REVIEW

Traditional Chinese medicine in COVID-19

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Abstract COVID-19 pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread across the globe, posing an enormous threat to public health and safety. Traditional Chinese medicine (TCM), in combination with Western medicine (WM), has made important and lasting contributions in the battle against COVID-19. In this review, updated clinical effects and potential mechanisms of TCM, presented in newly recognized three distinct phases of the disease, are summarized and discussed. By integrating the available clinical and preclinical evidence, the efficacies and underlying mechanisms of TCM on COVID-19, including the highly recommended three Chinese patent medicines and three Chinese medicine formulas, are described in a panorama. We hope that this comprehensive review not only provides a reference for health care professionals and the public to recognize the significant contributions of TCM for COVID-19, but also serves as an evidence-based in-depth summary and analysis to facilitate understanding the true scientific value of TCM.

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1. Introduction

The outbreak and spread of coronavirus disease-19 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has inflicted immense losses on human lives and properties all over the world. Globally, as of August 7, 2021, there have been more than two hundred million confirmed COVID-19 cases, including more than four million of deaths (WHO, https://covid19.who.int/). SARS-CoV-2 is an enveloped, single-stranded, positive-sense, β-coronavirus RNA virus that belongs to the sub-family Coronavirinae, family Coronaviridae, order Nidovirales. It shares about 79.6% identity of genome sequence with SARS-CoV and 96% similarity with bat coronavirus at the whole-genome level1,2. SARS-CoV-2 is transmitted from person to person via respiratory droplets, high concentration of aerosols, and occasionally feces or urine. Currently, no approved specific anti-viral drug is recommended to defeat COVID-19, which may lead to acute respiratory distress syndrome (ARDS), multiple organ dysfunction syndrome (MODS), and even death.

It is well documented that traditional Chinese medicine (TCM) has accumulated abundant clinical experience and effective prescriptions to control and treat infectious diseases in about 500 epidemics occurred in China over more than 3000 years in the past. The combined therapy of TCM and Western medicine (WM) had significantly reduced mortality, shortened duration of fever, decreased chest radiograph abnormalities, and relieved secondary fungal infections among patients receiving glucocorticoids in combating severe acute respiratory syndrome (SARS). Owing to the positive role of TCM in treating previous coronavirus pneumonias such as SARS, middle east respiratory syndrome (MERS), and other epidemic diseases3-9, the National Health Commission of China recommended to use TCM as one of the strategies for COVID-19 remedy. This epidemic was deemed as the category of “pestilence” with the pathological characteristics of “dampness, heat, toxin, deficiency, and stasis” under TCM theory10-12. Over the past year, TCM achieved remarkable efficacy in treating patients at all stages infected with SARS-CoV-2 in China. Typical clinical characteristics contain clinical manifestations, laboratory findings, and chest imaging features, as well as the pathogenesis of SARS-CoV-2 infection and therapeutic targets including SARS-CoV-2 invasion and replication, immune response, and cytokine storm, ARDS and MODS were outlined in published papers. In this review, the therapeutic efficacies and pharmacological mechanisms of TCM for this epidemic disease were systematically documented and discussed, aiming at displaying an in-depth understanding of TCM against COVID-19.

2. TCM in the treatment of COVID-19

2.1. Understanding COVID-19 in TCM theory

In the theory of TCM, COVID-19 is deemed as the category of “dampness–toxin pestilence”10. The distinct disease stages of TCM treatment can be divided into mild, moderate, severe, and critical. The main patterns in mild stage are cold–damp constraint and damp–heat accumulation in the lung, where dispersing lung and removing pathogenic factors, and resolve turbidity with aroma are needed; The main patterns in moderate stage are damp–toxin constraint in the lung and cold–damp obstructing the lung, where eliminating heat and dampness, detoxification, and invigorate spleen are needed; The main patterns in severe stage are epidemic toxin blocking the lung, blazing of both qi and yin, where tonifying qi and yin, ventilating lung qi, co-treatment of lung and intestines are needed. The main patterns in critical stage are internal blockage and external desertion, where tonifying qi and preventing exhaustion, cool blood and nourishing yin, and restore consciousness are needed13-15. Syndrome differentiation is one of the most important principles for TCM to treat COVID-19.

2.2. The recommended TCMs for distinct stages of COVID-19 treatment

According to the officially issued 7th and 8th trial version of Diagnosis and Treatment Protocol for COVID-19 in China and other references14,16-23, there are more than 18 recommended TCMs to prevent and treat COVID-19, covering from medical observation period (suspected cases) to clinical treatment period (confirmed cases) including distinct disease stages of mild, moderate, severe, and critical, as shown in Fig. 1. Among them, the highly recommended three Chinese patent medicines (CPMs) are Jinhua Qinggan granules, Lianhua Qingwen capsule (granules), and Xuebijing injection, and three Chinese medicine formulas are Qingfei Paidu decoction, Huashi Baidu formula, and Xuanfei Baidu formula, with proven efficacies in treating COVID-1924,25. Jinhua Qinggan granules clear heat and detoxifying, was an innovative CPM for the treatment of SARS in 200326,27. Xuebijing injection, a five-herbal injection medicine and with a clinical indication for clearing heat, diffusing the lung, and detoxifying, was an innovative CPM for the treatment of SARS in 200328,29. Xuebijing injection, a five-herbal injection medicine and with a clinical indication for resolving stasis and detoxifying, was derived from a modified Xuefu Zhuyu decoction and was developed and marketed during SARS. The Chinese medicine formula Qingfei Paidu decoction consists of 21 herbal medicines from five classic formulas of Treatise on Febrile Diseases. It clears the lung and calm panting, and is the first recommended universal treatment formula for all stages from mild to critical of COVID-1926,27. Huashi Baidu formula is composed of 14 medicinal herbs. It serves to clearing heat and detoxifying, removing dampness, mainly suitable for the treatment of mild, moderate, and severe COVID-19 patients30,31. Xuanfei Baidu formula is derived from classic formulas including Maxing Shigan decoction and Maxing Yigan decoction, and is composed of 13 medicinal herbs. It detoxifies and removes blood stasis, diffuse the lung, removes dampness, clears heat, and is mainly applicable to treat mild and moderate...
Beyond the above-mentioned medicines and formulas, Chinese herbal injections, including Xiyanping injection, Reduning injection, Tanreqing injection, Shenfu injection, Shengmai injection, and Shenmai injection, were more suitable as supplemental treatments for severe or critical COVID-19 cases with their advantages of fast absorption, high bioavailability, and clearer ingredients in contrast to orally administrated TCMs.

2.3. Clinical evidence of TCM for COVID-19

A total of 40 representative clinical trials, including 11 randomized controlled trials (RCTs), 16 retrospective cohort studies (RCSs), 5 multi-center clinical observations, and 8 others were completed and summarized. According to the available clinical data, integrated TCM and WM exhibited several clinical advantages in COVID-19 treatment, including the outcomes of 1) clinical manifestations, 2) lung features, and 3) laboratory findings as shown in Table 1. Furthermore, based on Table 1, the clinical evidence of TCM for typical characteristics of COVID-19 were analyzed and summarized in Table 2.

For mild or moderate stages: 1) the most typical clinical symptoms of fever, cough, and fatigue were relieved by Jinhua Qinggan granules, Lianhua Qingwen granules, Shufeng Jiedu capsule, Toujie Quwen granules, Lianhua Qingke granules, Xuanfei Baidu decoction, and Maxing Shigan decoction. Lianhua Qingwen granules and Shufeng Jiedu capsule improved the symptoms of short of breath and chest tightness; Jinhua Qinggan granules relieved the symptom of psychological anxiety, and Shufeng Jiedu capsule improved the symptoms of short of breath and chest tightness; Jinhua Qinggan granules relieved the symptom of psychological anxiety, and Shufeng Jiedu capsule improved the symptom of diarrhea. 2) Jinhua Qinggan granules, Shufeng Jiedu capsule, and Toujie Quwen granules promoted pneumonia inflammatory absorption or improve lung CT imaging. 3) Jinhua Qinggan granules, Lianhua Qingwen granules, Shufeng Jiedu capsule, and Maxing Shigan decoction increased white blood cell (WBC) or lymphocyte count; Lianhua Qingwen granules, Shufeng Jiedu capsule, Toujie Quwen granules, Xuanfei Baidu decoction, and Maxing Shigan decoction reduced the level of C-reactive protein (CRP). Shufeng Jiedu capsule decreased the level of interleukin-6 (IL-6).

