Review Articles

Acupuncture and Herbal Medicine

# Traditional Chinese medicine for long COVID-19: the potential roles of immunity remodeling

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**Abstract**

Given that the immunity imbalance in patients with Long COVID-19 (LC) may pose a significant global health and economic post-pandemic burden, there is an emergent need to identify therapeutic targets and treatment options. Traditional Chinese medicine (TCM), as an evidence-based therapeutic approach, can effectively improve the sequelae of LC patients by eliminating pathogenic factors. The purpose of this paper is to discuss how immune remodeling contributes to the pathogenesis of LC, the clinical evidence supporting TCM's treatment of LC, and the mechanism of TCM modulating immune remodeling and relieving chronic inflammation to develop new ideas for the treatment of LC as well as the development of drugs. Data were retrieved using appropriate keywords from a variety of internet databases, including PubMed and Web of Science. Current evidence shows that LC can affect multiple organ systems, and its prominent manifestations include respiratory complications, neurological symptoms and cardiovascular dysfunction. Immunoassay showed a characteristic increase in interleukin 6 (IL-6), interferon gamma (IFN-γ), and T helper (Th)17/regulatory T (Treg) imbalance. TCM interventions have shown great therapeutic potential, with active compounds such as baicalin reducing lung inflammation and ginsenosides improving heart function. Clinical research reports that Qingfei Paidu decoction (QFPD) can effectively alleviate respiratory symptoms, and Sini powder (SNP) has antidepressant effects. TCM interventions can be tailored based on the specific clinical symptoms of individual patients. This article elucidates the crucial role of inflammation and immune dysfunction in alleviating multiple organ symptoms of LC. TCM used in LC treatment is an important source of new molecules. These new molecules may act synergistically to combat adverse effects such as COVID-19 infection-induced inflammation and oxidative stress.

**Keywords:** Immunity remodeling, Inflammation, Long COVID-19, Multi-system complications, SARS-CoV-2, Traditional Chinese Medicine

**Graphical abstract:** https://links.lww.com/AHM/A192.

## Introduction

Due to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), Coronavirus disease 2019 (COVID-19) has been spreading around the world[1]. The increase in immunity, the development of vaccines, and new therapies have been developed, and especially novel rapid formulation have greatly reduced the death rates[2]. As the number of individuals recovering from SARS-CoV-2 infection continues to rise, an increasingly worrying issue is the long COVID-19 (LC)[3], which likely impacts over 62% of acute patients[4]. LC is a broad classification encompassing various ongoing or new-onset health issues that emerge following the initial recovery from a SARS-CoV-2 infection[5–6]. Due to the lack of medical information about LC, patients with LC experience feelings of being ignored and disbelieved, as well as the fear of having to live with these symptoms forever. With the continued spread of SARS-CoV-2 variants, millions of people worldwide are likely to suffer from LC symptoms[7–8].

According to recent joint guidelines, there are three phases of COVID-19 infection: "Acute COVID-19" (signs and symptoms occurring up to 4 weeks after infection), "ongoing symptomatic COVID-19" (up to 12 weeks after infection), and "post-COVID-19 syndrome" (beyond 12 weeks)[9–10]. Based on this classification, LC, also named as "chronic COVID," "Long Haulers" or "Post COVID syndrome," covers both "ongoing symptomatic COVID-19" phase and "post-COVID-19 syndrome" phase[11]. During the long period following SARS-CoV-2 infection, patients may present with a variety of clinical symptoms[11]. A current challenge of public

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health services is therefore to first understand the effects and complications of LC[12], and then to properly manage them.

LC exhibits a remarkably broad clinical scope, affecting individuals across all disease severity levels, from critical cases to mild-to-moderate infections, and spanning diverse populations. This includes children, adults, outpatients, discharged patients, and even those who have tested negative for SARS-CoV-2, highlighting its extensive reach beyond traditional disease classifications[13–17]. Clinically, the recovered patients from COVID-19 continue to have many symptoms for several months[13,16]. The median time from SARS-CoV-2 infection to the assessment was 141 days. A total of 201 individuals completed the baseline assessment, with a mean age of 45 years (ranging from 21 to 71 years). Notably, 42% of the individuals reported 10 or more symptoms, and 60% were diagnosed with severe post-COVID-19 syndrome. The most commonly reported symptoms included fatigue (98%), muscle aches (87%), breathlessness (88%), and headaches (83%)[13]. In addition, according to a cohort study based on data from 1,733 patients carried out 6 months after hospitalization, 75% of Wuhan hospital-discharged patients still suffered from physical or mental health symptoms. The most prevalent indicators included exhaustion or muscle weakness (63%), insomnia (26%), and depression or anxiety (23%)[18]. Some of the less common symptoms are cognitive difficulties, headaches, chest and joint pains, loss of smell and taste, coughing, loss of hair, arrhythmias, diarrhea, nausea, and metabolic disorders (Figure 1)[19–22].

Relevant evidence shows that traditional Chinese medicine (TCM) can treat clinical symptoms of LC such as shortness of breath, weakness, heartburn, chest tightness, breath-holding, cough, sweating, dry mouth, thirst, muscle aches, nasal congestion, sore throat, anxiety and depression, improve lung function, improve pulmonary fibrosis, reduce the inflammatory index of the body, and improve the immune function of patients in LC patients[23–24]. To provide new ideas for treatment and drug development for LC, we review the role of immune remodeling in the pathogenesis of LC, the clinical evidence, and the mechanism of TCM modulating immune remodeling to treat LC.

## Complications of LC

### *Respiratory system*

LC involves many systems of the body, and specific symptoms and duration vary from patient. The acute infection symptoms of COVID-19 usually last for days to weeks, while the symptoms of LC can last for weeks, months, or even years[9,25].

LC patients often experience respiratory symptoms, including dyspnea, coughing, shortness of breath, chest pain, and pulmonary fibrosis[26]. The reason for dyspnea is likely related to the fact that the respiratory system is the main target of SARS-CoV-2[27]. After infection, the virus enters the human body through the respiratory tract, causing diffuse alveolar damage and inflammation, which will then cause damage to the respiratory mucosa, affect the normal operation of the respiratory system, weaken the normal contraction and expansion of respiratory muscles, cause dyspnea, shortness of breath, hypoxia, and other uncomfortable symptoms[28].

SARS-CoV-2, as a respiratory infectious disease associated with pulmonary cell infection, can lead to excessive deposition of extracellular matrix components causing alveolar and pulmonary interstitial fibrosis. In addition, the virus invasion can initiate the immune defense cascade of the body, and the excessive immune response can trigger an inflammatory cytokine storm, leading to inflammatory damage and dysfunction of lung tissues and organs further enhancing the pulmonary fibrosis[29].

Cough is a common respiratory symptom, but the persistent presence of cough exacerbates the patient's subjective discomfort. As a result of residual virus of SARS-CoV-2, inflammatory cells invade the airways and lung tissues and release inflammatory mediators, leading to congestion and edema of the airway mucosa, damage and shedding of the mucosal epithelium. The inflammatory response of the cough receptor increases the neuronal sensitivity. Chronic inflammation of LC causes an increase in intracellular $Ca^{2+}$ which opens the pannexin channel and releases adenosine triphosphate that in turn stimulates and activates the airway sensory neurons. This leads to cell depolarization potentially triggering the opening of voltage-gated $Na^{+}$ channel causing cough[30].

### *Neurological system*

The neurological manifestations of LC involve the central nervous system (cognitive impairment, headache, memory issues, sleep disorders, depression, etc)[31] and the peripheral nervous system (muscle weakness, myalgias, hyposmia/hypogeusia, tinnitus, etc)[32–33]. The presence of SARS-CoV-2 implicates neurotropic effects in the pathogenesis of LC[34–35]. After the acute recovery period, inflammatory and immune responses to SARS-CoV-2 infection may endure for several months, leading to persistent systemic inflammation characterized by cytokines such as interferon gamma (IFN-γ), interleukin (IL)-2, IL-6, IL-17, and chemokine (C-X-C motif) ligand 10 (CXCL 10)[36].

The prolonged release of cytokines in LC patients with high macrophage scavenger receptor 1 leads to a disruption of the blood–brain barrier and neuropsychiatric manifestations[37]. Inflammatory molecules and immune cells spreading into the central nervous system may result in neuropsychiatric manifestations and induce a persistent neuroinflammatory response. In addition, the serum inflammatory marker IL-6 inhibits the cleavage of von Willebrand factor, promoting platelet aggregation[35], further leading to mitochondrial dysfunction or impaired cerebral autoregulation[32].

In contrast, persistent hyposmia is a manifestation of the peripheral nervous system that likely arises from the enduring impact of direct viral harm to the olfactory epithelium[36]. Due to the fact that SARS-CoV-2 can lead to persistent reduction of symbiotic organisms and dysbiosis of the gut microbiota in the gastrointestinal tract, long-term virus shedding can cause the microbial dysbiosis and may lead to dysfunction of the brain-gut axis[38].

