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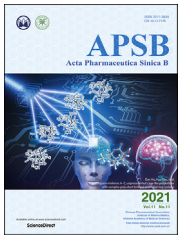

REVIEW

Traditional Chinese medicine in COVID-19

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Multiple organ dysfunction

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 subfamily Coronavirinae, family Coronavirdiae, order Nidovirales. It shares about 79.6% identity of genome sequence with SARS-CoV and 96% similarity with bat coronavirus at the whole-genome level[1,2]. 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[3]. 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)[4]. Owning to the positive role of TCM in treating previous coronavirus pneumonias such as SARS, middle east respiratory syndrome (MERS), and other epidemic diseases[4–9], 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 theory[10–12]. 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 efficacities 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 needed[13–15]. 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 references[14,16–23], 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-19[24,25]. Jinhua Qinggan granules clear heat and detoxifying, and diffuse the lung. It is composed of 12 herbal medicines originating from Maxingshigan–Yinqiaosan formula, which could shorten time to fever resolution in patients with H1N1 influenza virus infection occurred in 2009[26]. Lianhua Qingwen capsule (granules), containing 13 herbal medicines and with a clinical indication for clearing heat, diffusing the lung, and detoxifying, was an innovative CPM for the treatment of SARS in 2003[27,28]. Xuebijing injection, a five-herbal injection medicine and with a clinical indication for dissolving 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-19[25,29]. 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 patients[30,31]. 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, diffuses the lung, removes dampness, clears heat, and is mainly applicable to treat mild and moderate

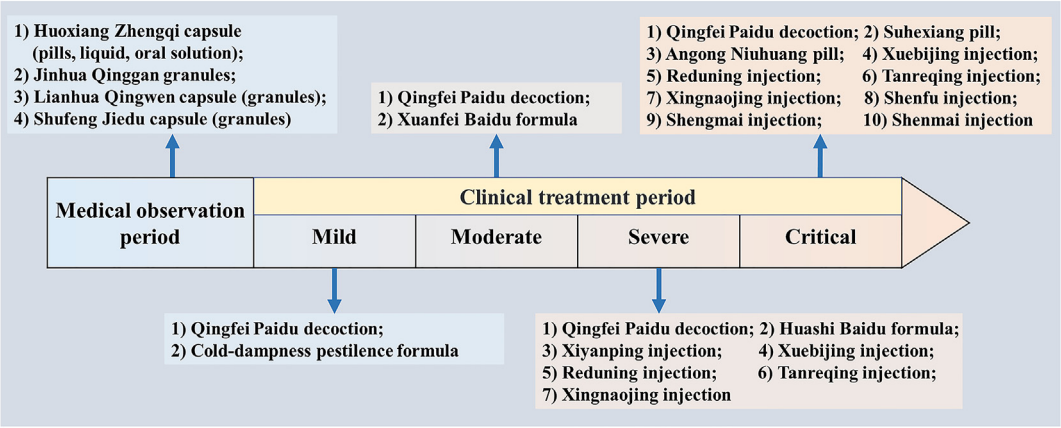

Figure 1 The recommended Chinese patent medicines or Chinese medicine formulas for distinct stages of COVID-19 treatment.

COVID-19 patients[32]. 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[33−35].

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[27,28,30−32,36−70]. 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[27,28,30−32,36−70]. Furthermore, based on Table 1, the clinical evidence of TCM for typical characteristics of COVID-19 were analyzed and summarized in Table 2[27,28,30−32,36−70].

For mild or moderate stages: 1) the most typical clinical symptoms of fever, cough, and fatigue were relieved by Jinhua Qinggan granules[37], Lianhua Qingwen granules[39], Shufeng Jiedu capsule[51,52], Toujie Quwen granules[57], Lianhua Qingke granules[56], Xuanfei Baidu decoction[32], and Maxing Shigan decoction[59]; Lianhua Qingwen granules[38] and Shufeng Jiedu capsule[51] improved the symptoms of short of breath and chest tightness; Jinhua Qinggan granules relieved the symptom of psychological anxiety[37], and Shufeng Jiedu capsule[53] improved the symptom of diarrhea. 2) Jinhua Qinggan granules[36], Shufeng Jiedu capsule[51], and Toujie Quwen granules[57] promoted pneumonia inflammatory absorption or improve lung CT imaging. 3) Jinhua Qinggan granules[36], Lianhua Qingwen granules[39], Shufeng Jiedu capsule[52], Xuanfei Baidu decoction[32], and Toujie Quwen granules[57] increased white blood cell (WBC) or lymphocyte count; Lianhua Qingwen granules[39], Shufeng Jiedu capsule[51], Toujie Quwen granules[57], Xuanfei Baidu decoction[32], and Maxing Shigan decoction[59] reduced the level of C-reactive protein (CRP). Shufeng Jiedu capsule decrease the level of interleukin-6 (IL-6)[54].

For severe or critical stages: 1) Xuebijing injection[43] and Qingfei Paidu decoction[45] improved the conditions of patients and reduced multiple organ dysfunction. 2) Xuebijing injection[43], Qingfei Paidu decoction[45], and Huashi Baidu formula[30] improved chest CT imaging or promoted lung lesions absorption; Chansu injection[61] ameliorated the respiratory function and shorten the respiratory support step-down time. 3) Both Xuebijing injection[43] and Chansu injection[61] improved the oxygenation index of PaO_2/FiO_2; Xuebijing injection[43] and Qingfei Paidu decoction[45] 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, MIP-1β, and RANTES[42]; Qingfei Paidu decoction decreased biochemical parameters of CK and LDH, and the level of blood urea nitrogen[45]; Maxing Shigan decoction increased $CD4^+$ T and $CD8^+$ T count[59]; Huashi Baidu formula[30] 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[62].