For severe or critical stages: 1) Xuebijing injection and Qingfei Paidu decoction improved the conditions of patients and reduced multiple organ dysfunction. 2) Xuebijing injection, Qingfei Paidu decoction, and Huashi Baidu formula improved chest CT imaging or promoted lung lesions absorption; Chansu injection ameliorated the respiratory function and shorten the respiratory support step-down time. 3) Both Xuebijing injection and Chansu injection improved the oxygenation index of PaO2/FiO2; Xuebijing injection and Qingfei Paidu decoction decreased the level of CRP, and increased WBC or lymphocyte count; In addition, Xuebijing injection reduced the level of inflammatory mediators of TNF-α, IP-10, and RANTES; Qingfei Paidu decoction decreased biochemical parameters of CK and LDH, and the level of blood urea nitrogen; Maxing Shigan decoction increased CD4+ T and CD8+ T count; Qingfei Baidu formula decreased CRP, erythrocyte sedimentation rate (ESR), serum ferritin, and myoglobin level; Yidu-toxicity blocking lung decoction reduced the levels of IL-6 and TNF-α.

For all stages: 1) Qingfei Paidu decoction and Qingfei Dayuan granules ameliorated extensive adverse symptoms such as fever, cough, fatigue, chest tightness, and headache; Xuanfei Huazhuo decoction relieved the symptoms of cough, fever, sputum, diarrhea, fatigue, and loss of appetite. 2) Qingfei Paidu decoction, Qingfei Dayuan granules, Xuanfei Huazhuo decoction, Keguan-1, Qingfei Touxie Fuzheng recipe, Ganlu Xiaodu decoction, and Matrine injection improved lung inflammation or lesions absorption. 3) Qingfei Paidu decoction, Qingfei Dayuan granules, Xuanfei Huazhuo decoction, Ganlu Xiaodu decoction, “Fei Yan No. 1”, Matrine and sodium chloride injection, and Diammonium glycyrrhizinate increased WBC or lymphocyte count; Qingfei Paidu decoction and Diammonium glycyrrhizinate decreased CRP, IL-6, and ESR; Qingfei Paidu decoction and Xuanfei Huazhuo decoction reduced the level of CRP and ESR, and the biochemical parameters of AST and ALT. What’s more, Qingfei Paidu decoction decreased the level of a thrombotic marker D-dimer.

A plentiful of clinical studies and analyses proved that integrated Chinese and Western medicine therapy are much better than pure use of WM for COVID-19. A recent systematic
| No. | Intervention                                      | Method                        | Object (T/C) | Disease stage     | Clinical manifestation                                                                                      | Laboratory finding                                      | Ref. |
|-----|--------------------------------------------------|-------------------------------|--------------|------------------|-----------------------------------------------------------------------------------------------------------|----------------------------------------------------------|------|
| 1   | Jinhua Qinggan granules + WM vs. WM              | Retrospective cohort study (RCS) | 44/36        | Moderate or severe | 1) Shorten the duration of nucleic acid turn negative  
2) Promote the absorption of pneumonia inflammatory exudate | Increase WBC and lymphocyte count                         | 36   |
| 2   | Jinhua Qinggan capsule + WM vs. WM               | Randomized controlled trial (RCT) | 82/41        | Mild              | Reduce the symptoms of fever, cough, fatigue, and sputum cough, and relieve the psychological anxiety  | Unreported                                               | 37   |
| 3   | Lianhua Qingwen capsule + WM vs. WM              | RCT                           | 142/142      | Mild or moderate  | 1) Shorten median time to symptom recovery  
2) Shorten time to recovery of fever, fatigue, and cough  
3) Improve the rate of chest CT manifestations and clinical cure | Unreported                                               | 27   |
| 4   | Lianhua Qingwen capsule + WM vs. WM              | RCS                           | 63/38        | All               | Relieve symptoms of fever, cough, weakness, and short of breath | Unreported                                               | 38   |
| 5   | Lianhua Qingwen capsule + arbidol vs. arbidol    | RCT                           | 147/148      | Mild or moderate  | Relieve symptoms of fever, fatigue, cough, dry throat, sore throat, and chest tightness | Lower the levels of CRP and procalcitonin, elevate WBC and lymphocyte count | 39   |
| 6   | Lianhua Qingwen capsule + WM                     | Before and after comparison   | 54/0         | Moderate          | Relieve the symptoms and reduce the duration of fever, fatigue, and cough.  
2) Reduce the utilization rate of anti-infective drugs and improve the prognosis of patients  
3) Block disease aggravation | Unreported                                               | 40   |
| 7   | Lianhua Qingwen capsule + Huoxiang Zhengqi dropping pills + WM vs. WM | RCT                           | 189/94       | All               | 1) Improve the symptoms of fever and diarrhea, especially fatigue, nausea and vomiting, chest tightness, shortness of breath and limb soreness  
2) Reduce the utilization rate of anti-infective drugs and improve the prognosis of patients  
3) Block disease aggravation | Unreported                                               | 28   |
| 8   | Lianhua Qingwen capsule + arbidol vs. arbidol    | RCS                           | 68/40        | Mild or moderate  | 1) Shorten the median time from admission to the first negative result of nucleic acid detection  
2) Reduce lung inflammation | 1) Increase lymphocytes count  
2) Lower the levels of serum amyloid A and CRP | 41   |
| 9   | Xuebijing injection + WM                         | Case analysis                 | 11/0         | Severe or critical | May ameliorate lung injury | Reduce the levels of TNF-α, IP-10, MIP-1β, and RANTES | 42   |
| 10  | Xuebijing injection + WM vs. WM                   | RCT                           | 40/20        | Severe            | Improve the conditions of patients, lower APACHE II score | 1) Improve the oxygenation index of PaO₂/FiO₂  
2) Increase WBC and lymphocyte count, decrease the levels of CRP and ESR | 43   |
| 11  | Xuebijing injection + antiviral treatment vs. antiviral treatment | RCS                           | 22/22        | Moderate          | Increase the effective rate of lung lesions absorption and the overall effective rate of treatment | Tend to improve WBC count, lymphocyte count, and the levels of CRP and ferritin | 44   |
| 12  | Qingfei Paidu decoction + WM vs. WM              | RCS                           | 37/26        | Severe            | 1) Relieve the symptoms and improve inflammation resolution in the lung  
2) Tend to mitigate the extent of multi-organ impairment | 1) Improve the levels of CRP, CK, creatine kinase-myocardial band, LDH, and blood urea nitrogen  
2) Increase lymphocyte count | 45   |
| 13  | Qingfei Paidu decoction + WM                     | Before and after              | 98/0         | All               | 1) Nearly all adverse symptoms including | Restore the levels of AST, ALT, D- | 46   |
| Comparison | Design | N | Outcome | Additional Findings |
|------------|--------|---|---------|---------------------|
| Qingfei Paidu decoction + antiviral treatment vs. antiviral treatment | RCS | 30/30 | All | 1) Shorten inpatient days and reduce the time of fever and cough 2) Improve lung CT imaging |
| Qingfei Paidu decoction + WM | RCS | 46/43 | All | 1) Reduce inflammation, enhance cellular immunity, improve renal function, lower hypercoagulability 2) Shorten the length of hospitalization and nucleic acid negative time |
| Qingfei Paidu decoction + WM vs. WM | Multi-center clinical observation | 199/96 | Mild or moderate | Unreported |
| Qingfei Paidu decoction + WM | Multi-center clinical observation | 782/0 | All | Shorten the time of recovery, viral shedding, and the duration of hospital stay |
| Xuanfei Baidu decoction + WM | RCT | 22/20 | Mild | Increase the disappearance rate of symptoms of fever, cough, fatigue, and loss of appetite |
| Huashi Baidu granule vs. WM | RCS | 23/32 | Severe | Improve chest CT imaging and lung lesion opacity |
| Huashi Baidu formula + TCM injection vs. Huashi Baidu formula + lopinavir–ritonavir vs. lopinavir–ritonavir | RCS | 20/20/20 | Mild or moderate | Shorten the clinical remission time |
| Shufeng Jiedu capsule + WM vs. WM | RCS | 34/34 | Moderate | 1) Improve the symptoms of cough, sputum, fatigue, chest tightness, and shortness of breath 2) Lower the rate of transferring to severe disease 3) Promote the absorption of lung inflammation and improve lung CT imaging |
| Shufeng Jiedu capsule + arbidol vs. arbidol | RCS | 100/100 | Mild | 1) Alleviate the symptoms of fever, cough, chest distress, and shortness of breath 2) Increase the absorption lung infected lesions |
| Shufeng Jiedu capsule + arbidol vs. arbidol | RCS | 40/30 | Mild or moderate | Unreported |
| Shufeng Jiedu capsule + arbidol vs. arbidol | RCS | 100/100 | Moderate | 1) Shorten defervescence time 2) Improve resolution of pneumonia on chest CT 3) Increase WBC and lymphocyte count |
| Hanshiyì formula + WM vs. WM | RCS | 430/291 | Mild or moderate | 1) Increase lymphocyte count 2) Decrease the levels of CRP, procalcitonin, and D-dimer 3) Increase lymphocyte count and lymphocyte percentage 4) Increase lymphocyte count and lymphocyte percentage 5) Increase WBC and lymphocyte count 6) Reduce the levels of CRP and IL-6 7) Reduce novel coronavirus negative conversion time |

