

“Three medicines and three formulas” in COVID-19: from bench to bedside

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Abstract

Chinese guideline has proven effective in the fight against coronavirus disease 2019 (COVID-19) during the global spread of the epidemic. Traditional Chinese medicine (TCM) is widely recognized for its effectiveness in alleviating symptoms, inhibiting disease progress, reducing mortality, and improving the cure rate of patients with COVID-19. During the pandemic, “three medicines and three formulas” (TMTFs) stood out from hundreds of others in registered clinical studies, which became highly recommended as TCM for COVID-19 treatment. The TMTFs not only effectively relieve the clinical symptoms of fever, cough, fatigue, and phlegm, but also substantially shorten the time of nucleic acid negative conversion, improve lung computed tomography imaging features and inflammation, ameliorate clinical biochemical indicators, and reduce sequelae. Their potential pharmacological mechanisms are mainly related to the crosstalk between viral toxicity, endothelial damage, cytokine storm, immune response, and microthrombus. In brief, the clinical effects and the potential mechanisms of TMTFs on COVID-19 were systematically analyzed and summarized covering the entirety of disease development, including virus invasion and replication, immune response and cytokine storm, and acute respiratory distress syndrome and multiple organ dysfunction syndrome. This review provides a theoretical basis and reference for the in-depth understanding of the positive role of TMTFs in COVID-19 treatment.

Keywords: Clinical research, COVID-19, Potential mechanism, SARS-CoV-2, Three medicines and three formulas

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Introduction

Coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared a public health emergency of international concern by the World Health Organization (WHO) on January 30, 2020. As an infectious disease, COVID-19 is highly contagious and has a wide range of symptoms, ranging from mild symptoms of fever, cough, and fatigue to severe symptoms of acute respiratory distress syndrome (ARDS) and multiple organ dysfunction syndrome (MODS)^[1-2]. In response to this sudden outbreak, without specific antiviral treatments for COVID-19, China quickly implemented policies of early detection, early quarantine,

and early treatment, and integrated traditional Chinese and Western medicine, which have been proved effectively^[3-4]. Such as traditional Chinese medicine (TCM) has attracted considerable attention from the international community.

Early TCM intervention can effectively prevent mild patients from becoming severe^[5-6]. For patients with severe COVID-19, treatment with TCM can recovery time by relieving symptoms^[6-7]. On January 22, 2020, *the Diagnosis and Treatment Protocol for COVID-19 (Trial Version 3)*, promulgated by the National Health Commission (NHC) of the People’s Republic of China, was the first to incorporate and recommend TCM for COVID-19 treatment. With the update and promulgation of *the Diagnosis and Treatment Protocol for COVID-19*, Jinhua Qinggan granules (JHQG) and Lianhua Qingwen capsule (LHQW) were recommended for fever, fatigue, and other symptoms of COVID-19 patients during clinical observation. Xuanfei Baidu formula (XFBD) and Huashi Baidu formula (HSBD) summarized in the guidelines regarding clinical treatment, can be prescribed to treat patients with COVID-19 experiencing mild and moderate symptoms. Xuebijing injection (XBJ) was recommended for the treatment of those with severe disease and in critical pathological stages, whereas Qingfei Paidu decoction (QFPD) can be used to treat patients with mild to critical diseases. JHQG, LHQW, XBJ, QFPD, XFBD, and HSBD are collectively known as the three medicines and three formulas (TMTFs). In this review, the clinical effects, and pharmacological mechanisms of the TMTFs on COVID-19 were systematically reviewed and summarized with the aim of providing a deeper understanding of the principles and characteristics of TCM in the treatment of COVID-19.

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TMTFs for different COVID-19 stages

Devastating epidemics have long swept across the world, including China. However, epidemics in China have been brought under control soon after outbreaks, while the Black Death and Spanish Flu, which killed millions of people in other countries. TCM has been used to prevent and treat conventional diseases and epidemics in China, gradually forming a complete and effective theoretical system for epidemic response through hundreds of successful experiences^[8-9]. Chinese herbs containing anti-viral active ingredients have been recorded in ancient TCM books^[10]. Since the early 2000s, TCM has often been used for the prevention and treatment of pandemics, such as severe acute respiratory syndrome caused by SARS-CoV in 2003, Middle East respiratory syndrome caused by Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012, and seasonal epidemics caused by influenza viruses and dengue virus^[11-12]. They not only verify the effectiveness of the theoretical TCM system in preventing and controlling epidemics but also increase our understanding of epidemics caused by viruses.

COVID-19 poses a serious threat to the health and safety of people worldwide. Due to its infectivity, symptoms, and climatic factors at the time of the outbreak, COVID-19 is classified as a “dampness–toxin pestilence” according to TCM theory^[13]. The pathogenesis of COVID-19 is generally thought to involve an interaction between dampness, heat, toxin, deficiency, and stasis. Under the basic principle of “reinforcing *qi* and eliminating pathogens,” with TCM, different treatment methods are adopted for different disease stages

(Figure 1). During the medical observation period, for cases experiencing fatigue, fever, and other symptoms, the use of Chinese patent medicines such as JHQQ and LHQW is recommended. In the mild stage after diagnosis, clinical symptoms include fever, fatigue, cough, myalgia, nausea, and vomiting. The cold–damp constraint and damp–heat accumulation in the lung are the main patterns, for which strategies should be adopted to disperse the lung remove pathogenic factors, and resolve turbidity with aroma. In the middle stage, the main patterns are dampness–toxin constraint in the lung and cold–damp obstructing the lung, and most of them have symptoms such as fever, expectoration, dyspnea, constipation, and diarrhea. Therefore, it is necessary to eliminate heat and dampness, detoxification, and invigorate spleen. In mild and moderate stages, JHQQ, LHQW, QFPD, XFBD, and HSBD are recommended. In the severe stage, owing to the further invasion of the lungs by the pestilent toxin and the serious injuries to the *qi* and blood by pathogenic heat, the patient develops high fever, dyspnea, hematemesis, and even unconsciousness. TCM states that while eliminating heat and dampness, and detoxification, it should tonify *qi* and *Yin*, should be tonified, and lung *qi* should be ventilated to relieve lung and heart dysfunction. Therefore, the use of XBJ, QFPD, and HSBD is recommended to tonify *qi* and *yin* For critically ill patients with multiple organ failure or shock, TCM practitioners mainly suggests the methods of tonifying *qi*, preventing exhaustion, cooling blood, nourishing *yin*, invigorating *qi*, strengthening *yang*, and restoring consciousness. At this stage, XBJ which recuperates collapsed *yang* and *qi* and