For all stages: 1) Qingfei Paidu decoction[46] and Qingfei Dayuan granules[63] 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[65]. 2) Qingfei Paidu decoction[45], Qingfei Dayuan granules[63], Xuanfei Huazhuo decoction[65], Keguan-1[66], Qingfei Touxie Fuzheng recipe[67], Ganlu Xiaodu decoction[68], and Matrine injection[69] improved lung inflammation or lesions absorption. 3) Qingfei Paidu decoction[46], Qingfei Dayuan granules[63], Xuanfei Huazhuo decoction[65], Ganlu Xiaodu decoction[68], "Fei Yan No. 1"[64], Matrine and sodium chloride injection[69], and Diammonium glycyrrhizinate[70] increased WBC or lymphocyte count; Qingfei Touxie Fuzheng recipe[67] and Diammonium glycyrrhizinate[70] decreased the level of CRP, IL-6, and ESR; Qingfei Paidu decoction[46,48] and Xuanfei Huazhuo decoction[65] 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[46].

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[71−80]. A recent systematic

Table 1 Clinical efficacies of integrated TCM and WM for COVID-19 treatment.

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.	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 PaO_2/FiO_2 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			fever, cough, asthma, and fatigue were relieved 2) Improve lung CT imaging	dimer, CRP, ESR, and the percentage of lymphocyte	
14	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) Promote lung CT improvement	Unreported	47
15	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	Reduce the level of IL-6 and increase the level of CD3	48
16	Qingfei Paidu decoction + WM *vs.* WM	Multi-center clinical observation	199/96	Mild or moderate	1) Reduce mean length of hospital stay, nucleic acid negative time and improve symptom of sputum 2) Improve lung CT imaging	Unreported	49
17	Qingfei Paidu decoction + WM	Multi-center clinical observation	782/0	All	Shorten the time of recovery, viral shedding, and the duration of hospital stay	Unreported	50
18	Xuanfei Baidu decoction + WM *vs.* WM	RCT	22/20	Mild	Increase the disappearance rate of symptoms of fever, cough, fatigue, and loss of appetite	1) Elevate WBC and lymphocyte count 2) Reduce the levels of CRP and ESR	32
19	Huashi Baidu granule *vs.* WM	RCS	23/32	Severe	Improve chest CT imaging and lung lesion opacity	Decrease the levels of CRP, ESR, serum ferritin, and myoglobin	30
20	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	No significant differences in biochemical indicators such as D-dimer, CRP, and IL-6	31
21	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	1) Increase lymphocyte count 2) Decrease the levels of CRP, procalcitonin, and D-dimer	51
22	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	Increase lymphocyte count and lymphocyte percentage	52
23	Shufeng Jiedu capsule + arbidol *vs.* arbidol	RCS	40/30	Mild or moderate	1) Shorten the antipyretic time and the disappearance time of dry cough, nasal congestion, runny nose, pharyngeal pain, fatigue, and diarrhea 2) Reduce novel coronavirus negative conversion time	Unreported	53
24	Shufeng Jiedu capsule + arbidol *vs.* arbidol	RCS	100/100	Moderate	1) Shorten defervescence time 2) Improve resolution of pneumonia on chest CT	1) Increase WBC and lymphocyte count 2) Reduce the levels of CRP and IL-6	54
25	Hanshiyi formula + WM *vs.* WM	RCS	430/291	Mild or moderate	Reduce the progression to severe disease	Unreported	55

(*continued on next page*)

Table 1 (*continued*)

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 PaO_2/FiO_2 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

					fatigue 2) Promote the absorption of pulmonary inflammation	2) Reduce the levels of CRP, ESR, total bilirubin, LDH, and the ratio of AST/ALT	
36	Keguan-1+WM *vs.* WM	RCT	24/24	All	1) Reduce ARDS development 2) Shorten the time to fever resolution 3) Tend to improve lung injury recovery	No significant difference in biochemical indicators such as ALT, AST, and D-dimer	66
37	Qingfei Touxie Fuzheng recipe + WM *vs.* WM	RCT	51/49	All	1) Alleviate the symptoms of fever, cough, expectoration, chest tightness, and shortness of breath 2) Promote the absorption of pulmonary lesions and improve oxygenation	Decrease the levels of ESR, CRP, and IL-6, tend to increase IFN-γ level	67
38	Ganlu Xiaodu decoction + Chinese medicine and WM	Case analysis	131/0	All	Increase the effective rate of lung lesions absorption	Increase WBC and lymphocyte count	68
39	Matrine injection + WM	Case analysis	40/0	All	1) Improve the symptoms of cough, fatigue, appetite, and digestive tract 2) Promote absorption of lung lesions, especially for grid-like and fibrotic lesions 3) Shorten nucleic acid clearance time	Alleviate absolute value and ratio of lymphocyte and CRP	69
40	Diammonium glycyrrhizinate + arbidol	Case analysis	46/0	All	Improve the symptoms of low-grade fever, cough, and fatigue	1) Increase lymphocyte count and decrease ESR level 2) Decrease the levels of CRP, IL-6, and procalcitonin	70

T/C, treatment/control.

review and meta-analysis of RCTs involving 2275 patients revealed that integration of TCM and WM group was more effective than WM treatment alone in the indicators of clinical cure rate, conversion rate from mild to critical, length of hospital stay, total score of clinical symptoms, symptoms of fever, cough and fatigue, TCM syndrome, negative conversion rate of viral nucleic acid, inflammatory biomarkers of CRP and lung CT without significant difference in adverse effects[81,82]. Another similar meta-analysis of RCTs including 1259 COVID-19 patients showed consistent results that TCM with 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[83].

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 count 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 is one of the important reasons for the rapid containment of this epidemic in China. Additional high-quality RCTs are needed to demonstrate the effectiveness and adverse events of TCM in the treatment of COVID-19.

