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Review



Traditional Chinese medicine against COVID-19: Role of the gut microbiota

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ABSTRACT

Coronavirus disease 2019 (COVID-19) is an acute respiratory infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and it has become a public health concern worldwide. In addition to respiratory symptoms, some COVID-19 patients also show various gastrointestinal symptoms and even consider gastrointestinal symptoms to be the first manifestation. A large amount of evidence has shown that SARS-CoV-2 infection could disrupt the gut microbiota balance, and disorders of the gut microbiota could aggravate the condition of COVID-19 patients. Therefore, maintaining the gut microbiota balance is expected to become a potential new therapeutic target for treating COVID-19. Traditional Chinese medicine (TCM) has significant effects in all stages of the prevention and treatment of COVID-19. It can adjust the gut microbiota and is an ideal intestinal microecological regulator. This review summarizes the advantages and clinical efficacy of TCM in the treatment of COVID-19 and expounds on the relationship between TCM and the gut microbiota, the relationship between COVID-19 and the gut microbiota, the mechanism of gut microbiota disorders induced by SARS-CoV-2, the relationship between cytokine storms and the gut microbiota, and the role and mechanism of TCM in preventing and treating COVID-19 by regulating the gut microbiota to provide new research ideas for TCM in the prevention and treatment of COVID-19.

1. Introduction

In late December 2019, several health institutions reported patients with unexplained pneumonia related to epidemiology in Wuhan, Hubei Province, China. On January 7, 2020, Chinese scientists isolated the pathogenic coronavirus for the first time from respiratory tract samples of patients in Wuhan and sequenced the full length of the genome [1]. On February 11, the International Committee on Taxonomy of Viruses

(ICTV) and the World Health Organization (WHO) named the virus and the disease that it caused severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease 2019 (COVID-19), respectively [2,3]. COVID-19 is extremely harmful, with the characteristics of rapid transmission, strong pathogenicity, and poor prognosis. On March 12, the WHO declared that the outbreak of COVID-19 constituted a global "pandemic" [4]. Because of the lack of drugs targeting SARS-CoV-2 specifically, as of February 26, 2022, the cumulative number of

Abbreviations: COVID-19, Coronavirus Disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TCM, traditional Chinese medicine; WHO, World Health Organization; CNKI, China National Knowledge Infrastructure Database; VIP, VIP Chinese Science and Technology Journal Database(VIP); CBM, Chinese BioMedical Literature Database; ARDS, acute respiratory distress syndromes; MODS, multiple organ dysfunction syndromes; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IL, interleukin; CK, creatine kinase; CK-MB, creatine kinase-myocardial band; LDH, lactate dehydrogenase; BUN, blood urea nitrogen; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Scr, serum creatinine; TNF, tumor necrosis factor; MERS-CoV, middle east respiratory syndrome coronavirus; ACE2, angiotensin-converting enzyme 2; TMPRSS2, transmembrane protease serine 2; G-SCF, granulocyte colony-stimulating factor; SCFAs, short-chain fatty acids.

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COVID-19 cases globally has surpassed 433 million in 216 countries, areas, and territories and more than 5.96 million confirmed deaths [5]. Although significant progress has been made in clinical and vaccine research, many countries are still experiencing or have experienced a second or third wave of the COVID-19 pandemic, mainly due to mutations of SARS-CoV-2 [6,7].

The initial symptoms of COVID-19 patients are mainly characterized by fever, fatigue, and a dry cough. Clinical studies have found that SARS-CoV-2 can also cause digestive symptoms, such as diarrhoea, abdominal pain, nausea, and vomiting [8–11]. Clinical data have shown that a considerable proportion of COVID-19 patients have symptoms related to intestinal flora disturbance, indicating that the SARS-CoV-2 virus could cause the problem of intestinal microecological imbalance, especially in critically ill patients with poor prognoses [11,12]. Compared with non-COVID-19 patients, the composition of the gut microbiota of COVID-19 patients has changed significantly, regardless of whether the patients have received medication [12,13]. Therefore, there could be a close relationship between the intestinal flora and SARS-CoV-2 infection [14]. The diagnosis and treatment of COVID-19 (8th trial edition) [15] clearly mentions that "intestinal microecological regulators could be used to maintain intestinal microecological balance and prevent secondary infection". Studies have shown that traditional Chinese medicine (TCM) is an effective microecological regulator that has the functions of adjusting imbalances in the intestinal flora, promoting the growth of beneficial bacteria, and inhibiting the excessive reproduction of harmful bacteria. In the prevention and control of this epidemic, TCM has been deeply involved in the whole process of prevention, treatment, and rehabilitation, complementing and cooperating with Western medicine, making important contributions and playing a unique role in the comprehensive control of the COVID-19 epidemic [16]. We performed the comprehensive retrieval of electronic databases in both Chinese and English (the China National Knowledge Infrastructure Database(CNKI), VIP Chinese Science and Technology Journal Database(VIP), WangFang Database, Chinese BioMedical Literature Database (CBM), PubMed and Embase) for collecting the published research from inception to December 10, 2021. Eventually, we summarized 69 representative clinical trials, including 19 randomized, controlled trials (RCTs), 24 retrospective cohort studies (RCSs), 10 case-control studies (CCSs), and 16 others. This review mainly summarizes the clinical efficacy of TCM in the prevention and treatment of COVID-19; the relationship between the gut microbiota and TCM; COVID-19, SARS-CoV-2, and inflammatory storms; and how TCM regulates the gut microbiota to prevent and treat COVID-19 to provide new strategies and new targets for the prevention and treatment of COVID-19.

2. The advantages of TCM for COVID-19

COVID-19 has the characteristics of rapid onset, strong infectivity, and easy spread. It belongs to the category of "dampness toxin epidemics" in TCM, and the main nature of the disease is as a dampness toxin. According to the theory of TCM, the disease is mainly located in the lungs and spleen. The basic pathogenesis is "dampness, toxin, heat, phlegm, blood stasis and deficiency" [17–20]. Early clinical manifestations of the disease can include fever or no fever, and fever is often accompanied by multiple symptoms of hiding fever, dry coughing, fatigue, vomiting, loose stools, diarrhoea, and other digestive symptoms. The tongue coating is generally greasy and has obvious dampness toxicity from the disease [21]. In the whole clinical process, attention must be paid to eliminating dampness, resolving turbidity, eliminating filth and removing toxicity, as well as the effects of blood stasis [19]. TCM has been used to treat epidemic diseases since ancient times and has accumulated abundant successful experience in the prevention and treatment of epidemic diseases for thousands of years [22–24]. The advantage of TCM is that, even if the cause of the disease is unknown, a set of corresponding prescriptions can be proposed based on the clinical symptoms under the guidance of the theory of syndrome differentiation

and treatment, which can relieve clinical symptoms, shorten the course of the disease, and prevent deterioration due to the disease [25,26].

3. Clinical efficacy of TCM in the prevention and treatment of COVID-19

In the prevention and treatment of COVID-19, TCM is an irreplaceable main force [27]. Zhang et al. [28] reported that early treatment with TCM could reduce the inflammatory response, regulate immune function, promote the absorption of pulmonary inflammation, and reduce mortality in patients with severe COVID-19. The integration of traditional Chinese and Western medicine had a good effect on COVID-19, and it could improve the rate of alleviation of fever, coughing, expectoration, fatigue, chest tightness, and anorexia; shorten the duration of fever and coughing; shorten the hospital stay; reduce the severity of illness; promote the absorption of pulmonary inflammation and nucleic acid negative conversion; and improve the overall response rate and cure rate [29–43].

We independently searched the clinical trials of TCM treating COVID-19 in the relevant databases, including the CNKI, VIP, Wanfang Database, CMB, PubMed, and Embase. The search time was from inception to December 10, 2021. On the one hand, the following terms for COVID-19 were adopted: "novel coronavirus pneumonia", "new coronary pneumonia", "NCP", "New Coronavirus", "2019 novel coronavirus", "COVID-19", "2019-nCoV", "coronavirus disease 2019", "coronavirus disease-19", "severe acute respiratory syndrome coronavirus 2", and "SARS-CoV-2". On the other hand, the search terms for TCM mainly included "traditional Chinese medicine", "Chinese medicine", "Chinese and Western medicine", and "prescription". A total of 69 representative clinical trials, including 19 randomized, controlled trials (RCTs), 24 retrospective cohort studies (RCSs), 10 case-control studies (CCSs), and 16 others, were completed and summarized [38,44–48, 50–67,69–93,95,97–112,114–116]. According to the available clinical data, there have been many clinical trials on the clinical advantages of TCM in the prevention and treatment of COVID-19, including suspected stages, mild stages, moderate stages, severe stages, critical stages, and convalescent stages, as shown in Fig. 1. The clinical evidence for TCM for COVID-19 is summarized in Table 1. In addition, the relationship of TCM with its constituents is depicted in Fig. 2.

For suspected COVID-19 patients: 1) Lianhua Qingwen granules [44, 45] and Xiaochaihu decoction combined with Yupingfeng powder [46] significantly improved the clinical symptoms of fever, cough, phlegm, fatigue, and shortness of breath; Lianhua Qingwen granules [45] relieved gastrointestinal symptoms; and 2) Xiaochaihu decoction combined with Yupingfeng powder [46] reduced the level of C-reactive protein (CRP) and improved lung CT imaging. For asymptomatic COVID-19 patients, Chaihu Ganlu decoction [47] and Lanxiang Jiedu oral liquid [48] could shorten the nucleic acid negative conversion time and hospital stay and prevent deterioration due to the disease.

COVID-19 patients have the most typical clinical symptoms of fever, coughing, and fatigue. Therefore, alleviating these clinical symptoms is crucial for the prevention and treatment of COVID-19 [49]. For mild or moderate COVID-19 patients: 1) Qingfei Paidu decoction [50], Lianhua Qingwen granules [51–53], Jinhua Qinggan granules [54], Shufeng Jiedu capsules [55,56], Maxing Shigan decoction [57], Xiyanning injection [58], Jinbei oral liquid [59], Huoxiang Zhengqi [60], Toujie Quwen granules [61], Jinqiang Xuanfei Jiedu mixture [62], Ganlu Xiaodu decoction [63], Lianhua Qingke granules [64], Jinyinhua oral liquid [65], and Sanxiaoyin modified and subtracted prescription [66] alleviated the main clinical symptoms of fever, coughing, and fatigue; Lianhua Qingwen granules [52], Ganlu Xiaodu decoction [63], Lianhua Qingke granules [64], Jinyinhua oral liquid [65,67], and Jinye Baidu granules [68] reduced the rate of conversion from mild or moderate cases to severe or critical cases; 2) Lianhua Qingwen granules [69], Qingfei Paidu decoction [50], Shufeng Jiedu capsules [55], Maxing Shigan decoction [57], Reduning injection [70], Xiyanning injection

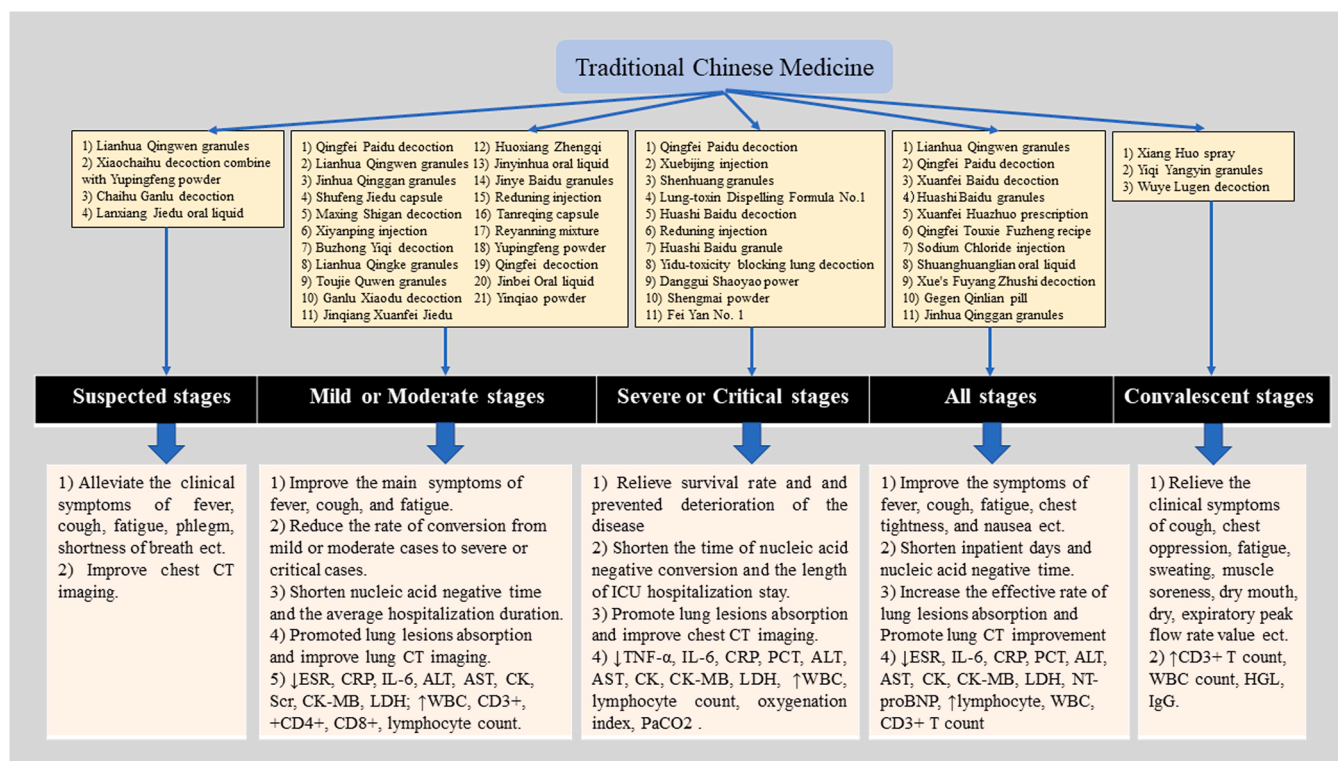


Fig. 1. Clinical advantages of TCM in the prevention and treatment of the COVID-19.