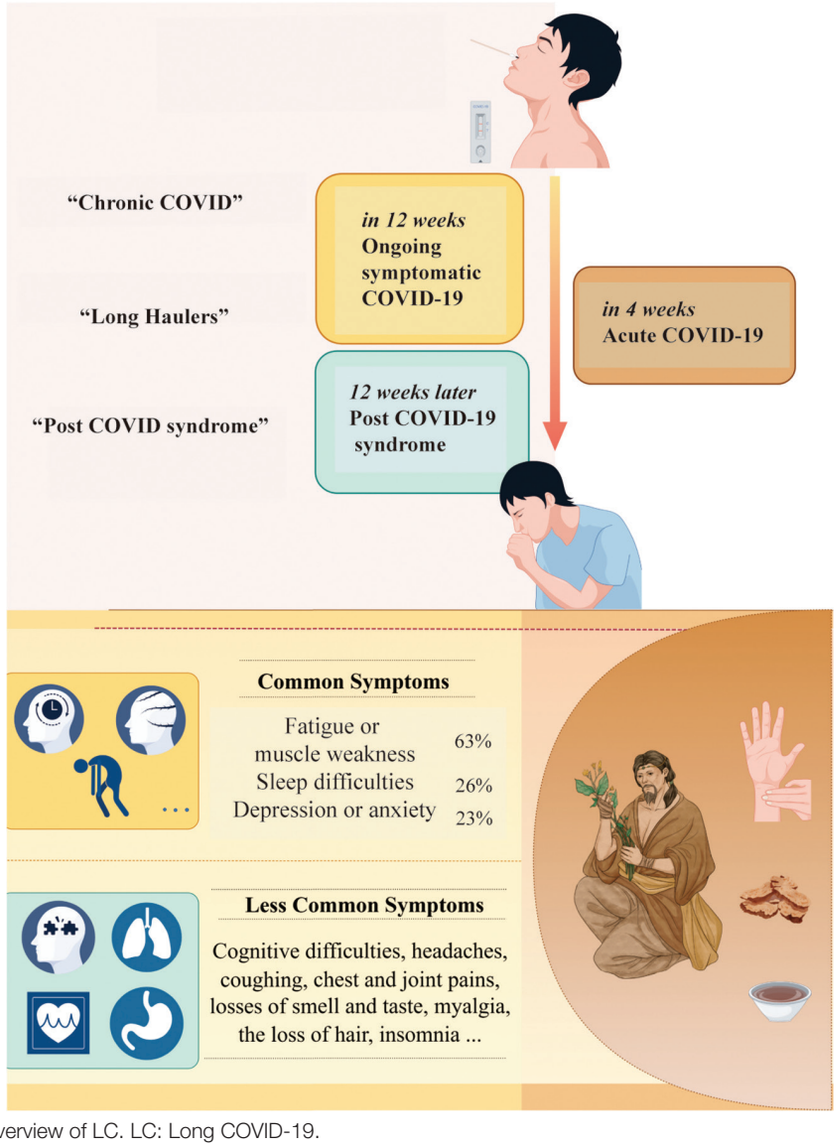



**Figure 1.** Definition and overview of LC. LC: Long COVID-19.

### *Cardiovascular system*

Long COVID syndrome is characterized by a wide range of cardiac complications, including myocardial inflammation, ventricular dysfunctions, arrhythmias, and cardiovascular autonomic vegetative dysregulation; in general, the severity of these symptoms correlates with the severity of acute COVID-19 infection[39–40]. Due to the large impact of COVID infection in the entire world, the vicious interaction between cardiac complications and LC is now considered of major concern in public health[39]. Mechanisms behind cardiovascular manifestations of LC are still unclear, but increasing evidence indicates that they can originate from not resolved cardiac tissue damage or caused by persistent systemic inflammation and oxidative stress[19,40–41].

Although the SARS-CoV-2 virus is generally cleared from the organism within a few weeks after the onset of the infection, and the presence of cardiac issues directly associated with it are normally resolved, longer viral permanence has also been observed[42].

The large spectrum of symptoms associated with cardiac LC clearly points to complex and likely multifactorial mechanisms, including both direct viral cell infection, systemic immune response, and autonomic dysfunctions leading to altered homeostatic responses. Viral infection of cardiac and vascular cells starts from the interaction between the virus and the angiotensin-converting enzyme 2 (ACE2) receptor and then progresses by activating a transductional cascade leading to myocardial inflammation and cardiac tissue damage and dysfunction. The presence of pro-inflammatory markers has indeed been detected in some patients with LC and persistent inflammation can trigger a maladaptive process ultimately leading to increased cardiac fibrosis. Interestingly, inflammation has not only been associated with myocardial infarction but also with the loss of electrical stability (atrial fibrillation, palpitations, and tachycardia) caused by $Ca^{2+}$ homeostasis dysregulation, reduction in $K^+$ currents, and altered cell-to-cell connection *via* Connexin 43. In an interesting study, Clemens et al.[43] evaluated the effect of viral infection on the electrophysiological properties of human induced pluripotent stem cell–derived cardiomyocytes. These authors observed the formation of cellular syncytia as well as the development of cellular arrhythmic behaviors and alterations in the $Ca^{2+}$ handling processes. Arrhythmic conditions (ie, sinus tachycardia

and prolonged QT interval[40]) have been reported, and this evidence may be associated with a direct effect of inflammatory stress at the cellular level. Indeed, inflammatory cytokines (eg, IL-6 and tumor necrosis factor alpha [TNF-α]) may alter cardiac repolarization due to inhibition of potassium currents. Pharmacological treatment with antibiotics and antivirals can also be proarrhythmic because of cardiac toxicity on $K^+$, $Na^+$, and $Ca^{2+}$ ion channels. However, some authors suggest that autonomic dysfunction also plays a major role in cardiac LC symptoms[41] since the continuous systemic and myocardial inflammation may lead to an initial overactivation of the vagal response, subsequently followed by a rebound effect due to exacerbated sympathetic activation. This sequela of events may well explain some of the often-reported arrhythmic conditions, such as sinus tachycardia and postural orthostatic tachycardia.

### *Endocrine system*

Endocrine imbalance is a significant feature of LC. Widespread damage of the endocrine system can worsen immune and metabolic disorders, such as endothelial dysfunction, hyperthyroidism, insulin resistance, and adrenal insufficiency[44–46]. SARS-CoV-2 infection can cause and exacerbate type 1 diabetes (T1DM) and type 2 diabetes (T2DM)[47]. Infection and inflammation are the powerful driving forces of diabetes[48]. Patients with diabetes are more likely to have syndromes because of the chronic inflammation of LC. There is a decrease in anti-inflammatory cytokines due to impaired insulin signaling, and the expression of pro-inflammatory cytokines which inhibit insulin signaling TNF-α, IL-6, and IL-1β is elevated, thereby increasing insulin resistance. The insulin resistance increases the risk of respiratory and cardiopulmonary symptoms in patients with LC.

The thyroid gland is the main organ that maintains many long-term functions of the body, especially cardiovascular, respiratory, and catabolic functions[49]. LC initiates the immune dysregulation leading to the release of inflammatory cytokines, especially IL-6 which leads to thyroid dysfunction by disrupting desiodases and thyroid transporters. The T3 level is inversely proportional to IL-6, while thyroid-stimulating hormone (TSH) and T4 slightly decrease, leading to the abnormalities of thyroid dysfunction[50]. Endocrine manifestation can also lead to multi-systemic manifestations.

### *Gastrointestinal system*

Gastrointestinal symptoms are common in acute COVID-19; indeed, loss of appetite, constipation, abdominal pain, diarrhea, nausea, and vomiting are commonly observed in LC patients[16,51–52]. These symptoms are probably related to the continuous replication of the virus which is present in the gastrointestinal tract even after the respiratory tract has become negative. Interestingly, since ACE2 receptors are mostly expressed in small gastrointestinal microvilli[53–54], SARS-CoV-2 may be amplified and transmitted through the gastrointestinal system. The high affinity of SARS-CoV-2 for the gastrointestinal system may thus explain why gastrointestinal symptoms appear before respiratory symptoms and why the virus can persist in stools even after the illness has subsided. The composition of individual gut microbiota may also affect the susceptibility and response of SARS-CoV-2 (Figure 2)[38].