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[4−9]. SARS-CoV-2 is genetically more similar with SARS-CoV (about 80%) than MERS-CoV (about 50%)[1,2,84]. 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[85−87]. 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[42,88−164], seen in Table 3[42,88−120] and Table 4 [109,115−117,121−164].

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 (IC_{50}) of 411.2 μg/mL[89], Liu Shen capsule[107] with an IC_{50} of 0.6 μg/mL, and Shuanghuanglian preparation[109] with an IC_{50} 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

Table 2 Clinical evidence of TCM for typical characteristics of COVID-19.

Clinical evidence	TCM
Clinical symptom	
Fever	Jinhua Qinggan granules[37], Lianhua Qingwen capsule[27,28,38-40], Qingfei Paidu decoction[46,47], Xuanfei Baidu decoction[32], Shufeng Jiedu capsule[52,53], Lianhua Qingke granules[56], Toujie Quwen granules[57], Reyanning mixture[58], Maxing Shigan decoction[59], Qingfei Dayuan granules[63], Xuanfei Huazhuo decoction[65], Qingfei Touxie Fuzheng recipe[67], Diammonium glycyrrhizinate[70]
Cough	Jinhua Qinggan granules[37], Lianhua Qingwen capsule[27,38–40], Qingfei Paidu decoction[46,47], Xuanfei Baidu decoction[32], Shufeng Jiedu capsule[51–53], Lianhua Qingke granules[56], Toujie Quwen granules[57], Reyanning mixture[58], Maxing Shigan decoction[59], Qingfei Dayuan granules[63], Xuanfei Huazhuo decoction[65], Qingfei Touxie Fuzheng recipe[67], Matrine injection[69], Diammonium glycyrrhizinate[70]
Fatigue	Jinhua Qinggan granules[37], Lianhua Qingwen capsule[27,28,39,40], Qingfei Paidu decoction[46], Xuanfei Baidu decoction[32], Shufeng Jiedu capsule[51,53], Lianhua Qingke granules[56], Toujie Quwen granules[57], Reyanning mixture[58], Maxing Shigan decoction[59], Qingfei Dayuan granules[63], Xuanfei Huazhuo decoction[65], Matrine injection[69], Diammonium glycyrrhizinate[70]
Dry throat	Lianhua Qingwen capsule[39], Shufeng Jiedu capsule[53], Lianhua Qingke granules[56], Toujie Quwen granules[57], Reyanning mixture[58]
Sore throat	Lianhua Qingwen capsule[39], 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[65], Qingfei Touxie Fuzheng recipe[67]
Shortness of breath	Lianhua Qingwen capsule[28,38], Qingfei Paidu decoction[46], Shufeng Jiedu capsule[51,52], Qingfei Dayuan granules[63], Qingfei Touxie Fuzheng recipe[67]
Myalgia	Lianhua Qingwen capsule[28], Shufeng Jiedu capsule[53], Qingfei Dayuan granules[63]
Diarrhea	Lianhua Qingwen capsule[28], Shufeng Jiedu capsule[53], Maxing Shigan decoction[59], Xuanfei Huazhuo decoction[65]
Duration of nucleic acid turn negative	Jinhua Qinggan granules[36], Lianhua Qingwen capsule[41], Qingfei Paidu decoction[48], Shufeng Jiedu capsule[53], Reyanning mixture[58], Honeysuckle oral liquid[60], "Fei Yan No. 1"[64], Matrine injection[69]
Time to symptom recovery	Lianhua Qingwen capsule[27], Xuebijing injection[44], Qingfei Paidu decoction[47–50], Huashi Baidu Decoction[31], Honeysuckle oral liquid[60], Yidu-toxicity blocking lung decoction[62], "Fei Yan No. 1"[64], Keguan-1[66]
The progression to severe disease	Shufeng Jiedu capsule[51], Hanshiyi formula[55]
Multiorgan injury	Xuebijing injection[44], Qingfei Paidu decoction[48]
Lung feature	
Lung inflammatory absorption	Jinhua Qinggan granules[36], Lianhua Qingwen capsule[41], Xuebijing injection[44], Qingfei Paidu decoction[45], Shufeng Jiedu capsule[52], "Fei Yan No. 1"[64], Xuanfei Huazhuo decoction[65], Ganlu Xiaodu decoction[68], Matrine injection[69]
CT imaging	Lianhua Qingwen capsule[27], Qingfei Paidu decoction[46,47], Huashi Baidu formula[30], Shufeng Jiedu capsule[51], Toujie Quwen granules[57], Reyanning mixture[58], Honeysuckle oral liquid[60]
Lung injury	Xuebijing injection[42], Lianhua Qingke granules[56], Qingfei Dayuan granules[63], Keguan-1[66]
Lung function	Chansu injection[61]
Laboratory finding	
WBC count	Jinhua Qinggan granules[36], Lianhua Qingwen capsule[39], Xuebijing injection[43,44], Xuanfei Baidu decoction[32], Shufeng Jiedu capsule[54], "Fei Yan No. 1"[64], Xuanfei Huazhuo decoction[65], Ganlu Xiaodu decoction[68]
Lymphocyte count	Jinhua Qinggan granules[36], Lianhua Qingwen capsule[39,41], Xuebijing injection[43,44], Qingfei Paidu decoction[45,46], Xuanfei Baidu decoction[32], Shufeng Jiedu capsule[51], Toujie Quwen granules[57], Qingfei Dayuan granules[63], Xuanfei Huazhuo decoction[65], Ganlu Xiaodu decoction[68], Matrine injection[69], Diammonium glycyrrhizinate[70]
Oxygenation index	Xuebijing injection[43], Chansu injection[61]
CRP	Lianhua Qingwen capsule[39], Xuebijing injection[43,44], Qingfei Paidu decoction[45], Xuanfei Baidu Decoction[32], Huashi Baidu formula[30], 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[65], Qingfei Touxie Fuzheng recipe[67], Matrine injection[69], Diammonium glycyrrhizinate[70]
IL-6	Xuebijing injection[42], Qingfei Paidu decoction[48], Shufeng Jiedu capsule[54], Yidu-toxicity blocking lung decoction[62], Qingfei Touxie Fuzheng recipe[67], Diammonium glycyrrhizinate[70]
TNF-α	Xuebijing injection[42], Yidu-toxicity blocking lung decoction[62]
ESR	Xuebijing injection[44], Qingfei Paidu decoction[46], Xuanfei Baidu Decoction[32], Huashi Baidu formula[30], Xuanfei Huazhuo decoction[65], Qingfei Touxie Fuzheng recipe[67], 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 Paidu decoction[46], Xuanfei Huazhuo decoction[65]
AST	Qingfei Paidu decoction[46], Xuanfei Huazhuo decoction[65]
Procalcitonin	Lianhua Qingwen capsule[39], Shufeng Jiedu capsule[51], Toujie Quwen granules[57], Qingfei Dayuan granules[63], Diammonium glycyrrhizinate[70]
D-dimer	Qingfei Paidu decoction[46], Shufeng Jiedu capsule[51], Toujie Quwen granules[57]
$CD4^+$ T cell	Maxing Shigan decoction[59]
$CD8^+$ T cell	Maxing Shigan decoction[59]