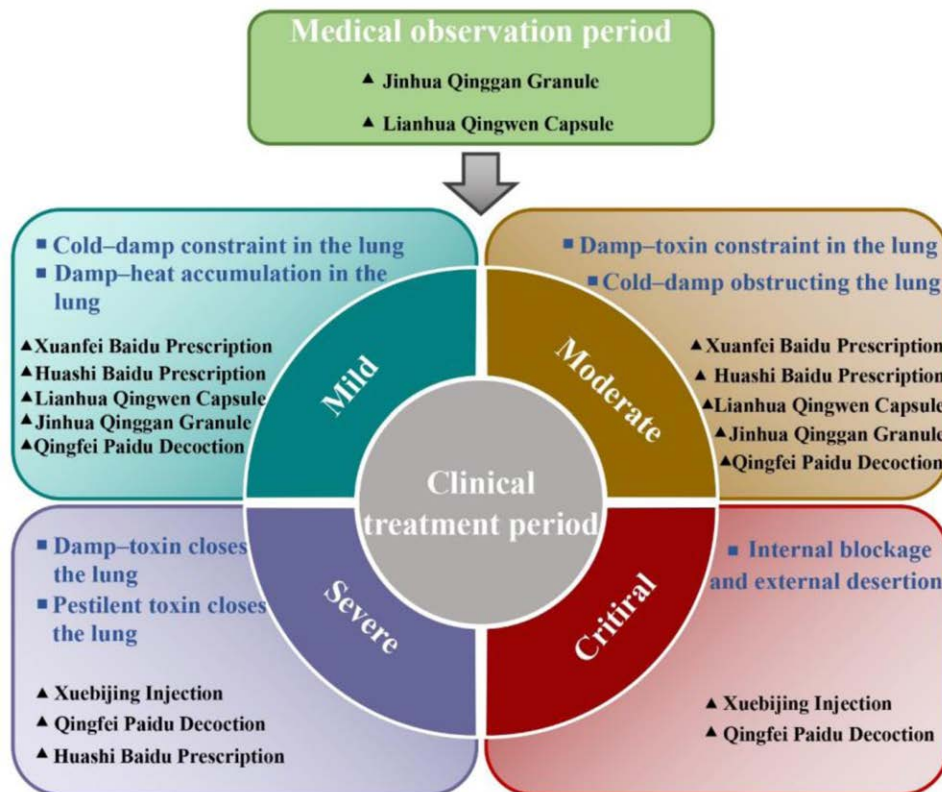


Figure 1. Main TCM patterns and recommended “TMTFs” for the treatment of the different stages of COVID-19. COVID-19: Coronavirus disease 2019; TCM: Traditional Chinese medicine; TMTFs: Three medicines and three formulas.

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restores consciousness, is recommended^[14-15]. The above describes the main TCM strategy to let the body's own immune function fight COVID-19 by regulating the damaged balance in the body; "syndrome differentiation and treatment" is a characteristic of and advantage provided by TCM.

Clinical studies of TMTFs for COVID-19 treatment

Since the outbreak of the pandemic, the NHC has successively issued ten versions of the Diagnosis and Treatment Protocol for COVID-19 to enable a more effective response, and the effectiveness of TCM in the treatment of COVID-19 has been proven^[13]. Figure 2 shows the Venn and chord diagrams drawn to present the common herbs shared in the TMTFs. The typical Clinical characteristics, including clinical symptoms, lung features, and laboratory findings of the TMTFs for COVID-19 treatment are presented in Figure 3.

Clinical studies of TMTFs in the treatment of mild-to-moderate with COVID-19

During the 2009 H1N1 pandemic, JHQG was developed by the expert group of TCM combined with two classical recipes, Maxing Shigan decoction and Yinqiao san, and it is very effective in the treatment of H1N1 influenza^[16]. JHQG dispels wind, disperses the lungs, clears heat, and detoxifies^[17-18]. Treatment with JHQG granules can substantially improve the clinical symptoms of fever, cough, fatigue, sputum, sore throat, dyspnea, headache, nasal obstruction, and expectoration patients with mild-to-moderate COVID-19^[17,19]. In a randomized clinical trial (RCT), JHQG treatment was found to relieve symptoms such as fever, fatigue, diarrhea, and especially fever and loss of appetite^[17]. When using JHQG with Western medicine, the use of antibiotics can be reduced to a certain extent^[17]. In addition,

JHQG treatment can effectively shorten the negative conversion time of the nucleic acid test and alleviate the inflammatory exudation of pneumonia in patients with COVID-19^[18].

LHQW, which was patented in China in 2003, has broad-spectrum anti-viral, anti-bacterial, and anti-inflammatory effects, and is commonly used in the treatment of influenza A and B^[20-21]. During the fight against COVID-19, LHQW showed excellent therapeutic effects and was included in the *Diagnosis and Treatment Protocol for COVID-19* (Trial Version 6) by the NHC in February 2020. LHQW was recommended for the treatment of patients with mild-to-moderate COVID-19 and can effectively mitigate the clinical symptoms of fever, cough, and fatigue, and increase the clinical cure rate^[22-23]. Clinical studies have found that LHQW evidently improved chest computed tomography (CT) findings and shortened the duration of clinical symptoms in patients with COVID-19^[24]. A meta-analysis of 217 experimental studies showed that treatment with LHQW substantially reduced the incidence of respiratory system injury, skin and accessory injury, nervous system injury, gastrointestinal system injury, and other adverse reactions in patients with COVID-19^[25]. In addition, LHQW is often clinically used in combination with other anti-viral drugs for the treatment of COVID-19. For example, LHQW in combination with ribavirin^[26], lopinavir/ritonavir^[27], and umifenovir^[28] can be the first choice of the treatment for patients with severe COVID-19 patients. When combined with macrolide antibiotics, Huoxiang Zhengqi dropping pills, treat nausea, vomiting, and limb soreness^[26], not only decrease the use of antibiotics but also reduce the progression of COVID-19 cases to severe disease^[26]. In a retrospective analysis of a large population-based cohort study, LHQW had a strong therapeutic effect on reducing the positive rate of COVID-19^[29].

XFBD is the first newly formulated TCM recipe for the treatment of COVID-19 and is improved from

