Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Biomedicine & Pharmacotherapy 137 (2021) 111310

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Review

Research progress of traditional Chinese medicine against COVID-19

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ARTICLE INFO

Keywords:
COVID-19
Traditional Chinese medicine
Prescriptions
Characteristic therapies
Underlying mechanism

ABSTRACT

Background: Currently, the number of confirmed cases and deaths of COVID-19 worldwide continues to rise, receiving great concern from the international community. However, there is no specific and widely accepted effective vaccines. The experience in controlling the outbreak in China has proven the effectiveness of traditional Chinese medicine (TCM).

Objectives: This review aims to evaluate the role of TCM in COVID-19 treatment, hoping to provide references for prevention and control of global pandemic.

Data sources: China National Knowledge Infrastructure, Web of Science, Baidu Scholar, ScienceDirect, Elsevier and PubMed were used to search literatures published from December 2019 to December 2020 by entering the keywords "Traditional Chinese medicine", "COVID-19", "Severe acute respiratory syndrome coronavirus 2", "Pathogenesis", "Syndrome differentiation", "Prescriptions" and their combinations. Hence, we have performed an extensive review of research articles, reviews and primary scientific studies to identify TCM against COVID-19.

Results: Among clinical treatments of COVID-19, several TCM prescriptions and characteristic therapies have been effectively suggested, the underlying mechanisms of which are mainly involved in antiviral, anti-inflammatory, immunomodulatory and organ-protective effects of multi-components acting on multi-targets at multi-pathways.

Conclusions: This review may provide meaningful and feasible information that can be considered for the treatment of COVID-19 pandemic globally.

Abbreviations: SARS-CoV, severe acute respiratory syndrome coronavirus; MERS-CoV, middle East Respiratory Syndrome Coronavirus; R0, the basic basic reproduction number; ACE2, angiotensin-converting enzyme-2; TMPRSS2, transmembrane protease, serine 2; S protein, spike protein; E protein, envelope protein; M protein, membrane protein; N protein, nucleocapsid protein; 3CLpro, 3C-like protease; PLpro, papain-like protease; RdRp, RNA dependent RNA polymerase; IgM, immunoglobulin M; IgG, immunoglobulin G; ARDS, acute respiratory distress syndrome; AKT1, AKT1 protein kinase; AGTR1, angiotensin receptor II type I; CRP, C-reactive protein; CCL-2, CC chemokine 2; CXCL-10, CXC chemokine 10; CASP3, caspase-3; DPP4, T cell surface antigen CD26; EGFR, epidermal growth factor receptor; ESR1, estrogen receptor 1; IL-1A, interleukin 1A; IL-1B, interleukin 1B; IL-1β, interleukin 1β; IL-1, interleukin 1; IL-2, interleukin 2; IL-6, interleukin 6; IL-10, interleukin 10; IP-10, interferon induced protein 10; IFN-γ, interferon γ; ICAM1, intercellular cell adhesion molecule-1; IFNG, interferon gene; MCP-1, monocyte chemoattractant protein 1; MIP-1A, macrophage inflammatory protein 1A; TNF-α, tumor necrosis factor-alpha; G-CSF, granulocyte colony-stimulating factor; PTGS2, prostaglandinendoperoxidesynthase 2; MAPK1, mitogen-activated protein kinase 1; MAPK8, mitogen-activated protein kinase 8; PI3K-Akt, PI3K-Akt signaling pathway; HIF-1, hypoxia inducible factor-1; MAPK3, mitogen-activated protein kinase 3; NOS2, nitric oxide synthase 2; TLR4, TLR4 signaling pathway.