angiotensin converting enzyme-2 (hACE2) transgenic mice *in vivo*[108]. Six herbal extracts of *Cibotium barometz* (Gouji), *Gentiana scabra* (Longdan), *Dioscorea batatas* (Shanyao), *Cassia tora* (Juemingzi), and *Taxillus chinensis* (Sangjisheng) were evaluated for the anti-SARS-CoV activities by screening out from more than 200 extracts of Chinese medicinal herbs using a Vero E6 cell-based assay[120]. Among them, Gouji and Shanyao could significantly inhibit 3CLpro protease activity of SARS-CoV with IC_{50} values of 39 and 44 μg/mL[120]. Another screen of 312 Chinese medicinal herb extracts discovered three widely used Chinese medicinal herbs of the family Polygonaceae involving *Rheum officinale* (Yaoyong Dahuang), *Polygonum multiflorum* (Heshouwu), and *Caulis polygoni multiflori* (Shouwuteng) blocking the interaction of SARS-CoV Spike protein and angiotensin converting enzyme 2 (ACE2) which may protect the host from virus invasion with the IC_{50} values ranged from 1 to 10 g/mL[117]. It was not difficult to find that although several TCMs like Liu Shen capsule and Dahuang showed a good performance in suppressing viral replication or activity, more studies are still necessary to be implemented to reveal more receivable anti-viral CPMs and herbal extracts especially the recommended CPMs *in vitro* and *in vivo*.

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 IC_{50} of 200 μmol/L[117], while hesperidin from *Citrus aurantium* (Suancheng) was predicted to target the binding between spike RBD and ACE2 with high affinity[124]. Besides, geniposide from *Gardenia jasminoides* (Zhizi) 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[126]. Seven isolated tanshinones derived from *Salvia miltiorrhiza* (Danshen) including tanshinone IIA, tanshinone IIB, methyl tanshinonate, crytotanshinone, tanshinone I, dihydrotanshinone I, and rosmariquinone showed marked inhibitory activities to both proteases of 3CLpro and PLpro[149]. Particularly, dihydrotanshinone I exerted powerful effects with IC_{50} values of 14.4 μmol/L regarding 3CLpro and 4.9 μmol/L regarding PLpro[149]. Furthermore, crytotanshinone exhibited the most potent nanomolar level inhibitory activity toward PLpro with an IC_{50} of 0.8 μmol/L[149]. Baicalin and baicalein, the major bioactive ingredients of Shuanghuanglian preparation, were characterized as the first noncovalent and non-peptidomimetic inhibitors of SARS-CoV-2 3CLpro, also possessed good anti-SARS-CoV-2 activity in Vero E6 cell-based system[109]. What's more, celastrol[143,144], tingenone[143], xanthoangelol E[150], and hesperetin[151] targeting 3CLpro, while hirsutenone[155], methyl tanshinoate, tanshinone I[149], xanthoangelol E[150], isobavachalcone, 4′-*O*-methylbavachalcone, psoralidin[157], and tomentin A-E[158] targeting PLpro, may have relatively strong anti-viral replication efficacy with IC_{50} below or near 10 μmol/L. Notably, the well-known anti-malarial[165], anti-tumor[166], and immune modulation[167] compound artemisinin from *Artemisia apiacea* (Qinghao), and its derivatives including arteannuin B, artesunate, dihydroartemisinin, arteether, and lumefantrine presented favorable anti-SARS-CoV-2 effects. Among these artemisinin derivatives, arteannuin B showed the highest anti-viral potential with an IC_{50} 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[137]. Significantly, lycorine from *Lycoris radiata* (Shisuan) had a powerful inhibitory effect on virus activity with an IC_{50} of 15.7 nmol/L and may serve as a candidate for the development of new anti-SARS-CoV-2 drug in the treatment of COVID-19[164]. 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 IC_{50} values ranging from 0.011 to 11.03 μmol/L. Among them, bufalin from toad venom (Chansu) exerted the antiviral effect with an IC_{50} of 18 nmol/L by targeting the ion transport function of Na^+/K^+-ATPase[139]. Theaflavin was predicted to exert anti-viral replication by inhibiting RdRp activity[130]. The binding affinities with the critical proteins of a portion of ingredients presented above were also predicted by *in silico* screening and molecular docking[124,168]. 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[169]. Except for the broad-spectrum antiviral activity, TCM process

Table 3 Potential mechanisms of TCM for COVID-19.