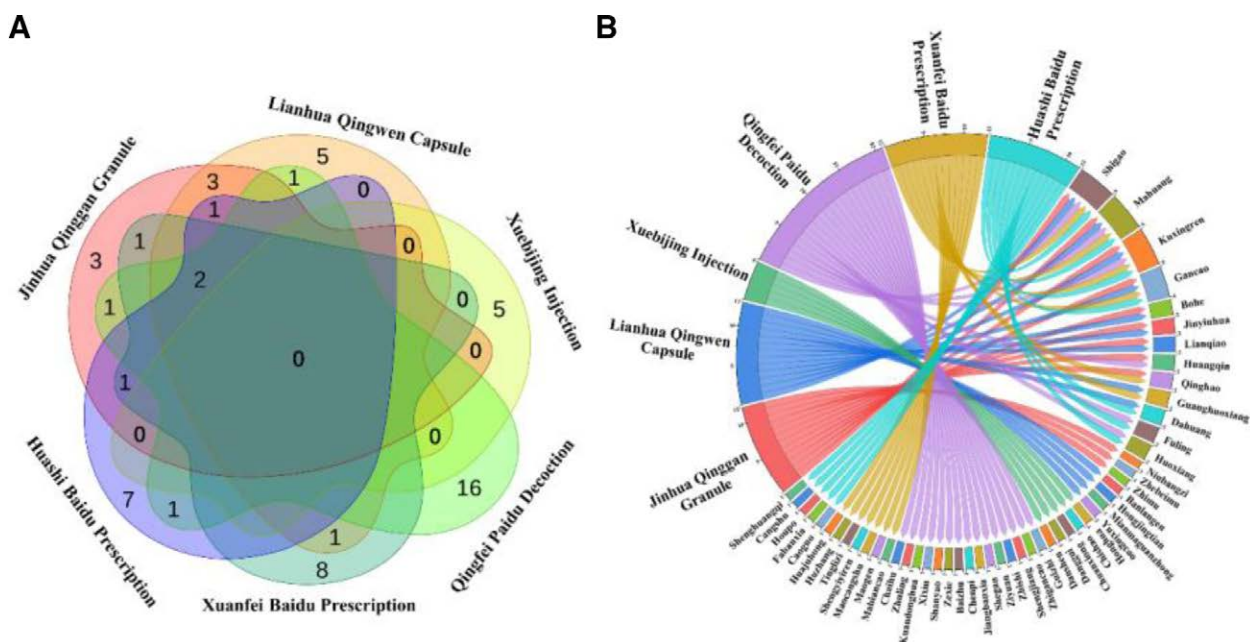


Figure 2. Herb distributions of TMTFs: (A) Venn and (B) Chord diagrams of the herbs present in the TMTFs. TMTFs: Three medicines and three formulas.

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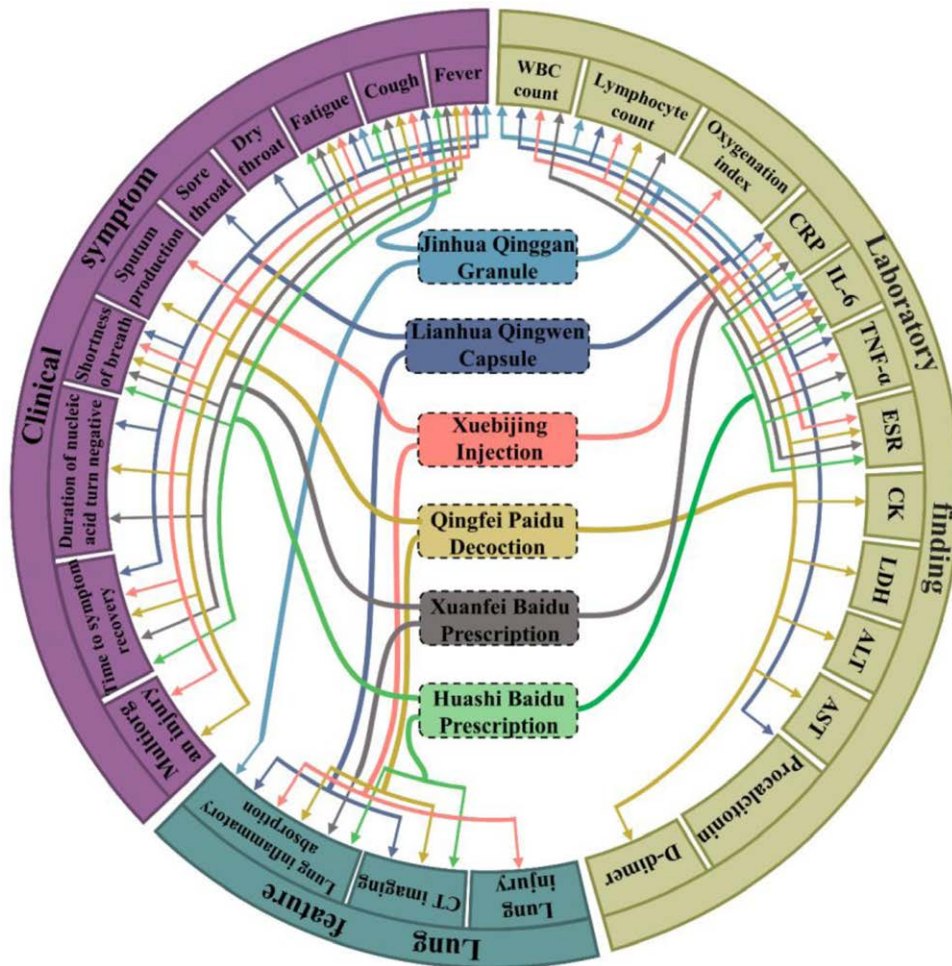


Figure 3. Clinical efficacy of the TMTFs against typical characteristics of COVID-19. AST: Aspartate aminotransferase; ATL: Adult T cell leukemia; CK: Serum creatine kinase; COVID-19: Coronavirus disease 2019; CRP: C-reactive protein; CT imaging: Computed tomography imaging; ESR: Erythrocyte sedimentation rate; IL-6: Interleukin-6; LDH: Lactate dehydrogenase; TMTFs: Three medicines and three formulas; TNF- α : Tumor necrosis factor- α ; WBC: White blood cell.

classic formulas such as Maxing Shigan decoction, Maxing Yigan decoction, Qianjin Weigan decoction and Tingli Dazao Xiefei decoction^[16]. The monarch medicines of XFBD are *Polygoni Cuspidata Cuspidati* Rhizoma (Huzhang) and *Verbenae Herba* (Mabiancao). Some Chinese herbs in this formula are effective in treating previous coronavirus infections. Among them, *Polygoni Cuspidata Cuspidati* Rhizoma (Huzhang) has the strongest anti-coronavirus effect, whereas *Verbenae Herba* (Mabiancao) has a strong therapeutic effect on the small airway injury and microthrombus caused by coronaviruses. XFBD is a prescription recommended by the Diagnosis and Treatment Protocol for COVID-19 (Trial Version 8) for the pattern of damp-toxin accumulation in the lungs, and is suitable for patients with mild and moderate symptoms of COVID-19. Clinical studies have confirmed that XFBD treatment can ameliorate fever, cough, fatigue, and other symptoms in patients with COVID-19 and decrease the conversion rate of mild/moderate to moderate/severe cases^[30]. Moreover, in an RCT of 42 patients with COVID-19, XFBD combined with conventional therapy considerably alleviated clinical symptoms such as fever, cough, fatigue, confusion, and loss of appetite; increased the number of leukocyte and lymphocytes, and reduced the

C-reactive protein content and erythrocyte sedimentation rate^[31].