[58], Tanreqing capsules [71], Reyanning mixture [72], Jinbei oral liquid [59], Jiawei Yupingfeng powder [73], Qingfei decoction [74], Ganlu Xiaodu decoction [63], Buzhong Yiqi decoction [75], Jinyinhua liquid [67], Yinqiao powder combined with modified Sanren decoction [76], and Sanxiaoyin modified and subtracted prescription [66] shortened nucleic acid negative time and the average hospitalization; Lianhua Qingwen granules [69], Qingfei Paidu decoction [50], Shufeng Jiedu capsules [56,77], Reduning injection [70], Qingfei decoction [74], Ganlu Xiaodu decoction [63], Lianhua Qingke granules [64], Jinyinhua liquid [67], Xuebijing injection [78], Reyanning mixture [72], and Sanxiaoyin modified and subtracted prescription [66] promoted the absorption of pulmonary inflammation or improved chest CT imaging; and 3) Sanxiaoyin modified and subtracted prescription [66], Lianhua Qingwen granules [79], Jiawei Yupingfeng powder [73], Toujie Quwen granules [61,80], and Buzhong Yiqi decoction [75] decreased the levels of erythrocyte sedimentation rate (ESR) or CRP, and increased lymphocyte count; Lianhua Qingwen granules [79] reduced the level of D-dimer and increased the levels of albumin and haemoglobin; Qingfei Paidu decoction [81] reduced the levels of CRP, creatine kinase (CK), creatine kinase-myocardial band (CK-MB), lactate dehydrogenase (LDH), and blood urea nitrogen (BUN); Moxing Shigan decoction [57] decreased the levels of CRP, interleukin-6 (IL-6), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and serum creatinine (Scr), and increased CD4 + T and CD8 + T cell counts; and Tanreqing capsule [71] increased CD3 + T cell counts.

Severe or critical COVID-19 patients have the main factors directly affecting mortality. Treating severe cases is crucial since they can easily develop into critical cases, or the patients can even eventually die without timely and effective treatment [26,82]. The Diagnosis and Treatment Protocol for COVID-19 (trial version 8 revision) [15], formulated by the National Health Commission of the People's Republic of China, pointed out that, in severe cases, dyspnoea and/or hypoxemia usually occur one week after disease onset, and some severe patients have rapid progression to acute respiratory distress syndrome (ARDS), septic shock, refractory metabolic acidosis, coagulation disorders, and

multiple organ failure. Therefore, to reduce the mortality rate of COVID-19, it is necessary to apply more active and effective treatments to prevent the development of COVID-19. For severe or critical COVID-19 patients: 1) Qingfei Paidu decoction [38,83], Xuebijing injection [84,85], Shenhuang granules [86], Lung-toxin Dispelling Formula No. 1 [87], and Huashi Baidu decoction [88] improved the survival rate and prevented deterioration due to the disease; Xuebijing injection [84] and Reduning injection [89] shortened the length of intensive care unit (ICU) hospitalization; 2) Qingfei Paidu decoction [38], Huashi Baidu granules [90] Reduning injection [89], Xuebijing injection [84, 85], "Fei Yan No. 1" [91], and Danggui Shaoyao powder [92] shortened the time of nucleic acid negative conversion or improved the ratio of nucleic acid negative conversion; Qingfei Paidu decoction [38,83], Huashi Baidu granules [90], Shengmai powder [93], Shenhuang granule [86], "Fei Yan No. 1" [91], and Danggui Shaoyao powder [92] promoted the absorption of pulmonary inflammation and improved chest CT imaging; and 3) Qingfei Paidu decoction [38,83], Reduning injection [89], Xuebijing injection [84], and Huashi Baidu decoction [88] reduced the levels of IL-6, tumour necrosis factor-α (TNF-α), and CRP and increased the white blood cell (WBC) count; Qingfei Paidu decoction [38] decreased the levels of ALT, AST, LDH, ESR, and procalcitonin (PCT) and improved lymphocyte counts; "Fei Yan No. 1" [91] and Danggui Shaoyao powder [92] decreased the level of CRP and leukocyte counts; Shengmai powder [93], Xuebijing injection [85], and Huashi Baidu decoction [88] reduced the level of ESR; Xuebijing injection [94] improved the oxygenation index, PaCO₂, and lymphocyte counts; and Yidu-toxicity blocking lung decoction [95] ameliorated inflammation by decreasing the levels of IL-6 and TNF-α.

For the clinical treatment period (mild, moderate, severe, and critical COVID-19 patients): 1) Lianhua Qingwen granules [96], Qingfei Paidu decoction [97–101], Xuanfei Baidu decoction [102], Huashi Baidu granules [103], Xuanfei Huazhuo prescription [104], and sodium chloride injection [105] relieved the clinical symptoms of fever, coughing, fatigue, chest tightness and loss of appetite; Gegen Qinlian pills [106] improved the clinical symptoms of coughing, chest tightness,

Table 1
The clinical evidence of TCM for COVID-19.

NO	Name of traditional Chinese medicine	Compositions	Type of study	Location of study	Intervention	Control	Severity classification	Treatment duration	Main findings	References
1	BuZhong YiQi decoction (BZYQ)	Huangqi (Astragali Radix), Renshen (Ginseng Radix Et Rhizoma), Gancao (Glycyrrhizae Radix Et Rhizoma), Baizhu (Atractylodis Macrocephalae Rhizoma), Chenpi (Citri Reticulatae Pericarpium), Danggui (Angelicae Sinensis Radix), Shengma (Cimicifugae Rhizoma), Chaihu (Bupleuri Radix)	Case-control studies(CCS)	Hubei 672 Orthopedic Hospital of Integrated Traditional Chinese and Western Medicine	BZYQ+C (n=36)	WMST (n=35)	Mild cases	10d	(1) Improve the clinical symptoms (2) Shorten the course of disease and improve the cure rate (3) Decrease the levels of CRP, ESR	[75]
2	Chaihu Ganlu decoction (CHGL)	Chaihu (Bupleuri Radix), Huangqin (Scutellariae Radix), Shichangpu (Acori Tatarinowii Rhizoma), Guang Huoxiang (Pogostemonis Herba), Doukou (Amomi Fructus Rotundus), Lianqiao (Forsythiae Fructus), Nanshashen (Adenophorae Radix), Yiyiren (Coicis Semen), Houpo (Magnoliae Officinalis Cortex), Fuling (Poria), Banxia (Pinelliae Rhizoma), Chenpi (Citri Reticulatae Pericarpium), Chantui (Cicadae Periostracum), Jiangcan (Bombyx Batryticatus), Kuxingren (Armeniacae Semen Amarum), Jiegeng (Platycodonis Radix), Maiya (Hordei Fructus Germinatus)	Before and after comparison	People's Hospital of Wanzhou District of Chongqing	CHGL+WMST (n=46)		Asymptomatic cases	5-22d	(1) Prevent deterioration of the disease (2) Shorten nucleic acid negative time (3) Improve chest CT imaging (4) Increase lymphocyte count	[47]

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Table 1 (continued)

NO	Name of traditional Chinese medicine	Compositions	Type of study	Location of study	Intervention	Control	Severity classification	Treatment duration	Main findings	References
3	Danggui Shaoyao powder (DGSY)	Danggui (Angelicae Sinensis Radix), Baishao (Paeoniae Radix Alba), Chuanxiong (Chuanxiong Rhizoma), Baizhu (Atractylodis Macrocephalae Rhizoma), Zexie (Alismatis Rhizoma), Fuling (Poria)	Before and after comparison	Wuhan Union Hospital	DGSY+WMST (n=100)		Severe cases	10d	(1) Relieve the symptoms fever, cough, fatigue, dry cough, chest tightness and shortness of breath (2) Improve the ratio of nucleic acid negative conversion (3) Improve chest CT imaging (4) Reduce the levels of CRP, ALT, AST and increase lymphocyte count	[92]
4	Ganlu Xiaodu decoction (GLXD)	Huashi (Talcum), Yinchen (Artemisiae Scopariae Herba), Huangqin (Scutellariae Radix), Shichangpu (Acori Tatarinowii Rhizoma), Mutong (Akebiae Caulis), Chuanbeimu (Fritillariae Cirrhosae Bulbus), Guanghuoxiang (Pogostemonis Herba), Doukou (Amomi Fructus Rotundus), Lianqiao (Forsythiae Fructus), Bohe (Menthae apocalycis Herba), Shegan (Belamcandae Rhizoma), Shanyao (Dioscoreae Rhizoma), Gancao (Glycyrrhizae Radix Et Rhizoma)	Retrospective cohort studies (RCS)	Wuhan Third Hospital	GLXD+C (n=115)	WMST (n=115)	Moderate cases	7-14d	(1) Improve the clinical symptoms of fever, cough, expectoration, chest tightness, fatigue, panting and shortness of breath. (2) Shorten hospitalization time and improve the cure rate. (3) Reduce the rate of severe cases worsening (4) Promote absorption of lung inflammation and Improve chest CT imaging (5) Decrease the levels of CRP, PCT and increased lymphocyte count	[63]
5	Gegen Qinlian pill (GGQL)	Huangqin (Scutellariae Radix), Huanglian (Coptidis Rhizoma), Gegen (Puerariae Lobatae Radix), Gancao (Glycyrrhizae Radix Et Rhizoma)	CCS	Hubei Provincial Hospital of traditional Chinese medicine	GGQL+C (n=58)	WMST (n=60)	All cases	7-14d	(1) Improve clinical symptoms of cough, chest tightness, nausea, vomiting and loose stool. (2) Shorten the time of nucleic acid negative conversion (3) Decrease the levels of hs-CRP and increase lymphocyte count	[106]

(continued on next page)

Table 1 (continued)

NO	Name of traditional Chinese medicine	Compositions	Type of study	Location of study	Intervention	Control	Severity classification	Treatment duration	Main findings	References
6	Huashi Baidu granule (HSBD)	Mahuang (Ehedraep Herba), Kuxingren (Armeniaca Semen Amarum), Shigao (Gypsum Fibrosum), Gancao (Glycyrrhizae Radix Et Rhizoma), Guanghuoxiang (Pogostemonis Herba), Houpo (Magnoliae Officinalis Cortex), Cangzhu (Atractylodis Rhizoma), Caoguo (Tsaoko Fructus), Banxia (Pinelliae Rhizoma), Fuling (Poria), Dahuang (Rhei Radix Et Rhizoma), Huangqi (Astragali Radix), Tinglizi (Descurainiae Semen Lepidii Semen), Chishao (Paeoniae Radix Rubra)	RCS	Wuhan Jinyintan Hospital	HSBD+C (n=23)	WMST (n=32)	Severe cases	16d	(1) Promote the absorption of pulmonary inflammation and improved chest CT imaging (2) Decrease the levels of CRP, ESR, serum ferritin, and myoglobin	[90]
			Randomized controlled trials(RCT)	Wuhan Jinyintan Hospital	HSBD+C (n=99)	WMST (n=96)	All cases	14d	(1) Relieve the clinical symptoms of fever, cough, fatigue, chest tightness, loss of appetite (2) Promote the absorption of pulmonary inflammation or improve chest CT imaging	[103]
			CCS	TheThird People's Hospital of Yichang	HSBD+C (n=25)	WMST (n=25)	Severe cases	15d	(1) Reduce the incidence of adverse reactions such as gastrointestinal bleeding (2) Improve WBC and lymphocyte count (3) Reduce the levels of CRP and ESR	[88]

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Table 1 (continued)

NO	Name of traditional Chinese medicine	Compositions	Type of study	Location of study	Intervention	Control	Severity classification	Treatment duration	Main findings	References
7	HuoXiang Zhengqi power (HXZQ)	Guanghuoxiang (Pogostemonis Herba), Cangzhu (Atractylodis Rhizoma), Chenpi (Citri Reticulatae Pericarpium), Fabanxia (Pinelliae Rhizoma Praeparatum), Fuling (Poria), Houpo (Magnoliae Officinalis Cortex), Jiegeng (Platycodonis Radix), Gancao (Glycyrrhizae Radix Et Rhizoma)	Before and after comparison	The Red Cross Hospital of Yulin	HXZQ+WMST (n=11)		Moderate cases	9-33d	(1) Improve clinical symptoms of fever, fatigue, cough, dizziness (2) Improve clinical cure rate (3) Reduce the rate of severe cases worsening (4) Reduce the levels of CRP, ESR, PCT, and LDH	[60]
8	Jiawei Yupingfeng powder (YPF)	Huangqi (Astragali Radix), Baizhu (Atractylodis acrocephalae Rhizoma), Fangfeng (Saposhnikovia Radix), Fuling (Poria), Cangzhu (Atractylodis Rhizoma), Guanghuoxiang (Pogostemonis Herba), Zisugeng (Perillae Caulis), Banxia (Pinelliae Rhizoma), Sharen (Amomi Fructus), Shengjiang (Zingiberis Rhizoma Recens)	RCS	TheThird People's Hospital of Jiujiang	YPF+C(n=30)	WMST (n=24)	Mild or Moderate cases	14d	(1) Improve the clinical symptoms (2) Shorten nucleic acid negative time and hospitalization time (3) Decrease the levels of hs-CRP, ESR and increase lymphocyte count	[73]
9	Jinbei oral liquid (JBOL)	Huangqi (Astragali Radix), Dangshen (Codonopsis Radix), Beishashen (Glehniae Radix), Danshen (Salviae Miltiorrhizae Radix Et Rhizoma), Danggui (Angelicae Sinensis Radix), Chuanxiong (Chuanxiong Rhizoma), Jinyinhua (Lonicerae Japonicae Flos), Lianqiao (Forsythiae Fructus), Huangqin (Scutellariae Radix), Chuanbeimu (Fritillariae Cirrhosae Bulbus), Banxia	RCS	The Third Hospital of Wuhan	JBOL+C (n=50)	WMST (n=46)	Mild or Moderate cases	15 d	(1) Relieve clinical symptoms of fever, fatigue, cough (2) Reduce the abnormal fluctuation of body temperature during the treatment (3) Improve the ratio of nucleic acid negative conversion	[59]

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Table 1 (continued)