(continued on next page)
| No. | Intervention | Method | Object (T/C) | Disease stage | Clinical manifestation | Laboratory finding | Ref. |
|-----|--------------|--------|--------------|---------------|-----------------------|--------------------|------|
| 26  | Lianhua Qingke granules + WM vs. WM | RCT | 25/32 | Mild or moderate | Ameliorate the symptoms of cough, sputum, fever, fatigue, dry throat, and sore throat, and shorten the duration of cough and sputum, reduce lung diseases, improve respiratory function | Unreported | 56 |
| 27  | Toujie Quwen granules + moxifloxacin + ambroxol vs. moxifloxacin + ambroxol | RCS | 32/33 | Mild or moderate | 1) Improve the symptoms of fever, cough, fatigue, expectoration, dry throat, and sore throat 2) Improve lung CT imaging | 1) Up-regulate lymphocyte count and neutrophil ratio 2) Down-regulate the levels of CRP, D-dimer, and procalcitonin | 57 |
| 28  | Reyanning mixture + WM vs. WM | Multi-center clinical observation | 26/23 | Moderate | 1) Improve the symptoms of dry throat, cough, fatigue, chest tightness, and headache, and shorten the duration of fever 2) Promote the improvement of lung CT 3) Improve nucleic acid negative conversion rate | No significant differences in neutrophil count, lymphocyte count and CRP level | 58 |
| 29  | Maxing Shigan decoction + WM | Before and after comparison | 40/0 | Moderate | Improve the symptoms of fever, cough, fatigue, hemoptysis, nausea, vomiting, diarrhea, and chest pain | Decrease CRP level, increase CD4⁺/T and CD8⁺/T count | 59 |
| 30  | Honeysuckle oral liquid + WM vs. WM | Multi-center clinical observation | 200/100 | Moderate | 1) Shorten the length of hospitalization and the time of nucleic acid negative conversion 2) Lower right lung CT score | No significant difference in the levels of ALT, AST, creatinine, and uric acid | 60 |
| 31  | Chansu injection + WM vs. WM | RCT | 25/25 | Severe or critical | Improve the respiratory function and shorten the respiratory support step-down time | Improve the respiratory function indicators of PaO₂/FiO₂ and ROX index | 61 |
| 32  | Yidu—toxicity blocking lung decoction + WM vs. WM | RCT | 15/24 | Severe | All patients are cured and discharged | Reduce the levels of IL-6 and TNF-α | 62 |
| 33  | Qingfei Dayuan granules + WM | Multi-center clinical observation | 451/0 | All | 1) Reduce the incidence of fever, cough, and fatigue 2) Improve the symptoms of aversion to cold, nasal obstruction, runny nose, sneezing, pharyngeal itch, sore throat, dyspnea, chest tightness, muscle ache or joint pain, dizziness, headache, tolerance, nausea and vomiting, abdominal distension, and loose stool 3) Thin white greasy moss, thick greasy moss, and yellow greasy moss, and improve tongue color 4) Decrease and thin lung lesion area | 1) Increase lymphocyte count 2) Reduce the levels of CRP and procalcitonin | 63 |
| 34  | “Fei Yan No. 1” + WM vs. WM | RCS | 49/35 | All | 1) Improve the rate of recovering from symptoms and shorten the time 2) Increase the proportion of testing negative for nucleic acid 3) Promote focal lung absorption and inflammation | Reduce leukocyte count and CRP level | 64 |
| 35  | Xuanfei Huazhuo decoction + WM | Case analysis | 40/0 | All | 1) Improve the symptoms of cough, fever, sputum, diarrhea, loss of appetite, and 1) Improve WBC count, lymphocyte, and neutrophil percentage | 65 |
In summary of clinical evidence, TCM is beneficial for treating COVID-19 in 1) relieving the typical symptoms of fever, cough, fatigue, dry throat, sore throat, sputum production, shortness of breath, myalgia, and diarrhea; shortening the duration of positive viral nucleic acid, reducing the time to symptom recovery and the progression to severe disease, and protecting against multi-organ injury; 2) improving the lung features including lung inflammatory absorption, CT imaging, lung injury, lung function, and oxygenation index; 3) regulating laboratory index including inflammatory and immune response related the level of WBC, lymphocyte, CD4+ T and CD8+ T, and the level of CRP, IL-6, TNF-α, and ESR, single or multi-organ injury related the level of procalcitonin, CK, LDH, ALT, and AST, and thrombosis related D-dimer level. Taking full advantage of integration of TCM and WM treatment could improve the amounts of severe and critical conversion, length of hospital stay, time of antipyretic, and resolution rate of fever, fatigue, and tachypnea.

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3. Potential mechanisms of TCM for COVID-19

The intervention of TCM for COVID-19 is greatly inspired by the successful experience of treating SARS in 2002—2003. SARS-CoV-2 is genetically more similar with SARS-CoV (about 80%) than MERS-CoV (about 50%). According to sequence alignment and homology modeling, the critical targets of spike, 3C-like protease (3CLpro), papain-like protease (PLpro), and RNA-dependent RNA polymerase (RdRp) protease share 76%, 96%, 83%, 96% sequence similarity between SARS-CoV and SARS-CoV-2, respectively. We collected and summarized TCMs and their ingredients to reveal the specific mechanisms of TCM for the three phases of distinct disease stages of COVID-19 seen in Table 3 and Table 4.

