SFT) is a well-known CHM formula used to tonify qi and yang, especially for patients with qi and yang collapse [159]. SFT is composed of Renshen and Fuzi (*Aconitum camichaelii*). An Gong Niu Huang Wan (AGNHW) and Zi Xue Dan (ZXD) are famous CHM formulas for clearing heat, opening the orifice of the heart and arousing the spirit [160]. AGNHW is composed of Niuhuang (*Calculus bovis*), Yujin (*Radix curcumae*), Huanglian, Huangqin, Zhizi, Shuiniujiao, Xionghuang (*Realgar*), Shexiang (*Moschus*), Bingpian (*Borneolum syntheticum*), Zhusha (*Cinnabaris*), Zhenzhu (*Pulvis pernnlae*) and Jinbo (*Native gold*). ZXD is composed of Shigao, Huashi, Cishi (*Magnetitum*), Xuanshen, Shengma (*Cimicifugae Rhizoma*), Shuiniujiao, Lingyangjiao (*Cornu saigae Tataricae*), Chenxiang (*Aquilaria agallocha*), Muxiang (*Radix Aucklandiae*), Gancao, Mangxiao (*Natrii sulfas*), Dingxiang (*Flos caryophylli*), Zhusha, Shexiang and Jinbo.

Several studies have demonstrated the efficacy of the above-mentioned formulas when administered in acute infectious diseases. For example, QYT does not only ameliorate brain tissue edema but also attenuates cytokine increases in brain tissue [161]. Aqueous extract of prepared Dihuang, an ingredient contained

in QYT, has demonstrated anti-inflammatory activity in the CNS by inhibiting IL-1 secretion [162]. Danshen in QYT can attenuate pulmonary fibrosis in mouse models by reducing the inflammatory reaction [163, 164]. Shuiniujiao in QYT demonstrates antipyretic activity in infectious hyperthermia by enhancing antioxidation enzyme activities and reducing prostaglandin E2 production [165, 166]. JGT exhibits anti-inflammatory effects by suppressing the expression of inflammatory mediators such as NF- $\kappa$ B [167]. Platycodin D in Jiegeng has demonstrated anti-inflammatory and immunomodulatory activities [168]. Jiegeng also attenuates airway inflammation by inhibiting mucus hypersecretion and inflammatory cell infiltration [162]. SMS has demonstrated its ability to reduce systemic inflammatory reactions by inhibiting high-sensitivity C-reactive protein (hs-CRP) and inflammatory cytokine levels [169]. Renshen has also improved influenza vaccination outcomes by modulating cytokines to reduce immunopathology during influenza virus infection [170]. Shenfu injection, an herbal extract originated from SFT, can reduce the expression of TNF- $\alpha$ , improve systemic microcirculation, and prolong the hypoxia tolerance duration [171]. A systematic review has shown that Shenfu injection can also increase mean arterial pressure, normalize heart rate, clear serum lactate, and reduce mortality in patients with septic shock [172]. In animal studies, AGNHW has exhibited antipyretic and anti-inflammatory effects associated with reduced expression of TNF- $\alpha$  [173, 174]. Niuhuang in AGNHW has not only demonstrated antipyretic effects but also improvements in oxidative stress injury in rats with acute lung injury [175]. Shigao, an ingredient contained in ZXD, has demonstrated antipyretic effects against LPS-induced pyrexia in rats [176].

### The convalescent stage

Severe COVID-19 infection is highly associated with myocardial injuries and cardiac arrhythmia, probably due to dysregulation of the RAS/ACE2 system and a cytokine storm, as evidenced by the release of IL-6 and IL-17 during the infection [177]. Pulmonary fibrosis is more likely to develop in patients after severe clinical conditions, especially in the convalescent stage.

### *The syndrome of dual qi and yin deficiency*

In the convalescent period of a febrile disease, multiple organ injuries need to be repaired, which usually belongs to the phase of dual deficiency of Qi and yin in TCM. We suggest herbal regimens to supplement Qi and nourish Yin and several herbs that can improve the microcirculation. SMS, a CHM formula that has been used for thousands of years for improving Qi and Yin, is designed to treat patients with severe dyspnea, sweating and palpitations. SMS has demonstrated protective effects in many types of heart failure. SMS consists of Renshen, Maidong and Wuweizi. Schisandrin, a major ingredient identified in Wuweizi, has demonstrated the ability to protect human umbilical vein endothelial cells from hypoxia/reoxygenation injury, increases cell viability, nitric oxide (NO) content and decreases lactate dehydrogenase (LDH) leakage, MDA content and reactive oxygen species generation [178]. In addition, SMS has shown that it can preserve right ventricular function during chronic intermittent hypoxia in mice [156] and inhibit particulate matter (PM)-induced acute lung injury via the TLR4-mTOR-autophagy pathway [179]. In a meta-analysis of 27 randomized controlled trials involving 2,045 subjects with chronic cor pulmonale heart failure showed that combined therapy with SMS (injection form) improved heart function more effectively than conventional therapy alone [180]. Thus, SMS is believed to be helpful in the convalescence stage by supplementing Qi-Yin and improving heart and lung function.