Clinical studies of TMTFs in the treatment of severe-to-critical patients with COVID-19

As the only injection in the TMTFs, XBJ is widely used in clinical practice to treat systemic inflammatory response syndrome and MODS^[32–33]. Based on a large amount of clinical evidence, XBJ has significant anti-inflammatory, anti-viral, bacteriostatic, and immune-regulating effects, it has been included in *the Diagnosis and Treatment Protocol for COVID-19 (Trial Version 5)* to treat COVID-19 patients with severe or even critical illness^[34–35]. After 42 patients with COVID-19 were treated with XBJI combined with routine treatment, the body temperature, time to negative nucleic acid test, lung CT feature, and interleukin-6 (IL-6) levels were remarkably improved^[36]. In addition, in a randomized controlled trial of 710 patients with severe COVID-19, XBJ substantially improved the primary endpoint of the pneumonia severity index, as well as secondary clinical outcomes such as mortality, duration of mechanical ventilation, and total length of stay in intensive care unit (ICU)^[37]. In another study of 675 patients, XBJ exhibited higher efficacy in

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the treatment of severe community-acquired pneumonia, particularly those presenting with elevated lymphocyte and diminished neutrophil counts^[38]. XBJ substantially enhances the conversion of severe patients with severe COVID-19 to moderate, while also decreasing the rate of conversion from severe to critical disease^[39]. In conclusion, multitudinous clinical studies have revealed that XBJ can effectively improve the clinical symptoms of patients with severe COVID-19, such as fever, cough, fatigue and shortness of breath, and reduce the mortality of severe patients by inhibiting inflammatory factor storm and restoring blood oxygen levels^[40–41]. A retrospective case series showed that a four-drug combination of Huashi Baidu granules with Xiyanping, Xuebijing, and Shenmai injections was effective for SARS-CoV-2 RNA clearance, promoted lung lesion opacity, and reduced inflammation in severe patients with severe COVID-19^[42]. A clinical study of 640 patients demonstrated that XBJ can improve the renal function of patients with sepsis and kidney injury; its therapeutic effect was considerably stronger than that of Western medicine, demonstrating clinical application value^[43].

HSBD, which is an improvement over the classic formula, is recommended by *the Diagnosis and Treatment Protocol for COVID-19 (Trial Version 7)* to treat severe epidemic toxins that block lung syndrome^[44]. The results of an unblinded cluster-RCT suggested that HSBD, combined with conventional treatment could prevent the deterioration of the condition of patients with mild COVID-19^[7]. For severe patients with severe COVID-19, HSBD had the positive effect of shortening the time required to relieve blood oxygen saturation in a single-center retrospective cohort study^[9]. In a single-center, open-label, randomized controlled trial of 204 patients with COVID-19, HSBD substantially improved symptoms such as fever, cough, fatigue, and lung CT findings, and did not cause observed serious adverse events^[45]. Furthermore, the findings of a retrospective cohort study conducted at a single center have revealed that HSBD treatment notably reduced the duration until negative nucleic acid conversion and the length of hospitalization in patients infected with the SARS-CoV-2 Omicron variant^[46–47]. In addition, HSBD can enhance the therapeutic effect of lopinavir-ritonavir on COVID-19, and it can also show advantages when used in combination with TCM injections to treat COVID-19, especially by shortening the clinical remission time^[48–49].

Clinical study of TMTFs in the treatment of all stages of patients with COVID-19

QFPD comprises four classic TCM prescriptions: the Maxing Shigan decoction, Shegan Mahuang decoction, Xiaochaihu decoction, and Wuling powder^[50]. The QFPD recommended by *the Diagnosis and Treatment Protocol for COVID-19 (Trial Version 6)* showed significant efficacy in the clinical treatment of patients with COVID-19^[51–52]. During the clinical efficacy observation of 214 patients with COVID-19 in Shanxi, Hebei, Heilongjiang, and Shaanxi provinces of China, the total efficacy rate of QFPD was higher than 90%^[53]. More than 60% of the patients showed notable improvement in clinical symptoms and imaging manifestations, and

30% experienced stable symptoms without aggravation^[53]. In a retrospective multi-center cohort study of 782 patients with COVID-19 administered QFPD treatment, the results indicated that the earlier QFPD intervention was initiated after symptom onset, the greater the likelihood of recovery, the faster the recovery, the shorter the time to viral shedding, and the shorter the hospitalization^[51]. Furthermore, QFPD reduced COVID-19 inpatient-related mortality by 50% with no additional risk of acute liver injury or acute kidney injury, according to the results of a national retrospective registry study^[52]. Clinically, QFPD is often used in combination with Western medicine. Compared with Western medicine alone, QFPD can markedly alleviate the patient's pulmonary inflammation, reduce the length of hospital stay, and improve clinical symptoms and lung CT^[54]. Notably, no serious adverse reactions related to QFPD were observed^[55]. As the only TCM therapy for the treatment of all stages of COVID-19, QFPD has cured thousands of COVID-19 patients and also prevented the transition of patients from mild to severe stage^[56]. Additionally, QFPD combined with Western medicine treatments reduced the symptom aggravation rate, increased clinical efficacy, shortened the durations of viral shedding and hospital stay, and decreases adverse events^[57]. A recent systematic review and meta-analysis that included 15 studies with 10,390 patients have shown that QFPD could substantially improve the cure rate and improve the lung CT of patients with COVID-19, reduce the number of patients progressing to a critical condition or death, shorten the time for nucleic acid test conversion and the length of hospital stay, change laboratory indices, and quickly relieve symptoms without adverse effects^[58].

Potential mechanisms through which TMTFs treat COVID-19

The occurrence and development of COVID-19 can be divided into three main stages; SARS-CoV-2 invasion and replication, immune response and cytokine storm, and ARDS and MODS. The crosstalk between viral toxicity, vascular endothelial cell injury, cytokine storm, immune response, and microthrombus is an important factor in the pathogenesis and exacerbation of COVID-19^[13]. Although clinical studies have shown that TMTFs can be used to effectively treat COVID-19 at distinct stages, their mechanism of action remains unclear. Therefore, we reviewed and summarized the relevant literature to clarify the mechanisms through which TMTFs function in the prevention and treatment of COVID-19, as shown in Figure 4.

Potential mechanisms through which TMTFs affect SARS-CoV-2 invasion and replication

JHQG is recommended for the treatment of patients with mild to moderate COVID-19. Patients with mild COVID-19 are in the initial stage of infection, which is dominated by viral invasion and replication^[13]. SARS-CoV-2 invades host cells through interaction with the receptor-binding domain (RBD) of the spike (S) protein and human angiotensin-converting enzyme 2 (ACE2),