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) Anhydrosafflor 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 anti-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	93–95
8	Qingfei Paidu decoction	SARS-CoV-2	NP, molecular docking, molecular verification	NA	1) Exhibit the effects of immune regulation, anti-infection, anti-inflammation, 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-κB, PTGS1/2, CYP1A1, and CYP3A4 activity, and increase IL-10 expression 4) Reduce platelet aggregation.	96
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

					2) Protect pulmonary alveolar-capillary barrier and alleviate pulmonary edema 3) Regulate immune response and decrease fever	
14	Maxing Shigan decoction	SARS-CoV-2	NP, molecular docking, molecular verification	NA	1) Inhibit IL-6 mediated JAK-STAT signal pathway 2) Amygdalin is predicted to bind ACE2, 3CLpro, and RdRp	102
15	Cold-damp plague formula	SARS-CoV-2	NP, molecular docking	NA	1) Regulate free radical production and blood circulation 2) Exert antiviral, immune-regulatory, and anti-inflammatory by targeting ACE2 and IL-6	103
16	Dayuanyin	SARS-CoV-2	NP, molecular docking	NA	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-methyl, isoflavone, naringenin, and formononetin target IL-6, IL-1β, and CCL2 with high affinity	104,105
17	Reduning injection	SARS-CoV-2	Infected Vero E6 cells, CPE, NP	103.420 μg/mL	1) Exert antiviral effect 2) Regulate ACE2, 3CLpro, and PLpro activity 3) Modulate inflammation-related expressions of MAPKs, PKC, and NF-κB	106
18	Liu Shen capsule	SARS-CoV-2	Infected Vero E6 cells and Huh-7 cells, CPE, plaque reduction assay	0.6 μg/mL	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-IκBα, and p-p38 MAPK expression	107
19	Pudilan Xiaoyan oral liquid	SARS-CoV-2	Infected Vero E6 cells, CPE	1.08 mg/mL	Inhibit viral replication *in vitro* and *in vivo*	108
20	Shuanghuanglian preparation	SARS-CoV-2	1) Infected Vero cells 2) Enzyme inhibition assay	1) 0.93−1.2 μL/mL 2) 0.06−0.09 μL/mL	1) Inhibit viral replication 2) Inhibit 3CLpro activity	109
21	Yinqiao powder	SARS-CoV-2	NP, molecular docking, surface plasmon resonance (SPR) analysis	NA	Regulate TNF, T-cell receptor, Toll-like receptor, and MAPK signaling pathways	110
22	Pudilan prescription	SARS-CoV-2	NP, GSEA enrichment, molecular docking	NA	1) Prevent SARS-CoV-2 entrance by blocking ACE2 2) Inhibit cytokine storm of CRP, IFN-γ, IL-6, IL-10, TNF, EGFR, CCL5, and TGF-β1	111
23	Matrine injection	SARS-CoV-2	NP, molecular docking	NA	1) 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	112,113
24	Shenfu decoction	SARS-CoV-2	NP, molecular docking	NA	Play antiviral role through multi-component, multi-target, and multi-pathway approach, and exert anti-inflammation, immune regulation, and multi-organ protection effects	114
25	*Andrographis paniculate* (Chuanxinlian)	SARS-CoV-2	Infected Calu-3 cells, CPE	0.036 μg/mL	Exert antiviral effect	115
26	*Scutellaria baicalensis* (Huangqin)	SARS-CoV-2	1) Enzyme inhibition assay 2) Infected Vero cells, CPE	1) 8.52 mg/mL 2) 0.74 mg/mL	1) Inhibit 3CLpro activity 2) Exert antiviral effect	116
27	*Rheum officinale* (Yaoyong Dahuang)	SARS-CoV	Infected Vero E6 cells, CPE, biotinylated ELISA	1−10 μg/mL	Block spike−ACE2 interaction	117

(*continued on next page*)

Table 3 (*continued*)

No.	TCM	Coronavirus	Model/method	IC_{50} (EC_{50}) or dosage	Potential mechanism	Ref.
28	*Polygonum multiflorum* (Heshouwu)	SARS-CoV	Infected Vero E6 cells, CPE, Biotinylated ELISA	1–10 μg/mL	Block spike–ACE2 interaction	117
29	*Houttuynia cordata* (Yuxingcao)	SARS-CoV	Flow cytometry, ELISA, enzyme inhibition assay, etc.	0–800 μg/mL	1) Stimulate the proliferation of mouse splenic lymphocytes 2) Increase the proportion of $CD4^+$ and $CD8^+$ T cells 3) Increase in the secretion of IL-2 and IL-10 in mouse splenic lymphocytes 4) Inhibit 3CLpro and RdRp activity	118
30	*Rheum palmatum* (Zhangye Dahuang)	SARS-CoV	Enzyme inhibition assay	13.76 μg/mL	Inhibit 3CLpro activity	119
31	*Cibotium barometz* (Gouji)	SARS-CoV	1) Infected Vero E6 cells, CPE 2) Enzyme inhibition assay	1) 8.42 μg/mL 2) 39 μg/mL	1) Inhibit viral replication 2) Inhibit 3CLpro activity	120
32	*Dioscorea batatas* (Shanyao)	SARS-CoV	1) Infected Vero E6 cells, CPE 2) Enzyme inhibition assay	1) 8.06 μg/mL 2) 44 μg/mL	1) Inhibit viral replication 2) Inhibit 3CLpro activity	120

advantages in regulating immune response, suppressing cytokine storm through multiple avenues[170–172]. Beyond inhibiting virus replication, Lianhua Qingwen capsule[89] 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[90]. 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[101]. As same as Maxing Shigan decoction, Qingfei Paidu decoction showed multiple immune regulation, anti-inflammation, and lung injury–repair activities with its main ingredients of baicalin, glycyrrhizin, hesperidin, and hyperoside by targeting proteins including TNF-α, IL-6, IL-10, and CCL2[93–96]. Furthermore, several ingredients such as baicalin and glycyrrhizin of Qingfei Paidu decoction could inhibit platelet aggregation[96]. Dayuanyin 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[63,104]. 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[54], Yidu-toxicity blocking lung decoction[62], Qingfei Touxie Fuzheng recipe[67], and diammonium glycyrrhizinate[70] 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[137], 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[183] (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 cytotoxins[42,184–189]. Xuebijing injection

Table 4 Potential mechanisms of TCM ingredients for COVID-19.