3.1. Potential mechanisms of TCM for SARS-CoV-2 invasion and replication

Although the direct evidence is still lacking, increasing reports suggested that TCM resource holds great promises for agents against SARS-CoV-2 invasion and replication. Numerous efforts had been made to identify the antiviral effects of CPMs and herbals, as shown in Table 3. Lianhua Qingwen capsule with a half maximal inhibitory concentration (IC50) of 411.2 μg/mL89, Liu Shen capsule107 with an IC50 of 0.93–1.2 μL/mL were confirmed to inhibit SARS-CoV-2 replication in Vero E6 cells. In addition, Pudilan Xiaoyan oral liquid not only inhibited SARS-CoV-2-stimulated Vero E6 cells in vitro, but also showed the potential efficacy on SARS-CoV-2-infected human cells.
| Clinical symptom | Clinical evidence |
|------------------|-------------------|
| **Fever**        | Jinhua Qinggan granules[^37], Lianhua Qingwen capsule[^7,28,38-40], Qingfei Paidu decoction[^46,47], Xinfei Baidu decoction[^25], Shufeng Jiedu capsule[^53], Lianhua Qingke granules[^46], Toujie Quwen granules[^57], Reyanning mixture[^59], Maxing Shigan decoction[^39], Qingfei Dayuan granules[^63], Xuanfei Huazhuo decoction[^5], Qingfei Touxie Fuzheng recipe[^6], Diammonium glycyrrhizinate[^70] |
| **Cough**        | Jinhua Qinggan granules[^37], Lianhua Qingwen capsule[^7,28,38-40], Qingfei Paidu decoction[^46,47], Xinfei Baidu decoction[^25], Shufeng Jiedu capsule[^51-53], Lianhua Qingke granules[^56], Toujie Quwen granules[^57], Reyanning mixture[^59], Maxing Shigan decoction[^39], Qingfei Dayuan granules[^63], Xuanfei Huazhuo decoction[^5], Qingfei Touxie Fuzheng recipe[^6], Matrine injection[^6], Diammonium glycyrrhizinate[^70] |
| **Fatigue**      | Jinhua Qinggan granules[^37], Lianhua Qingwen capsule[^7,28,39,40], Qingfei Paidu decoction[^46,47], Xinfei Baidu decoction[^25], Shufeng Jiedu capsule[^51-53], Lianhua Qingke granules[^56], Toujie Quwen granules[^57], Reyanning mixture[^59], Maxing Shigan decoction[^39], Qingfei Dayuan granules[^63], Xuanfei Huazhuo decoction[^5], Matrine injection[^6], Diammonium glycyrrhizinate[^70] |
| **Dry throat**   | Lianhua Qingwen capsule[^27], Shufeng Jiedu capsule[^52], Lianhua Qingke granules[^56], Toujie Quwen granules[^57], Reyanning mixture[^59] |
| **Sore throat**  | Lianhua Qingwen capsule[^27], Lianhua Qingke granules[^56], Toujie Quwen granules[^57], Qingfei Dayuan granules[^63] |
| **Sputum production** | Jinhua Qinggan granules[^37], Qingfei Paidu decoction[^49], Lianhua Qingke granules[^56], Xuanfei Huazhuo decoction[^5], Qingfei Touxie Fuzheng recipe[^57] |
| **Shortness of breath** | Lianhua Qingwen capsule[^38], Qingfei Paidu decoction[^46], Shufeng Jiedu capsule[^52], Qingfei Dayuan granules[^63], Qingfei Touxie Fuzheng recipe[^57] |
| **Myalgia**      | Lianhua Qingwen capsule[^39], Shufeng Jiedu capsule[^53], Lianhua Qingke granules[^56], Toujie Quwen granules[^57], Qingfei Dayuan granules[^63] |
| **Diabetes**     | Lianhua Qingwen capsule[^39], Shufeng Jiedu capsule[^53], Maxing Shigan decoction[^59], Xuanfei Huazhuo decoction[^5] |
| **Duration of nucleic acid turn negative** | Jinhua Qinggan granules[^36], Lianhua Qingwen capsule[^41], Qingfei Paidu decoction[^48], Shufeng Jiedu capsule[^52], “Fei Yan No. 1”[^64], Matrine injection[^6], Diammonium glycyrrhizinate[^70] |
| **Time to symptom recovery** | Lianhua Qingwen capsule[^27], Xuebijing injection[^42], Qingfei Paidu decoction[^46], Shufeng Jiedu capsule[^51,52], Xuanfei Huazhuo decoction[^5], “Fei Yan No. 1”[^64], Keguan-1[^66] |
| **The progression to severe disease** | Shufeng Jiedu capsule[^2], Banshiy formula[^3] |
| **Laboratory finding** | Xuebijing injection[^42], Qingfei Paidu decoction[^6] |
| **WBC count**    | Jinhua Qinggan granules[^36], Lianhua Qingwen capsule[^39], Xuebijing injection[^43,44], Xinfei Baidu decoction[^2], Shufeng Jiedu capsule[^52], “Fei Yan No. 1”[^64], Xuanfei Huazhuo decoction[^65], Ganlu Xiaodu decoction[^68], Matrine injection[^69] |
| **Lymphocyte count** | Jinhua Qinggan granules[^36], Lianhua Qingwen capsule[^39], Xuebijing injection[^43,44], Xuanfei Paidu decoction[^45,46], Xinfei Baidu decoction[^2], Shufeng Jiedu capsule[^51,52], Toujie Quwen granules[^57], Qingfei Dayuan granules[^63], Xuanfei Huazhuo decoction[^65], Matrine injection[^69], Diammonium glycyrrhizinate[^70] |
| **Oxygenation index** | Xuebijing injection[^42], Banshiy formula[^3] |
| **CRP**          | Lianhua Qingwen capsule[^38], Xuebijing injection[^43,44], Qingfei Paidu decoction[^45], Xinfei Baidu Decoction[^1], Huashi Baidu formula[^4], Shufeng Jiedu capsule[^51,54], Toujie Quwen granules[^57], Maxing Shigan decoction[^59], Qingfei Dayuan granules[^63], “Fei Yan No. 1”[^64], Xuanfei Huazhuo decoction[^5], Qingfei Touxie Fuzheng recipe[^6], Matrine injection[^6], Diammonium glycyrrhizinate[^70] |
| **IL-6**         | Xuebijing injection[^42], Qingfei Paidu decoction[^48], Shufeng Jiedu capsule[^54], “Fei-tycoy blocking lung decoction[^1], Qingfei Touxie Fuzheng recipe[^6], Diammonium glycyrrhizinate[^70] |
| **TNF-α**        | Xuebijing injection[^42], “Fei-tycoy blocking lung decoction[^1] |
| **ESR**          | Xuebijing injection[^42], Qingfei Paidu decoction[^48], Xinfei Baidu Decoction[^32], Huashi Baidu formula[^30], Xuanfei Huazhuo decoction[^65], Qingfei Touxie Fuzheng recipe[^6], Diammonium glycyrrhizinate[^70] |
| **CK**           | Qingfei Paidu decoction[^45] |
| **LDH**          | Qingfei Paidu decoction[^45], Xuanfei Huazhuo decoction[^65] |
Table 2 (continued)

| Clinical evidence | TCM |
|-------------------|-----|
| ALT               | Qingfei Pai duo decoction*9, Xuanfei Huazhuo decoction*9 |
| AST               | Qingfei Pai duo decoction*9, Xuanfei Huazhuo decoction*9 |
| Procalcitonin     | Lianhua Qingwen capsule*9, Shufeng Jiedu capsule*1, Toujie Quwen granules*57, Qingfei Dayuan granules*9, Diamonium glycyrrhizinate |
| D-dimer           | Qingfei Pai duo decoction*9, Shufeng Jiedu capsule*21, Toujie Quwen granules*57 |
| CD4+ T cell       | Maxing Shigan decoction*9 |
| CD8+ T cell       | Maxing Shigan decoction*9 |

Noticeably, a considerable number of ingredients derived from TCMs were found to have anti-viral invasion and anti-viral replication activities by targeting diverse molecules, as seen in Table 4. The interaction between spike protein and ACE2, primed by serine protease transmembrane protease serine 2 (TMPRSS2), is the key step for SARS-CoV-2 host invasion. Emodin from Yaoyong Dahuang was able to inhibit S protein and ACE2 interaction with an IC50 of 200 μmol/L, while hesperidin from Citrus aurantium (Shouwuteng) was predicted to target the binding between spike RBD and ACE2 with high affinity. Besides, geniposide from Gardenia jasminoides (Zhizhi) was found through virtual screening of 2140 compounds with pharmacophoric features, which could target the active site residues of TMPRSS2 with a binding energy score of −14.69, and is even greater than that of the standard inhibitor of camostat mesylate. Seven isolated tanshinones derived from Salvia miltiorrhiza (Danshen) including tanshinone IIA, tanshinone IIB, methyl tanshinonate, cryptotanshinone, tanshinone I, dihydrotanshinone I, and rosmanquinone showed marked inhibitory activities to both proteases of 3CLpro and PLpro. Particularly, dihydrotanshinone I exerted powerful effects with IC50 values of 14.4 μmol/L regarding 3CLpro and 4.9 μmol/L regarding PLpro. Furthermore, cryptotanshinone exhibited the most potent nanomolar level inhibitory activity toward PLpro with an IC50 of 0.8 μmol/L. Baicalin and baicalein, the major bioactive ingredients of Shuanghuanglian preparation, were characterized as the first noncovalent and nonpeptidomimetic inhibitors of SARS-CoV-2 3CLpro, also possessed good anti-SARS-CoV-2 activity in Vero E6 cell-based assay. What’s more, celastrol, tingenone, xanthoangelol E, and hesperetin targeting 3CLpro, while hirsutenone, methyl tanshinoate, tanshinoine I, xanthoangelol E, isobavachalcone, 4′-O-methylbavachalcone, psoralidin, and tomentin A-E targeting PLpro, may have relatively strong anti-viral replication efficacy with IC50 below or near 10 μmol/L. Notably, the well-known anti-malarial, anti-tumor, and immune modulation compound artemisinin from Artemisia apiacea (Qinghao), and its derivatives including artenannuin B, artemesunate, dihydroartemisinin, arteether, and lumefantrine presented favorable anti-SARS-CoV-2 effects. Among these artemisinin derivatives, artenannuin B showed the highest anti-viral potential with an IC50 of 10.28 μmol/L, while lumefantrine exerted therapeutic promise owing to its high plasma and lung concentrations after multiple dosing. The deeper pharmacological mechanism analysis revealed that these two compounds acted at the post-entry step of SARS-CoV-2 infection. Significantly, lycorine from Lycoris radiata (Shisuan) had a powerful inhibitory effect on virus activity with an IC50 of 15.7 μmol/L and may serve as a candidate for the development of new anti-SARS-CoV-2 drug in the treatment of COVID-19. In addition, a Vero E6 cell-based large-scale anti-SARS-CoV-2 activity of 1058 natural compounds were screened, and 17 newly discovered compounds showed strong anti-virus propagation effects with the IC50 values ranging from 0.011 to 11.03 μmol/L. Among them, bufalin from toad venom (Chansu) exerted the antiviral effect with an IC50 of 18 mmol/L by targeting the ion transport function of Na+/K+ - ATPase. Theaflavin was predicted to exert anti-viral replication by inhibiting RdRp activity. The binding affinities with the critical proteins of a portion of ingredients presented above were also predicted by in silico screening and molecular docking. Whether these TCM ingredients could be used to combat COVID-19 need further in vitro and in vivo validation. Pharmacokinetic profiles including absorption, distribution, metabolism, and excretion (ADME) on the promising leads should be further studied.