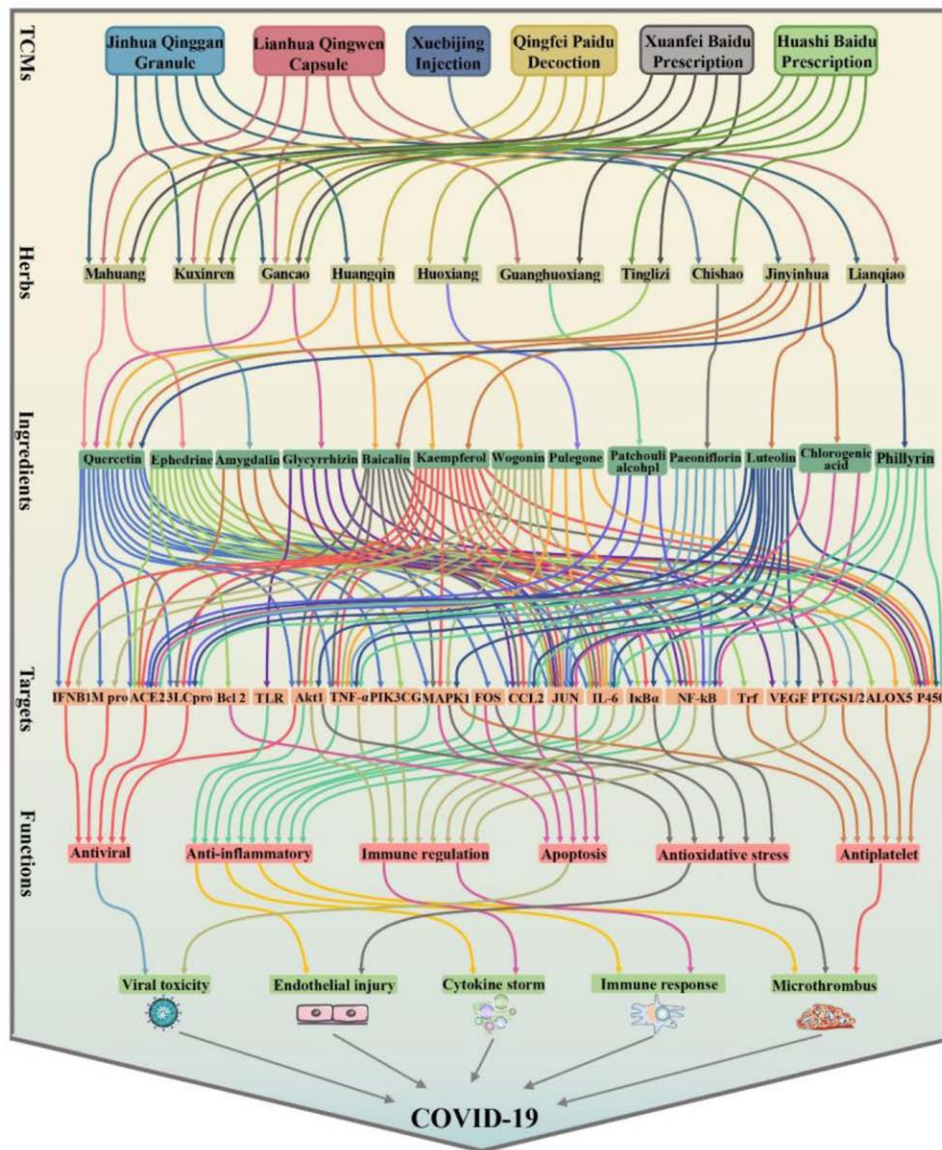


Figure 4. The herb–ingredient–target–function network of frequently used herbs in TMTFs, main ingredients, key targets, and functions against COVID-19. COVID-19: Coronavirus disease 2019; TCM: Traditional Chinese medicine; TMTFs: Three medicines and three formulas.

which initiates transcription and replication^[59]. The results of network pharmacology analysis showed that JHQG down-regulates the expression of ACE2 by regulating transcription factors (TFs) and microRNAs (miRNAs), which could be attributed to its active ingredients such as quercetin, glabridin, and chrysoeriol^[60]. The results of network pharmacology and molecular docking revealed that the active ingredients in JHQG such as kaempferol, baicalin, and oroxylin A have a strong ability to bind with ACE2 and can regulate a variety of targets such as prostaglandin-endoperoxide synthase 1 (PTGS1), prostaglandin-endoperoxide synthase 2 (PTGS2), B cell lymphoma/leukemia-2 (BCL2), heat shock protein 90 kDa alpha B1 (HSP90AB1), heat shock protein 90 kDa alpha A1 (HSP90AA1), nuclear receptor coactivator 2 (NCOA2), and caspase-3 (CASP3)^[16]. In addition, the results of informatics analysis reveal that the *Scutellariae Radix* (Huangqin), *Anemarrhenae Rhizoma* (Zhimu), and *Arctii Fructus* (Niubangzi) in JHQG can inhibit the transcription

and replication of SARS-CoV-2 through 3C-like protease (3CL^{pro}), which is a key enzyme in mediating viral replication^[61].

As a broad-spectrum anti-viral medicine, LHQW mainly exerts therapeutic effects through anti-viral, anti-inflammatory, and immune regulation, especially during COVID-19 treatment^[21]. In the initial stage of the disease, LHQW mainly prevents the replication of SARS-CoV-2 *via* blocking the combination of SARS-CoV-2 and ACE2 and inhibiting the activation of 3CL^{pro}. The blocking of the binding of SARS-CoV-2 to ACE2 is mainly related to the actions of Chinese herbs such as *Lonicera japonica* Thunb (Jinyinhua), *Forsythia suspensa* (Lianqiao), and *Radix Glycyrrhizae* (Gancao), whereas *Rheum officinale* (Dahuang) and *Houttuynia cordata* Thunb (Yuxingcao) mainly inhibit the activation of 3CL^{pro}^[21,45]. Based on the results of network pharmacology and molecular docking, it has been revealed that forsythin, forsythoside A, neochlorogenic acid, and other active ingredients in LHQW were found to have

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signaling pathway, which is one of the key links in the treatment of severe patients with COVID-19^[40,68]. TCM network pharmacology study has indicated that anhydrosafflor yellow B (AHSYB), salvianolic acid B (SAB), and rutin can combine with crucial COVID-19 proteins and play a role in anti-inflammatory, anti-viral, and immune responses in the treatment of COVID-19^[76].

Treatment with QFPD can inhibit the production of IL-6, TNF- α , MCP-1, IFN- γ , and other pro-inflammatory factors and the polarization of macrophages, which may be one of the important mechanisms through which the immune response is regulated and cytokine storm^[77-78]. Another study also reveals that six key components in QFPD, such as quercetin, luteolin, berberine, hederagenin, shionone, and kaempferol, could substantially inhibit the high expressions of chemokine (C-X-C motif) receptor 4 (CXCR4), intercellular cell adhesion molecule-1 (ICAM1), C-X-C motif chemokine ligand 8 (CXCL8), C-X-C motif chemokine ligand 10 (CXCL10), IL-6, interleukin-2 (IL-2), CCL-2, interleukin 1-beta (IL1B), interleukin-4 (IL-4), and IFNG in patients with severe COVID-19^[56]. The key molecules related to the effects of QFPD in the treatment of COVID-19 were also determined *via* utilizing a systems pharmacological approach, which identified four important active components of baicalin, glycyrrhizic acid, hesperidin, and hypericin, and seven key targets of AKT1, TNF- α , IL-6, PTGS2, heme oxygenase 1 (HMOX1), interleukin-10 (IL-10), and TP53^[79]. It also indicates that QFPD has multiple functions, anti-viral, immune regulatory, anti-inflammatory, and multi-organ protection^[79]. Additionally, the gut microbiome plays an important role in regulating immune responses and inflammation in patients with COVID-19^[80-81]. Short-term intervention with QFPD dose-dependently modulates host metabolism and gut microbiota of rats, which may be part of its mechanism of action in the treatment of COVID-19^[80,82]. QFPD may effectively regulate damage due to oxidative stress and inflammatory symptoms induced by SARS-CoV-2^[83]. Both QFPD and XFBD decreased pro-inflammatory cytokine expression levels, inhibited activation of the NF- κ B signaling pathway, and reduced pinocytosis activity in THP-1-derived macrophages^[84]. Computer-aided drug design in combination with network pharmacology through overlapping the targets of QFPD and COVID-19 was used to identify eight common targets (retinol-binding protein 4 (RBP4), interleukin-1 receptor antagonist (IL1RN), prealbumin (TTR), Fyn-related kinase (FYN), surfactant, pulmonary-associated protein D (SFTPD), TP53, serine/arginine protein kinase1 (SRPK1), and AKT1) of the 62 active components in QFPD^[85]. QFPD potently inactivates CYP3A and substantially modulates the pharmacokinetics of CYP3A substrate drugs^[86]. The comprehensive pharmacokinetic behavior of QFPD *in vivo* illustrates that QFPD exhibits therapeutic effect *via* immune regulation, anti-infection, anti-inflammatory activities, thereby ameliorating the symptoms of metabolic disorders^[87]. QFPD improved immune function and reduced inflammation in a mouse model of pneumonia by remodeling the gut microbiota and host metabolism^[88]. Thus, QFPD and wogonoside may regulate ubiquitin-specific peptidase