NO	Name of traditional Chinese medicine	Compositions	Type of study	Location of study	Intervention	Control	Severity classification	Treatment duration	Main findings	References
10	Jinhua Qinggan granules (JHQG)	(Pinelliae Rhizoma), Gancao (Glycyrrhizae Radix Et Rhizoma) Jinyinhua (Lonicerae Japonicae Flos), Shigao (Gypsum Fibrosum), Niubangzi (Arctii Fructus), Zhebeimu (Fritillariae Thunbergii Bulbus), Kuxingren (Armeniaca Semen Amarum), Mahuang (Ehdraep Herba), Huangqin (Scutellariae Radix), Lianqiao (Forsythiae Fructus), Qinghao (Artemisiae Annuae Herba), Zhimu (Anemarrhenae Rhizoma), Bohe (Menthae Haplocalycis Herba), Gancao (Glycyrrhizae Radix Et Rhizoma)	CCS	Hubei Provincial Hospital of Integrated Traditional Chinese and Western Medicine	JHQG+C (n=82)	WMST (n=41)	Mild cases	5d	(1) Alleviate the clinical symptoms of fever, cough, expectoration and anxiety	[54]
8			RCS	Beijing YouAn Hospital Affiliated to Capital Medical University	JHQG+C (n=44)	WMST (n=36)	Moderate or Severe cases	7d	(1) Shorten the length of hospitalization or nucleic acid negative time (2) Promote the absorption of pulmonary inflammation or improve chest CT imaging	[110]
11	Jinjiang Xuanfei Jiedu mixture (JQXF)	Xuanshen (Scrophulariae Radix), Jinyinhua (Lonicerae Japonicae Flos), Lianqiao (Forsythiae Fructus), Kuxingren (Armeniaca Semen Amarum), Chenpi (Citri Reticulatae Pericarpium), Doukou (Amomi Fructus Rotundus), Huangqin (Scutellariae Radix), Shegan (Belamcandae Rhizoma), Bohe (Menthae aplocalycis)	RCS	Wuhan Union Hospital	JQXF+C (n=99)	WMST (n=60)	Mild or Moderate cases	7d	(1) Improve clinical symptoms of fever, cough, sore throat, loss of appetite. (2) Reduce inflammatory reaction	[62]

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Table 1 (continued)

NO	Name of traditional Chinese medicine	Compositions	Type of study	Location of study	Intervention	Control	Severity classification	Treatment duration	Main findings	References
12	Jinyinhua oral liquids (JYH)	Herba, Fangfeng (Saposhnikoviae Radix), Chaihu (Bupleuri Radix), Banlangen (Isatidis Radix), Gancao (Glycyrrhizae Radix Et Rhizoma), Banxia (Pinelliae Rhizoma), Jiegeng (Platycodonis Radix), Cangzhu (Atractylodis Rhizoma), Qianghuo (Notopterygii Rhizoma Et Radix), Sangbaipi (Mori Cortex), Baibu (Stemonae Radix) Jinyinhua (Lonicerae Japonicae Flos)	CCS	The First People's Hospital of Jiangxia District	JYH+C (n=100)	WMST (n=100)	Mild or Moderate cases	10d	(1) Shorten nucleic acid negative time and hospitalization time (2) Improve chest CT imaging (3) Reduce the rate of severe cases worsening	[67]
			CCS	The First People's Hospital of Jiangxia District	JYH+C(n=80)	WMST (n=40)	Moderate cases	10d	(1) Alleviate the main clinical symptoms of fever, cough, and fatigue (2) Reduce the rate of conversion from mild or moderate cases to severe or critical cases	[65]
13	Lanxiang Jiedu oral liquid (LXJD)	Guanghuoxiang (Pogostemonis Herba), Peilan (Eupatorii Herba), Cangzhu (Atractylodis Rhizoma), Houpo (Magnoliae Officinalis Cortex), Chenpi (Citri Reticulatae Pericarpium), Shengjiang (Zingiberis Rhizoma Recens), Fuling (Poria), Banxia (Pinelliae Rhizoma), Jinyinhua (Lonicerae Japonicae Flos),	CCS	The Fifth Hospital of Shijiazhuang	LXJD+C(n=8)	WMST (n=8)	Asymptomatic cases	7d	(1) Improve the ratio of nucleic acid negative conversion (2) Shorten hospitalization time	[48]

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Table 1 (continued)

NO	Name of traditional Chinese medicine	Compositions	Type of study	Location of study	Intervention	Control	Severity classification	Treatment duration	Main findings	References
14	Lianhua Qingke granule (LHQK)	Lianqiao (Forsythiae Fructus), Mianmaguanzhong (Dryopteridis Crassirhizomatis Rhizoma), Taoren (Persicae Semen), Jiegeng (Platycodonis Radix), Gancao (Glycyrrhizae Radix Et Rhizoma) Mahuang (Ehedaep Herba), Shigao (Gypsum Fibrosum), Lianqiao (Forsythiae Fructus), Huangqin (Scutellariae Radix), Sangbaipi (Mori Cortex), Kuxingren (Armeniaca Semen Amarum), Shanyinhua (Lonicerae Flos), Dahuang (Rhei Radix Et Rhizoma), Qianhu (Peucedani Radix), Banxia (Pinelliae Rhizoma), Chenpi (Citri Reticulatae Pericarpium), Zhebeimu (Fritillariae Thunbergii Bulbus), Niubangzi (Arctii Fructus), Jiegeng (Platycodonis Radix), Gancao (Glycyrrhizae Radix Et Rhizoma)	RCT	Tangshan Infectious Diseases Hospital; The Third People's Hospital of Hengshui City; Cangzhou People's Hospital	LHQK+C (n=32)	WMST (n=25)	Mild or Moderate cases	14d	(1) Improve the symptoms of fever, fatigue, dry pharynx and sore throat (2) Shorten the duration of cough and expectoration symptoms (3) Promote the absorption of pulmonary inflammation and improve chest CT imaging (4) Reduce the rate of severe cases worsening	[64]
15	Lianhua Qingwen granules (LHQW)	Jinyinhua (Lonicerae Japonicae Flos), Dahuang (Rhei Radix Et Rhizoma), Mahuang (Ehedaep Herba), Chenpi (Citri Reticulatae Pericarpium), Sangbaipi (Mori Cortex), Banxia (Pinelliae Rhizoma), Kuxingren (Armeniaca Semen Amarum), Shigao (Gypsum Fibrosum), Zhebeimu (Fritillariae Thunbergii Bulbus),	RCT	Puren Hospital Affiliated to Wuhan University of Science and Technology; The Ninth Hospital of Wuhan; CR & WISCO General Hospital, Wuhan University of Science and Technology	LHQW+C (n=51)	WMST (n=51)	Moderate cases	7d	(1) Improve clinical symptoms including fever, fatigue, cough, expectoration, shortness of breath, chest distress and appetite loss. (2) Enhance the effective rate of cardinal symptom. (3) Reduce the proportion of normal to heavy	[52]

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Table 1 (continued)

NO	Name of traditional Chinese medicine	Compositions	Type of study	Location of study	Intervention	Control	Severity classification	Treatment duration	Main findings	References
		Gancao (Glycyrrhizae Radix Et Rhizoma), Qianhu (Peucedani Radix), Huangqin (Scutellariae Radix), Niubangzi (Arctii Fructus), Jiegeng (Platycodonis Radix)	CCS	CR & WISCO General Hospital Affiliated to Wuhan University of Science and Technology	LHQW+C (n=63)	WMST (n=38)	Pediatric cases	10d	(1) Relieve clinical symptoms including fever, fatigue, cough, short breath (2) Improve the disappearance rates of short breath and moist crackles	[44]
			RCS	Xiangyang No.1 People's Hospital	LHQW+C (n=42)	WMST (n=41)	Pediatric cases	5d	(1) Improve symptoms of fever, cough, phlegm, shortness of breath, and gastrointestinal symptoms	[45]
			RCS	The Ninth Hospital of Wuhan; CR & WISCO General Hospital, Wuhan University of Science and Technology	LHQW+C (n=21)	WMST (n=21)	Moderate cases	Unreported	(1) Improve the clinical symptoms of fever, cough, expectoration and shortness of breath	[53]
			Before and after comparison	The Puren affiliated Hospital of Wuhan University of Science and Technology	LHQW+WMCT (n=54)		Moderate cases	7d	(1) Relieve clinical symptoms of fever, weakness, and cough, and reducing their duration	[51]
			RCS	Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology	LHQW+C (n=90)	WMST (n=158)	Moderate cases	5-7d	(1) Decrease the levels of ESR and D-dimer (2) Increase the levels albumin and hemoglobin lymphocyte count	[79]
			RCS	Ruijin Hospital and Tongji Hospital	LHQW+C (n=113)	WMST (n=49)	Moderate or Severe cases	Unreported	(1) relieve the clinical symptoms of fever, cough, fatigue, chest tightness, loss of appetite (2) Shorten the length of hospitalization or	[69]

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Table 1 (continued)

NO	Name of traditional Chinese medicine	Compositions	Type of study	Location of study	Intervention	Control	Severity classification	Treatment duration	Main findings	References
16	Lung-toxin dispelling formula No.1 (LDF1)	Renshen (Ginseng Radix Et Rhizoma), Jingjie (Schizonepetae Herba), Fengfang (Vespae Nidus), Jinyinhua (Lonicerae Japonicae Flos), Lianqiao (Forsythiae Fructus), Zaojiaoci (Gleditsiae Spina), Xuanshen (Scrophulariae Radix), Kuxingren (Armeniacae Semen Amarum), Gancao (Glycyrrhizae Radix Et Rhizoma)	Before and after comparison	Zhumadian City of Chinese medicine Hospital and The First Affiliated Hospital of Henan University of Chinese Medicine	LDF1+WMST (n=6)		Severe or Critical cases		nucleic acid negative time (3) Improve chest CT imaging (1) Promote the absorption of pulmonary inflammation (2) Shorten nucleic acid negative time	[87]
17	Maxing Shigan decoction (MXS)	Mahuang (Ehedraep Herba), Kuxingren (Armeniacae Semen Amarum), Shigao (Gypsum Fibrosum), Gancao (Glycyrrhizae Radix Et Rhizoma)	Before and after comparison	Chongqing Three Gorges Central Hospital	MXS+WMST (n=40)		Moderate cases	3d	(1) Relieve the main clinical symptoms of fever, cough, and fatigue (2) Shorten nucleic acid negative time (3) Decrease the levels of CRP, ALT, AST, and Scr, and increase CD4+ T and CD8+ T count	[57]
18	Pneumonia No.1 (PN1)	Huangqin (Scutellariae Radix), Binglang (Arecae Semen), Zhimu (Anemarrhenae Rhizoma), Banxia (Pinelliae Rhizoma), Dangshen (Codonopsis Radix), Baishao (Paeoniae Radix Alba), Gancao (Glycyrrhizae Radix Et Rhizoma), Chaihu (Bupleuri Radix), Chenpi (Citri Reticulatae Pericarpium), Houpo (Magnoliae Officinalis Cortex), Gualou (Trichosanthis	RCS	Hubei Provincial Hospital of Traditional Chinese medicine and Hanchuan People's Hospital	PN1+C(n=47)	WMST (n=40)	Moderate or Severe cases	Unreported	(1) Shorten the time of nucleic acid negative conversion (2) Relieve the clinical symptoms	[91]

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Table 1 (continued)

NO	Name of traditional Chinese medicine	Compositions	Type of study	Location of study	Intervention	Control	Severity classification	Treatment duration	Main findings	References
19	Qingfei decoction (QFD)	Fructus), Caoguo (Tsaoko Fructus), Huzhang (Polygoni Cuspidati Rhizoma Et Radix) Gualou (Trichosanthis Fructus), Banxia (Pinelliae Rhizoma), Huangqin (Scutellariae Radix), Baibu (Stemonae Radix), Qianhu (Peucedani Radix), Baiqian (Cynanchi Stauntonii Rhizoma Et Radix), Gancao (Glycyrrhizae Radix Et Rhizoma)	Before and after comparison	Wuhan Jiangxia Fangcang Shelter Hospital	QFD+WMST (n=152)		Mild or Moderate cases	14d	(1) Relieve the symptoms fever, cough, fatigue, dry cough, and chest tightness (2) Improve the ratio of nucleic acid negative conversion (3) Improve chest CT imaging (4) Reduce the rate of severe cases worsening (5) play an auxiliary role in reducing blood pressure	[74]
20	Qingfei Paidu decoction (QFPD)	Gancao (Glycyrrhizae Radix Et Rhizoma), Kuxingren (Armeniaca Semen Amarum), Shigao (Gypsum Fibrosum), Guizhi (Cinnamomi Ramulus), Zexie (Alismatis Rhizoma), Zhuling (Polyporus), Baizhu (Atractylodis Macrocephalae Rhizoma), Fuling (Poria), Shanyao (Dioscoreae Rhizoma), Chaihu (Bupleuri Radix), Huangqin (Scutellariae Radix), Banxia (Pinelliae Rhizoma), Ganjiang (Zingiberis Rhizoma), Guanghuoxiang (Pogostemonis Herba), Ziwang (Asteris Radix Et Rhizoma), Kuandonghua (Farfarae Flos), Shegan (Belamcandae Rhizoma), Xixin (Asari Radix Et Rhizoma), Zhishi	RCS	Department of Traditional Chinese Medicine, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology	QFPD+C (n=12)	WMST (n=12)	Severe or Critical cases	7d	(1) Prevent early and mid term cytokine storm and improve clinical symptoms (2) Decrease the levels of CRP, IL-2R, IL-6, IL-10, and TNF-α	[83]

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Table 1 (continued)

NO	Name of traditional Chinese medicine	Compositions	Type of study	Location of study	Intervention	Control	Severity classification	Treatment duration	Main findings	References
	(Aurantii Fructus Immaturus), Chenpi (Citri Reticulatae Pericarpium)		RCS	Xiangyang No. 1 People's Hospital, affiliated hospital of Hubei University of Medicine	QFPD+C (n=37)	WMST (n=26)	Mild or Moderate cases	6d	(1) Reduce the levels of CRP, CK, CK-MB, LDH, and BUN (2) Mitigate the extent of multi-organ impairment	[81]
			RCS	The First Affiliated Hospital of Anhui University of Traditional Chinese Medicine	QFPD+WMST (n=782)		All cases	Unreported	(1) Improve the cure rate Shorten duration of hospital stay (2) Shorten the time of nucleic acid negative conversion	[108]
			CCS	Wuchang Makeshift Hospital; Jingkai Makeshift Hospital; JiangHan Makeshift Hospital; Xinzhou Makeshift Hospital; Qiankou Makeshift Hospital	QFPD+WMST (n=96)	QFPD (n=96)	Mild or Moderate cases	Unreported	(1) Shorten nucleic acid negative time and hospitalization time (2) Improve chest CT imaging	[50]
			RCS	East Hospital of Renmin Hospital of Wuhan University	QFPD+C (n=43)	WMST (n=46)	All cases	15d	(1) Shorten nucleic acid negative time and hospitalization time (2) Decrease the level of IL-6 and increase CD3 count	[107]
			Before and after comparison	Infectious Disease Hospital of Heilongjiang Province; The First Hospital of Suihua City; Harbin Infectious Hospital; Jincheng People's Hospital; Mudanjiang Kangan Hospital; Suining Central Hospital; The Affiliated Traditional Chinese Medicine Hospital of Southwest Medical University; Xingtai Hospital of Traditional Chinese Medicine; Chengde Hospital of Traditional Chinese Medicine; Yongwu Hospital, People's Hospital of Guangxi Zhuang Autonomous Region	QFPD+WMST (n=50)		Severe cases	6d	(1) Relieve the symptoms fever, cough, fatigue, dry cough, anorexia and asthma (2) Shorten nucleic acid negative time and hospitalization time (3) Promote the absorption of pulmonary inflammation (4) Reduce the levels of ESR, CRP, ALT, AST, and PCT and	[38]