## The inflammatory and immunological dysfunction of LC patients

The persistent and recurrent LC symptoms are caused by sequelae of organ damage, persistent virus, chronic

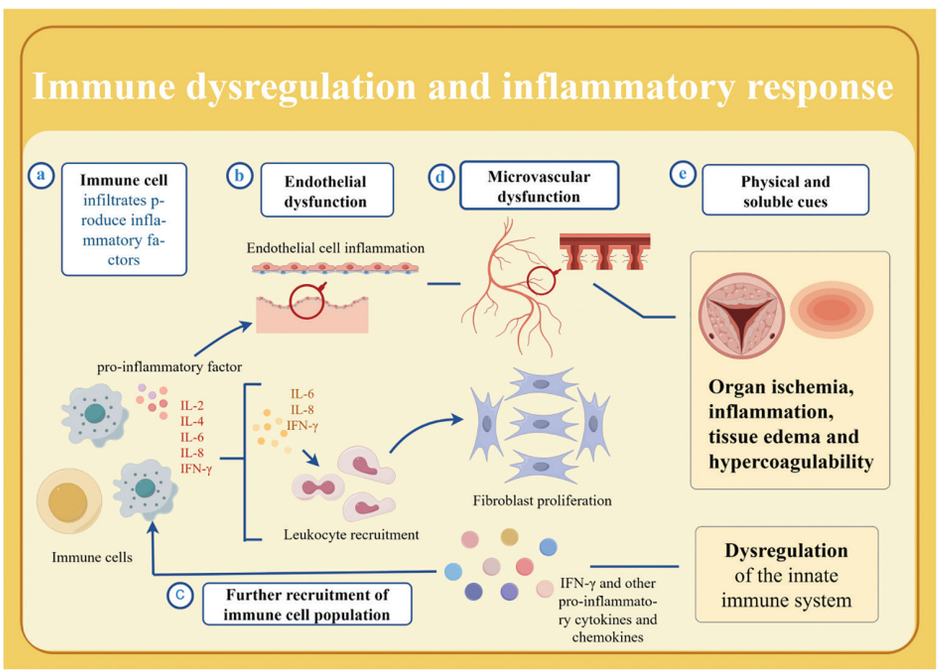



**Figure 2.** LC symptoms and their effects on several organs with various pathologies. The effects of extended long COVID-19 on multiple organs are demonstrated, along with a wide range of symptoms. IFN-γ: Interferon gamma; IL: Interleukin; LC: Long COVID-19.

inflammation, and/or immune response/autoantibody production[55–57]. Notably, inflammatory and immunological dysfunctions play key roles in maintaining LC. Indeed, the persistence of clinical symptoms following the resolution of the initial infection is associated with immunological alterations characterized by inflammation and reduced immune regulation[58–60]. The persistence or reinfected virus[56] contributes to the pathogenesis of LC by inducing chronic inflammation, triggering excessive activation of the adaptive immune system, and prompting immune dysregulation, and the process can then progress to immune exhaustion, often leading to impaired tissue repairment (Figure 3)[42,56,61].

### *Chronic inflammation in LC*

Chronic inflammation is one of the main underlying causes of LC[62–63]. Typical ongoing clinical manifestations of chronic inflammation in LC patients are chest pain, dyspnea, cough, fatigue, headache, depression, and anxiety[64–65]. The chronic inflammation state with higher inflammatory markers induces not only direct cellular damage and endothelial dysfunction but also a dysregulated inflammatory response. According to available data, the most concerned and frequently described biomarkers reported in LC patients are: increased pro-inflammatory levels of IL-2[66], IL-6[67], IL-8[68], and IFN-γ[68]. However, it has also been reported an increase in anti-inflammatory factors such as IL-4 and IL-10[69–70].

Pro-inflammatory cytokines like IL-6, IL-8, and IFN-γ are pivotal in chronic inflammation. These cytokines promote leukocyte recruitment to preserve chronic inflammation and induce fibroblast proliferation[71]. Endothelial activation by pro-inflammatory cytokines is a part of the normal immune system defense, but long-term inflammatory stimulation can lead to sustained endothelial dysfunction[72]. Endothelial dysfunction is the primary factor contributing to microvascular dysfunction by altering the vascular equilibrium toward vasoconstriction, consequently resulting in organ ischemia, inflammation, tissue edema, and hypercoagulability[73]. IL-6, which has multiple potential targets and plays an essential role in cardiovascular complications, could potentially induce T lymphocyte activation and thus it is implicated in the inflammatory response[74–76]. Inflammatory responses may cause endothelial dysfunction, resulting in diffuse thrombotic microangiopathy. This may contribute to heart thrombosis and result in myocardial infarction[77–78]. It is believed that the resultant nervous symptoms of LC are caused by the same ongoing inflammation. Fatigue is an important aspect of one of the most manifestations in LC with a prevalence in patients of about 60%[64,79] and it is likely that fatigue may be caused by systemic chronic inflammation and cell-mediated immune mechanisms[80]. A large number of epidemiological and genetic studies have also demonstrated that inflammatory cytokines are associated with the development of neuropsychiatric symptoms in patients with LC[11,81]. Chronic inflammation

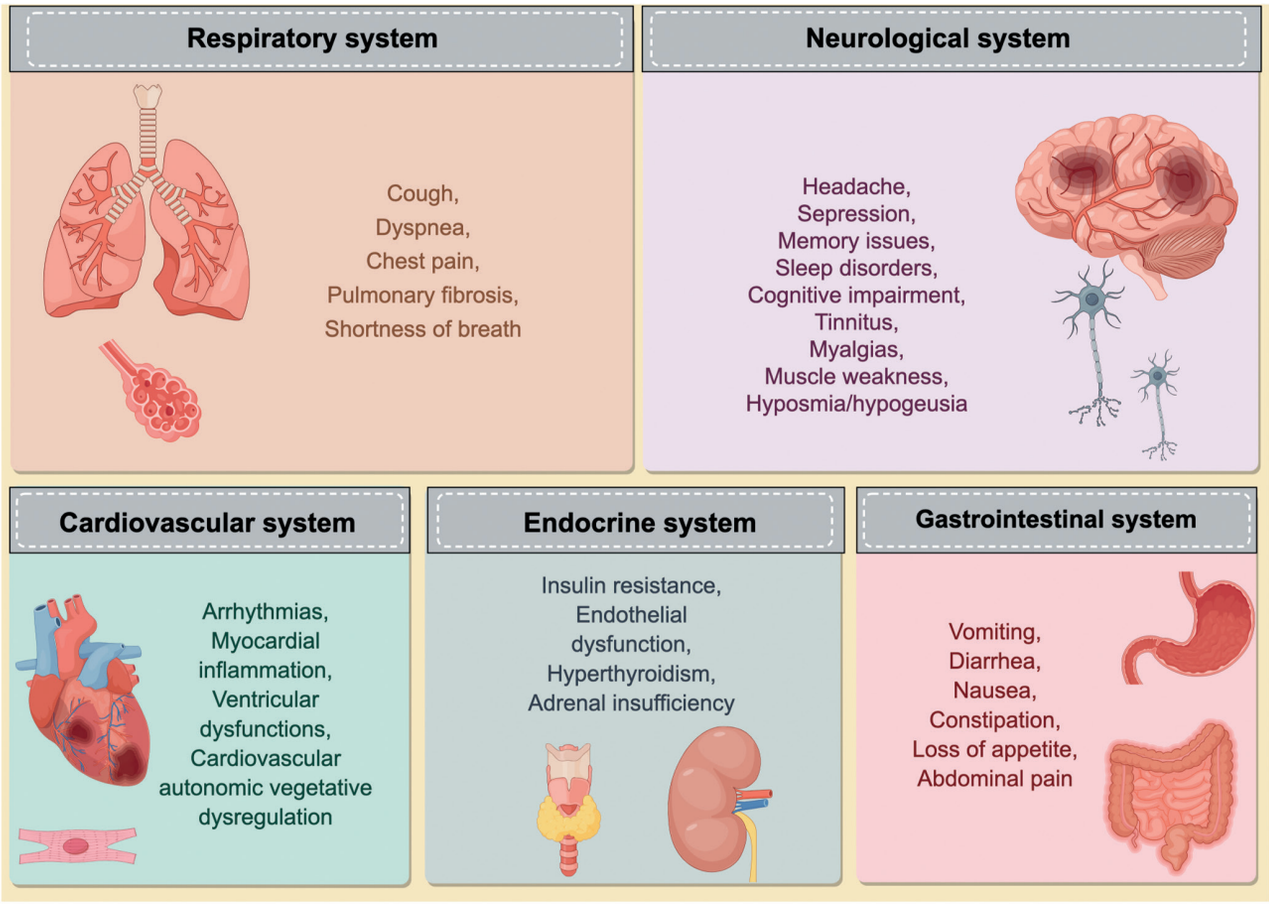



**Figure 3.** LC Immune dysregulation and inflammatory response. The persistence or reinfection of the virus induces chronic inflammation, triggers excessive activation of the adaptive immune system, and promotes immune dysfunction. LC: Long COVID-19.

is linked to fatigue and IL-6 could be the possible cause of this symptom[81].

Chronic inflammation persists in patients who recover from COVID-19, leading to irreversible fibrotic interstitial lung disease, although abnormal respiratory function may be reversed over time[63,82–83]. The pro-inflammatory cytokine IL-8 is an important cytokine that chemoattracts neutrophils and causes tissue damage, thus playing a critical role in mediating the destruction of normal airway structure, airway structural remodeling, and long-term persistence of airway inflammation[84–85]. When IL-8 damages endothelial and epithelial cells of the lung, fibroblasts proliferate, migrate, and differentiate into myofibroblasts with resultant deposition of collagen and fibronectin[86]. Dyspnea can result from irreversible fibrotic interstitial lung disease caused by chronic inflammation[82]. High levels of IFN-γ can impact the resolution of inflammation-induced lung injury and thrombosis which is associated with prolonged symptoms related to coagulation disorders and immune-mediated tissue damage[70,87]. A hyper-inflammatory response in LC patients, together with chronic inflammation, is a potential trigger for LC heterogeneous symptoms. Clearly, inflammasome activation and the resulting innate and adaptive immunity dysregulation impair the organ function.