Sha Shen Mai Dong Tang (SSMDT) is composed of Beishashen (*Radix glehniae*), Maidong, Yuzhu (*Polygonati odorati*), Tianhuafen (*Radix trichosanthis*), Sangye (*Folium mori*) and Gancào. SSMDT is also used to nourish Qi and Yin, but is more focused on the fluid-humor depletion of the stomach and lung. Several clinical reports have shown that SSMDT alleviates radiation-induced xerostomia in cancer patients [181-183]. The saponins from Tianhuafen have been proven to be antioxidative [184] and neuroprotective [185]. Sangye, the leaf of *Morus alba* L. (Moraceae) used in SSMDT, promotes macrophagic differentiation by regulating cytokines such as TNF- $\alpha$ , IL-1 $\beta$ , IL-6, and IL-10 [186].

### *The syndrome of dual deficiency of the lung-spleen*

Gut microbiota plays an important role in human immunity, metabolism and diseases. Alteration of gut microbiota is often observed in patients with infectious diseases [187]. Shen Ling Bai Zhu San (SLBZS) is traditionally used for gastrointestinal diseases, especially functional dyspepsia when characterized as Qi-Yin deficiency of the spleen, in TCM theory. The improvement of symptoms associated with SLBZS treatment has been linked to its modulation of gut microbiota [188-190]. In addition, SLBZS promotes the integrity of the intestinal barrier and reduces levels of intestinal inflammatory cytokines [191]. The concept of Qi-Yin deficiency of the spleen is usually applied during the convalescent period of an infection or other immune disorder, such as inflammatory bowel disease [192].

### *The syndrome of damage to the lung vessels*

Pulmonary fibrosis is another problem in patients recovered from COVID-19. To prevent pulmonary fibrosis, TCM theory recommends the use of CHMs such as Taoren (*Semen persicae*), Honghua (*Flos carthami*) and Danshen, which are capable of activating blood circulation and dissipating blood stasis. Single components from CHMs, such as flavonoids, terpenes, or alkaloids, have proven beneficial in pulmonary fibrosis [193]. Safflor yellow is the effective part of the aqueous extract from Honghua. In a study of 70 patients with pulmonary fibrosis, combined treatment with Honghua and methylprednisolone yielded higher FEV1/forced vital capacity (FVC) values than methylprednisolone monotherapy [194]. Tanshinone IIA extracted from Danshen has been shown to protect bleomycin-induced pulmonary fibrosis in mice through the ACE2/ANG (1-7) axis and immunomodulation [195, 196].

### **Conclusion**

Based on the disease progression and stages of coronavirus infection, we propose the application of the corresponding principles of CHM treatment in clinical practice. Especially for cancer patients with worse clinical outcomes, CHMs exert antitumor effects by modulating immune response to ameliorate the risk of coronavirus infection. Evil-qi invading lung-wei presents with symptoms similar to coronavirus