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https://doi.org/10.1016/j.biopha.2021.111310
Received 25 October 2020; Received in revised form 4 January 2021; Accepted 21 January 2021
Available online 3 February 2021

1. Introduction

On March 11, 2020, the novel coronavirus disease 2019 (COVID-19) caused by a novel coronavirus (SARS-CoV-2), was declared as a global pandemic by World Health Organization (WHO) [1]. As of January 5, 2021, over 80 million confirmed cases have been reported across over 230 countries, areas, and territories, resulting in over 1.8 million deaths (according to data from WHO). The critical timeline in COVID-19 outbreak from December 2019 to December 2020 is shown in Fig. 1. The number of confirmed cases worldwide is still soaring. More than hundreds of preclinical studies and clinical trials have been conducted to search a way against COVID-19, however, there is no approved treatment for this widespread disease [2]. As the pandemic continues to escalate rapidly, it is urgent to discover safe and effective drugs or potential adjuvant treatments. Among them, traditional Chinese medicine (TCM) is utilized to effectively reduce symptoms of COVID-19 patients and inhibit disease progression from mild to severe, bringing remarkable clinical response [3]. It has been shown that over 70,000 COVID-19 patients in China have received TCM treatment, with the total effective rate over 90 % [4]. Here, we briefly review the characteristic, epidemiology and clinical features of SARS-CoV-2 infection, which may help to give a comprehensive understanding of this outbreak. Additionally, several prescriptions and characteristic therapies concluded from TCM in controlling COVID-19 are reviewed and analyzed. We also analyze the mechanisms of TCM prescriptions with multi-components acting on multi-pathways and summarize the high frequency used herbs, the related components and signaling pathways, hoping to provide references for developing further anti-SARS-CoV-2 drugs to control the global outbreak.

1.1. Comparison of SARS-CoV-2, MARS-CoV and SARS-CoV

The comparison of SARS-CoV, MERS-CoV and SARS-CoV-2 are listed in Table 1, including characteristics, epidemiology and TCM treatments. Similar to SARS-CoV and MARS-CoV, SARS-CoV-2 also belongs to a member of β coronavirus and single stranded RNA viruses, but its genome sequence is significantly distinct from those of SARS-CoV and MERS-CoV [5]. Several vital protein molecules encoded by these three coronavirus may be considered as possible targets for inhibiting viral infection and replication, including S protein, M protein, E protein, N protein, ACE2, 3CLpro, PLpro and RdRp [6]. Structural analysis showed that the receptor-binding domain of SARS-CoV-2 has approximately 10 times higher affinity to ACE2 than SARS-CoV [7]. The human-to-human transmission is mainly via respiratory droplets, contacts and aerosols [8,9]. As the epidemic progresses, *Wenling Wang et, al.* reported that live SARS-CoV-2 is detected in human's feces, suggesting the possible existance of fecal transmission route [10]. During the asymptomatic period, it is also highly contagious with 44 % transmission rate before symptoms appearing [11]. Reports showed that the consensus estimate for R_0 value of SARS-CoV-2 is between 2 and 3, which is concluded from a mathematical model on the affected countries from the WHO situation published on 27 February 2020 [12,13]. All people are susceptible to these three coronaviruses, especially suffering from diseases like cardiovascular problems, diabetes and cancers [14]. SARS-CoV-2 has a tendency to attack elderly populations because of their higher ACE2 expression [15]. In terms of time distribution, SARS-CoV basically conforms to the epidemic of respiratory infectious diseases in winter and spring. Since 2014, the peak of MERS-CoV epidemic has been concentrated in April-May and September-October. Nevertheless, since March 2020, SARS-CoV-2 infections have shown rapid growth, forming a global pandemic and becoming a serious threat to human health. In this case, TCM shows its special advantages in treating epidemic. Several classic prescriptions, Chinese patent medicine and TCM extracts are recommended in the treatment of three coronavirus infections (Table 1). Mechanisms of TCM treatments mainly involve anti-viral replication, anti-inflammation, immune regulation and target organs protection. In the development of TCM against coronavirus, specific targets proteins corresponding to SARS-CoV, MERS-CoV and SARS-CoV-2 are 3CLpro and RdRp, N protein and S protein, and ACE2, 3CLpro and PLpro, respectively.