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Table 1 (continued)

NO	Name of traditional Chinese medicine	Compositions	Type of study	Location of study	Intervention	Control	Severity classification	Treatment duration	Main findings	References
			Before and after comparison	27 hospitals in 8 provinces(cities) (The fifth hospital of Shijiazhuang; Xingtai Hospital of Traditional Chinese Medicine; Chengde Hospital of Traditional Chinese Medicine;The First Hospital of Suihua City, ect.)	QFPD+WMST (n=119)		All cases	6d	increase WBC and lymphocyte count (1) Relieve the symptoms fever, cough, fatigue, dry cough, anorexia and asthma (2) Shorten nucleic acid negative time and hospitalization time (3) Promote the absorption of pulmonary inflammation	[98]
			Before and after comparison	36 hospitals in 9 provinces (municipalities) (The Affiliated Traditional Chinese Medicine Hospital of Southwest Medical University; Harbin Infectious Hospital; Chongqing Hospital of Traditional Chinese Medicine, ect.)	QFPD+WMST (n=157)		All cases	6d	(1) Relieve the symptoms fever, cough, fatigue, and asthma (2) Shorten nucleic acid negative time and hospitalization time (3) Promote the absorption of pulmonary inflammation (4) Reduce the levels of CRP and LDH, and increase lymphocyte count	[97]
			Before and after comparison	17 hospitals in eight provinces/autonomous regions/municipalities. Qiqihar Hospital of Infectious Diseases; The Affiliated Traditional Chinese Medicine Hospital of Southwest Medical University; Mianyang Hospital of Traditional Chinese Medicine, ect)	QFPD+WMST (n=49)		All cases	6d	(1) Relieve the symptoms fever, cough, fatigue (2) Shorten nucleic acid negative time	[101]
			Before and after comparison	28 hospitals in eight provinces/autonomous regions/municipalities. (Qiqihar Hospital of Infectious Diseases; The Affiliated Traditional Chinese Medicine Hospital of Southwest Medical University; Harbin Infectious Hospital, ect)	QFPD+WMST (n=124)		All cases	6d	(1) Relieve the symptoms fever, cough, fatigue, dry cough and asthma (2) Shorten nucleic acid negative time (3) Promote the absorption of pulmonary inflammation	[100]

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Table 1 (continued)

NO	Name of traditional Chinese medicine	Compositions	Type of study	Location of study	Intervention	Control	Severity classification	Treatment duration	Main findings	References
			RCS	14 hospitals (The Public Health Clinical Center of Chengdu, Sichuan Province; The First Hospital of Suihua City, Heilongjiang Province; ect)	QFPD+C (n=23)	WMST (n=22)	All cases	6d	(4) Reduce the levels of CK and CK-MB, and increase WBC and lymphocyte count (1) Relieve the symptoms and fever, cough, dry cough, fatigue, sore throat and anorexia (2) Shorten nucleic acid negative time and hospitalization time (3) Reduce the levels of ESR, CRP, ALT, and AST, and increase lymphocyte count	[99]
21	Qingfei Touxie Fuzheng reccipe (QFTX)	Mahuang (Ehedraep Herba), Shigao (Gypsum Fibrosum), Kuxingren (Armeniacae Seman Amarum), Jinyinhua (Loniceræ Japonicæ Flos), Lianqiao (Forsythiæ Fructus), Lugen (Phragmitis Rhizoma), Yiyiren (Coicis Semen), Jiangcan (Bombyx Batryticatus), Chantui (Cicadae Periostracum), Huzhang (Polygoni Cuspidati Rhizoma Et Radix), Jianghuang (Curcumæ Longæ Rhizoma), Baishao (Paeoniae Radix Alba), Taizishen (Pseudostellariæ Radix), Gancao (Glycyrrhizæ Radix Et Rhizoma)	RCT	General Hospital of Central Theater Command of Chinese People's Liberation Army	QFTX+C (n=51)	WMST (n=49)	All cases	10d	(1) Alleviate the symptoms of fever, cough, expectoration, chest tighness, shortness of breath (2) Promote the absorption of pulmonary lesions, improve oxygenation (3) Decrease the levels of ESR, CRP, and IL-6	[112]
22	Qingre KangDu oral liquid (QRKD)	Shigao (Gypsum Fibrosum), Banlangen (Isatidis Radix), Shengma (Cimicifugæ Rhizoma),	CCS	The Fifth Hospital of Shijiazhuang	QRKD+C (n=11)	WMST (n=11)	Moderate cases	10d	(1) Improve clinical symptoms, fever, cough, fatigue, lung disease absorption rate >	[48]

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NO	Name of traditional Chinese medicine	Compositions	Type of study	Location of study	Intervention	Control	Severity classification	Treatment duration	Main findings	References
23	Reduning injection (RDN)	Guanghuoxiang (Pogostemonis Herba), Pugongying (Taraxaci Herba), Huanglian (Coptidis Rhizoma), Mudanpi (Moutan Cortex), Baimaogen (Imperatae Rhizoma) Qinghao (Artemisiae Annuae Herba), Jinyinhua (Lonicerae Japonicae Flos), Zhizi (Gardeniae Fructus)	RCT	Lianyungang Fourth People's Hospital affiliated to Kangda College, Nanjing Medical University and The Third People's Hospital of Yichang	RDN+C(n=27)	WMST (n=23)	Mild cases	14d	50% and shorten the duration of fever (1) Relieve the symptoms fever, fatigue, cough, wheezes, and sputum (2) Shorten nucleic acid negative time and hospitalization time (3) Improve chest CT imaging	[70]
24			RCS	The second Affiliated Hospital of Chongqing Medical University	RDN+C(n=32)	WMST (n=26)	Severe cases	5-7d	(1) Decrease the levels of WBC, CRP, IL-6, IL-17 and improve the level of IL-4 (2) Shorten hospitalization time	[89]
25	Sanxiaoyin modified and subtracted prescription (SXY)	Caoguo (Tsaoko Fructus), Houpo (Magnoliae Officinalis Cortex), Huangqin (Scutellariae Radix), Baishao (Paeoniae Radix Alba), Zhimu (Anemarrhenae Rhizoma), Gancao (Glycyrrhizae Radix Et Rhizoma), Dahuang (Rhei Radix Et Rhizoma), Jiangcan (Bombyx Batryticatus), Chantui (Cicadae Periostracum), Mumianhua (Gossampini Flos), Niuxi (Achyranthis Bidentatae Radix)	RCS	The Second Hospital of Jingzhou	SXY+C(n=26)	WMST (n=26)	Mild or Moderate cases	7d	(1) Alleviate the clinical symptoms of fever, cough, fatigue, dry throat, anorexia, poor mental state, and poor sleep quality (2) Shorten the average hospitalization duration (3) Improve chest CT imaging (4) Decrease the levels of CRP, ESR, and PCT, and increase lymphocyte count	[66]

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Table 1 (continued)

NO	Name of traditional Chinese medicine	Compositions	Type of study	Location of study	Intervention	Control	Severity classification	Treatment duration	Main findings	References
26	Shengmai injection (SM)	Hongshen (Ginseng Radix Et Rhizoma Rubra), Maidong (Ophiopogonis Radix), Wuweizi (Schisandrea Chinensis Fructus)	RCT	Hubei 672 Orthopedic Hospital of Integrated Traditional Chinese and Western Medicine	SM+C(n=34)	WMST (n=30)	Moderate or Severe cases	7d	(1) Improve the symptoms of dry throat, thirst, fatigue and night sweat (2) Promote the absorption of pulmonary inflammation and improve oxygen saturation (3) Shorten the time of nucleic acid negative conversion	[93]
27	Shenhuang granule (SHG)	Renshen (Ginseng Radix Et Rhizoma), Dahuang (Rhei Radix Et Rhizoma), Pugongying (Taraxaci Herba), Fuzi (Aconiti Lateralis Radix Praeparata), Shuizhi (Hirudo), Daxueteng (Sargentodoxae Caulis)	RCT	Leishenshan Hospital of Wuhan, Tongji Hospital, Wuhan Mental Health Center, and Huangshi Hospital of TCM.	SHG+C(n=57)	WMST (n=54)	Severe or Critical cases	14d	(1) Improve survival rate and prevent deterioration of the disease (2) Promote the absorption of pulmonary inflammation and improve chest CT imaging	[86]
28	Shuanghuanglian oral liquid (SHL)	Jinyinhua (Lonicerae Japonicae Flos), Huangqin (Scutellariae Radix), Lianqiao (Forsythiae Fructus)	RCT	Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology ect.	SHL+C (n=176)	WMST (n=59)	All cases	14d	(1) Shorten nucleic acid negative time (2) Promote the absorption of pulmonary inflammation or improved chest CT imaging (3) Reduce the level of NT-proBNP	[109]
29	Shufeng Jiedu capsule (SFJD)	Huzhang (Polygoni Cuspidati Rhizoma Et Radix), Lugen (Phragmitis Rhizoma), Chaihu (Bupleuri Radix), Lianqiao (Forsythiae Fructus), Baijiangcao (Patriniae Herba), Mabiancao (Verbenae Herba), Banlangen (Isatidis Radix), Gancao (Glycyrrhizae Radix Et Rhizoma)	RCS	Bozhou People's Hospital	SFJD+C (n=40)	WMST (n=30)	Mild or Moderate cases	10d	(1) Alleviate dry cough, nasal congestion, runny nose, sore throat, fatigue, and diarrhea (2) Shorten the time of nucleic acid negative conversion	[55]
				Bozhou People's Hospital	SFJD+C (n=40)	WMST (n=40)	Mild or Moderate cases	10d	(1) Reduce clinical symptoms of	[56]

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Table 1 (continued)

NO	Name of traditional Chinese medicine	Compositions	Type of study	Location of study	Intervention	Control	Severity classification	Treatment duration	Main findings	References
			Randomized controlled trials						fever, dry cough, nasal congestion, sore throa (2) Promote the absorption of lung inflammation lesions (3) Enhance immunity, promote the recovery of lymphocytes and white blood cells, and reduce the infection index	
			RCT	The Central Hospital of Wuhan	SFJD+C (n=100)	WMST (n=100)	Mild cases	14d	(1) Improve the clinical symptom of fever (2) Improve chest CT imaging (3) Increase WBC and lymphocyte count	[77]
30	Sodium Chloride Injection (SCI)		Before and after comparison	Jingzhou Hospital of Infectious Disease (Chest Hospital) of Hubei Province	SCI+WMST (n=40)		All cases	Unreported	(1) Alleviate the clinical symptoms of fever, cough, fatigue, and loss of appetite (2) Shorten the length of hospitalization and nucleic acid negative time (3) Promote the absorption of pulmonary inflammation and improved chest CT imaging (4) Decrease the levels of hs-CRP, PCT, ALT, AST, and LDH, and increase lymphocyte count	[105]
31	Tanreqing Capsule (TRQ)	Huangqin (Scutellariae Radix), Xiongdanfen (Bear BilePowder), Shanyangjiao (Cornu Caprae Hircus), Jinyinhua(Lonicerae Japonicae Flos),	RCS	Shanghai Public Health Clinical Center	TRQ+C(n=25)	WMST (n=57)	Mild or Moderate cases	Unreported	(1) Shorten nucleic acid negative time or hospitalization time (2) Increase the level of CD3+ T cells	[71]

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NO	Name of traditional Chinese medicine	Compositions	Type of study	Location of study	Intervention	Control	Severity classification	Treatment duration	Main findings	References
32	Toujie Quwen granules (TJQW)	Lianqiao (Forsythiae Fructus)	RCT	Guangzhou Eighth People's Hospital	TJQW+C (n=37)	WMST (n=36)	Mild or Moderate cases	10d	(1) Relieve the symptoms fever, cough, fatigue, expectoration, dry pharynx and sore throat, chest tightness, (2) Reduce the rate of severe cases worsening (3) Reduce the levels of CRP and PCT and increase lymphocyte count and neutrophil ratio	[61]
		Lianqiao (Forsythiae Fructus), Shancigu (Cremastrae Pseudobulbus Pleiones Pseudobulbus), Jinyinhua (Lonicerae Japonicae Flos), Huangqin (Scutellariae Radix), Daqingye (Isatidis Folium), Chaihu (Bupleuri Radix), Qinghao (Artemisiae Annuae Herba), Chantui (Cicadae Periostracum), Qianhu (Peucedani Radix), Chuanbeimu (Fritillariae Cirrhosae Bulbus), Zhebeimu (Fritillariae Thunbergii Bulbus), Fuling (Poria), Wumei (Mume Fructus), Xuanshen (Scrophulariae Radix), Huangqi (Astragali Radix), Taizishen (Pseudostellariae Radix)								
			RCT	Guangzhou Eighth People's Hospital	TJQW+C (n=32)	WMST (n=33)	Moderate cases	15d	(1) Relieve the symptoms fever, cough, fatigue, dry pharynx and sore throat, chest tightness (2) Improve the cure rate (3) Reduce the level of CRP and increase lymphocyte count	[80]
33	Wuye Lugen decoction (WYLG)	Bohe (Menthae apocalycis Herba), Guanghuoxiang (Pogostemonis Herba), Heye (Nelumbinis Folium), Peilan (Eupatorii Herba), Pipaye (Eriobotryae Folium),	Before and after comparison	Jiangmen Wuyi Hospital of Traditional Chinese Medicine Affiliated to Ji'nan University	WYLG+CWMT (n=18)		Convalescent cases	moderate cases	(1) Improve the clinical symptoms of fatigue, dry mouth, insomnia, anxiety (2) Increase lymphocyte and WBC counts, and the levels of	[116]