### *Immune dysregulation*

It is thought that long-lasting symptoms may be caused by the immune response, like other chronic viral infections[56,88]. Innate and adaptive immune systems make up the human immune system. Continuous immune activation can cause tissue damage, early aging, and immune exhaustion[61]. The virus components trigger the innate immune response, which is further propagated by tissue damage and dysbiosis[61]. Increased IL-6 cytokine levels impact negatively on natural killer (NK) cells and affect viral clearance and immune regulation[89]. Patients with LC exhibit elevated levels of IFN-γ and IL-2, which trigger the stimulation of effector T cells with pro-inflammatory characteristics and enable the production of a robust immune response to combat the virus. However, without the necessary signals to attract activated T cells, the inflammatory conditions resulting from these cytokines are inadequate for generating an effective antiviral response[70,90]. High concentrations of IL-6 and IL-10 have been demonstrated to stimulate the activation of myeloid cells, oxidative stress, and damage to the endothelial cells[91]. Dysregulation of the innate immune system is certainly one of the major contributing factors of LC[61,92].

Adaptive immune responses play a very important role as well[56,93]. SARS-CoV-2, like other chronic viral infections, appears to severely damage the functional subsets of cluster of differentiation $CD4^+$ and $CD8^+$ T cells[56,94]. Proper T cell activation, but ineffective T cell recruitment, is a feature of the failed antiviral response observed in LC patients supporting the persistence of virus. Chronic infection can result in a rapid loss of antigen-specific $CD4^+$ T cells and promote $CD4^+$ T cell exhaustion with diminished effector functionality[95–96] $CD4^+$ Tex (exhausted T cells) form a T cell lineage different from the clearly defined $CD4^+$ T cell phenotypes and accelerate $CD8^+$ T cell exhaustion by producing IL-10[95,97]. Increased levels of IL-10 and IL-4 inhibit T-cell responses, causing exhaustion of T-cells and regulatory T cell polarization that evades the antiviral immune response[70,98]. Furthermore, the programmed death-1 (PD-1) as well as T cell immunoglobulin domain and mucin domain-3 (Tim-3) subpopulations, which represent T cell exhaustion, are increased in patients with LC[99]. During chronic viral infections, T cell exhaustion is the main cause of immune dysfunction[100]. The adaptive immunity of LC patients also showed a Th1-predominance[59]. Th1-mediated inflammatory cytokine may play a potential role in myocardial damage[18,101]. Increased IL-6 levels lead to the transformation of activated T helper (Th) cells to Th17 lineage in patients. IL-6 signal activates Th cells, inhibits regulatory T (Treg) cells, and promotes Th17 to Treg imbalance[102–104]. Th17/Treg dysregulation involved in processes such as learning, emotion, sleep-related brain processes, and neuronal energy metabolism provides a reasonable link that can explain how chronic inflammation manifests as fatigue and sleeping difficulties of LC[74,81,104].

## TCM formulae clinically alleviate LC by immunity remodeling

There is a limitation of LC treatment medications. Considering the pathophysiology of LC discussed previously, therapeutic strategies should focus on immunity remodeling. By reviewing the relevant literature, we summarize the scientific basis for the use of TCM to treat LC based on immunity remodeling.

TCM drugs used in LC treatment represent an important source of novel molecules that may synergistically act to contrast both COVID-19 infection and undesired side effects such as the inflammation processes and oxidative stress (Figure 4).

### *Respiratory system*

Several studies have shown that Chinese herbal formulas improve pulmonary fibrosis in COVID-19 patients. Convalescent COVID-19 prescription (CCP) has an anti-fibrotic effect by inhibiting TNF-α, IL-6, transforming growth factor beta 1 (TGF-β1), and matrix metalloproteinase 9 (MMP9)[105]. As a result of downregulating vascular endothelial growth factor (VEGF) expression, Shenling Baizhu powder (SLBZ) can reduce the symptoms of pulmonary fibrosis[106]. In a recent study, the effect of Buzhong Yiqi decoction (BZYQ) on the recovery period of COVID-19 was examined, and results confirmed that this drug could eliminate inflammation, reduce lung damage, and regulate immunity[107]. Qingfei Paidu decoction (QFPD) and Xuanfei Baidu decoction (XFBD) can improve cough and sputum by reducing IL-6 and TNF-α levels, inhibiting nuclear factor-kappa B (NF-κB) activities, while attenuating macrophage exocytosis[107].

In addition, Bufei Huoxue capsules (BFHX) greatly reduce the residual lung damage and impair exercise tolerance in convalescent patients infected with COVID-19 and promote their recovery[108]. By reducing inflammation and pathological responses, BFHX significantly reduces IL-4,

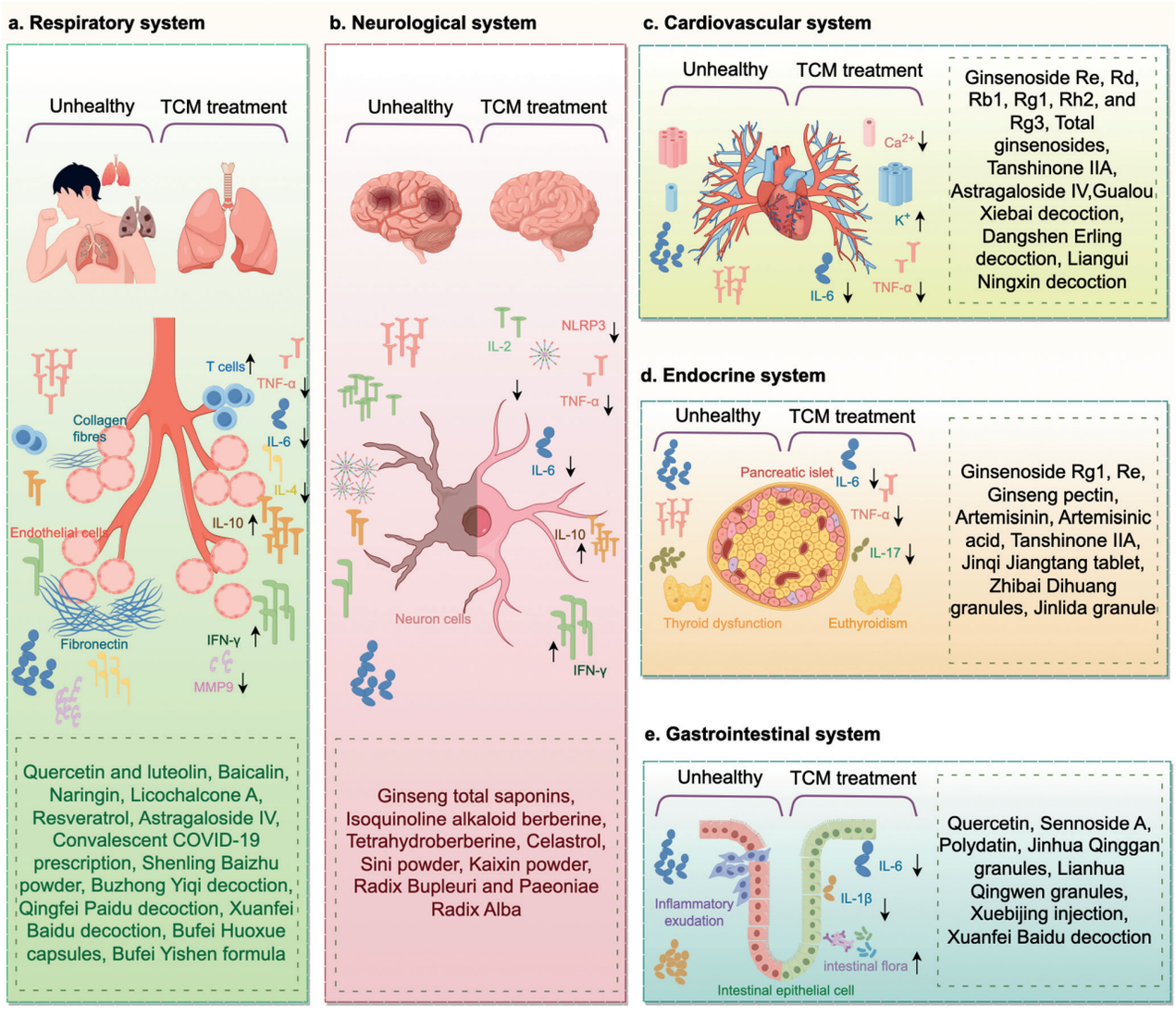



**Figure 4.** TCM immunity remodeling and anti-inflammation. IFN-γ: Interferon gamma; IL: Interleukin; MMP9: Matrix metalloproteinase 9; NLRP3: Nod-like receptor protein 3; TCM: Traditional Chinese medicine; TNF: Tumor necrosis factor.

IL-6, IL-10, IL-8, and TNF-α and keratinocyte growth factor as well as secretory immunoglobulin A and collagen fibers for improving lung function[107]. Moreover, the Bufei Yishen formula (BYF) restores the balance of Th17/Treg, enhances anti-inflammatory cytokine production, and decreases pro-inflammatory cytokine production, all of which contribute to improving lung function[109].

Chinese herbal formulae exhibit unique combinatorial principles for immune regulation. These formulae establish network-level actions across immune cells, cytokine networks, and oxidative stress systems, demonstrating systemic advantages in immune homeostasis restoration.