1.2. Clinical features of COVID-19

The averincubation period of SARS-CoV-2 is 1−14 days, most of which is 3−7 days. However, cases with 24-day incubation period have also been reported [16]. Here, we summarize the clinical features of COVID-19 patients with different types such as asymptomatic cases, suspected cases and confirmed cases [17]. As shown in Table 2, for asymptomatic cases, there is no obvious related clinical symptoms such as fever, fatigue, and nonproductive cough, however, respiratory specimen tests are positive, including SARS-CoV-2 nucleic acid test, serum specific IgM antibody test or specific IgG antibody test. Besides, *Yongchen Zhang et, al.* reported that asymptomatic cases exhibit later production and lower titer of plasma antibody than that of symptomatic cases, which may be attributed to fewer viruses [18]. The difference between suspected cases and confirmed cases are embodied in the results of respiratory samples tests. Additionally, confirmed cases could be divided into mild cases, common cases and severe cases because of their different clinical manifestations. Patients with mild symptoms are characterized by low-grade fever and mild fatigue. In the early 41 patients, the most common features of COVID-19 were fever, fatigue, cough, and bilateral distribution of ground glass shadows under chest CT scan imaging. In addition, some patients also exhibited runny nose, sore throat and diarrhea [19]. Symptoms of dyspnea and hypoxemia are

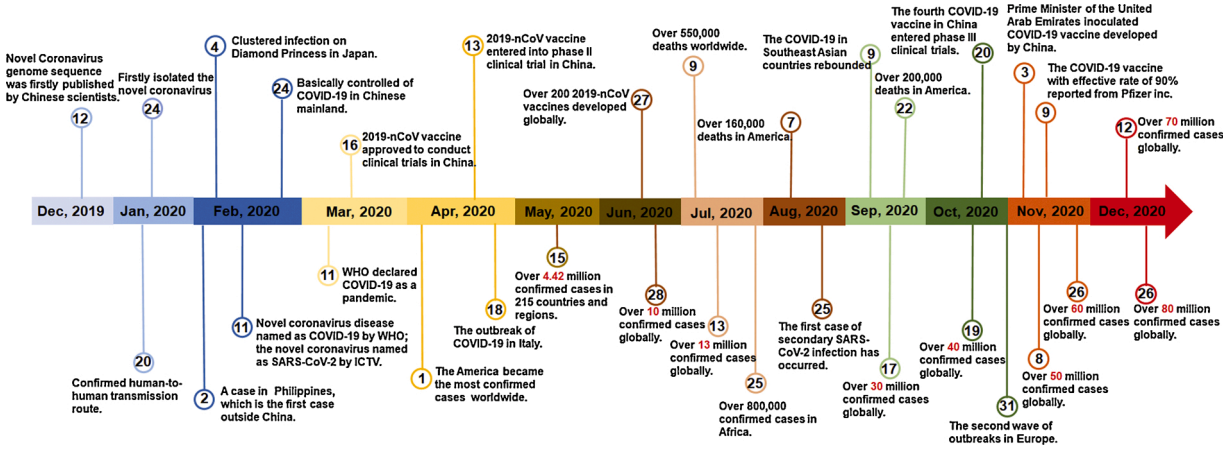

Fig. 1. The critical timeline in COVID-19 outbreak from December 2019 to December 2020.

Table 1
The comparison of SARS-CoV, MERS-CoV and SARS-CoV-2.