infection in the early phase and can be treated with CHM of YQS and MXGST, which possess anti-viral activity and anti-inflammatory effects. Single herbs including Jinyinhua, Lianqiao, Jingjie, Danzhu, Mahuang, Gancao, Dahuang, Jianghuang, Hohsaing, Zuling, Zexie and Cangzhu can be applied to treat the main syndromes, “heat-toxicity invades lung-wei”, “damp-heat obstructs lung-wei” and “superficial cold and interior heat with damp”. Jinyinhua, Lianqiao, Gancao, Dahuang and Jianghuang have been demonstrated antitumor effects. Additionally, Dahuang was reported inhibitory effect of metastasis. The hyperthermic reaction in the intermediate stage of coronavirus infection can be divided into four syndrome types: “dual exterior and interior heat”; “retained dampness-heat toxin”; “dampness-heat obstructing the Shaoyang”; and “intense heat toxin”. CHMs that are used in this stage have mainly antiviral and anti-inflammatory effects, to prevent the disease from developing into a severe stage. The purpose of TCM treatment in the severe stage of disease is to restore normal lung function and improve consciousness. The principles of treatment for cancer patients in intermediate and severe stage are similar with general population. QYT and JGT are prescribed in the treatment of phlegm and blood stasis obstructing the lung syndrome; SMS of dual deficiency of qi and yin syndrome; SFT, AGNHW and ZXD are administered for internal block and external collapse syndrome. In TCM theory, patients in the convalescent period present mostly with the syndrome of either dual deficiency of qi-yin or of the lung-spleen; however, the syndrome of damage to lung vessels persists throughout the entire disease spectrum. Herbal formulas of SMS, SSMDT, SLBZS and their composition herbs are helpful for patients’ pulmonary and vascular recovery from COVID-19 infection in this period. Baizhu used in convalescent stage had both immunomodulatory activity and antitumor effect. SSMDT was reported alleviating radiation-induced xerostomia in cancer patients. We recommend that combining Chinese and Western medicine in clinical practice will synergize the advantages offered by each system of healthcare, ameliorate the disease progression and hasten cancer patients’ recovery in the most effective way.

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### Disclosure of conflict of interest

None.

### Abbreviations

ACE2, angiotensin converting enzyme 2; CHM, Chinese herbal medicine; CNS, central nervous system; COVID-19, coronavirus disease 2019; COX-2, cyclooxygenase-2; H1N1, hemagglutinin type 1 and neuraminidase type 1; IFN- $\gamma$ , interferon gamma; IL, interleukin; iNOS, inducible nitric oxide synthase; LDH, lactate dehydrogenase; MCP-1, monocyte chemoattractant protein-1; MDA, malondialdehyde; MMP, matrix metalloproteinase; MODS Mpro (3-CL protease), multiple organ dysfunction syndrome main protease, (3 chymotrypsin-like protease); NF- $\kappa$ B, nuclear factor kappa-light-chain-enhancer of activated B cells; NO, nitric oxide; PGE2, prostaglandin E2; PI3K/AKT, phosphatidylinositol 3-kinase and protein kinase B; RSV, respiratory syncytial virus; RT-qPCR, real-time quantitative polymerase chain reaction; SARS, severe acute respiratory syndrome; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TCM, traditional Chinese medicine; TLR2, toll-like receptor transmembrane protease, serine 2; TNF- $\alpha$ , tumor necrosis factor alpha; WHO, World Health Organization.

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**Supplementary Table 1.** Reference of TCM patterns between Chinese and English

| English translation                                      | Chinese characters | Pin Yin                       |
|--|--------------------|-------------------------------|
| Syndrome of heat-toxicity invading lung-wei              | 熱毒侵襲肺衛證            | Re Du Chin Si Fei Wei Jheng   |
| Syndrome of damp-heat obstructed lung-wei                | 濕熱阻遏肺衛證            | Shih Re Zu E Fei Wei Jheng    |
| Syndrome of superficial cold and interior heat with damp | 表寒裡熱夾濕證            | Biao Han Li Re Jia Shih Jheng |
| Syndrome of dual exterior and interior heat              | 表裡熱熾證              | Biao Li Re Chih Jheng         |
| Syndrome of retained dampness-heat toxin                 | 濕熱蘊毒證              | Shih Re Yun Du Jheng          |
| Syndrome of dampness-heat obstructing the Shaoyang       | 濕熱鬱阻少陽證            | Shih Re Yu Zu Shao Yang Jheng |
| Syndrome of intense heat toxin                           | 熱毒熾盛證              | Re Du Chih Sheng Jheng        |
| Syndrome of phlegm and blood stasis obstructing the lung | 痰瘀壅阻肺絡證            | Tan Yu Yong Zu Fei Luo Jheng  |
| Syndrome of dual deficiency of qi and yin                | 氣陰兩傷證              | Chi Yin Liang Shang Jheng     |
| Syndrome of internal block and external collapse         | 內閉外脫證              | Nei Bi Wai Tuo Jheng          |
| The syndrome of dual qi and yin deficiency               | 氣陰兩傷證              | Chi Yin Liang Shang Jheng     |
| The syndrome of dual deficiency of the lung-spleen       | 肺脾兩虛證              | Fei Pi Liang Syu Jheng        |
| The syndrome of damage to the lung vessels               | 肺絡瘀阻證              | Fei Luo Yu Zu Jheng           |