Many herbs have a significant role in immune remodeling. Several botanical drugs, such as *Codonopsis pilosula* (Franch.) Nannf., *Ophiopogon japonicus* (Thunb.) Ker Gawl., *Atractylodes macrocephala* Koidz., *Adenophora triphylla* (Thunb.) A.DC. *and Astragalus membranaceus* Fisch. ex Bunge, have been shown to increase leukocytes, stimulate T and B lymphocyte proliferation, improve phagocyte capacity, and balance immunity[110–111].

Many compounds also participate in immune remodeling to alleviate respiratory symptoms. Flavonoids can boost immunity and reduce damage to the immune system[112]. During COVID-19 recovery, quercetin and luteolin can regulate immune function, promote T lymphocyte differentiation, and suppress pathological $CD4^+$ T lymphocytes[113]. As a primary flavonoid monomer in *Scutellaria baicalensis* Georgi, baicalin exerts anti-asthma effects by reducing IL-4, IL-6, IL-8, and IL-17 levels, rebalancing Th17 and Treg responses, and increasing IL-10 and IFN[114–115]. Moreover, baicalin reduces TGF-β1 and VEGF levels for airway remodeling in asthmatic mice[116]. The compound naringin, derived from *Citrus maxima* (Burm.) Merr., an effective TCM remedy for cough, suppresses airway hyperreactivity (AHR) and inflammation by inhibiting eosinophils and Th2 cells and by enhancing Th1 cells[117]. A component of *Glycyrrhiza glabra* L., licochalcone A (LA) can inhibit Th2-type cytokines, prevent monocyte adhesion, and reduce inflammation and oxidative stress to treat asthma[118].

Resveratrol, a natural phenol extracted from *Reynoutria japonica* Houtt., suppresses AHR, reduces eosinophilia and mucus hypersecretion by inhibiting IL-4 and IL-5; in addition, it also reduces pulmonary inflammation and superoxide production by regulating the expression of adenosine 5'-monophosphate-activated protein kinase (AMPK) in the lungs[119].

Furthermore, Astragaloside IV (AS-IV), the principal active ingredient found in *Astragalus membranaceus* Fisch. ex Bunge, has shown effective activity in decreasing inflammation and oxidative stress, reducing AHR, collagen deposition, mucus production by increasing Tregs and IFN-γ levels to treat asthma[120].

Phytochemicals with immunomodulatory effects share a "structure-target" regulatory model. Their functional groups (eg, phenolic hydroxyls, glycosidic chains) bind immune signal molecules, exerting multi-target effects on Th cell balance, oxidative stress, and cytokines. This forms a bidirectional mechanism: suppressing excessive immunity while boosting deficits. Such structure-based modulation defines a universal paradigm for phytomedicines in immune diseases, linking chemical structure to immunological balance.

### Neurological system

Sini powder (SNP) can effectively combat depression[121]. Research has shown that SNP can prolong sleep time and regulate the circadian rhythm of patients with depression[122]. In addition, animal experiments have shown that SNP can regulate hypothalamic pituitary adrenal axis, downregulate serum corticosterone and plasma adrenocorticotropin, and increase levels of hippocampal glucocorticoid receptors to treat depression[123].

The Kaixin powder (KXP), an herbal formula, can effectively improve depressive symptoms by reducing the levels of IL-1β, IL-2, and TNF-α in the hippocampus of mice[124].

In addition, the *Radix Bupleuri* and *Paeoniae Radix Alba* drug combination is widely accepted among the many classical antidepressant prescriptions in TCM[125]. To treat depression through reducing oxidative stress damage and inflammation, drug combinations of the *Radix Bupleuri* and *Paeoniae Radix Alba* are effective at reducing peroxidation products, and inhibiting nod-like receptor protein 3 (NLRP3) inflammasome expression, IL-6, and TNF-α secretion[125–126].

These formulae demonstrate systems-level therapeutic strategies that contrast with single-target pharmaceuticals by concurrently addressing: (1) neuroendocrine dysfunction, (2) neuroinflammatory cascades, and (3) oxidative damage—representing a paradigm of network pharmacology that aligns with the multicomponent pathology of depression and neurodegenerative diseases. Their multitarget mechanisms support enhanced efficacy in treatment-resistant cases with favorable safety profiles.

A variety of TCMs exhibit anti-fatigue properties, with particular efficacy in alleviating fatigue symptoms subsequent to viral infections. Persistent fatigue ranks among the most prevalent manifestations of LC. Ginseng, which primary bioactive constituents include saponins and polysaccharides, is closely implicated in neuroprotective effects and the modulation of neurotransmission, with a distinct therapeutic role in managing fatigue[127]. Furthermore, the administration of acanthopanax senticosus injections has been shown to mitigate postoperative fatigue syndrome, while extracts of acanthopanax senticosus also exert a significant fatigue-improving effect[127].

Ginseng total saponins (GTS) serve as antidepressants by reducing inflammation. Research has shown that GTS treatment alleviates depression-like behavioral impairments and decreases IL-6 and TNF-α mRNA in the hippocampus[128]. The isoquinoline alkaloid berberine, isolated from *Coptis chinensi*s Franch., also shows an antidepressant-like effect by improving mitochondrial and spinal morphology in the hippocampus[129]. As a result, the chemical reactions initiated by berberine convert tyrosine into dopamine, which can lead to better brain functioning[130].

A compound from Corydalis Rhizoma called tetrahydroberberine shows antianxiety properties and plays a significant neuroprotective role in Parkinson disease by blocking ATP-sensitive $K^+$ ion channels in the substantia nigra pars compacta[131]. The compound celastrol, from *Tripterygium wilfordii* Hook.f., relieves neuroinflammatory pain by inhibiting the expression of cyclooxygenase-2, upregulating the expression of sterile- and armadillo-motif-containing proteins, and reducing levels of IL-6, IL-17, and TNF-α[132–133].

Key neuroactive compounds show immunomodulatory effects *via* multiple mechanisms. These compounds bidirectionally regulate neural circuits and immune responses, addressing neuropsychiatric disorders by targeting neuroplasticity and neuroinflammation.

### Cardiovascular system

The Gualou Xiebai decoction (GLXB) possesses significant inflammatory and cardiac-protecting properties. GLXB can protect myocardial structure and ameliorate cardiac function by decreasing the level of IL-6[134]. Dangshen Erling decoction (DSEL) can downregulate IL-6 and TNF-α to improve myocardial inflammation, remodel heart function, and reduce myocardial fibrosis[135]. Liangui Ningxin decoction (LGNX), an effective antiarrhythmic formula, can shorten the duration and alleviate the severity of arrhythmias by maintaining intracellular $Ca^{2+}$ homeostasis[136].

These formulae exemplify the TCM principle of "simultaneous treatment of the symptomatic and root causes" by addressing immediate electrophysiological abnormalities (eg, arrhythmias), while systemically modulating the inflammatory microenvironment that drives cardiovascular pathology progression, offering advantages over single-target conventional drugs in chronic cardiovascular disease management.

Herbal products typically used in cardiovascular TCM target specific cardiac ion channels. Ginseng has been considered an effective herb for treating diseases for centuries, but its effects on cardiovascular diseases have only recently been confirmed through research[137]. $Ca^{2+}$ channels can be inhibited by ginsenosides, including Re, Rh2, and Rg3. Hypertensive remodeling can be reduced by Ginsenoside Rd by reversing $Ca^{2+}$ channel[138]. Ginsenoside Re modulates cardiac $K^+$ channel activation

through nitric oxide[139]. As well as regulating ion channels, total ginsenosides inhibit right ventricular hypertrophy[139]. In addition, ginsenoside Rg1 protects from left ventricular hypertrophy[140–141]. Ginsenoside Rb1 reduces myocardial infarction, ginsenoside Re inhibits electromechanical alternans[142].

Tanshinone IIA (Tan IIA), the main component of *Codonopsis pilosula* Nannf., has anti-inflammatory and anti-oxidant effects and has been used for treating cardiomyopathy, arrhythmia, and congenital heart defects[143]. Tan IIA regulates immune cell activation through a reduction in inflammation mediators and a restoration of abnormal signaling pathways that are crucial for immune cell development and function[144].

The saponin component AS-IV isolated from *Astragalus membranaceus* Fisch. ex Bunge can improve cardiac function, inhibit cardiac hypertrophy and ventricular remodeling by reducing oxidative stress, inhibiting calpain-1 activation, enhancing mitochondrial superoxide dismutase and catalase activity, and inhibiting transcription factor p65 (p65) and NF-κB[145]. AS-IV increases nuclear factor erythroid-2–related factor 2 and regulates the $Ca^{2+}$-mediated calcineurin signaling pathway for improving ventricular function and structure[146]. Additionally, AS-IV can reduce inflammation mediators such as TNF-α and IL-6[147].

The key cardiovascular-active compounds demonstrate dual cardioprotective and immunomodulatory properties through distinct mechanisms. These compounds collectively represent a class of "cardio-immunomodulators" that uniquely bridge electrophysiological stabilization and immune homeostasis.