No.	TCM ingredient	Source	Coronavirus	Model/method	IC_{50} (EC_{50}) 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* (Yingxing)	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) Infected Vero E6 cells, CPE 2) Enzyme inhibition assay	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	*Lithospermum 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) Molecular docking 2) Infected Vero cells	7.91 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 Vero-E6 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*)

Table 4 (*continued*)

No.	TCM ingredient	Source	Coronavirus	Model/method	IC_{50} (EC_{50}) or dosage	Potential mechanism	Ref.
						TNF-α, IL-6, IL-1β, MCP-1, and IP-10 3) Suppress NF-κB signaling pathway	
23	Catechin	Green tea	SARS-CoV-2	Molecular docking	Unclear	Bind to 3CLpro, cathepsin L, RBD of S protein, NSP6, and nucleocapsid protein	131,136
24	Artemisinin	*Artemisia annua* (Qinghao)	SARS-CoV-2	Infected Vero E6 cells, CPE	64.45 μmol/L	Inhibit viral replication	137
25	Artesunate	Artemisinin derivative	SARS-CoV-2	Infected Vero E6 cells, CPE	12.98 μmol/L	Inhibit viral replication	137
26	Cepharanthine	*Stephania japonica* (Qianjinteng)	SARS-CoV-2	Infected Vero E6 cells, CPE	0.98 μmol/L	Inhibit viral entry and 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	*Brucea 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 Vevo E6 cells, CPE	31.3−250 μmol/L	Target two-pore channel 2	140
30	Andrographolide	*Andrographis paniculate* (Chuanxinlian)	SARS-CoV-2	Infected Calu-3 cells, CPE	0.034 μmol/L	Exert antiviral effect	115
31	Glycyrrhizin + vitamin C	*Glycyrrhiza uralensis* (Gancao)	SARS-CoV-2	NP	Unclear	Elevate immunity and suppress inflammatory stress	141
32	Chlorogenic acid	*Lonicera 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	Tingenone	*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	149
40	Xanthoangelol E	*Angelica keiskei* (Mingriye)	SARS-CoV	Enzyme inhibition assay	11.4 μmol/L	Inhibit 3CLpro activity	150
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 3CLpro activity	153,154
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

47	Crytotanshinone	*Salvia miltiorrhiza* (Danshen)	SARS-CoV	Enzyme inhibition assay	0.8 μmol/L	Inhibit PLpro activity	149
48	Dihydrotanshinone I	*Salvia miltiorrhiza* (Danshen)	SARS-CoV	Enzyme inhibition assay	4.9 μmol/L	Inhibit PLpro activity	149
49	Xanthoangelol E	*Angelica keiskei* (Mingriye)	SARS-CoV	Enzyme inhibition assay	1.2 μmol/L	Inhibit PLpro activity	150
50	Terrestrimine	*Tribulus terrestris* (Cijili) *fruits*	SARS-CoV	Enzyme inhibition assay	15.8 μmol/L	Inhibit PLpro activity	156
51	Isobavachalcone	*Psoralea corylifolia* (Buguzhi) seeds	SARS-CoV	Enzyme inhibition assay	7.3 μmol/L	Inhibit PLpro activity	157
52	Psoralidin	*Psoralea corylifolia* (Buguzhi) seeds	SARS-CoV	Enzyme inhibition assay	4.2 μmol/L	Inhibit PLpro activity	157
53	Tomentin A-E	*Paulownia tomentosa* fruits (Maopaotong)	SARS-CoV	Enzyme inhibition assay	5.0–12.5 μmol/L	Inhibit PLpro activity	158
54	Glycyrrhizin	*Glycyrrhiza uralensis* (Gancao)	SARS-CoV	Infected Vero cells, CPE	0.3 mg/mL	Inhibit virus replication	159–161
55	Cepharanthine	*Stephania japonica* (Qianjinteng)	SARS-CoV	Infected Vero E6 cells, CPE	6.0–9.5 μg/mL	Exert antiviral effect	162
56	Ginsenoside Rb1	*Panax ginseng* (Renshen)	SARS-CoV	Infected Vero E6 cells, CPE	100 μmol/L	Exert antiviral effect	163
57	Aescin	*Aesculus chinensis* (Qiyeshu)	SARS-CoV	Infected Vero E6 cells, CPE	6.0 μmol/L	Inhibit viral replication	163
58	Reserpine	*Ophiorrhiza japonica* (Shegencao)	SARS-CoV	Infected Vero E6 cells, CPE	3.4 μmol/L	Inhibit viral replication	163
59	Lycorine	*Lycoris radiata* (Shisuan)	SARS-CoV	Infected Vero E6 cells, CPE	15.7 nmol/L	Exert antiviral effect	164

was able to improve the oxygenation index of PaO_2/FiO_2 and reduce the level of pro-inflammatory cytokines of TNF-α, IP-10, MIP-1β, and RANTES in the treatment of COVID-19[42,43]. 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[190–193]. 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[194–199]. 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[96].