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Table 1 (continued)

NO	Name of traditional Chinese medicine	Compositions	Type of study	Location of study	Intervention	Control	Severity classification	Treatment duration	Main findings	References
34	Xiang Huo Spray (XHS)	Lugen (Phragmitis Rhizoma), Dongguazi (Benincasae Semen) Guanguoxiang (Pogostemonis Herba), Xiangru (Moslae Herba), Aiye (Artemisiae Argyi Folium), Dingxiang (Caryophylli Flos), Bohe (Menthae apocalycis Herba), Bingpian (Borneolum)	RCT	Hubei Provincial Hospital of Traditional Chinese medicine	XHS+C(n=60)	WMST (n=60)	Convalescent cases	7d	(1) Improve the total clinical efficiency (2) Alleviate the clinical symptoms of cough, chest oppression, fatigue, sweating, muscle soreness, stuffy nose and sore throat	[114]
35	Xiaochaihu decoction combined with Yupingfeng powder (XCY)	Chaihu (Bupleuri Radix), Huangqin (Scutellariae Radix), Banxia (Pinelliae Rhizoma), Mianmaguanzhong (Dryopteridis Crassirhizomatis Rhizoma), Jinyinhua (Loniceræ Japonicæ Flos), Lianqiao (Forsythiae Fructus), Taizishen (Pseudostellariae Radix), Huangqi (Astragali Radix), Fangfeng (Saposhnikoviae Radix), Baizhu (Atractylodis Macrocephalae Rhizoma), Gancao (Glycyrrhizae Radix Et Rhizoma)	RCS	Affiliated Hospital of Liaoning University of Traditional Chinese Medicine	XCY+C(n=18)	WMST (n=14)	Pediatric cases	5d	(1) Improve the symptoms of fever, cough, expectoration, sore throat, shortness of breath, appetite, and chills (2) Shorten the course of fever, cough, and expectoration (3) Improve chest CT imaging	[46]
36	Xiyanping injection (XYP)	Andrographolide sulfonates	RCT	the Second Affiliated Hospital of Nanchang University ect.	XYP+C(n=65)	WMST (n=65)	Mild or Moderate cases	28d	(1) Alleviate the main clinical symptoms of fever, cough, and fatigue (2) Reduce the time virus clearance (3) Shorter time to achieve negative SARS-CoV-2 RNA tests	[58]
37	Xuanfei Baidu decoction (XFBD)	Mahuang (Ehedraep Herba), Kuxingren (Armeniacæ Seman Amarum), Shigao (Gypsum Fibrosum),	RCT	Wuhan Pulmonary Hospital	XFBD+C (n=22)	WMST (n=22)	All cases	7d	(1) Reduce the disappearance rate of clinical symptoms such as fever, cough,	[102]

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Table 1 (continued)

NO	Name of traditional Chinese medicine	Compositions	Type of study	Location of study	Intervention	Control	Severity classification	Treatment duration	Main findings	References
		Yiyiren (Coicis Semen), Cangzhu (Atractylodis Rhizoma), Guanghuoxiang (Pogostemonis Herba), Qinghao (Artemisiae Annuae Herba), Huzhang (Polygoni Cuspidati Rhizoma Et Radix), Mabiancao (Verbenae Herba), Lugen (Phragmitis Rhizoma), Tinglizi (Descurainiae Semen Lepidii Semen), Huajuhong (Citri Grandis Exocarpium), Gancao (Glycyrrhizae Radix Et Rhizoma)							fatigue and loss of appetite (2) Decrease the levels of CRP and ESR, and increase WBC and lymphocyte counts	
38	Xuanfei Huazhuo prescription (XFHZ)	Mahuang (Ehedraep Herba), Lianqiao (Forsythiae Fructus), Qianhu (Peucedani Radix), Banxia (Pinelliae Rhizoma), Cangzhu (Atractylodis Rhizoma), Guanghuoxiang (Pogostemonis Herba), Qianghuo (Notopterygii Rhizoma Et Radix), Dahuang (Rhei Radix Et Rhizoma), Chenpi (Citri Reticulatae Pericarpium), Huangqin (Scutellariae Radix)	Before and after comparison	Affiliated Hospital of Gansu University of Chinese Medicine	XFHZ+WMST (n=40)		All cases	8-23d	(1) Relieve the symptoms cough, fever, sputum, diarrhea, loss of appetite and fatigue (2) Shorten the time of nucleic acid negative conversion (3) Promote the absorption of pulmonary inflammation (4) Promote WBC, lymphocyte percentage, neutrophil percentage, lymphocyte absolute value, CRP, ESR, total bilirubin (TBIL), AST/ALT and LDH to return to the normal range	[104]
39				Chongqing public health medical treatment center			Unreported	14d		[111]

(continued on next page)

Table 1 (continued)

NO	Name of traditional Chinese medicine	Compositions	Type of study	Location of study	Intervention	Control	Severity classification	Treatment duration	Main findings	References
	Xue's Fu Yang Zhu Shi decoction cutting (XFYZS)	Dangshen (Codonopsis Radix), Baizhu (Atractylodis Macrocephalae Rhizoma), Fuzi (Aconiti Lateralis Radix Praeparata), Fuling (Poria), Houpo (Magnoliae Officinalis Cortex), Banxia (Pinelliae Rhizoma), Ganjiang (Zingiberis Rhizoma), Chaihu (Bupleuri Radix), Shengma (Cimicifugae Rhizoma), Huangqi (Astragali Radix), Huangqin (Scutellariae Radix), Lugen (Phragmitis Rhizoma)	Before and after comparison		XFYZS+WMST (n=36)				(1) Relieve the clinical symptoms of fever, cough, sputum, and sore throat (2) Promote the negative rate of nucleic acid (3) Improve the improvement rate of chest CT	
40	Xuebijing injection (XBJ)	Chishao (Paeoniae Radix Rubra), Honghua (Carthami Flos), Danggui (Angelicae Sinensis Radix), Chuanxiong (Chuanxiong Rhizoma), Danshen (Salviae Miltiorrhizae Radix Et Rhizoma)	RCT	The First People's Hospital of Jingzhou	XBJ+C(n=30)	WMST (n=30)	Severe cases	14d	(1) Improve survival rate and prevent deterioration of the disease (2) Reduce the rate of mechanical ventilation, rate of septic shock, (3) Decrease the levels of IL-6 IL-8, and TNF- α and increase lymphocyte count (4) Shorten the length of ICU hospitalization stay	[84]
			CCS	North Hospital of the First Hospital of Changsha City	XBJ+C(n=20)	WMST (n=20)	Severe cases	7d	(1) Reduce the rate of severe cases worsening (2) Decrease the levels of CRP, ESR, and acute physiology and chronic health evaluation II (APACHEII) score, and increase lymphocyte count	[85]
			RCT	Affiliated Dongfeng Hospital, Hubei University of Medicine	XBJ+C(n=22)	WMST (n=22)	Moderate cases	7d	(1) Improve the cure rate	78]

(continued on next page)

Table 1 (continued)

NO	Name of traditional Chinese medicine	Compositions	Type of study	Location of study	Intervention	Control	Severity classification	Treatment duration	Main findings	References
41	Yidu-toxicity blocking lung decoction (YTBL)	Kuxingren (Armeniacae Semen Amarum), Shigao (Gypsum Fibrosum), Gualou (Trichosanthis Fructus), Dahuang (Rhei Radix Et Rhizoma), Mahuang (Ehedralp Herba), Tinglizi (Descurainiae Semen Lepidii Semen), Taoren (Persicae Semen), Caoguo (Tsaoko Fructus), Binglang (Arecae Semen), Cangzhu (Atractylodis Rhizoma)	RCT	The First Affiliated Hospital of Anhui Medical University	YTBL+C (n=15)	WMST (n=24)	Severe cases	29d	(1) All patients are cured and discharged (2) Decrease the levels of IL-6 and TNF- α (2) Promote the absorption of lung pulmonary infection	[95]
42	Yinqiao powder combined with modified Sanren decoction (YCS)	Pugongying (Taraxaci Herba), Lugen (Phragmitis Rhizoma), Yiyiren (Coicis Semen), Jinyinhua (Lonicerae Japonicae Flos), Lianqiao (Forsythiae Fructus), Chaihu (Bupleuri Radix), Huangqin (Scutellariae Radix), Kuxingren (Armeniacae Semen Amarum), Doukou (Amomi Fructus Rotundus), Jiegeng (Platycodonis Radix), Guanghuoxiang (Pogostemonis Herba)	RCS	the Second Hospital of Nanjing	YCS+C(n=20)	WMST (n=16)	Moderate cases	7d	(1) Relieve clinical symptoms such as fever, cough, fatigue, muscle soreness, dry mouth (2) Shorten the time of returning to normal body temperature (3) Increase the ratio of nucleic acid negative conversion	[76]
43	Yiqi Yangyin granules (YQYY)	Dangshen (Codonopsis Radix), Maidong (Ophiopogonis Radix), Baihe (Lilii Bulbus), Fuling (Poria), Baizhu (Atractylodis Macrocephalae)	RCT	Jiangxia Wuhan District Hospital of Traditional Chinese Medicine; The First Hospital of Wuhan; Huai'an Hospital of Traditional Chinese Medicine; Yangzhou Hospital of Traditional Chinese Medicine; The Third People's Hospital of Zhenjiang	YQYY+C (n=30)	WMST (n=30)	Convalescent cases	14d	(1) Alleviate the clinical symptoms of fatigue, short of breath, dry mouth, dry pharynx, vexing heat in chest, palms and soles	[115]

(continued on next page)

Table 1 (continued)

NO	Name of traditional Chinese medicine	Compositions	Type of study	Location of study	Intervention	Control	Severity classification	Treatment duration	Main findings	References
		Rhizoma), Chenpi (Citri Reticulatae Pericarpium), Maiya (Hordei Fructus Germinatus), Hehuampi (Albiziae Cortex), Digupi (Lycii Cortex), Gancao (Glycyrrhizae Radix Et Rhizoma)							(2) Improve expiratory peak flow rate value (3) Increase CD3+ T count	

WMST: Western medicine routine symptomatic treatment.

vomiting and loose stools, and nausea; 2) Lianhua Qingwen granules [96], Qingfei Paidu decoction [97–99, 101, 107, 108], Gegen Qinlian pills [106], Shuanghuanglian oral liquid [109], Jinhua Qinggan granules [110], Xue’s Fuyang Zhushi decoction [111], and sodium chloride injection [105] shortened the length of hospitalization or nucleic acid negative time; Lianhua Qingwen granules [96], Qingfei Paidu decoction [97,98,100,101,107], Shuanghuanglian oral liquid [109], Huashi Baidu granules [103], Xuanfei Huazhuo prescription [104], Jinhua Qinggan granules [110], Xue’s Fuyang Zhushi decoction [111], and sodium chloride injection [105] promoted the absorption of pulmonary inflammation or improved lung CT imaging; and 3) Qingfei Paidu decoction [97, 99–101, 107] reduced the levels of IL-6, CRP, ALT, AST, CK, CK-MB, and LDH and increased lymphocytes, WBC, CD3 + T cell counts; and Qingfei Touxie Fuzheng recipe [112] decreased the levels of ESR, CRP, and IL-6; in addition, sodium chloride injection [105] and Gegen Qinlian pills [106] decreased the levels of high-sensitivity C-reactive protein (hs-CRP) and PCT and increased lymphocyte counts; Xuanfei Baidu decoction [102] increased lymphocyte and WBC counts and reduced the levels of CRP and ESR; and Shuanghuanglian oral liquid reduced the levels of N-terminal brain natriuretic peptide (NT-proBNP).

For convalescent COVID-19 patients, TCM can remove residual evil, help vital Qi, improve symptoms, promote the repair of injured organs and tissues, and expedite the process of rehabilitation [113]. Xiang Huo spray [114] improved the total clinical efficiency and alleviated the clinical symptoms of coughing, chest tightness, fatigue, sweating, muscle soreness, stuffy nose, and sore throat; Yiqi Yangyin granules [115] alleviated the clinical symptoms of fatigue, shortness of breath, dry mouth, vexing heat in the chest, palms, and soles, and dry pharynx; improved the expiratory peak flow rate value; and increased CD3 + T cell counts. Wuye Lugen decoction [116] could improve the clinical symptoms of fatigue, dry mouth, insomnia, and anxiety and increase lymphocyte and WBC counts and the levels of haemoglobin (HGL), CRP, and IgG.

4. The relationship between the gut microbiota and TCM

The normal gut microbiota consists of bacteria, viruses, fungi, and archaea in numbers up to 10¹³-10¹⁴. On the one hand, under normal physiological conditions, the gut microbiota can interact with the host through complex dynamic network regulatory mechanisms, participate in regulating the host’s material metabolism and immune defence, and protect the integrity of the intestinal mucosal barrier structure [117–119]. On the other hand, beneficial bacteria can produce antibacterial substances that are more beneficial to the body and resist the invasion of pathogens by competing for nutrients and occupying favourable sites [120]. When the homeostasis of the intestinal microecology is disrupted, beneficial bacteria decline, harmful bacteria increase, the intestinal barrier is damaged, and the function of the immune system is disrupted, thus triggering a variety of diseases and threatening human health. It has been reported that the gut microbiota is closely related to the inflammatory response induced by novel coronaviruses and could be highly correlated with individual susceptibility to COVID-19 [121]. Numerous studies have shown that respiratory virus infection of the host causes alteration of the gut microbiota, increasing the colonization of pathogenic bacteria and decreasing the number of probiotics. In turn, alteration of the gut microbiota can reduce the level of the host’s antiviral immune response and aggravate the lung injury caused by viral infection. In addition, the gut microbiota can act directly on viruses through its structural components or metabolites or indirectly influence the body’s immune response, ultimately affecting the outcome of viral infection [122]. Probiotics can enhance the antiviral ability of the body by regulating innate immunity, maintaining the integrity of the intestinal wall, and activating adaptive immune responses [123].