### *Endocrine system*

There is evidence suggesting that chronic low-grade inflammation causes insulin resistance, which in turn leads to T2DM. The inflammatory markers associated with diabetes include adipokines, chemotactic proteins, TNF-α, IL-1β, and IL-17[148]. Diabetes patients can benefit from Jinqi Jiangtang Tablet (JQJTT)[149]. There is evidence that JQJTT could reduce the circulating Th17 frequency and serum IL-17 levels, as well as decrease C-reactive protein concentrations and NF-κB phosphorylation levels[149].

Zhibai Dihuang granule (ZBDH) can alleviate hyperthyroidism by regulating complement activation and inflammatory response, and by improving antigen recognition ability[150].

Jinlida granule are used to treat T2DM, improving insulin resistance, promoting insulin secretion, and lowering blood lipid levels[151–153]. With anti-inflammatory effects involving the NF-κB pathway, it could significantly improve hypothalamic-pituitary-thyroid axis dysfunction in DM[154].

Traditional Chinese endocrine formulae exhibit integrated metabolic-immune modulation through sophisticated multicomponent approaches. These formulae embody the TCM principle of "holistic regulation" by simultaneously addressing metabolic disorders and their underlying inflammatory drivers, offering a multidimensional therapeutic approach superior to single-target antidiabetic medications in managing diabetes-associated immune dysregulation.

*Radix Ginseng* can alleviate insulin resistance and promote immune homeostasis[155]. Ginsenoside is a significant active component in *Panax ginseng* C.A.Mey. and is known to elicit proven pharmacological effects. Ginsenoside Rg1 can improve insulin resistance and reduce the expression level of IL-1β in the blood[156]. Ginsenoside Re can regulate insulin resistance, modulate glucose metabolism, and regulate inflammatory cytokines[157]. Additionally, ginseng pectin can inhibit hyperglycemia and immune dysfunction independently or synergistically[158].

Artemisinin isolated from *Artemisia annua* L. can restore islet function and improve the microcirculation of the pancreas[159]. Artemether, as a derivative of artemisinin, is capable of reducing fasting blood glucose levels, improving insulin sensitivity, and increasing glucose tolerance[160]. Artemisinic acid, which is isolated from artemisinin, is also capable of significantly reducing IL-6 and improving insulin resistance[161]. Tan IIA can also reduce glucose intolerance and insulin resistance by regulating AMPK signaling and decreasing TNF-α and IL-6 levels[162].

The key endocrine-active compounds demonstrate dual metabolic and immunoregulatory properties through distinct mechanisms. These compounds collectively represent a class of "immunometabolic regulators" that bridge endocrine function and immune balance, offering advantages over conventional antidiabetic drugs by simultaneously targeting metabolic dysfunction and chronic low-grade inflammation.

### *Gastrointestinal system*

Jinhua Qinggan granule (JHQG)[163], Lianhua Qingwen granule (LHQW)[164], Xuebijing injection (XBJ)[165], Huashi Baidu granule (HSBD)[166], QFPD, and XFBD[167] were all highly effective in preventing and controlling COVID-19, and have played a crucial role in combating epidemics by treating diseases according to the patient's personality[168–169]. Considering gastrointestinal disorders, LHQW is the most effective for nausea, XBJ is the most effective for diarrhea, LHQW is the best for vomiting, JHQG is the best for inappetence[168]. XFBD reduces weight loss and tissue damage of the colon, attenuates intestinal disorders associated with inflammation, and improves intestinal flora[170]. This drug also modulates intestinal immunity by remodeling the Th1/Th2 ratio and has a therapeutic effect on respiratory disorders, such as pulmonary fibrosis and acute lung injury[171–173].

Traditional Chinese gastrointestinal formulae exhibit integrated gut-immune modulation through sophisticated multicomponent strategies. These formulae achieve superior clinical outcomes compared to single-target therapies by holistically addressing both gastrointestinal symptoms and their immunopathological underpinnings.

Flavonoids can alleviate COVID-19–induced gastrointestinal symptoms. Quercetin is extracted from natural plants and can inhibit viral entry into host cells and reduce diarrhea induced by SARS-CoV-2[174]. Quercetin can inhibit the inflammatory storm associated with

**Table 1**

**Potential immunity remodeling effects of TCM**

| Systems | Categories | Compounds/formulas name | Mechanism | Symptoms/ disease | Reference |
|---|---|---|---|---|---|
| Respiratory system | Compounds | *Codonopsis pilosula* (Franch.) Nannf.; *Ophiopogon japonicus* (Thunb.) Ker Gawl.; *Atractylodes macrocephala* Koidz.; *Adenophora triphylla* (Thunb.) A.DC.; *Astragalus membranaceus* Fisch. ex Bunge | Increase leukocytes, stimulate T and B lymphocyte proliferation, improve phagocyte capacity, and balance immunity | - | [120, 183] |
| | | Quercetin and luteolin | Regulate immune function, promote T lymphocyte differentiation, and suppress pathological $CD4^+$ T lymphocytes | LC | [113] |
| | | Baicalin | Reduce IL-4, IL-6, IL-8, IL-17, TGF-β1 and VEGF levels, rebalance Th17 and Treg responses, and increase IL-10 and IFN | Asthma | [114–116, 184] |
| | | Naringin | Inhibit eosinophils and Th2 cells, enhancing Th1 cells | Cough | [117] |
| | | Licochalcone A | Inhibit Th2-type cytokines, prevent monocyte adhesion, and reduce inflammation and oxidative stress | Asthma | [118] |
| | | Resveratrol | Inhibit IL-4 and IL-5 | Asthma | [119, 185] |
| | | Astragaloside IV | Decrease the levels of TNF-α and increasing Tregs and IFN-γ | Asthma | [120, 183] |
| | Formulas | Convalescent COVID-19 prescription | Inhibit TNF-α, IL-6, TGF-β1 and MMP9 | LC, Pulmonary fibrosis | [105] |
| | | Shenling Baizhu powder | Downregulate VEGF expression | Pulmonary fibrosis | [106] |
| | | Buzhong Yiqi decoction | Eliminate inflammation, reduce lung damage, and regulate immunity | LC | [107] |
| | | Qingfei Paidu decoction; Xuanfei Baidu decoction | Reduce IL-6 and TNF-α levels, inhibit NF-κB activities | - | [186] |
| | | Bufei Huoxue capsules | Reduce IL-4, IL-6, IL-10, IL-8, and TNF-α and keratinocyte growth factor as well as secretory immunoglobulin A and collagen fibers | LC | [107–108] |
| | | Bufei Yishen formula | Restores the balance of Th17/Treg, enhance anti-inflammatory cytokine production and decrease pro-inflammatory cytokine production | Chronic obstructive pulmonary disease | [109, 187] |
| Neurological system | Compounds | Ginseng total saponins | Alleviate depression-like behavioral impairments and decreases IL-6 and TNF-α mRNA | Depression | [128] |
| | | Isoquinoline alkaloid berberine | Improve mitochondrial and spinal morphology | Depression | |
| | | Tetrahydroberberine | Block ATP-sensitive $K^+$ ion channels | Anxiety | [131] |
| | | Celastrol | Reduce levels of IL-6, IL-17, and TNF-α | Neuroinflammatory pain | [133, 188–189] |
| | Formulas | Sini powder | Disrupt neurogenesis, increasing blood–brain barrier connections, balancing fibrinolytic activity, inhibiting NLRP3 and IL-6, and balancing the fibrinolytic system | Depression; sleep disorders | [122, 190–191] |
| | | Kaixin powder | Reduce the levels of IL-2, IL-6, TNF-α and increase IL-10, IFN-γ levels | Depression | [192] |
| | | *Radix Bupleuri* and *Paeoniae Radix Alba* | Reduce peroxidation products, and inhibit NLRP3 inflammasome expression, IL-6, and TNF-α secretion | Depression | [125–126] |