14 (USP14) to promote activating transcription factor 2 (ATF2) degradation^[89].

The weakened immune response and cytokine storm due to SARS-CoV-2 infection are the two main characteristics of deterioration in patients with mild disease. Notably, 12% of the enriched pathways regulated by XFBD for the treatment of COVID-19 are related to immune regulation^[66]. The Toll-like receptor (TLR) and nucleotide-binding oligomerization domain (NOD)-like receptor signaling pathways, which play a key role in the immune response to microbial infection, are the key pathways associated with XFBD, and its target genes including TNF- α , phosphoinositide-3-kinase, catalytic, gamma polypeptide (PIK3CG), and PTGS1/2^[66]. The *Polygoni Cuspidata Cuspidati* Rhizoma (Huzhang), *Imperatae* Rhizoma (Maogen), and *Citri Grandis* Exocarpium (Huajuhong) in XFBD could markedly suppressed macrophage activation, a result related to their active ingredients, including polydatin, isoliquiritin, and acteoside^[66,90]. The active ingredients in *Artemis Annuae* Herba (Qinghao) and *Ephedrae* Herba (Mahuang) such as ephedrine, atractylide, and kaempferol, inhibited the migration of endogenous macrophages^[66]. The inhibitory effect of XFBD on IL-6, TNF- α , monocyte chemoattractant protein-1 (MCP-1), CXCL10, and other pro-inflammatory factors may be one of the main pathways through which its inhibition of cytokine storm is inhibited^[68,90]. The key anti-inflammatory and anti-viral targets of XFBD, including repetitive Extragenic Palindromic (REP), TTR, AKT1, FYN, and TP53, were discovered using a new reverse-finding^[91]. In addition, vascular endothelial growth factor A (VEGFA), which is considered to play a pro-inflammatory role during SARS-CoV-2 infection, is downregulated after XFBD intervention^[66,92]. XFBD treatment attenuated intestinal disorders associated with the inhibition of inflammation, remodeling of intestinal immunity, and improvement in intestinal flora. These findings provide a scientific basis for the clinical use of XFBD and offer a potential therapeutic approach for treating patients with COVID-19 with intestinal symptoms^[93]. Mechanistically, XFBD increases mitochondrial fusion by upregulating Mfn1 and attenuated NOD-like receptor thermal protein domain associated protein 3 (NLRP3) inflammasome activation by repressing Casp11 to inhibit the NF- κ B and MAPK pathways, respectively, thus repressing pro-inflammatory macrophage polarization. XFBD exerts anti-ALI and anti-inflammatory effects by restoring mitochondrial dynamics and reducing inflammasome activation, providing a biological illustration of the clinical efficacy of XFBD in treating patients with COVID-19^[94]. XFBD increased the immune levels of immunoglobulin A (IgA), immunoglobulin G (IgG), and immunoglobulin M (IgM), modified the gut bacteria structure according to principal component analysis, and partially restored the relative abundance of intestinal microflora in rats with bacterial disorder caused by antibiotics. The mechanism of action of XFBD may be related to the regulation of intestinal flora composition^[95]. The important active chemical components in XFBD, such as I-SPD, pachypodol and vestitol, reduce the inflammatory response and apoptosis by inhibiting the activation of NLRP3, and

reduce the production of inflammatory factors and the chemotaxis of inflammatory cells by inhibiting the activation of colony-stimulating factor 2 (CSF2). Therefore, XFBD can effectively alleviate the clinical symptoms of COVID-19 *via* NLRP3 and CSF2. XFBD played a crucial role in the protection against immunosuppression in cyclophosphamide (CY)-treated mice *via* reductions in the TNF- α , IFN- γ , IgG, and IgM levels in the serum and in IL-2, IL-4, and IL-6 expressions in the spleen^[96]. The results of a pharmacokinetic study have shown higher absorption rates of eight chemicals, including ephedrine and bitter amygdalin^[97].

The results of network pharmacology analysis indicate that the key targets of HSBD in the treatment of COVID-19 are mitogen-activated protein kinase 3 (MAPK3), mitogen-activated protein kinase 8 (MAPK8), tumor protein p53 (TP53), caspase-3 (CASP3), IL-6, TNF, mitogen-activated protein kinase 1 (MAPK1), CCL-2, and PTGS2; and the main pathways regulated by HSBD include TNF signaling pathway, PI3K-Akt signaling pathway, NOD-like receptor signaling pathway, MAPK signaling pathway, and hypoxia-inducible factor1 (HIF-1) signaling pathway^[67]. Through the network pharmacology analysis of ACE2-related disease targets screened from the reported single-cell sequence data of colon epithelial cells, 84 targets of HSBD in regulating COVID-19 disease were found, among which the main targets included ACE, estrogen receptor1 (ESR1), recombinant adrenergic receptor alpha 1A (ADRA1A) and human recombinant (HDAC1), Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis was also used to screen important pathways such as the renin-angiotensin system, renin secretion, NF- κ B pathway, arachidonic acid metabolism, and AMPK signaling pathway^[98]. The results of *in vitro* experiments revealed that HSBD substantially reduces the expressions of IL-6 and TNF- α in cell models^[99]. These are the potential mechanisms through which HSBD exerts immunomodulatory effects and suppresses cytokine storm. Six compounds (magnolol, glycyrrhisoflavone, licoisoflavone A, emodin, echinatin, and quercetin) exhibited dose-dependent inhibitory effects against SARS-CoV-2 infection. Among these, echinatin and quercetin were identified as inhibitors of main protease (3CL^{pro}), while glycyrrhisoflavone and licoisoflavone A were found to inhibit the RNA-dependent RNA polymerase (RdRp). Additionally, three anti-inflammatory components, namely licochalcone B, echinatin, and glycyrrhisoflavone, were identified in a SARS-CoV-2-infected inflammatory cell model^[100]. From network pharmacological analysis, eight common targets, including FYN, SFTPD, P53, retinol-binding protein 4 (RBP4), IL1RN, TTR, serine/arginine protein kinase1 (SRPK1), and AKT1, were identified by overlapping the targets of HSBD and COVID-19. Using P53 and AKT1 as the receptor proteins for macromolecular docking to evaluate the main active ingredients in HSBD, kaempferol 2 and kaempferol 3, which were found to be the two most active ingredients, showed potential as supplements for the treatment of COVID-19^[101]. *Via* integrating Chemical Bioinformatics Analysis, HSBD and its key active components in plasma (quercetin, emodin, and rhein) can decrease the levels of pro-inflammatory factors (IL-6 and TNF- α), decrease the expression of

MDA, increase expression of T-SOD, and decrease cell apoptosis in an inflammatory environment. HSBD has a strong anti-inflammatory and anti-oxidative stress effect and can decrease cell apoptosis in the treatment ALI^[102].