3.2. Potential mechanisms of TCM for immune and inflammatory regulation

Antiviral monotherapy for patients hospitalized with COVID-19 is quite not enough, especially for severely and critically ill patients. Except for the broad-spectrum antiviral activity, TCM process...
| No. | TCM                  | Coronavirus | Model/method                                      | IC_{50} (EC_{50}) or dosage | Potential mechanism                                                                                     | Ref. |
|-----|----------------------|-------------|---------------------------------------------------|-----------------------------|--------------------------------------------------------------------------------------------------------|------|
| 1   | Jinhua Qinggan       | SARS-CoV-2  | Network pharmacology (NP), molecular docking      | Not applicable (NA)         | 1) Regulate TNF, PI3K/Akt, and HIF-1 signaling pathways via binding angiotensin converting enzyme 2 (ACE2) and acting on targets such as PTGS2, HSP90AB1, HSP90AA1, PTGS1, and NCOA2  
2) Formononetin, stigmasterol, β-sitosterol, and anhydroicaritin have a high affinity with 3CLpro and ACE2 | 88   |
| 2   | Lianhua Qingwen capsule | SARS-CoV-2 | Infected Vero E6 cells and Huh-7 cells, cytopathic effect (CPE), plaque reduction assay | 411.2 μg/mL                  | 1) Inhibit virus replication and decrease the number of virus particles  
2) Reduce pro-inflammatory cytokines of TNF-α, IL-6, MCP-1, and IP-10 production | 89   |
| 3   | Lianhua Qingwen formula | SARS-CoV-2 | NP                                                 | NA                          | 1) Exert antiviral effect and repair lung injury  
2) Modulate inflammatory process and relieve cytokine storm  
3) Improve ACE2 expression disorder caused symptoms | 90   |
| 4   | Xuebijing injection  | SARS-CoV-2  | Infected Vero E6 cells and Huh-7 cells, CPE, plaque reduction assay | 11.75 mg/mL                  | 1) Exert antiviral effect and reduce plaque formation  
2) Inhibit the expression and release of TNF-α, IL-6, MIP-1β, RANTES, and IP-10 | 42   |
| 5   | Xuebijing injection  | SARS-CoV-2  | NP, molecular docking                              | NA                          | 1) Quercetin, luteolin, apigenin, and other compounds may target TNF, MAPK1, and IL6  
2) Anhydrosaflor yellow B, salvianolic acid B, and rutin play the role of anti-inflammatory, antiviral, and immune response | 91   |
| 6   | Xuebijing injection  | SARS-CoV-2  | NP                                                 | NA                          | Exert ant-inflammatory and immunoregulatory effects through RAS, NF-κB, PI3K, Akt, MAPK, VEGF, TLR, TNF, and TRP signaling pathways | 92   |
| 7   | Qingfei Paidu decoction | SARS-CoV-2 | NP, molecular docking                              | NA                          | 1) Exert antiviral and anti-inflammatory activities, regulate metabolic programming, and repair lung injury  
2) Glycyrrhizin in one of the main ingredients inhibits TLR agonists induced IL-6 production in macrophage | 93   |
| 8   | Qingfei Paidu decoction | SARS-CoV-2 | NP, molecular docking, molecular verification      | NA                          | 1) Exhibit the effects of immune regulation, anti-infection, anti-inflammatory, and multi-organ protection  
2) Four compounds of baicalin, glycyrrhizin, hesperidin, and hyperoside act on the targets including AKT1, TNF-α, IL-6, PTGS2, HMOX1, IL10, and TP53  
3) Inhibit IL-6, CCL2, TNF-α, NF-κβ, PTGS1/2, CYP1A1, and CYP3A4 activity, and increase IL-10 expression  
4) Reduce platelet aggregation | 94   |
| 9   | Huashi Baidu formula | SARS-CoV-2  | NP, molecular docking                              | NA                          | 1) Regulate TNF, PI3K-Akt, NOD-like, MAPK, and HIF-1 signaling pathways  
2) Baicalein and quercetin are the top two compounds with a high affinity to ACE2 | 97   |
| 10  | Xuanfei Baidu        | SARS-CoV-2  | NP                                                 | NA                          | Regulate viral, parasites and bacterial infections, and modulate energy metabolism, immunity, and inflammation | 98   |
| 11  | Shufeng Jiedu capsule | SARS-CoV-2 | NP                                                 | NA                          | Regulate the key targets of RELA, MAPK1, MAPK14, CASP3, CASP8, and IL-6 | 99   |
| 12  | Shufeng Jiedu capsule | SARS-CoV-2 | NP, molecular docking                              | NA                          | Regulate immunomodulatory and anti-inflammatory related targets on multiple pathways | 100  |
| 13  | Maxing Shigan decoction | SARS-CoV-2 | NP                                                 | NA                          | 1) Reduce inflammation and suppress cytokine storm | 101  |
| No. | Name                          | SARS-CoV-2 Source | Method                          | Description                                                                                                                                                                                                 |
|-----|-------------------------------|------------------|---------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 14  | Maxing Shigan decoction       | SARS-CoV-2       | NP, molecular docking,          | 2) Protect pulmonary alveolar-capillary barrier and alleviate pulmonary edema 1) Inhibit IL-6 mediated JAK-STAT signal pathway 2) Amygdalin is predicted to bind ACE2, 3CLpro, and RdRp 1) Regulate free radical production and blood circulation 2) Exert antiviral, immune-regulatory, and anti-inflammatory by targeting ACE2 and IL-6 |
| 15  | Cold-damp plague formula      | SARS-CoV-2       | NP, molecular docking           | 1) Play an anti-inflammatory and immunoregulatory role via acting on IL-6, IL-1β, and CCL2 2) Decrease the level of IL-6 in mild, moderate, and severe clinical cases 3) The ingredients of kaempferol, quercetin, 7-methoxy-2-methylisoflavone, naringenin, and formononetin target IL-6, IL-1β, and CCL2 with high affinity 1) Exert antiviral effect 2) Regulate ACE2, 3CLpro, and PLpro activity 3) Modulate inflammation-related expressions of MAPKs, PKC, and NF-κB |
| 16  | Dayuanyin                     | SARS-CoV-2       | NP, molecular docking           | 1) Inhibit IL-6 mediated JAK-STAT signal pathway 2) Exert antiviral, immune-regulatory, and anti-inflammatory by targeting ACE2 and IL-6 1) Regulate free radical production and blood circulation 2) Decrease the level of IL-6 in mild, moderate, and severe clinical cases 3) The ingredients of kaempferol, quercetin, 7-methoxy-2-methylisoflavone, naringenin, and formononetin target IL-6, IL-1β, and CCL2 with high affinity 1) Exert antiviral effect 2) Regulate ACE2, 3CLpro, and PLpro activity 3) Modulate inflammation-related expressions of MAPKs, PKC, and NF-κB |
| 17  | Reduning injection            | SARS-CoV-2       | Infected Vero E6 cells, CPE,    | Inhibit viral replication in vitro and in vivo 1) Inhibit virus replication and reduce plaque formation 2) Reduce pro-inflammatory cytokines of TNF-α, IL-6, IL-1β, IL-8, MCP-1, and IP-10 production, and inhibit p-NF-κB p65, p-p38, and p-gp38 MAPK expression |
| 18  | Liu Shen capsule              | SARS-CoV-2       | Infected Vero E6 cells and      | Inhibit viral replication 1) Inhibit viral replication 2) Inhibit 3CLpro activity 3) Regulate TNF, T-cell receptor, Toll-like receptor, and MAPK signaling pathways |
| 19  | Pudilian Xiaoayan oral liquid | SARS-CoV-2       | Infected Vero E6 cells, CPE,    | Inhibit viral replication in vitro and in vivo 1) Inhibit virus replication and reduce plaque formation 2) Reduce pro-inflammatory cytokines of TNF-α, IL-6, IL-1β, IL-8, MCP-1, and IP-10 production, and inhibit p-NF-κB p65, p-p38, and p-gp38 MAPK expression |
| 20  | Shuanghuangliang preparation  | SARS-CoV-2       | Infected Vero E6 cells, CPE     | Inhibit viral replication in vitro and in vivo 1) Inhibit virus replication and reduce plaque formation 2) Reduce pro-inflammatory cytokines of TNF-α, IL-6, IL-1β, IL-8, MCP-1, and IP-10 production, and inhibit p-NF-κB p65, p-p38, and p-gp38 MAPK expression |
| 21  | Yinqiao powder                | SARS-CoV-2       | NP, molecular docking, surface | Regulate TNF, T-cell receptor, Toll-like receptor, and MAPK signaling pathways |
| 22  | Pudilian prescription         | SARS-CoV-2       | NP, GSEA enrichment, molecular  | Regulate TNF, T-cell receptor, Toll-like receptor, and MAPK signaling pathways |
| 23  | Matrine injection             | SARS-CoV-2       | NP, molecular docking           | Regulate TNF, T-cell receptor, Toll-like receptor, and MAPK signaling pathways |
| 24  | Shenfu decoction              | SARS-CoV-2       | NP, molecular docking           | Regulate TNF, T-cell receptor, Toll-like receptor, and MAPK signaling pathways |
| 25  | Andrographis paniculate       | SARS-CoV-2       | Infected Calu-3 cells, CPE      | Inhibit viral replication, host cell apoptosis and inflammation by targeting the TNF-α, IL-6, and CASP3 in TNF signaling pathway 2) Reduce lung tissue damage and lung index 3) Decrease the production of IL-6, IL-10, TNF-α, IFN-γ, as well as the viral load in lung tissue 4) Increase the percentage of CD4⁺ T cells, CD8⁺ T cells and B cells in peripheral blood 5) Prevent SARS-CoV-2 entrance by blocking ACE2 6) Inhibit cytokine storm of CRP, IFN-γ, IL-6, IL-10, TNF, EGFR, CCL5, and TGF-β1 |
| 26  | Scutellaria baicalensis        | SARS-CoV-2       | 1) Enzyme inhibition assay      | Inhibit viral replication, host cell apoptosis and inflammation by targeting the TNF-α, IL-6, and CASP3 in TNF signaling pathway 2) Reduce lung tissue damage and lung index 3) Decrease the production of IL-6, IL-10, TNF-α, IFN-γ, as well as the viral load in lung tissue 4) Increase the percentage of CD4⁺ T cells, CD8⁺ T cells and B cells in peripheral blood 5) Prevent SARS-CoV-2 entrance by blocking ACE2 6) Inhibit cytokine storm of CRP, IFN-γ, IL-6, IL-10, TNF, EGFR, CCL5, and TGF-β1 |
| 27  | Rheum officinale              | SARS-CoV-2       | Infected Vero E6 cells, CPE,    | Block spike–ACE2 interaction 1) Inhibit 3CLpro activity 2) Exert antiviral effect |