*(Continued)*

**Table 1**
**(Continued)**

| Systems | Categories | Compounds/formulas name | Mechanism | Symptoms/ disease | Reference |
|---|---|---|---|---|---|
| Cardiovascular system | Compounds | Ginsenoside Re, Rh2, and Rg3 | Inhibit $Ca^{2+}$ channels | Hypertension | [138] |
| | | Ginsenoside Rd | Reverse $Ca^{2+}$ channel | Hypertension | [138] |
| | | Ginsenoside Re | Modulate cardiac $K^{+}$ channel activation through nitric oxide | - | [139] |
| | | Total ginsenosides | Inhibit right ventricular hypertrophy | - | [139] |
| | | Ginsenoside Rg1 | Protect left ventricular hypertrophy | - | [140–141] |
| | | Ginsenoside Rb1 | Inhibit electromechanical alternans | Myocardial infarction | [142] |
| | | Tanshinone IIA | Regulate immune cell activation through a reduction in inflammation mediators and a restoration of abnormal signaling pathways | Cardiomyopathy; arrhythmia; congenital heart defects | [144] |
| | | Astragaloside IV | Reduce oxidative stress, inhibit calpain-1 activation, enhance mitochondrial superoxide dismutase and catalase activity, and inhibit p65 and NF-κB; increase nuclear factor erythroid-2–related factor 2 and regulates the $Ca^{2+}$-mediated calcineurin signaling pathway; reduce TNF-α and IL-6 | Cardiac hypertrophy and ventricular remodeling | [146–147, 193] |
| | Formulas | Gualou Xiebai decoction | Reduce IL-6 | Cardiac dysfunction | [134] |
| | | Dangshen Erling decoction | Downregulate IL-6 and TNF-α | Myocardial inflammation, myocardial fibrosis | [135] |
| | | Liangui Ningxin decoction | Maintain intracellular $Ca^{2+}$ homeostasis | Arrhythmias | [136] |
| Endocrine system | Compounds | Ginsenoside Rg1 | Reduce IL-1β | Insulin resistance | [156] |
| | | Ginsenoside Re | Modulate glucose metabolism and regulate inflammatory cytokines | Insulin resistance | [157] |
| | | Ginseng pectin | - | Hyperglycemia and immune dysfunction | [158] |
| | | Artemisinin | Reduce fasting blood glucose levels, improve insulin sensitivity, and increase glucose tolerance significantly | Insulin resistance | [160] |
| | | Artemisinic acid | Reduce IL-6 | Insulin resistance | [161] |
| | | Tanshinone IIA | Regulate AMPK signaling and decrease TNF-α and IL-6 levels | Glucose intolerance and insulin resistance | [162] |
| | Formulas | Jinqi Jiangtang tablet | Reduce the circulating Th17 frequency and serum IL-17 levels, as well as decrease C-reactive protein concentrations and NF-κB phosphorylation levels | Diabetes | [149, 194] |
| | | Zhibai Dihuang granule | Regulate complement activation and inflammatory response, and improve antigen recognition ability | Hyperthyroidism | [150, 195] |
| | | Jinlida granule | Improve hypothalamic-pituitary-thyroid axis dysfunction; regulate NF-κB pathway | T2DM | [151–154] |
| Gastrointestinal system | Compounds | Quercetin | Inhibit viral entry into host cells; inhibit inflammatory storm; regulate gastrointestinal hormones and increase gastrointestinal motility | Diarrhea; inappetence; constipation | [174–178] |
| | | Sennoside A | Regulate the expression of aquaporin, accelerate the peristaltic movement of the colon, and regulate the gut microbiota | Constipation | [179] |

*(Continued)*

**Table 1**
**(Continued)**

| Systems | Categories | Compounds/formulas name | Mechanism | Symptoms/ disease | Reference |
|---|---|---|---|---|---|
| | | Polydatin | Reduce colonic oxidative stress and improve colon epithelial barrier dysfunction | Diarrhea and abdominal pain | [180–181] |
| | Formulas | Jinhua Qinggan granule | - | Inappetence | [163] |
| | | Lianhua Qingwen granule | - | Nausea | [164] |
| | | Xuebijing injection | - | Diarrhea | [165] |
| | | Xuanfei Baidu decoction | Reduce weight loss and colonic tissue damage, and improve intestinal flora | Intestinal disorders associated with inflammation | [170–173] |

AMPK: Adenosine 5'-monophosphate-activated protein kinase; IFN-γ: Interferon gamma; IL: Interleukin; LC: Long coronavirus disease 2019; MMP9: Matrix metalloproteinase 9; NF-κB: Nuclear factor-kappa B; NLRP3: Nod-like receptor protein 3; T2DM: Type 2 diabetes; TCM: Traditional Chinese Medicine; TGF-β1: Transforming growth factor beta 1; Th: T helper; TNF-α: Tumor necrosis factor alpha; Treg: Th cells inhibits regulatory T; VEGF: Vascular endothelial growth factor.

viral or bacterial infections and improve the appetite of COVID-19 patients[175–177]. Moreover, quercetin can improve constipation by regulating gastrointestinal hormones and increasing gastrointestinal motility[178].

Sennoside A is a laxative compound extracted from *Senna alexandrina* Mill. Sennoside A can improve constipation by regulating the expression of aquaporin, accelerating the peristaltic movement of the colon, and regulating the gut microbiota[179]. Furthermore, Polydatin is a phenolic glucoside extracted from *Reynoutria japonica* Houtt. In addition to improving symptoms of diarrhea and abdominal pain, polydatin reduces oxidative stress of the colon and improves colon epithelial barrier dysfunction[180–181].

The key gastrointestinal-active compounds demonstrate dual gut-protective and immunoregulatory properties through distinct mechanisms. These compounds collectively target the gut-immune axis through both luminal and systemic mechanisms, offering advantages over conventional gastrointestinal drugs by concurrently addressing symptoms and underlying mucosal immune dysfunction (Tables 1 and 2).

## Conclusion

LC impacts multiple organs; for example, it causes abnormalities in nervous, respiratory, cardiovascular, gastrointestinal, and muscle systems. Millions of people worldwide have already been affected by it, and the number keeps increasing[1,107]. It is important to raise public awareness of LC's risk factors and take appropriate measures to manage it. Currently, there are few diagnostic and treatment options, and clinical trials are necessary to confirm the underlying biological mechanisms, such as persistence of the virus, chronic inflammation, and/or immune response/autoantibody production. Further research is needed to verify the importance of immune perturbations within affected organs, the immune response to acute infection, chronic inflammation, and immune recovery after infection.

Clinical symptoms of LC patients can be effectively improved by TCM[182] since data support TCM actions in promoting the repair of damaged organ tissues and suggest a possible action in reducing the side effects of glucocorticoids, improving cardiopulmonary function, and relieving anxiety. Immune dysregulation contributes to the pathogenesis of LC patients; regulating the immune remodeling of the body may thus represent an important mechanism for the treatment of LC in TCM. However, there are still undefined aspects associated with the treatment of LC with TCM. The effectiveness of TCM in treating LC is supported by extensive evidence-based medicine, but there is a lack of guidance and tracking management for patients with TCM in home rehabilitation. The research and treatment methods of TCM that relate to LC must be further organized and optimized. The efficacy and mechanism of TCM in treating LC needs to be clarified in the future through clinical trials and basic research, as well as through the development of more effective rehabilitation plans based on a combination of Chinese and Western medicine.

## Conflict of interest statement

Mirko Baruscotti is an editorial board member of this journal. The other authors declare no conflict of interest.

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## Author contributions

Yanyan Wang and Mirko Baruscotti performed conceptualization, writing—review and editing, supervision. Qianru Zhao, Annalisa Bucchi, and Zhihua Yang performed writing—original draft preparation. Qianru Zhao and David Molla performed visualization. Yanyan Wang performed project administration. All authors have read and agreed to the published version of the manuscript.

**Table 2**

**Composition of formulas**

| Systems | Formulas | Herb name | References |
|---|---|---|---|
| Respiratory system | CCP | Astragali Radix (Huang qi)<br>Codonopsis Radix (Dang shen)<br>Atractylodes macrocephala Koidz. (Bai zhu)<br>Adenophprae Ae Radix (Nan sha shen)<br>Glehniae Radix (Bei sha shen)<br>Citrus Reticulata (Chen pi)<br>Poria (Fu ling)<br>Ophiopogonis Radix (Mai dong)<br>Radix Salviae (Dan shen)<br>Fritillariae Thunbrgii Bulbus (Zhe bei mu)<br>Hirudinis Rhynchobdellae (Shui zhi)<br>Crataegi Folium (Shan zha)<br>Massa Medicata Fermentata (Shen qu)<br>Hordei Fructus Germinatus (Mai ya)<br>Rhizoma Dioscoreae (Shan yao)<br>Eupolyphaga Steleophaga (Tu bie chong)<br>Glycyrrhizae Radix et Rhizoma (Gan cao)<br>Pinelliae Rhizoma (Ban xia) | [105] |
| | SLBZ | Glycyrrhizae Radix et Rhizoma (Gan cao)<br>Radix Ginseng (Ren shen)<br>Amomi Fructus (Sha ren)<br>Atractylodis Macrocephalae Rhizoma (Bai zhu)<br>Lablab Semen Album (Bai bian dou)<br>Poria (Fu ling)<br>Rhizoma Dioscoreae (Shan yao)<br>Coicis Semen (Yi yi ren)<br>Nelumbinis Semen (Lian zi)<br>Platycodon Grandiforus (Jie geng) | [106] |
| | BZYQ | Astragali Radix (Huang qi)<br>Atractylodes macrocephala Koidz. (Bai zhu)<br>Citrus Reticulata (Chen pi)<br>Cimicifugae Rhizoma (Sheng ma)<br>Radix Bupleuri (Chai hu)<br>Radix Ginseng (Ren shen)<br>Glycyrrhizae Radix et Rhizoma (Gan cao)<br>Angelicae Sinensis Radix (Dang gui) | [107, 196] |
| | QFPD | Asari Radix et Rhizoma (Xi xin)<br>Belamcandae Rhizoma (She gan)<br>Rhizoma Dioscoreae (Shan yao)<br>Farfarae Flos (Kuan dong hua)<br>Aurantii Fructus Immaturus (Zhi shi)<br>Asteris Radix Et Rhizoma (Zi wan)<br>Amygdalus Communis Vas (Ku xing ren)<br>Citrus Reticulata (Chen pi)<br>Zingiberis Rhizoma Recens (Sheng jiang)<br>Scutellariae Radix (Huang qin)<br>Cinnamomi Ramulus (Gui zhi)<br>Ephedra Herba (Ma huang)<br>Pinelliae Rhizoma Praeparatum (Jiang ban xia)<br>Poria (Fu ling)<br>Pogostemonis Herba (Huo xiang)<br>Glycyrrhizae Radix et Rhizoma (Gan cao)<br>Gypsum Fibrosum (Shi gao)<br>Alismatis Rhizoma (Ze xie)<br>*Polypori Umbellati Rhizoma* (Zhu ling)<br>Atractylodes macrocephala Koidz. (Bai zhu)<br>Radix Bupleuri (Chai hu)<br>Belamcandae Rhizoma (She gan) | [107] |