There is a close relationship between TCM and gut microbiota, as

shown in Fig. 3. On the one hand, TCM can influence the composition and metabolism of the gut microbiota; on the other hand, the gut microbiota can metabolize Chinese herbal medicinal components [124]. A large number of studies have shown that TCM can significantly adjust the alteration of the gut microbiota, promote the growth of beneficial bacteria, inhibit the overproliferation of harmful bacteria, and balance the number of these probiotic and pathogenic bacteria, thus maintaining a healthy intestinal environment [125,126]. Most TCM is administered orally and is selectively metabolized in the intestine by intestinal secretory enzymes into active or absorbable components; TCM thus exerts a therapeutic effect. In addition, the gut microbiota will be affected by TCM while transforming it. The composition of the gut microbiota will be changed under the effects of TCM. On the one hand, TCM can alleviate disease-induced gut microbiota disorders by regulating the composition of the gut microbiota and then treating the disease; on the other hand, changes in the composition of the gut microbiota can also lead to changes in its metabolic ability, thus triggering gut microbiota-mediated interactions of Chinese herbal medicinal components. The gut microbiota in the body plays an important role in the pharmacological effects of oral TCM, and TCM helps to maintain the balance of the gut microbiota. The interaction between them is of great significance in preventing and treating diseases and promoting health [127].

5. The relationship between COVID-19 and gut microbiota

The initial symptoms of COVID-19 patients are mainly fever, coughing, and fatigue. With in-depth research on the disease, it has also not been uncommon to find gastrointestinal symptoms caused by SARS-CoV-2 infection in clinical practice [128], especially in critically ill patients with poor prognoses [9–11]. Available evidence suggests that SARS-CoV-2 can directly damage the digestive system, disrupt the intestinal microecological balance, and cause associated clinical manifestations [11,129,130]. Gastrointestinal symptoms are present in approximately 2–79.1% of patients [9, 49, 131–133], and these symptoms can appear early in the onset of the disease, even earlier than fever and respiratory symptoms [134–136]. By studying 1099 patients with COVID-19, Nanshan Zhong's team found that the clinical manifestations of gastrointestinal symptoms, such as nausea, vomiting, and diarrhoea, could be 8.7%, and gastrointestinal symptoms were more common in severe patients, accounting for 12.7% [49]. Another study [9] found that 11.4% of COVID-19-infected people presented with gastrointestinal symptoms, such as abdominal pain, diarrhoea, nausea, and vomiting. Moreover, a study [137] confirmed that some COVID-19 patients had their first symptoms in the digestive tract, suggesting that gastrointestinal symptoms are another major manifestation of COVID-19 patients, in addition to respiratory symptoms. The Renmin Hospital of Wuhan University reported "atypical" cases in which patients with COVID-19 presented with gastrointestinal symptoms only, without fever or respiratory symptoms [138]. Wang et al. [132] found that the proportion of COVID-19 patients with gastrointestinal symptoms as initial symptoms accounted for approximately 10.12%, and the patients only had diarrhoea symptoms at the onset of the disease, followed by fever, dyspnoea, and other symptoms. Currently, SARS-CoV-2 has been identified and isolated from the stool specimens of COVID-19 patients [139,140], and disorders of the intestinal microecology have been detected in COVID-19 patients with gastrointestinal symptoms [130]. These findings suggest that SARS-CoV-2 might cause alterations in the gut microbiota along with pulmonary infection, which could be the main reason for the nausea, vomiting, diarrhoea, and other gastrointestinal symptoms in patients.

Alteration of the gut microbiota is closely related to the severity of COVID-19 patients [11,141]. A study found that COVID-19 patients with diarrhoea were in more serious conditions and had higher rates of receiving noninvasive ventilation and transferring to the intensive care unit and a higher case fatality rate than those without diarrhoea [11, 142]. Another study that included 74 COVID-19 patients with gastrointestinal symptoms and 577 COVID-19 patients without gastrointestinal symptoms found that the proportion of COVID-19 patients with gastrointestinal symptoms who were in severe or critical condition was as high as 22.97% – higher than the 8.14% of patients without gastrointestinal symptoms [9]. In 138 COVID-19 study subjects, the incidence of gastrointestinal symptoms was higher in severely ill patients than in ordinary patients, and severely ill patients presented with abdominal pain, whereas mildly ill patients did not [143]. Numerous retrospective studies have indicated that more than half of COVID-19 patients are complicated with underlying diseases, such as diabetes mellitus, hypertension, and hyperlipidaemia, with poor tolerance and rapid disease progression, and they are prone to becoming severe and critical high-risk patients [49,131,132]. In an interview with a CCTV reporter, the academician Li Lanjuan mentioned that severe and critical COVID-19 patients mostly have gut microbiota disorders. Severe and critical COVID-19 patients are predominantly elderly patients complicated with underlying diseases [144]. The intestinal microecological stability and diversity of elderly individuals decrease, and infection with SARS-CoV-2 causes gut microbiota disorders, which tend to affect the absorption of nutrients and reduce mucosal barrier immunity; the risk of nosocomial infections is thus increased [145]. In summary, there are many links between the gut microbiota and COVID-19. On the one hand, COVID-19 patients have gut microbiota disorders and impaired barrier function; could have gastrointestinal symptoms, such as nausea, vomiting, and diarrhoea; and could also have gastrointestinal symptoms as the first manifestation. On the other hand, gut microbiota disorders can aggravate the condition of COVID-19 patients.

6. Mechanism of gut microbiota disorder induced by SARS-CoV-2

SARS-CoV-2 is the third coronavirus to emerge in humans over the past 20 years after severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) [146,147]. Studies have shown that the pathogenic process of SARS-CoV-2 infection is associated with the binding of angiotensin-converting enzyme 2 (ACE2) [129]. Current studies have shown that, similar to SARS-CoV, SARS-CoV-2 uses ACE2 with the help of transmembrane protease serine 2 (TMPRSS2) as a cellular receptor in the host cell [148–150]. There are many ACE2 proteins in alveolar epithelial cells. After SARS-CoV-2 enters alveolar epithelial cells, virus replication causes an immune response in the body, and excessive cytokine production eventually forms a cytokine storm, in turn triggering inflammation, which is an important cause of lung injury, acute respiratory distress syndrome (ARDS), and multiple organ failure or even death [25,151]. Notably, ACE2 is highly expressed not only in alveolar cells but also in oesophageal epithelial cells, gastrointestinal epithelial cells, and hepatobiliary duct cells [152–154]. The above evidence suggests that SARS-CoV-2 might not only infect the respiratory system but also directly infect the digestive system and cause related clinical manifestations [155]. The high expression of ACE2 in the intestine can regulate the composition of the gut microbiota [156]. ACE2 is necessary for the expression of the neutral amino acid transporter BOAT1 protein in intestinal epithelial cells, and it participates in the absorption of tryptophan [157]. When the level of ACE2 expression in

the digestive tract is reduced, tryptophan is not efficiently absorbed, small intestinal mTOR pathway activity is reduced, and small intestinal antimicrobial peptide expression is inhibited, ultimately leading to alteration of the gut microbiota and an increase in endotoxin. These effects in turn trigger endotoxaemia and cytokine storms, leading to tissue damage and even ARDS and MODS [157–159]. Thus, the dysregulation of gut microbiota in COVID-19 might be related to decreased intestinal ACE2 expression caused by the binding of SARS-CoV-2 to the ACE2 receptor on the surface of intestinal epithelial cells, as shown in Fig. 4.

7. The relationship between cytokine storms and the gut microbiota

A cytokine storm, also known as a cytokine cascade or hyper-cytokinaemia, is essentially a more intense inflammatory response and an excessive immune response of the body to pathogenic microorganisms (such as bacteria and viruses) [160]. When pathogens invade the organism, a moderate immune response is activated, which can hinder viral replication and rapidly clear the pathogens. However, an excessive immune response leads to an imbalance in the immune regulatory network, and an excessive inflammatory response occurs in the body, prompting a large release of multiple inflammatory factors and cytokines into the body fluids in a short period and producing systemic inflammatory damage, resulting in lung injury, ARDS and multiple organ dysfunction syndromes (MODS) and even death [161]. Test reports of COVID-19 patients have shown that the absolute value of lymphocytes was reduced in most patients, suggesting that SARS-CoV-2 could mainly act on lymphocytes, especially T lymphocytes. The viral particles spread through the respiratory mucosa, infect other cells, induce a cytokine storm in vivo, produce a series of immune responses, and cause peripheral blood changes in immune cells, such as leukocytes and lymphocytes [131]. Clinical studies have shown that plasma levels of IL-2, IL-7, IL-10, granulocyte colony-stimulating factor (G-CSF), interferon- γ -inducible protein-10 (IP-10), monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1 α (MIP-1 α), and TNF- α in COVID-19 patients are elevated [131,151], and critically ill patients usually exhibit reduced peripheral blood T lymphocytes [132]. Abundant evidence has suggested that cytokine storms play an important role in the progression of COVID-19, especially in critically ill patients [11, 162,163]. A recent COVID-19 clinical study [151] showed that a high level of inflammatory cytokine expression, the "cytokine storm", was found in critically ill patients infected with SARS-CoV-2, suggesting a possible correlation between cytokine storms and the severity of patients' infections. Cytokine storms are now considered a turning point in the progression of COVID-19 patients to severe and critical illnesses. Some patients with COVID-19 had mild disease in the early stages, with sudden aggravation in the later stages and eventual death from MODS, with exacerbation mainly due to a cytokine storm [164]. Reports have indicated that the cytokine storm in severe COVID-19 patients is closely associated with severe lung pathological injury and the occurrence and development of ARDS, and it is one of the main causes of death in patients [131,151,165].

Numerous studies in recent years have shown that intestinal microorganisms play important roles in regulating the immunity of the body and that changes in the gut microbiota are closely associated with local and systemic inflammation [166]. The microecological imbalance of the gut microbiota leads to the release of inflammatory mediators caused by intestinal endotoxin and gut microbiota displacement, directly or indirectly promoting the occurrence and development of the COVID-19 inflammatory storm. After SARS-CoV-2 infection, especially in elderly

patients or those with underlying diseases, alteration of the gut microbiota increases the production of various toxins, including endotoxins, and impairs intestinal barrier function, causing a large number of toxins to enter the bloodstream. These toxins can directly damage lung structure and function, or they can aggravate the systemic and pulmonary inflammatory response by inducing inflammation and creating inflammatory factor storms, leading to severe disease. It was found that, among COVID-19 patients, the elderly and those with underlying diseases, such as diabetes, hypertensive disease, coronary heart disease, and extreme obesity, are susceptible to SARS-CoV-2, are prone to developing acute and critical illness, and have a higher risk of death [132,167–169]. Previous studies [170,171] have shown that the richness, evenness, and diversity of the gut microbiota in this population were significantly reduced, and the dominant flora was significantly decreased, with an imbalance in intestinal microecology. Infection with SARS-CoV-2 further aggravates gut microbiota disorders, leading to disruption of the intestinal mucosal barrier, the release of inflammatory mediators caused by intestinal endotoxin and gut microbiota displacement, and the formation of an inflammatory factor storm to exacerbate systemic and pulmonary inflammatory responses. It is now believed that the cause of severe pneumonia is not the virus itself but the excessive immune response induced by infection. The unbalanced inflammatory factor system in the body is an important cause of pneumonia and ALI [172, 173]. The above studies suggest that the gut microbiota is closely associated with the inflammatory storm in COVID-19 patients; that is, imbalance of the gut microbiota after SARS-CoV-2 infection, disruption of the intestinal mucosal barrier, and release of inflammatory mediators caused by intestinal endotoxin and gut microbiota displacement can directly or indirectly promote the occurrence and development of the COVID-19 "inflammatory storm".

8. TCM regulation of the gut microbiota to prevent and treat COVID-19

8.1. Regulation of gut microbiota structure

Many studies have been reported on the direct regulation of the gut microbiota composition by TCM, including the regulation of the gut microbiota by a single TCM or a single extracted component, and on the forms of Chinese herbal medicinal ingredients that act. Guo et al. [174] found that extracts of *Ginseng radix et rhizome rubra* and *Coicis semen* could promote the growth of probiotics such as *Lactobacillus* and *Bifidobacterium* and inhibit the growth of pathogenic bacteria such as *Escherichia*, *Staphylococcus*, and *Salmonella* in vitro. Chang et al. [175] reported the effect of adding *Ganoderma* extract to the food of mice fed a high-fat diet and found that *Ganoderma* extract not only reduced the elevated ratio of the *Firmicutes/Bacteroides* phylum and the level of endotoxin-producing *Proteobacteria* induced by a high-fat diet but also maintained the integrity of the intestinal mucosal barrier and reduced the occurrence of endotoxaemia. The compatibility of essential oil from *Atractylodis macrocephalae rhizoma* and total ginsenosides reduced the relative abundance of opportunistic pathogens, such as *Bacteroides*, *Anaerotruncus*, and *Desulfovibrio* [176]. Dong et al. [177] found that Shenling Baizhu powder could effectively regulate antibiotic-induced gut microbiota imbalances and reduce endotoxin production by promoting the proliferation of probiotics, such as *Lactobacillus* and *Bifidobacterium*, in the intestinal tract. The single Chinese medicines *Ginseng radix et rhizoma*, berberine, *Lonicerae japonicae flos*, *Rehmanniae radix praeparata*, *Artemisiae argyi folium*, and emodin had proliferative effects on intestinal probiotics such as *Lactobacillus* in the gut microorganisms of different disease models [127]. HuoXiang Zhengqi [178] could