Potential mechanisms of TMTFs in treatment of ARDS and MODS

To explore the underlying mechanisms of XBJ in the treatment of complications in patients with COVID-19 who are critically ill, a combination of network pharmacology and RNA sequencing was used^[103]. The results indicated that seven genes, including CCL-2, CXCL8, protein c-Fos (FOS), interferon beta (IFNB1), IL-1A, interleukin-1 β (IL-1B), and plasminogen activator inhibitor 1 (SERPINE1), were the key targets for XBJ in the treatment of cardiac insufficiency caused by COVID-19^[103]. Fos and quercetin showed the closest binding based on the molecular docking results^[103]. In addition, we have already used a combination of network pharmacology, molecular docking, and target validation to reveal that the 10 most important targets in the multi-functional regulation and multi-organ protection produced by XBJ treatment of COVID-19 are TNF, IL-6, transforming growth factor beta-1 proprotein [Cleaved into: latency-associated peptide (TGFB1), IL-1B, epidermal growth factor receptor (EGFR), signal transducer and activator of transcription 3 (STAT3), MAPK1, IL-10, Matrix metalloproteinase-9 (MMP9), and PTGS2; the most relevant classical signaling pathways include the hepatic fibrosis signaling pathway, neuroinflammation signaling pathway, IL-6 signaling, coronavirus pathogenesis pathway, HIF1 α signaling, acute phase response signaling, IL-10 signaling, and HMGB1 signaling. The results of bioinformatics analysis indicate the underlying protective effect provided by XBJ against COVID-19, especially COVID-19-induced cardiac dysfunction^[103]. XBJ ameliorates H2S-induced ARDS by promoting claudin-5 expression *via* the PI3K/AKT/Forkhead box protein O1 (FOXO1) signaling pathway^[104]. XBJ produced a strong protective effect on sepsis-induced myocardial injury (SIMI) and may act by inhibiting apoptosis and promoting autophagy *via*, at least partially, activating PI3K/AKT/mTOR pathway in the early stage of sepsis, as well as promoting apoptosis and inhibiting autophagy *via* suppressing PI3K/AKT/mTOR pathway in the late stage of sepsis^[105]. One of the main bioactive compounds is XBJ-benzoylpaeniflorin (BPF). BPF treatment alleviated LPS-induced lung damage and dose-dependently inhibited. LPS-induced IL-6, TNF- α , and CXCL1 production in peritoneal macrophages. The research shows that BPF is a potential drug for the treatment of sepsis and various inflammatory diseases^[106]. Senkyunolide I (SEI), a component of XBJ, is protected against CLP (a murine model of cecal ligation and puncture)-induced lung injury in mice. SEI treatment can substantially reduce NET formation^[107]. XBJ is protected against sepsis-induced lung injury by reversing GSDMD-related pathways to inhibit NET formation^[108]. XBJ ameliorates pulmonary endothelial injury, systemic inflammation, and coagulation dysfunction in early sepsis^[109]. The results from metabolomics and network pharmacology studies have shown that XBJ has the characteristics of

multi-target, multi-channel, and multi-component action in the treatment of pulmonary fibrosis caused by paraquat (PQ)^[110]. XBJ efficiently alleviates PQ-induced pulmonary fibrosis in mice through the inhibition of TG2 expression and the Wnt-1/ β -catenin signaling pathway^[104]. XBJ prevents DDVP*** poisoning-induced lung injury by attenuating the inflammatory response through downregulation of the TLR4 and NF- κ B expression^[111]. XBJ combined with cefoperazone sodium and sulbactam sodium (CSSS) strengthened the inflammatory responses of the body, intestinal tract barrier function, and hepatic function, showing satisfactory efficacy in the treatment of hepatitis B-induced liver cirrhosis (HBLC) complicated by spontaneous bacterial peritonitis (SBP)^[112]. The hepatoprotective effect of XBJ may be through up-regulation of GSK-3 β (Ser9) and increasing the binding of p-CREB to CBP, thereby alleviating the inflammatory response^[113]. The study into the early stages of sepsis in a rat model indicated that as an adjuvant therapy to antibiotics, XBJ increased renal perfusion and oxygenation, suppressed renal inflammation, and ameliorated kidney dysfunction^[114]. The results of a network pharmacology study evidence that LHQW may alleviate LPS-induced ALI by inhibiting the p53-mediated intrinsic apoptotic pathway^[115].

QFPD has multiple functions, including anti-viral, immune regulatory, anti-inflammatory, and multi-organ protection actions^[79]. The baicalin, glycyrrhizic acid, hesperidin, and hypericin in QFPD can play a multi-organ protective role in the treatment of COVID-19, which is related to the regulation of the expressions of AKT1, TNF- α , IL-6, PTGS2, heme oxygenase 1 (HMOX1), IL-10, and TP53 according to the results of a systems pharmacological study^[79].

Scientific connotation of TMTFs for COVID-19 treatment

Although the TMTFs have shown efficacy against COVID-19, their use is specific for patients with different disease severities. Therefore, the potential mechanisms of TMTFs act in the prevention and treatment of COVID-19 are also quite different. With the purpose of elucidating the role of the TMTFs in the different stages of COVID-19 more intuitively and clearly, we combined and integrated the three phases of the development of COVID-19 with the targets and mechanisms, to help further understand the scientific connotation of COVID-19 treated with TMTFs, as shown in Figure 5.