(continued on next page)
Table 3 (continued)

| No. | TCM                     | Coronavirus Model/method | IC₅₀ or dosage | Potential mechanism                                                                 |
|-----|-------------------------|--------------------------|----------------|--------------------------------------------------------------------------------------|
| 28  | Polygonum multiflorum   | SARS-CoV Infected Vero E6 cells, CPE, e₁₀₀µg/mL | Block spike e₁₀₀µg/mL | 1) Block spike e₁₀₀µg/mL 2) Increase the proportion of CD₈⁺ and CD₄⁺ T cells 3) Increase in the secretion of IL-2 and IL-10 in mouse splenic lymphocytes 4) Inhibit 3CLpro activity |
| 29  | Houttuynia cordata      | SARS-CoV Flow cytometry, ELISA, 0₈₀₀µg/mL | 1) Stimulate the proliferation of mouse splenic lymphocytes and CD₈⁺ T cells 2) Increase the proportion of CD₄⁺ T cells 3) Increase in the secretion of IL-2 and IL-10 in mouse splenic lymphocytes 4) Inhibit 3CLpro and RdRp activity |
| 30  | Rheum palmatum (Zhangye) | SARS-CoV Enzyme inhibition assay 13.76 µg/mL | 1) Inhibit viral replication 2) Inhibit viral replication |
| 31  | Chlorophyllum buxifolium (Guogu) | SARS-CoV Enzyme inhibition assay 2.139 µg/mL | 1) Inhibit 3CLpro activity 2) Inhibit 3CLpro activity |
| 32  | Dioscorea batatas (Shanyao) | SARS-CoV Infected Vero E6 cells, CPE, 2₄₄µg/mL | 1) Inhibit viral replication 2) Inhibit viral replication |

Advantages in regulating immune response, suppressing cytokine storm through multiple avenues [179–177]. Beyond inhibiting virus replication, Lianhua Qingwen capsule 136 and Liu Shen capsule 107 reduced pro-inflammatory cytokines production such as TNF-α, IL-6, MCP-1, and IP-10 in SARS-CoV-2 infected Huh-7 cells. In addition, Lianhua Qingwen capsule was analyzed to repair lung injury by modulating inflammatory process and cytokine storm 115. Maxing Shigan decoction is the basic prescription of “three medicines and three formulas” apart from Xuebijing injection, was revealed to regulate immunity and reduce cytokine storm, as well as protect alveolar-capillary barrier of lung and relieve pulmonary edema by utilizing integrated network pharmacological approaches 105. As same as Maxing Shigan decoction, Qingfei Paidu decoction showed multiple immune regulation, anti-inflammatory, and lung injury—repair activities with its main ingredients of baicalin, glycyrrhizic acid, hesperidin, and hyperoside by targeting proteins including TNF-α, IL-6, IL-10, and CCL2 95–96. Furthermore, several ingredients such as baicalin and glycyrrhizin of Qingfei Paidu decoction could inhibit platelet aggregation 98. Dayuanxin is the basic formula of Qingfei Dayuan granules that might process an anti-inflammatory and immunoregulatory effects via acting on IL-6, IL-₁β, and MCP-1, with its ingredients containing kaempferol, isoflavone, and formononetin 102,103. Glycyrrhizin is an anti-viral agent and clinically used anti-inflammatory ingredient from Glycyrrhiza uralensis (Gancao) was determined to elevate immunity and suppress inflammatory stress through T cell receptor and VEGF signaling pathways 141,159,173. Matrine was not only predicted to suppress host cell apoptosis and inflammation by targeting the TNF-α, IL-6, and CASP3 in the TNF signaling, but also validated to reduce lung tissue damage and lung index by decreasing the production of IL-6, IL-₁₀, TNF-α, and IFN-γ, increasing the percentage of CD4⁺ T cells, CD8⁺ T cells, and B cells in peripheral blood, and lessening viral load in lung tissue in a mouse model combining human coronavirus pneumonia with cold—dampness pestilence attacking the lung 112,113. Although systems pharmacology is a convenient and effective tool to propose the mechanism of action of TCM at a holistic level, all the results above need to be further validated. IL-6 was considered as one of the most important molecules in cytokine storm 174–182. Administration with Dayuanyin reduced the level of IL-6 in mild, moderate, and even severe clinical stages of COVID-19 104. Besides, Shufeng Jiedu capsule 105, Yidu-toxicity blocking lung decoction 62, Qingfei Toujie Fuzheng recipe 97, and diammonium glycyrrhizinate 100 were confirmed to decrease the level of IL-6 in COVID-19 patients, as seen in Table 1. Interestingly, except for the strong anti-SARS-CoV-2 activity 37, artemisinin and its derivatives regulated multiple immune cells including macrophage, monocyte, dendritic cell, and T cell to inhibit pro-inflammatory cytokine release and cytokine storm outbreak to protect tissues from injury 185 (Table 3).