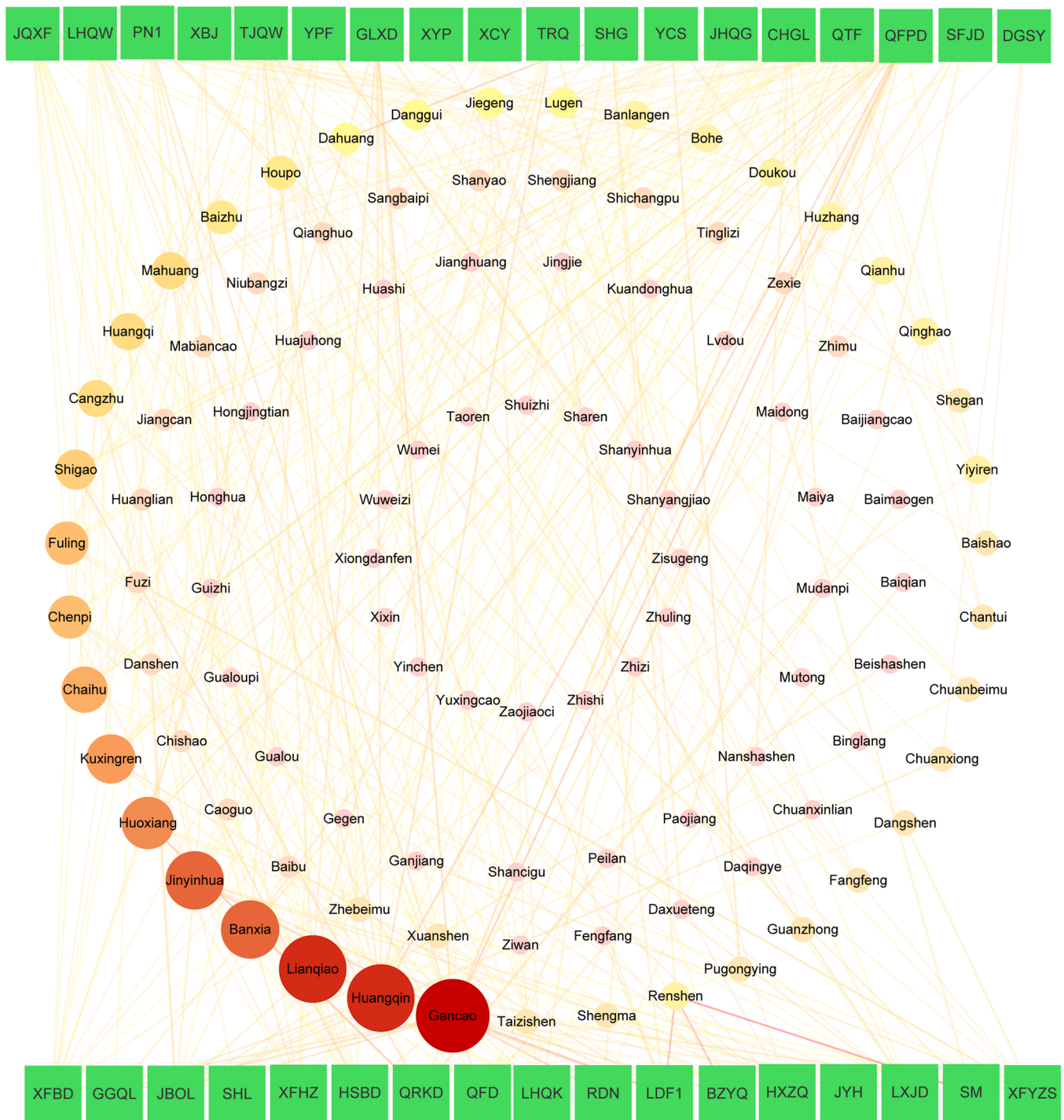


Fig. 2. The relationship of TCM with its constituents. Note: The green square nodes represent TCM. The red, yellow, and light red circular nodes represent the constituents of TCM. The size and darkness of the nodes represent the frequency of appearance of each constituent. The size from small to large and the darkness of the nodes from dark to light are illustrated in ascending order of frequency of appearance. The connecting lines indicate that each node is related. The width of the connecting lines was based on the frequency of appearance of constituents, and the colour and rule were the same as the circular nodes. JQXF: Jinjiang Xuanfei Jiedu mixture; LHQW: Lianhua Qingwen capsule; PN1: Pneumonia No.1; XBJ: Xuebijing injection; TJQW: Toujie Quwen granules; YPF: Jiawei Yupingfeng powder; GLXD: Ganlu Xiaodu decoction; XYP: Xiyanping injection; XCY: Xiaochaihu decoction combined with Yupingfeng powder; TRQ: Tanreqing injection; SHG: Shenhuang granule; YCS: Yingqiao powder combined with modified Sanren decoction; JHQQ: Jinhua Qinggan granules; CHGL: Chaihu Ganlu decoction; QTF: Qingfei Touxie Fuzheng recipe; QFPDD: Qingfei Paidu decoction; SFJD: Shufeng Jiedu capsule; DGSY: Danggui Shaoyao power; XFBD: Xuanfei Baidu decoction; GGQL: Gegen Qinlian pill; JBOL: Jinbei oral liquid; SHL: Shuanghuanglian oral liquid; XFHZ: Xuanfei Huazhuo prescription; HSBD: Huashi Baidu decoction; QRKD: Qingre KangDu oral liquid; QFD: Qingfei decoction; LHQK: Lianhua Qingke granules; RDN: Reduning injection; LDF1: Lung-toxin dispelling formula No.1; BZYQ: BuZhong Yiqi decoction; HXZQ: HuoXiang Zhengqi power; JYH: Jinyinhua oral liquid; LXJD: Lanxiang Jiedu oral liquid; SM: Shengmai power; XFYZS: Xue's Fu Yang Zhu Shi decoction cutting.

support the growth of normal intestinal flora and promote the proliferation of beneficial bacteria (*Bifidobacterium* and *Lactobacillus*). Gegen Qinlian decoction could reverse the reduction in the richness of the gut microbiota, change its structure, and significantly increase the relative abundances of short-chain fatty acid (SCFA)-producing bacteria, including *Akkermansia*, *Bacteroides*, *Clostridium*, *Ruminococcus*, and *Phascolarctobacterium* [179]. *Coptidis rhizoma* extracts could improve intestinal microecology. Pathogens such as *Enterobacter* and *Enterococcus* were inhibited, and probiotics such as *Lactobacilli* and *Bifidobacteria* were notably promoted by *Coptidis rhizoma* extracts [180]. Fermented Yupingfeng polysaccharides exhibited greater beneficial effects in improving the gut microbiota, including augmenting flora diversity and the abundance of cellulolytic bacteria and reducing the abundance of *Enterococcus* spp and *Streptococcus* spp [181]. Based on 16S rDNA sequencing, Wu et al. [182] found that Qingfei Paidu decoction significantly modulated the composition of rat gut microbiota, upregulating the relative abundance of *Romboutsia*, *Turcibacter*, and *Clostridium sensu stricto 1* and downregulating the relative abundance of *norank_f_Lachnospiraceae*, suggesting that the clinical efficacy of Qingfei Paidu decoction might be related to the regulation of gut microbiota composition.

8.2. Regulation of the intestinal mucosal barrier to prevent bacterial translocation

In addition to influencing the composition and number of gut microbiota constituents, TCM can indirectly affect the positioning of the flora by protecting the intestinal mucosal barrier. The normal intestinal mucosal barrier effectively prevents intestinal bacteria and endotoxin from crossing the intestinal mucosa, avoiding gut-derived infection. A variety of single TCMs, Chinese herbal medicinal ingredients, and TCM preparations have been found to have significant protective effects on the intestinal mucosal barrier. A modern pharmacological study showed that *Rhei radix et rhizoma* can effectively block the cascade response of inflammatory mediators, reduce the number of intestinal *Escherichia coli* bacteria in severely infected rats, inhibit the expression of Toll-like receptor 2 (TLR2) and TLR4 mRNA, block the intestinal inflammatory response, maintain the function of the intestinal mucosal immune barrier, and inhibit the translocation of bacteria in the early stage of

septicaemia, with important therapeutic effects on acute lung injury [183]. Chang et al. [175] found that *Ganoderma lucidum* was able to protect the barrier function of the intestinal mucosa in mice, thus resisting the invasion of pathogenic microorganisms and preventing bacterial translocation. Fermented Yupingfeng polysaccharides (FYP) maintain intestinal barrier integrity and functionality by upregulating the mRNA levels of ZO-1, claudin, polyimmunoglobulin receptor, trefoil factor, and epidermal growth factor in the jejunum and ileum, achieving a protective effect on the mechanical and immune barriers of the intestinal mucosa [184]. *Rhei radix et rhizoma* can maintain intestinal mucosal immune barrier function by regulating the gut microbiota and suppressing intestinal inflammatory responses [183].

8.3. Regulating immunity

Recent studies have suggested that the causes of exacerbation and even death in viral infectious diseases such as COVID-19 are not only related to pulmonary viral infection but also closely related to immune dysfunction of the body [185,186]. Therefore, in the process of preventing and treating COVID-19, it is very important to improve the body's own immune ability and regulate the immune balance. In addition to the direct or indirect antiviral effects of TCM in the prevention and treatment of COVID-19, the greatest advantage of TCM lies in its excellent immunomodulatory effects and reduced toxicity and side effects [187]. TCM has played an important role in the prevention and treatment of COVID-19. Among its effects, the immunomodulatory effect of TCM cannot be ignored. There have been many reports on the direct regulation of immunity by TCM, not only in the form of a single extracted ingredient or single Chinese medicine but also in the form of a compound prescription of TCM.

8.3.1. Single extracted ingredients of Chinese medicine regulate immunity

Poria Cocos polysaccharides [188] could improve immunity by reducing the content of IL-10 and regulating the secretion of Th1/Th2. *Radix glycyrrhizae* polysaccharides [189] could regulate cellular immunity disorders in tumour-bearing mice by decreasing the proportion of Treg cells and increasing the spleen lymphocyte transformation ratio. Bordbar et al. [190] found that glycyrrhizin could enhance the expression of the surface differentiation antigens CD80 and CD86 and the

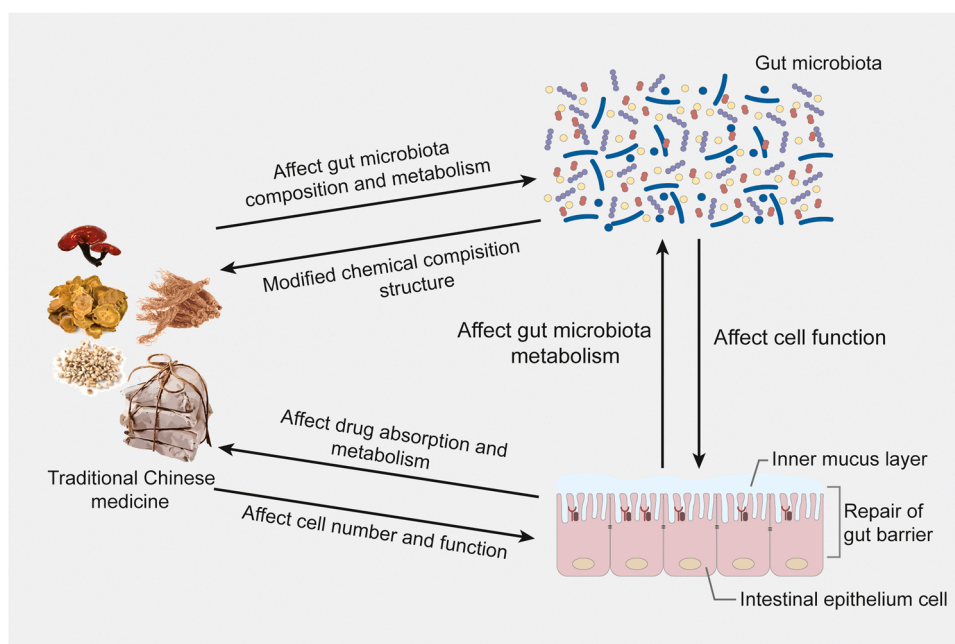


Fig. 3. The interaction between TCM and gut microbiota.

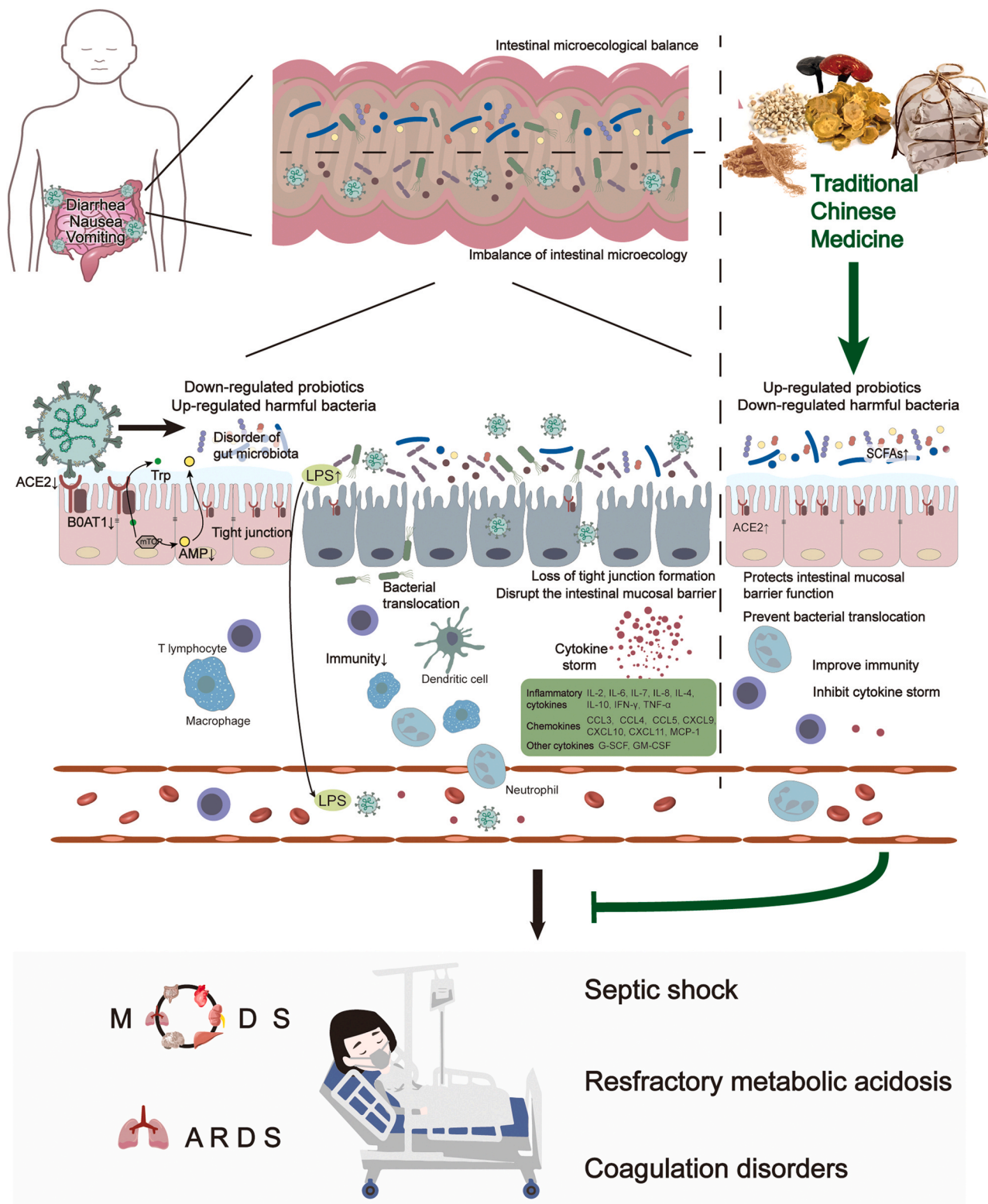


Fig. 4. Mechanism of gut microbiota disorders induced by SARS-CoV-2 and the mechanism by which TCM regulates the gut microbiota to prevent and treat COVID-19. The binding of SARS-CoV-2 to the ACE2 receptor could reduce the expression of ACE2 and affect the absorption of tryptophan by small intestinal epithelial cells. It could also reduce the activity of the mTOR pathway in the small intestine and inhibit the expression of small intestinal antimicrobial peptides, leading to intestinal flora imbalance (a decrease in the number of beneficial bacteria and an increase in the number of harmful bacteria) and displacement, the destruction of the intestinal mucosal barrier, and an increase in intestinal endotoxins. The above process causes the excessive release of inflammatory mediators, the occurrence of endotoxaemia and cytokine storms, and tissue damage. In severe cases, ARDS and MODS can occur. However, TCM can help to suppress inflammatory storms and maintain the immune barrier function of the intestinal mucosa, thereby improving the body's immunity and preventing the deterioration of the condition because of TCM's ability to adjust the intestinal flora imbalance, promote the growth of beneficial bacteria, inhibit the excessive reproduction of harmful bacteria, and promote the production of SCFAs.