Conclusions and perspectives

The representative TMTFs have been proved effectively in practice. COVID-19 is innovatively divided into three phases ranging from mild to critical clinical. The TMTFs are beneficial in the prophylaxis and treatment of COVID-19 by alleviating typical symptoms such as fever, coughing, fatigue, phlegm, and diarrhea; shortening the conversion time of the nucleic acid test to negative conversion time, improving CT image feature and lung inflammation, reversing adverse clinical biomarkers; and reducing the frequency and severity of complications. Furthermore, the main potential mechanisms of

action of TMTFs have been revealed, including inhibiting SARS-CoV-2 invasion and replication; regulating cytokine storm and immune response; and protecting against ARDS and MODS by reducing the crosstalk of viral toxicity, endothelial damage, cytokine storm, immune response, and microthrombus. With the purpose of using TCM to deal with the more global health threats like COVID-19 several issues need to be addressed: (1) Due to the lack of in-depth understanding, the effectiveness of TCM in treating COVID-19 has been questioned. More randomized controlled trials with high accuracy, a large sample size, rigorous design, and an in-depth mechanism exploration should be conducted, the results of which can provide more reliable evidence for the effectiveness and rationality of TCM, especially the “three medicines and three formulas”; (2) The results on the potential mechanisms of TCM in the treatment of COVID-19 have partly been obtained from virtual screening or network pharmacology analysis, which has led to ambiguous results. Therefore, new strategies and techniques must urgently be adopted to directly identify the targets of TCM in COVID-19 intervention. This may include employing the CETSA-MS-based marker-free method to explore the targets of the complex components in TMTFs; (3) The treatment of COVID-19 should not be limited to discharge criteria; and its sequelae should also be considered. Over time, the sequelae of COVID-19 have become prominent, involving physical, mental, and cognitive impairment^[116–117]. Although TCM can reduce the number and severity of sequelae of COVID-19, evidence-based research on TCM needs to be strengthened to further understand the entire process through which TCM intervention in COVID-19^[118]. (4) More attention should be paid to the patients with COVID-19 who are experiencing common symptoms such as fatigue or muscle weakness, sleep deprivation, and anxiety or depression especially for children with low immunity and the elderly with comorbidities including chronic diseases. (5) There is numerous evidence proved from bench to bedside, but the connection between them is scarce. The studies on QFPD are recommended to refer as the drug-metabolizing enzymes of CYP3A and metabolites distribution in organs are revealed, which may provide critical guidance for narrowing the gap from pharmacology to clinic^[186,119].

In conclusion, the purpose of this review was to sort out the clinical effects and potential mechanisms of the TMTFs in combating COVID-19 scientifically and systematically. TCM is worth the honor for fighting with COVID-19.

Conflict of interest statement

Yan Zhu is the editorial board member of this journal.

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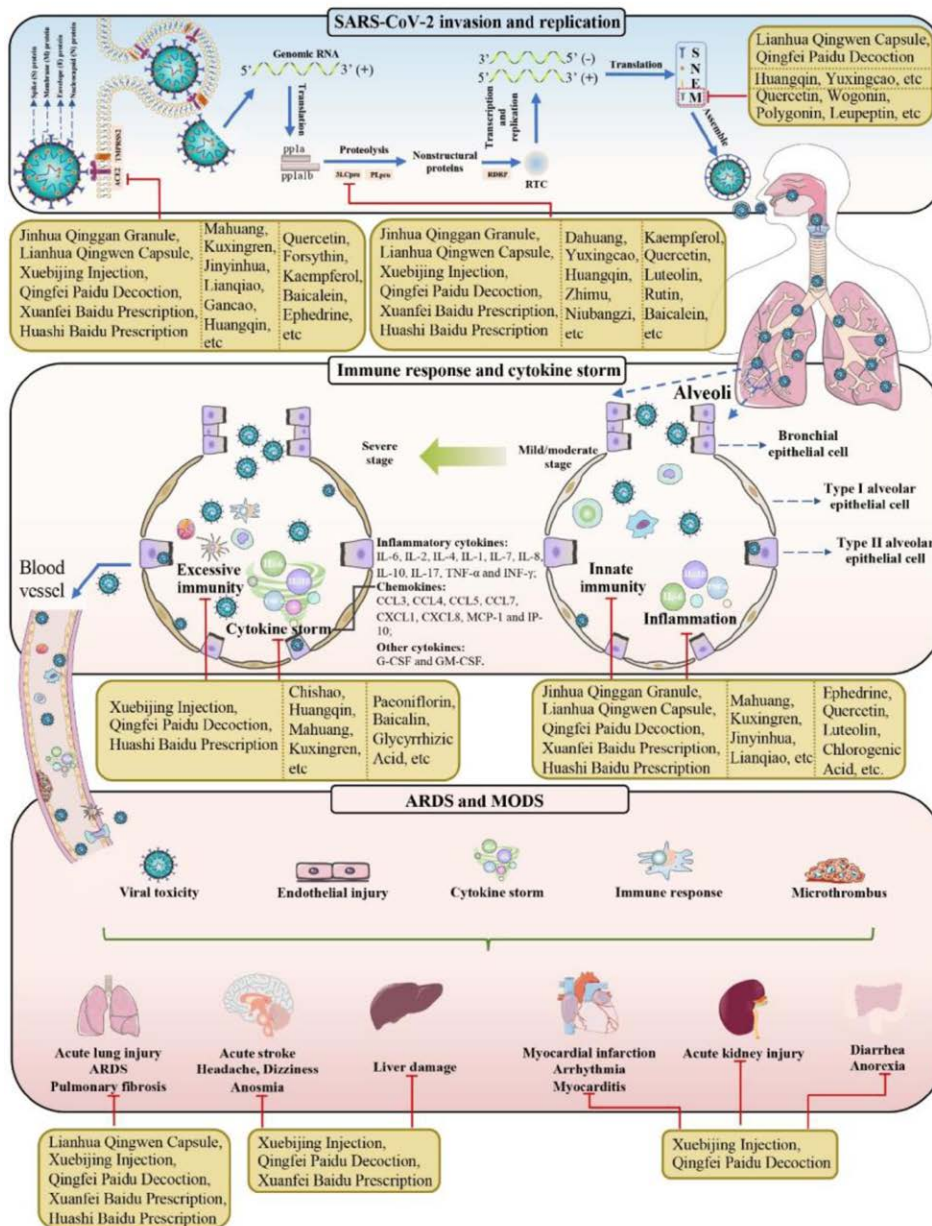


Figure 5. Overview of the pathogenesis of COVID-19 and the potential mechanisms of TMTFs in treating the different stages of the disease. CCL3: Chemokine(C-C motif)ligand 3; CCL4: Chemokine(C-C motif)ligand 4; CCL5: Chemokine(C-C motif)ligand 5; CCL7: Chemokine(C-C motif)ligand 7; COVID-19: Coronavirus disease 2019; CXCL1: C-X-C motif chemokine ligand 1; CXCL8: C-X-C motif chemokine ligand 8; G-CSF: Granulocyte colony-stimulating factor; GM-CSF: Granulocyte-macrophage colony stimulating factor; IFN- γ : Interferon; IL-2: Interleukin-2; IL-4: Interleukin-4; IL-6: Interleukin-6; IL-7: Interleukin-7; IL-8: Interleukin-8; IL-10: Interleukin-10; IL-17: Interleukin-17; IP-10: Inducible protein 10; MCP-1: Monocyte chemoattractant protein-1; TMTFs: Three medicines and three formulas; TNF- α : Tumor necrosis factor- α .

Author contributions

Ming Lyu conceived, designed, wrote, and revised the manuscript. Guangxu Xiao wrote and revised the manuscript. Simeng Wang, Ruijiao Wang, Shibo Ma, Li Tan, Shuang He, Guanwei Fan, and Yan Zhu contributed to the revision of the manuscript.

Ethical approval of studies and informed consent

Not applicable.

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Data availability

All data generated or analyzed during this study are included in this published article.

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