3.3. Potential mechanisms of TCM for ARDS and MODS treatment

In contrast with WM therapy, TCM is adept at treating complications of COVID-19 such as ARDS and MODS which are likely caused by the concurrence of viral toxicity, endothelial damage, cytokine storm, excessive immune, and microthrombus holistically (Table 3). Xuebijing injection was certified to treat severe pneumonia, sepsis, coagulopathy, SIRS, and MODS, owing to its various effects on cytokine reduction, immunoregulation, microcirculation improvement, anti-coagulation, pro-angiogenesis, and neutralization of released bacterial cytokinins 42,184–189. Xuebijing injection...
| No. | TCM ingredient | Source | Coronavirus | Model/method | IC₅₀ (EC₅₀) or dosage | Potential mechanism | Ref. |
|-----|----------------|--------|-------------|--------------|-----------------------|---------------------|-----|
| 1   | Rhein          | Rheum palmatum (Yaoyong Dahuang) | SARS-CoV-2 | Enzyme inhibition assay, molecular docking, and surface plasmon resonance (SPR) analysis | 18.33 µmol/L | Inhibit ACE2 activity | 121 |
| 2   | Forsythoside A | Forsythiae fructus (Lianqiao) fruit | SARS-CoV-2 | Enzyme inhibition assay, molecular docking, SPR analysis | Unclear | Inhibit ACE2 activity | 121 |
| 3   | Neochlorogenic acid | Lonicera japonica (Jingyinhua) | SARS-CoV-2 | Enzyme inhibition assay, molecular docking, SPR analysis | ~40 µmol/L | Inhibit ACE2 activity | 121 |
| 4   | Quercetin      | Ginkgo biloba (Yinxing) | SARS-CoV-2 | Enzyme inhibition assay | 4.48 µmol/L | Inhibit ACE2 activity | 122 |
| 5   | Ephedrine      | Ephedrae Herba (Mahuang) | SARS-CoV-2 | Molecular docking, SPR analysis | Unclear | Inhibit ACE2 activity | 123 |
| 6   | Hesperidin     | Citrus aurantium (Suancheng) | SARS-CoV-2 | Target-based virtual ligand screening | Unclear | Block spike—ACE2 interaction. | 124,125 |
| 7   | Geniposide     | Gardenia jasminoides (Zhizi) | SARS-CoV-2 | Molecular docking | Unclear | Inhibit TMPRSS2 activity | 126 |
| 8   | Baicalin       | Scutellaria baicalensis (Huangqin) | SARS-CoV-2 | 1) Enzyme inhibition assay 2) Infected Vero E6 cells, CPE | 1) 27.87 µmol/L 2) 6.41 µmol/L | 1) Inhibit viral replication 2) Inhibit 3CLpro activity | 109 |
| 9   | Baicalein      | Scutellaria baicalensis (Huangqin) | SARS-CoV-2 | 1) Enzyme inhibition assay 2) Infected Vero cells | 1) 0.39 µmol/L 2) 2.9 µmol/L | 1) Inhibit 3CLpro activity 2) Exert antiviral infection effect | 116 |
| 10  | Shikonin       | Lithospernum erythrorhizon (Zicao) | SARS-CoV-2 | Enzyme inhibition assay | 15.75 µmol/L | Inhibit 3CLpro activity | 127 |
| 11  | EGCG           | Green tea | SARS-CoV-2 | Enzyme inhibition assay | 0.017 µmol/L | Inhibit 3CLpro activity | 128 |
| 12  | Theaflavin     | Black tea | SARS-CoV-2 | Enzyme inhibition assay | 0.015 µmol/L | Inhibit 3CLpro activity | 128 |
| 13  | Scutellarein   | Scutellaria baicalensis (Huangqin) | SARS-CoV-2 | Enzyme inhibition assay | 5.8 µmol/L | Inhibit 3CLpro activity | 116 |
| 14  | Myricetin      | Myrica rubra (Yangmei) | SARS-CoV-2 | Enzyme inhibition assay | 2.86 µmol/L | Inhibit 3CLpro activity | 116 |
| 15  | Cannabidiol    | Cannabis sativa (Dama) | SARS-CoV-2 | 1) Enzyme inhibition assay 2) Infected Vero cells | 1) 7.91 µmol/L 2) 1.55 µmol/L | 1) Bind to PLpro 2) Exert antiviral effect | 129 |
| 16  | Theaflavin     | Black tea | SARS-CoV-2 | Molecular docking | Unclear | Inhibit RdRp activity | 130,131 |
| 17  | Digitoxin      | Digitalis purpurea (Yangdihuang) | SARS-CoV-2 | Infected Vero cells, CPE | 0.23 µmol/L | Exert antiviral effect | 132 |
| 18  | Tetrandrine    | Stephania tetrandra (Fengfangji) | SARS-CoV-2 | Infected Vero cells, CPE | 3 µmol/L | Exert antiviral effect | 132 |
| 19  | Glycyrrhizin   | Glycyrrhiza uralensis (Gancao) | SARS-CoV-2 | Infected Vero E6 cells, CPE | 0.53 µmol/L | Exert antiviral effect | 133 |
| 20  | Resveratrol    | Polygonum cuspidatum (Huzhang) | SARS-CoV-2 | Infected Vero E6, Calu-3 and primary human bronchial epithelium cells, CPE | 66 µmol/L | Exert antiviral effect | 134 |
| 21  | Pterostilbene  | Pterocarpus santalinus (Zitan) | SARS-CoV-2 | Infected Vero E6, Calu-3 and primary human bronchial epithelium cells, CPE | 19 µmol/L | Exert antiviral effect | 134 |
| 22  | Phillyrin       | Forsythiae fructus (Lianqiao) | SARS-CoV-2 | Infected VeroE6 cells and Huh-7 cells, CPE | 1) 63.9 µg/mL 2) and 3) 62.5—250 µg/mL | 1) Inhibit viral replication 2) Reduce the production of proinflammatory cytokines of | 135 |

(continued on next page)
| No. | TCM Ingredient | Source | Coronavirus | Model/method | IC₅₀ (EC₅₀) or dosage | Potential mechanism | Ref. |
|-----|----------------|--------|-------------|--------------|----------------------|---------------------|------|
| 23  | Catechin       | Green tea | SARS-CoV-2 | Molecular docking | Unclear | 3) Suppress NF-κB signaling pathway | 131,136 |
| 24  | Artemisinin    | Artemisia annua (Qinghao) | SARS-CoV-2 | Infected Vero E6 cells, CPE | 64.45 μmol/L | Bind to 3CLpro, cathepsin L, RBD of S protein, NSP6, and nucleocapsid protein | 137 |
| 25  | Artesunate     | Artemisinin derivative (Qianjinteng) | SARS-CoV-2 | Infected Vero E6 cells, CPE | 12.98 μmol/L | Inhibit viral replication | 137 |
| 26  | Cepharanthine  | Stephania japonica | SARS-CoV-2 | Infected Vero E6 cells, CPE | 0.98 μmol/L | Inhibit viral replication | 138 |
| 27  | Bufalin        | Toad venom (Chansu) | SARS-CoV-2 | Infected Vero E6 cells, CPE | 18 nmol/L | Exert antiviral effect by targeting Na⁺/K⁺-ATPase | 139 |
| 28  | Bruceine A     | Brueca javanica (Yadanzi) | SARS-CoV-2 | Infected Vero E6 cells, CPE | 11 nmol/L | Exert antiviral effect | 139 |
| 29  | Naringenin     | Gardenia jasminoides (Zhishi) | SARS-CoV-2 | Infected Vero E6 cells, CPE | 31.3–250 μmol/L | Target two-pore channel 2 | 140 |
| 30  | Andrographolide | Andrographis paniculata (Chuanxinlian) | SARS-CoV-2 | Infected Calu-3 cells, CPE | 0.034 μmol/L | Exert antiviral effect | 142 |
| 31  | Glycyrrhizin + vitamin C | Glycyrrhiza uralensis (Gancao) | SARS-CoV-2 | NP | Unclear | Elevate immunity and suppress inflammatory stress | 141 |
| 32  | Chlorogenic acid | Lonicer japonica (Jinyinhua) | SARS-CoV-2 | NP | Unclear | Exert antiviral effect by targeting NFE2L2, PPARG, ESR1, ACE, IL-6, and HMOX1 | 142 |
| 33  | Emodin         | Rheum palmatum (Yaoyong Dahuang) | SARS-CoV | Infected Vero E6 cells, CPE, biotinylated ELISA | 200 μmol/L | Block spike–ACE2 interaction | 117 |
| 34  | Celastrol      | Celastrus orbiculatus (Nansheteng) | SARS-CoV | Enzyme inhibition assay | 10.3 μmol/L | Inhibit 3CLpro activity | 143,144 |
| 35  | Tingenonol     | Euonymus alatus (Weimao) | SARS-CoV | Enzyme inhibition assay | 9.9 μmol/L | Inhibit 3CLpro activity | 143 |
| 36  | Curcurmin      | Curcuma longa (Jianghuang) | SARS-CoV | 1) Enzyme inhibition assay; 2) Infected Vero E6 cells, CPE | 1) 23.5 μmol/L 2) 40 μmol/L | 1) Inhibit 3CLpro activity; 2) Inhibit viral replication | 145,146 |
| 37  | Quercetin      | Ginkgo biloba (Yingxing) | SARS-CoV | Enzyme inhibition assay | 73 μmol/L | Inhibit 3CLpro activity | 147,148 |
| 38  | Tanshinone IIA | Salvia miltiorrhiza (Danshen) | SARS-CoV | Enzyme inhibition assay | 89.1 μmol/L | Inhibit 3CLpro activity | 149 |
| 39  | Dihydrotanshinone I | Salvia miltiorrhiza (Danshen) | SARS-CoV | Enzyme inhibition assay | 14.4 μmol/L | Inhibit 3CLpro activity | 150 |
| 40  | Xanthoangelol E | Angelica keiskei (Mingriye) | SARS-CoV | Enzyme inhibition assay | 11.4 μmol/L | Inhibit 3CLpro activity | 151 |
| 41  | Sinigrin       | Isatis indigotica root (Banlangen) | SARS-CoV | Enzyme inhibition assay | 217 μmol/L | Inhibit 3CLpro activity | 151 |
| 42  | Hesperetin     | Isatis indigotica root (Banlangen) | SARS-CoV | Enzyme inhibition assay | 8.3 μmol/L | Inhibit 3CLpro activity | 151 |
| 43  | Pectolinarin   | Cirsium japonicum (Daji) | SARS-CoV | Enzyme inhibition assay | 37.78 μmol/L | Inhibit 3CLpro activity | 152 |
| 44  | Luteolin       | Jinyinhua | SARS-CoV | 1) Infected Vero E6 cells, CPE; 2) Enzyme inhibition assay | 1) 9.02 μmol/L 2) 20.2 μmol/L | 1) Exert antiviral effect; 2) Inhibit PLpro activity | 153,154,149 |
| 45  | Hirsutenone    | Alnus japonica (Chiyang) | SARS-CoV | Enzyme inhibition assay | 4.1 μmol/L | Inhibit PLpro activity | 155 |
| 46  | Tanshinone IIB | Salvia miltiorrhiza (Danshen) | SARS-CoV | Enzyme inhibition assay | 10.7 μmol/L | Inhibit PLpro activity | 149 |
was able to improve the oxygenation index of PaO2/FiO2 and reduce the level of pro-inflammatory cytokines of TNF-α, IL-10, MIP-1β, and RANTES in the treatment of COVID-19. It was also reported that Xuebijing injection could downregulate the expression of IL-6, IL-1, TLR4, MAPK, and NF-κB, maintain the balance of Tregs and Th17 cells in acute lung injury. Besides, Xuebijing injection processed the potential to alleviate liver damage, acute lung injury-induced left ventricular ischemia/reperfusion, sepsis-induced acute kidney injury, and sepsis-induced myocardial injury via inhibiting inflammation, apoptosis, and endothelial injury. Systems pharmacological analysis revealed that Qingfei Paidu decoction could protect multi-organ including nervous system, sensory system, digestive system, and circulatory system by regulating key enzymes, G protein-coupled receptors, ion channels, and transporters.