major histocompatibility complex II (MHC II) of dendritic cells (DCs), improve the production of IL-12, enhance the proliferation of allogeneic T cells, increase the expression of IFN- γ and IL-10, and regulate the Th1-type immune response. Forsythia leaf polysaccharides [191] could significantly increase the thymus index, spleen index, macrophage phagocytosis, spleen lymphocyte proliferation, serum IL-2 and IL-4 levels, haemolysin content, and number of haemolytic plaques in immunosuppressed mice induced by cyclophosphamide. Baicalein [192] could play an immunomodulatory role by balancing CD4⁺/CD8⁺ and regulating the balance of T lymphocytes and their Th1/Th2 and Th17/Treg subsets. Chrysophanol [193] had an immunomodulatory effect in immunocompromised mice, which could enhance the proliferation of T and B lymphocytes, increase the spleen index and thymus index, upregulate the levels of serum IL-2 and IL-4, and promote an increase in haemolysin levels and the production of antibody cells. Flos Loniceræ polysaccharides [194] could regulate the immune function of immunosuppressed mice induced by cyclophosphamide, effectively increasing the organ index of the mice, enhancing the activity of NK cells and the phagocytosis of macrophages, promoting the proliferation of spleen lymphocytes, and enhancing the immunomodulatory activity of the immunosuppressed mice. In addition, Jia et al. [195] found that Flos Loniceræ polysaccharides could promote IFN- γ secretion by regulating immune function, stimulating an increase in the immune organ index and enhancing immune function. Liu et al. [196] found that *Astragalus* polysaccharides could improve the phagocytosis rate of macrophages and the spleen and thymus indices of mice.

8.3.2. Single Chinese medicines regulate immunity

Astragali radix, *Scutellariae radix*, *Isatidis radix*, *Pulsatillae radix*, *Polygoni cuspidati rhizoma et radix*, *Herba hedyotidis*, and *Andrographis herba* could regulate the balance of anti-inflammatory cytokines and proinflammatory cytokines in the lungs of mice infected with H1N1 influenza virus and then improve immune dysfunction, truncate the storm of cytokines, reduce the inflammatory injury of lung tissue, and promote the repair of inflammatory lesions of lung tissue [197–200]. *Astragali radix* [197] reduced the mRNA expression of the proinflammatory cytokines TNF- α , IL-1, and IL-6, significantly increased the mRNA expression of the anti-inflammatory cytokines IL-10 and IFN- γ in the lungs of mice, and significantly inhibited and repaired immune-inflammatory injury in lung tissue in mice. *Scutellariae radix* [198] inhibited the protein and gene expression of TNF- α , IL-1 and IL-6 in the lungs, promoted the protein and gene expression of IL-10 and IFN- γ , reduced the immune-inflammatory injury of lung tissue, and promoted the repair of inflammatory lesions in lung tissue. *Isatidis radix*, *Pulsatillae radix*, *Polygoni cuspidati rhizoma et radix*, and *Herba hedyotidis* can inhibit the expression of TNF- α , IL-1 and IL-6 and promote the expression of IL-10 and IFN- γ in the lung [199]. *Andrographis herba* [200] effectively regulated the concentrations of TNF- α , INF- γ and IL-10 in the peripheral blood of mice, increased the percentage of CD3⁺ T lymphocytes, regulated the CD4⁺/CD8⁺ ratio, improved the cellular immune function of mice, and regulated the balance of proinflammatory and anti-inflammatory factors.

8.3.3. Chinese medicine compound prescriptions regulate immunity

Clinical studies have shown that Qingfei Paidu decoction can significantly improve the CD3⁺ and CD4⁺ cell counts of COVID-19 patients and enhance the body's immune function [107,201]. Toujie Quwen granules [80] could significantly increase the CD4⁺ count and the ratio of CD4⁺/CD8⁺ in patients with COVID-19, promote the recovery of immune function and reduce the injury of cellular immunity. Lianhua Qingwen capsules [202] significantly inhibited the phosphorylation of p65 protein in the NF- κ B pathway and significantly reduced the expression levels of TNF- α , IL-6, KC, MCP-1, IL-1 β , and IP-10 in the lung tissue of H1N1-infected mice, suggesting that its immunomodulatory effect might be related to its inhibition of the NF- κ B pathway. Jinhua Qinggan granules reduced the levels of serum CRP and IFN- γ in

patients with influenza and improved immune function [203,204]. Xuebijing injection [205] reduced the levels of TNF- α and IL-6 in the lungs of mice infected with the influenza virus. In addition, clinical studies showed that, compared with human immunoglobulin alone, Xuebijing injection combined with human immunoglobulin could significantly shorten the antipyretic time, coughing, and asthma regression time and significantly reduce the levels of hs-CRP, IL-6, and TNF- α in patients with severe viral pneumonia [206]. Reduning injection [207,208] increased the level of IFN- γ in the lung tissue of virus-infected mice, decreased the levels of IL6 and TNF- α , decreased the levels of phosphorylated nuclear factor kappa B inhibitor protein (p-I κ B) and NF- κ B protein, decreased the expression of IL-1 β mRNA and increased the gene expression of interferon-induced transmembrane protein 3 (IFITM3) and mitochondrial antiviral signal protein (MAVS). Tanreqing injection [209–211] could significantly improve the pathological injury of lung tissue in virus-infected mice, enhance the function of T and B lymphocytes, increase the content of IL-4 and IFN- γ in the lungs, downregulate the transcriptional activity of the transcription factor NF- κ B, inhibit the content of TNF- α in the lungs, regulate the balance of Th1 and Th2 cells, reduce lung injury and corresponding inflammatory reactions, and enhance antiviral immune function. Buzhong Yiqi decoction [212] could significantly increase the serum CD3⁺ and CD4⁺ cell counts and the ratio of CD4⁺/CD8⁺ in patients with recurrent respiratory tract infections and improve the immune function of patients. Maxing Shigan decoction [213] upregulated the body mass, spleen index, and thymus index of mice infected with influenza virus, reduced the levels of TNF- α , IL-1 β , and IL-6 in the lungs, downregulated the expression of MyD88 and tumour necrosis factor receptor-associated protein 6 (TRAF6) mRNA and protein in lung tissue, increased the level of IL-2 in lung tissue and decreased the levels of IL-4 and TNF- α . Wang et al. [214] found that Sijunzi decoction could increase the levels of acetic acid, propionic acid, and butyric acid in the intestine; reduce the levels of the splenic index and serum inflammatory factors IL-2 and IFN- γ ; and increase the ratio of CD4⁺/CD8⁺ in spleen-deficient mice, suggesting that Sijunzi decoction could increase the major SCFAs in the intestine and improve immunity in spleen-deficient rats.

8.4. Regulation of gut microbiota and its metabolites

The gut microbiota and their metabolites can affect the local or systemic immune function of the host. SCFAs are important products of dietary fibre fermentation by beneficial intestinal bacteria. The most common SCFAs are propionic acid, acetic acid, and butyric acid, with *Bacteroidetes* producing mainly propionic acid and acetate and *Firmicutes* producing mainly butyrate [215]. SCFAs not only have an important function in the metabolism of the body but also play a role in regulating inflammation and immune homeostasis [216]. Immunomodulatory effects associated with SCFAs include enhancing the barrier function of intestinal epithelial cells, reducing the induction of proinflammatory cytokines, stimulating the production of regulatory T cells, promoting intestinal mucosal homeostasis, preventing colonic inflammation, and enhancing the proinflammatory state of intestinal epithelial cells and leukocytes [217,218]. SCFAs can induce the production and differentiation of regulatory T cells, thus promoting the production of the anti-inflammatory cytokine IL-10, and they can strongly reduce the release of the proinflammatory chemokines CCL3, CCL4, CCL5, CXCL9, CXCL10, and CXCL11, thereby inhibiting leukocyte migration with a strong anti-inflammatory effect [219]. Studies have found that *Firmicutes* is an important source of butyrate, which is a major energy substrate for cells. The decrease in the ratio of *Firmicutes* to *Bacteroidetes* could directly affect the metabolism of dietary fibre by the gut microbiota, resulting in lower concentrations of SCFAs, and the decrease in *Firmicutes* could induce or exacerbate local inflammatory responses [220]. *Prevotella*, *Ruminococcus*, *Coprococcus*, *Clostridium butyricum*, and *Lactobacillus* all increase the content of SCFAs in the intestine, induce the production and differentiation of regulatory T cells in the intestine of

mice, promote IL-10 production, and exert inflammatory inhibitory effects [221–223]. In contrast, overgrown *Escherichia coli* or *Klebsiella pneumoniae* could promote the expression of chemokines such as CCL5 and CXCL10, thereby aggravating the degree of inflammatory injury [224]. A previous study showed that influenza A virus infection could cause structural disorders of the gut microbiota and immune dysfunction in mice, and Maxingshigan decoction had a protective effect against influenza virus-induced intestinal immune damage by upregulating the relative abundance of *Firmicutes*, *Lactobacillus*, and *Coprococcus* and downregulating the relative abundance of *Proteobacteria* and *Escherichia*, regulating the structure of the gut microbiota and affecting the production of chemokines [225]. Other studies have indicated that Chinese medicine could increase the production of SCFAs by modulating the gut microbiota to improve the barrier function of the intestine and inhibit the inflammatory response of the intestinal mucosa [179,226]. Zhang et al. [227] reported that Shenling Baizhu powder could increase the relative abundance of SCFA-producing bacteria (including *Bifidobacterium* and anaerobic bacteria) in the intestine of obese rats, reduce the levels of serum endotoxin, TNF- α , and IL-1 β , and reduce systemic inflammation. TCM regulates the gut microbiota to prevent and treat COVID-19, as shown in Fig. 4.

9. Conclusions and prospects

In the prevention and control of this epidemic, early intervention, full participation, and classified treatment of TCM have made important and lasting contributions to the comprehensive control of the COVID-19 epidemic. Clinical studies have confirmed that TCM has certain advantages in improving the clinical symptoms of COVID-19 patients, inhibiting the storm of inflammatory factors, promoting the absorption of pulmonary inflammation, shortening the course of treatment, and promoting recovery. Currently, the focus and difficulties in the treatment of COVID-19 concern mainly the more severe and critical cases, which are also the main factors directly affecting mortality [27]. There is no definite and effective treatment for the more severe and critical COVID-19 patients in modern medicine, but the intervention of TCM or integrated traditional Chinese and Western medicine according to the clinical symptoms of the more severe and critical COVID-19 patients can help to reduce mortality and improve prognosis [22,25,27,228]. The gut microbiota in severe and critical COVID-19 patients is disordered, rendering it prone to bacterial infection and further aggravating the disease. Therefore, it is essential to maintain the balance of the gut microbiota.

There are many relationships between the gut microbiota and COVID-19. On the one hand, COVID-19 patients have gut microbiota disorders and intestinal barrier function damage; on the other hand, the gut microbiota can regulate the local and systemic immune system, becoming the turning point of the prognosis of the disease. Therefore, restoring and regulating the balance of gut microbiota are helpful for the rehabilitation of COVID-19 patients. In the Guideline on Diagnosis and Treatment of COVID-19 (trial 8th edition) [15], formulated by the National Health Commission of the People's Republic of China, it is mentioned that, for more severe and critical COVID-19 patients, microecological regulators should be selected in a timely and reasonable manner to restore and maintain intestinal homeostasis and prevent bacterial infection. In addition, the "four antibodies and two balances" suggested by the academician Lanjuan Li, that is, anti-virus, anti-shock, anti-hypoxaemia, anti-secondary infection, maintaining water-electrolyte acid-base balance and microecological balance, also clearly indicate the importance of using microecological agents to maintain the balance of intestinal bacteria in improving patients' immunity and preventing secondary infection. TCM plays a positive role in promoting the prognoses of patients with coronavirus infection or COVID-19 by maintaining the dynamic balance between the type and number of the gut microbiota and improving body immunity, but its mechanism remains to be further elucidated. From the perspective of

TCM, research on maintaining the gut microbiota balance and correcting gut microbiota imbalances and finding new targets and new ideas for the treatment of COVID-19, whether for the treatment of the sick or the health care of the undiseased, are of great significance.

CRedit authorship contribution statement

Shuping Wang was responsible for the entire manuscript; Zhihua Yang, Yangxi Liu, Lin Wang and Shanshan Lin conceived, designed, wrote and revised the manuscript; Zhihua Yang and Yangxi Liu have contributed equally to this work and shared first authorship; Xiangdong Dai, Haifeng Yan contributed to draw diagram; Zhao Ge, Qian Ren, Hui Wang, Feng Zhu revised the manuscript and discussed interpretation. All authors have read and approved the final submission.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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