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, antioxidant stress, anti-apoptosis, and anti-pulmonary fibrosis were summarized and categorized. According to their chemical structures, these were divided into flavonoids (*e.g.*, luteolin, baicalein), 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)[200]. In addition, a systematic review and meta-analysis of 19 eligible RCTs including Tanreqing injection, Shengmai injection, Shenfu injection, Danshen injection, Reduning injection, and Xuebijing injection demonstrated that Chinese medicine injections were adjuvant therapy with great potential benefits for the treatment of ALI/ARDS[33]. 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 PaO_2, Tanreqing injection was proved to improve lung injury, pulmonary infection, airway inflammation, and airway mucus hypersecretion[201–204]. Reduning injection was demonstrated to prevent pulmonary neutrophil infiltration, lung injury and severe pneumonia which may attribute to downregulating IL-1β, IL-18, TNF-α, NF-κB, and pyrin domain containing 3 levels, lowering myeloperoxidase activities, and reducing reactive oxygen species production[205–207]. Xiyanping injection, a famous Chinese medicinal preparation of andrographolide sulfonate, 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[208,209]. Besides, Xiyanping injection and Reduning injection were used to treat diarrhea in children. Xiyanping injection could ameliorate colitis by inhibiting Th1/Th17 response in mice[210].

Cardiovascular disease is a high frequent comorbidity and complication of COVID-19. Three Chinese injection medicines including Shenfu injection, Shengmai injection, and Shenmai injection, have both pulmonary and cardiac protective effects. For instance, Shenfu 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[211–221]. Moreover, Shenfu injection has a protective effect on gastrointestinal tract and intestinal mucosa[222,223]. Xingnaojing injection and Angong Niuhuang pill are different preparations share similar ingredients for stroke treatment in clinic. Both of them ameliorate cerebral

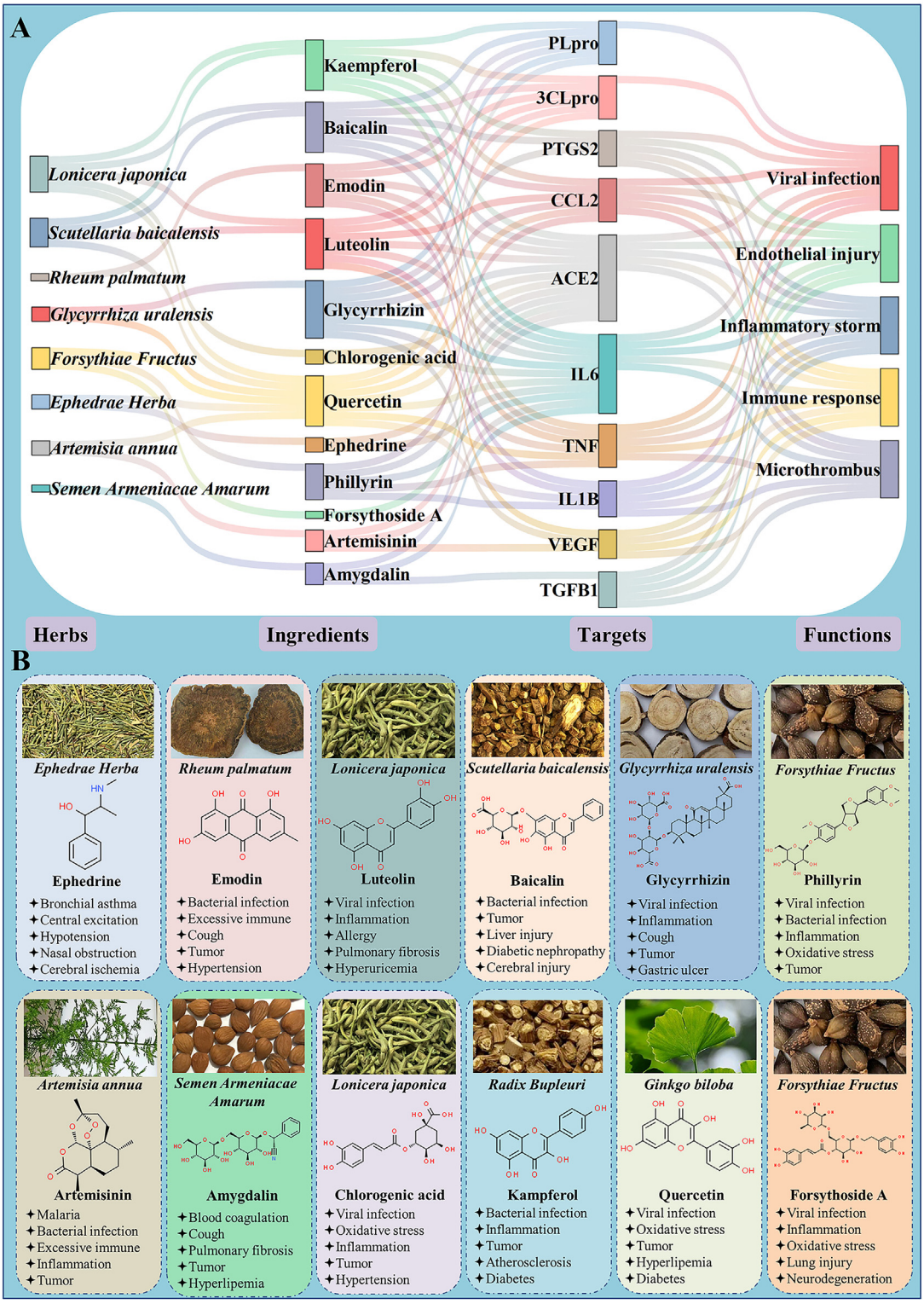

Figure 2 Representative herbs and their main active ingredients and functions for COVID-19. (A) The herb-ingredient-target-function network of frequently used herbs and their main ingredients, as well as their key targets and functions for COVID-19. (B) The chemical structures of main active ingredients and their main functions of commonly used herbs for COVID-19.