In the background of great demands for acute lung injury and ARDS therapy of COVID-19, more than one hundred of natural products from TCM with their potential benefits and underlying mechanisms of anti-inflammation, antioxidative stress, anti-apoptosis, and anti-pulmonary fibrosis were summarized and categorized. According to their chemical structures, these were divided into flavonoids (e.g., luteolin, baicalin), alkaloids (e.g., berberine, matrine), terpenoids (e.g., pogostone, andrographolide), polyphenols (e.g., honokiol, curcumin), quinonoids (e.g., emodin, shikonin), and other compounds (e.g., osthole, imperatorin). In addition, a systematic review and meta-analysis of 19 eligible RCTs including Tanreqing injection, Shengmai injection, Reduning injection, and Xuebijing injection demonstrated that Chinese medicine injections were adjuvant therapy with great potential benefits for the treatment of ALI/ARDS. For example, based on the effects of inhibiting inflammatory cytokines of IL-6, IL-8, IL-1β, and TNF-α, regulating immune, and elevating the oxygenation index of PaO2, Tanreqing injection was proved to improve lung injury, pulmonary infection, airway inflammation, and airway mucus hypersecretion. Reduning injection was demonstrated to prevent pulmonary neutrophil infiltration, lung injury and severe pneumonia which may attribute to downregulating IL-1β, IL-8, TNF-α, NF-κB, and pyrin domain containing 3 levels, lowering myeloperoxidase activities, and reducing reactive oxygen species production. Xiyangping injection, a famous Chinese medicinal preparation of andrographolide sulfate, was reputed as one of the most effective alternatives to antibiotics, which has been widely used to ameliorate lung damage, bronchitis and community acquired pneumonia probably through inhibiting NF-κB and MAPK-mediated inflammatory responses. Besides, Xiyangping injection and Reduning injection were used to treat diarrhea in children. Xiyangping injection could ameliorate colitis by inhibiting TH1/TH17 response in mice.

Cardiovascular disease is a high frequent comorbidity and complication of COVID-19. Three Chinese injection medicines including Shengmai injection, Shennai injection, and Shenfu injection, have both pulmonary and cardiac protective effects. For instance, Shengmai injection is effective in the treatment of heart failure, myocardial hypertrophy, cardiac arrest, myocardial ischemia-reperfusion injury, myocardial fibrosis, and acute viral myocarditis, partly through suppressing apoptosis and inflammation, improving microcirculation, reducing mitochondrial damage and coagulation-fibrinolysis disorders. Moreover, Shengmai injection has a protective effect on gastrointestinal tract and intestinal mucosa. Xingmaojing injection and Angong Niuhuang pill are different preparations share similar ingredients for stroke treatment in clinic. Both of them ameliorate cerebral...
Figure 2  Representative herbs and their main active ingredients and functions for COVID-19. (A) The herb-ingredient-target-function network of frequently used herbs and their main ingredients, as well as their key targets and functions for COVID-19. (B) The chemical structures of main active ingredients and their main functions of commonly used herbs for COVID-19.
Figure 3  An overview of pathogenesis of COVID-19 and the potential mechanisms of TCM remedy in distinct disease stages.
ischemia/reperfusion injury, cerebral infarction, cerebral edema, blood–brain barrier disruption, and acute cerebral hemorrhage because of their benefits in brain microvascular endothelial cells, hippocampal and cortical neurons protection, and their anti-inflammation and anti-apoptosis effects.

3.4. Potential mechanisms of the representative and commonly used herbs in the treatment of COVID-19

Analyses of the main compositions of the “three medicines and three formulas” and other related literatures identified G. uralensis (Gancao), Ephedrae Herba (Mahuang), Semen Armeniacae Amurum (Kuxingren), Scutellaria baicalensis (Huangqin), Forsythiae Fructus (Lianqiao), Lonicera japonica (Jingyinhua), Rheum palmatum (Dahuang), and Artemisia annua (Qinghao) as the representative and commonly used herbs for COVID-19.

Gut microbiome is involved in disease severity and host inflammatory and immune response by targeting inflammatory cytokines such as IL-1, TNF-

In summary of preclinical evidence, the anti-COVID-19 effects and mechanisms of TCM include but not limited to 1) inhibiting SARS-CoV-2 infection and replication by targeting the key proteins of spike, ACE2, TMPRSS2, 3CLpro, PLpro, RdRp, and spike–ACE2 interaction; 2) regulating immune and inflammatory response by targeting inflammatory cytokines such as IL-1, TNF-α, and IL-8, and chemokines like CCL5, CCL2, and IP-10, which are secreted by monocytes, macrophages, dendritic cells, CD4+ T cells, and CD8+ T cells; 3) protecting against ARDS and MODS by suppressing the crosstalk of viral toxicity, endothelial damage, cytokine storm, excessive immune, and microthrombus by targeting IL-6, CRP, D-dimer, and procalcitonin.

Finally, by integrating the clinical evidence and potential mechanisms of TCM for COVID-19, a panorama is drawn in Fig. 3, hoping that the effect and mechanism of TCM for COVID-19 could be viewed and understood within a single framework.

4. Conclusions and perspectives

Although a great quantity of review articles have been published on the topic of TCM in COVID-19, our work offers something unique. 1) To our knowledge, this is the first review of TCM on COVID-19 that integrates evidence-based scientific findings from bedside to bench with the most comprehensive and updated literatures. 2) The pathogenesis and potential mechanisms of TCM remedy in three phases corresponding to distinct stages for COVID-19 are first systematically described and presented within a single panorama by integrating available clinical and fundamental evidence. A valuable lesson learned from China’s COVID-19 battle is that perseverance in combination of TCM and WM is the right and sensible choice. Looking ahead, several critical issues need to be addressed as we prepare to face similar or even more serious global health threats in the future. Firstly, as the pandemic continues to evolve, the pathogenesis of COVID-19 is not fully elucidated. It is reasonable to postulate that the crosstalk of viral toxicity, endothelial damage, cytokine storm, excessive immune, and microthrombus are essential contributors for severely or critically ill patients with COVID-19, which need to be validated further. Secondly, due to a lack of in-depth understanding, there are still some skepticism on the validity of treating COVID-19 with TCM. More RCTs with high accuracy, clinical safety, rigorous design, and large sample, as well as in-depth mechanistic explorations with compatibility principal should be conducted to provide more reliable evidence for TCM in COVID-19 intervention, especially for the highly recommended three CPMS and three Chinese medicine formulas. Thirdly, the rehabilitative effects of TCM ought to be continuous concerned and long-term medical observed for the COVID-19 patients in recovery phase, especially for the aged. A recent paper published in The Lancet on 6-month consequences of 1733 COVID-19 patients revealed that those with severe disease discharged from hospital showed common syndromes of fatigue or muscle weakness, sleep difficulties, and anxiety or depression. Meanwhile, a comparison of 425 non-treatment with 143 TCM-treated COVID-19 patients post discharge showed that TCM was beneficial for decreasing IL-6 and procalcitonin, and increasing red blood cell, hemoglobin, and platelet count.

Overall, the purpose of this review is to scientifically and systematically evaluate the roles of TCM in combating COVID-19. The efficacies and potential mechanisms of TCM remedy in three phases of distinct stages of COVID-19 are discussed and presented comprehensively within a single panorama by integrating available clinical and preclinical evidence. Finally, although the availability of anti-COVID-19 vaccines and a global vaccination program have brought great hope for the ultimate control of the disease, threat of viral variants and new epidemics still exist. Therefore, it is of scientific value to historically and objectively summarize the contribution of TCM during the pandemic, which could be deployed in the future to combat against COVID-19 and other infectious diseases around the world.
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Author contributions

Boli Zhang, Yan Zhu, Junhua Zhang, Yuanlu Cui, and Jigang Wang conceived, designed, and revised the manuscript; Ming Lyu, Guanwei Fan, and Guangyu Xiao wrote and revised the manuscript; Taiyi Wang, Dong Xu, Jie Gao, Shaoqin Ge, Qinglin Li, Yuling Ma, and Han Zhang revised the manuscript and discussed interpretation.

Conflicts of interest

The authors declare no conflicts of interest.

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