*(Continued)*

**Table 2**
**(Continued)**

| Systems | Formulas | Herb name | References |
|---|---|---|---|
| | XFBD | Citri Grandis Exocarpium (Hua ju hong)<br>Verbenae Herb (Ma bian cao)<br>Ephedra Herba (Ma huang)<br>Glycyrrhizae Radix et Rhizoma (Gan cao)<br>Amygdalus Communis Vas (Ku xing ren)<br>Gypsum Fibrosum (Shi gao)<br>Artemisiae Annuae Herba (Qing hao)<br>Polygoni Cuspidati Rhizoma et Radix (Hu zhang)<br>Lepidii Semen Descurainiae Semen (Ting li zi)<br>Coicis Semen (Yi yi ren)<br>Pogostemonis Herba (Guang huo xiang)<br>Atractylodis Rhizoma (Cang zhu)<br>Imperatae Rhizoma (Mao gen) | [107, 197] |
| | BFHX | Psoraleae Fructus (Bu gu zhi)<br>Astragali Radix (Huang qi)<br>Radix Paeoniae Rubra (Chishao) | [108] |
| | BYF | Radix Ginseng (Ren shen)<br>Astragali Radix (Huang qi)<br>Corni Fructus (Shan zhu yu)<br>Lycii Fructus (Gou qi zi)<br>Schisandrae Chinensis Fructus (Wu wei zi)<br>Fritillariae Thunbrgii Bulbus (Zhe bei mu)<br>Perilla Frutescens (Zi su)<br>Citrus Reticulata (Chen pi)<br>Epimrdii Herba (Yin yang huo)<br>Radix Paeoniae Rubra (Chi shao)<br>Pheretima (Di long)<br>Ardisiae Japonicae Herba (Ai di cha) | [109] |
| Neurological system | SNP | Radix Bupleuri (Chai hu)<br>Aurantii Fructus Immaturus (Zhi shi)<br>Paeoniae Radix Alba (Bai shao)<br>Glycyrrhizae Radix et Rhizoma (Gan cao) | [191] |
| | KXP | Radix Ginseng (Ren shen)<br>Poria (Fu ling)<br>Polygalae Radix (Yuan zhi)<br>Acoritataninowii Rhizoma (Shi chang pu) | [192] |
| | *Radix Bupleuri* and *Paeoniae Radix Alba* | Radix Bupleuri (Chai hu)<br>Paeoniae Radix Alba (Bai shao) | [125] |
| Cardiovascular system | GLXB | Trichosanthes Kirilowii Maxim (Gua lou)<br>Allii Macrostemonis Bulbus (Xie bai) | [134] |
| | DSEL | Odonopsis Radix (Dang shen)<br>Atractylodis Macrocephalae Rhizoma (Bai zhu)<br>Smilacis Glabrae Rhixoma (Tu fu ling)<br>Saposhnikoviae Radix (Fang feng)<br>Morindae Officinalis Radix et Rhizoma (Ba ji tian)<br>Glycyrrhizae Radix et Rhizoma (Gan cao) | [135] |
| | LGNX | Coptidis Rhizoma (Huang lian)<br>Ophiopogonis Radix (Mai dong)<br>Radix Puerariae (Ge gen)<br>Citrus Reticulata (Chen pi)<br>Pinelliae Rhizoma (Ban xia)<br>Poria (Fu ling)<br>Cinnanmomi Cortex (Rou gui)<br>Corydalis Rhizoma (Yan hu suo)<br>Glycyrrhizae Radix et Rhizoma (Gan cao) | [136] |
| Endocrine system | JQJTT | Coptidis Rhizoma (Huang lian)<br>Astragali Radix (Huang qi)<br>Lonicerae Japonicae Flos (Jin yin hua) | [149] |

*(Continued)*

**Table 2**
**(Continued)**

| Systems | Formulas | Herb name | References |
|---|---|---|---|
| | ZBDH | Corni Fructus (Shan zhu yu)<br>Rehmanniae Radix Praeparata (Shu di huang)<br>Rhizoma Dioscoreae (Shan yao)<br>Phellodendri Chinrnsis Cortex (Huang bo)<br>Anemarrhenae Rhizoma (Zhi mu)<br>Cortex Moutan (Mu dan pi)<br>Alismatis Rhizoma (Ze xie)<br>Poria (Fu ling) | [195] |
| | Jinlida granule | Radix Ginseng (Ren shen)<br>Polygonati Rhizoma (Huang jing)<br>Atractylodis Rhizoma (Cang zhu)<br>Sophorae Flavescentis Radix (Ku shen)<br>Ophiopogonis Radix (Mai dong)<br>Radix Rehmanniae Recens (Di huang)<br>Polygonum Multiflorum Radix Praeparata (He shou wu)<br>Corni Fructus (Shan zhu yu)<br>Coptidis Rhizoma (Huang lian)<br>Anemarrhenae Rhizoma (Zhi mu)<br>Epimrdii Herba (Yin yang huo)<br>Codonopsis pilosula Nannf.<br>Radix Salviae (Dan shen)<br>Poria (Fu ling)<br>Eupatorium Fortunei Turcz (Pei lan)<br>Litchi Semen (Li zhi he)<br>Lycii Cortex (Di gu pi) | [151] |
| Gastrointestinal system | JHQG | Lonicerae Japonicae Flos (Jin yin hua)<br>Gypsum Fibrosum (Shi gao)<br>Ephedra Herba (Ma huang)<br>Amygdalus Communis Vas (Ku xing ren)<br>Scutellariae Radix (Huang qin)<br>Forsythiae Fructus (Lian qiao)<br>Fritillariae Thunbrgii Bulbus (Zhe bei mu)<br>Anemarrhenae Rhizoma (Zhi mu)<br>Fructus Arctii (Niu bang zi)<br>Artemisiae Annuae Herba (Qing hao)<br>Menthae Herba (Bo he)<br>Glycyrrhizae Radix et Rhizoma (Gan cao) | [163] |
| | LHQW | Forsythiae Fructus (Lian qiao)<br>Lonicerae Japonicae Flos (Jin yin hua)<br>Ephedra Herba (Ma huang)<br>Amygdalus Communis Vas (Ku xing ren)<br>Isatidis Radix (Ban lan gen)<br>Dryopteridis Crassirhizomatis Rhizoma (Mian ma guan zhong)<br>Houttuyniae Herba (Yu xing cao)<br>Pogostemonis Herba (Guang huo xiang)<br>Radix Rhei Et Rhizome (Da huang)<br>Rhodiolae Crenulatae Radix et Rhizoma (Hong jing tian)<br>Glycyrrhizae Radix et Rhizoma (Gan cao)<br>Mentholum (Bo he nao)<br>Gypsum Fibrosum (Shi gao) | [164] |
| | XBJ | Chuanxiong Rhizoma (Chuan xiong)<br>Radix Salviae (Dan shen)<br>Radix Paeoniae Rubra (Chi shao)<br>Carthami Flos (Hong hua)<br>Angelicae Sinensis Radix (Dang gui) | [165] |

*(Continued)*

**Table 2**
**(Continued)**

| Systems | Formulas | Herb name | References |
|---|---|---|---|
| | HSBD | Ephedra Herba (Ma huang)<br>Amygdalus Communis Vas (Ku xin gren)<br>Glycyrrhizae Radix et Rhizoma (Gan cao)<br>Pogostemonis Herba (Huo xiang)<br>Atractylodis Rhizoma (Cang zhu)<br>Pinelliae Rhizoma (Ban xia)<br>Poria (Fu ling)<br>Radix Paeoniae Rubra (Chi shao)<br>Radix Rhei Et Rhizome (Da huang)<br>Astragali Radix (Huang qi)<br>Gypsum Fibrosum (Shi gao) | [166] |

BFHX: Bufei Huoxue capsules; BYF: Bufei Yishen formula; BZTQ: Buzhong Yiqi decoction; CCP: Convalescent coronavirus disease 2019 prescription; DSEL: Dangshen Erling decoction; GLXB: Gualou Xiebai decoction; HSBD: Huashi Baidu granule; JHQG: Jinhua Qinggan granule; JQJTT: Jinqi Jiangtang tablet; KXP: Kaixin powder; LGNX: Liangui Ningxin decoction; LHQW: Lianhua Qingwen granule; QFPD: Qingfei Paidu decoction; SLBZ: Shenling Baizhu powder; SNP: Sini powder; XBJ: Xuebijing injection; XFBD: Xuanfei Baidu decoction; ZBDH: Zhibai Dihuang granule.

## 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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