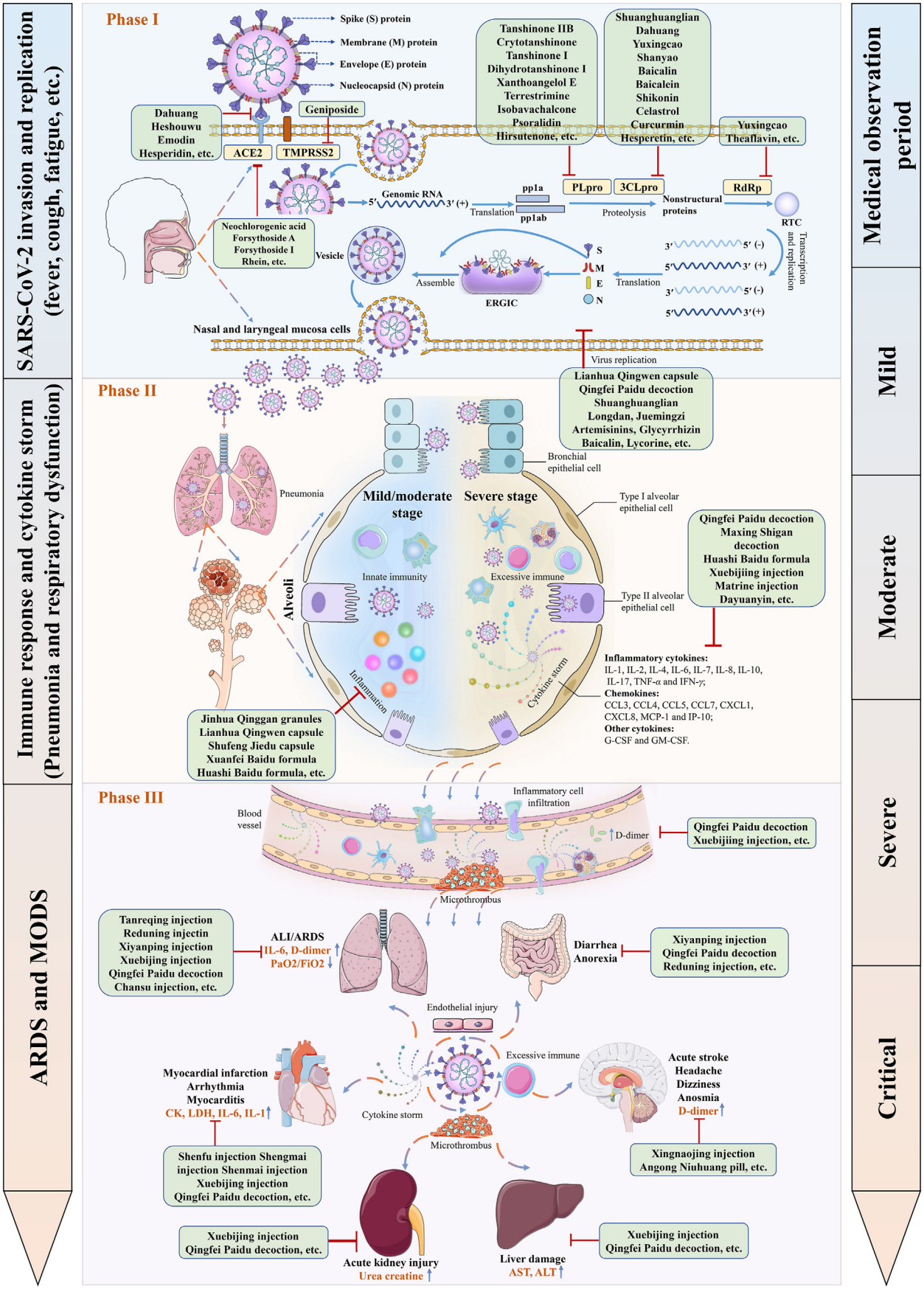

Figure 3 An overview of pathogenesis of COVID-19 and the potential mechanisms of TCM remedy in distinct disease stages.

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[224−231].

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 Amarum* (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[3,81,232]. Herb−ingredient−target−function action network is established to elucidate the potential mechanisms of the frequently used herbs for COVID-19. In this relationship network, 8 commonly used herbs, 12 main ingredients, 10 key targets and 5 pivotal functions are involved, as shown in Fig. 2A. The portraits of commonly used herbs, chemical structures of ingredients, and main functions are illustrated in Fig. 2B.

Gut microbiome is involved in disease severity and host inflammatory and immune responses in COVID-19 patients[233]. It is worth noting that the anti-COVID-19 effects and mechanisms of TCM may be exerted *via* the gut−lung axis and mediated by gut microbiota[234−236]. For example, short-term intervention of Qingfei Paidu decoction dose-dependently regulates the host metabolism and gut microbiome in rats, indicating that altering gut microbiota composition may be part of the anti-COVID-19 mechanisms of Qingfei Paidu decoction[237]. It is of particularly significance to consider that the solubility and bioavailability of certain TCM ingredients, such as resveratrol, quercetin, baicalin, curcumin, emodin, and tanshinone IIA, are limited, leading to poor absorption into the bloodstream after oral administration. These ingredients may exert their therapeutic effects though interplaying with gut microbiota[238]. For instance, resveratrol could also alleviate intestinal inflammation and oxidative damage by modulating the composition of gut microbiota in addition to the direct antiviral effect[239]. What's more, to improve the bioavailability, a nano-micellar form of curcumin was used to decrease IL-6 and IL-1β expression and secretion in patients with COVID-19[240].

In summary of preclinical evidence, the anti-COVID-19 effects and mechanisms of TCM include but not limited to 1) inhibiting SARS-CoV-2 invasion 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[13,14,19,23,25,35,71,87,168,171,241−277], 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[71,249]. 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 skepticisms on the validity of treating COVID-19 with TCM[278−280]. 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[281,282]. 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[283].

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 Guangxu 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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