	SARS-CoV	MERS-CoV	SARS-CoV-2
Year	November, 2002	June, 2012	December, 2019
Origin	Guangdong, China	Saudi Arabia	unknown
Genus	β coronavirus and single stranded RNA viruses		
Cellular receptor	ACE2	CD26 (DPP4)	ACE2
Possible host	Rhinolophus sinicus	bats, camels	bats, pangolin
Routes of transmission	droplets, contact	droplets, contact	droplets, aerosol, fecal
Basic reproductive number (R0)	1.7−1.9	0.7	2−3 (consensus)
Incubation period	1−16 days, mostly 3−5 days	7−14 days	1−14 days, mostly 3−7 days
Susceptible population	all people	all people (especially older males)	all people
Time distribution	winter spring season	spring season	a rapid growth since December, 2019
Regional distribution	from Guangdong, China to Mainland China, Hongkong, Macao and Taiwan	from Saudi Arabia to the Middle East and more than 20 countries around the world	global pandemic
Mechanism of TCM treatments	anti-viral replication, anti-inflammation, immune regulation and target organs protection		
Target protein	3CLPro, RdRp	N protein, S protein	ACE2, 3CLPro, PLpro
Recommend TCM prescriptions	*Maxing Shigan* decoction, *Dayuan* decoction, *Shenfu* decoction, *Shengmai* powders, *Dushen* decoction, *Xuanbai Chengqi* decoction, *Angong Niuhuang* pills, etc.	*Daqinglong* decoction, *Xiaochaihu* decoction, *Gegen Qinlian* decoction, *Huopu Xialing* decoction, etc.	*Maxing Shigan* decoction, *Qingfei Paidu* decoction, *Dayuan* decoction, *Huashi Baidu* formula, *Shufeng Jiedu* formula, etc.
Chinese patent medicine	*Yinqiao* powders, *Qingkailing* injection, *Yuxingcao* injection, *Banlangen* granules, etc.	*Lianhua Qingwen* capsules, *Ganmaoling* granules, *Xuebijing* injection, *Reduning* injection, etc.	*Lianhua Qingwen* capsules, *Huoxiang Zhengqi* capsules, *Jinhua Qinggan* granules, *Toujie Quwen* granules, *Xuebijing* injection, etc.
TCM and its extracts	3CLPro: *Isatis indigotica* Fort.; 3CLpro, RdRp: *Houttuynia cordata*, *Gentiana manshuric*, *Artemisia annua L.*	N protein: Resveratrol; S protein: Dihydrotanshinone, Lycorine, Cephaeline	ACE2: *Pueraria lobata*, *Morus alba L.*, *Lonicera japonica*, *Forsythia suspensa*, *Fritillaria thunbergii.*; 3CLpro: *Polygonum cuspidatum*; PLpro: *Rheum palmatum L*, *Fritillaria thunbergia*, *Trichosanthes kirilowii*,

Table 2
Clinical features of COVID-19.

	Asymptomatic cases	Suspected cases	Confirmed cases		
			Mild cases	Common cases	Severe and critical cases
fever	–	+	+	+	+/#
fatigue	–	+	+	+	+
nonproductive cough	–	+	+	+	+
diarrhea	–	+	+	+	+
dyspnea	–	–	–	–	+
white blood cell counts	–	-/↓	-/↓	-/↓	↓
lymphocyte counts	–	-/↓	-/↓	-/↓	↓
hyoxemia	–	–	–	–	+
ARDS	–	–	–	–	+
septic shock	–	–	–	–	+
coagulation disorders	–	–	–	–	+
multiple organ dysfunction	–	–	–	–	+
pneumonia	–	+	+	+	+
pulmonary imaging	–	+	+	+	+
SARS-CoV-2 nucleic acid	+	–	+	+	+
specific IgM antibody	+	–	+	+	+
specific IgG antibody	+	–	+	+	+

Note: "+" means positive index; "-" means negative index; "#" means some severe patients with no fever symptom; "↓" means decreasing index.

appeared in severe cases after a week onset, rapidly deteriorating into ARDS, septic shock, coagulation dysfunction, and multiple organ failure [19]. Most patients exhibit good prognosis, except few critical cases. In addition, the poor prognosis in elderly and those with underlying chronic diseases has been observed [20].

2. Role of TCM in COVID-19 treatment

2.1. TCM understanding of COVID-19

The symptoms of COVID-19 are similar to those explained in *Huang Di Nei Jing* (Inner Canon of the Yellow Emperor), for *plague* category, being highly infectious and epidemic. The ancient Chinese people had

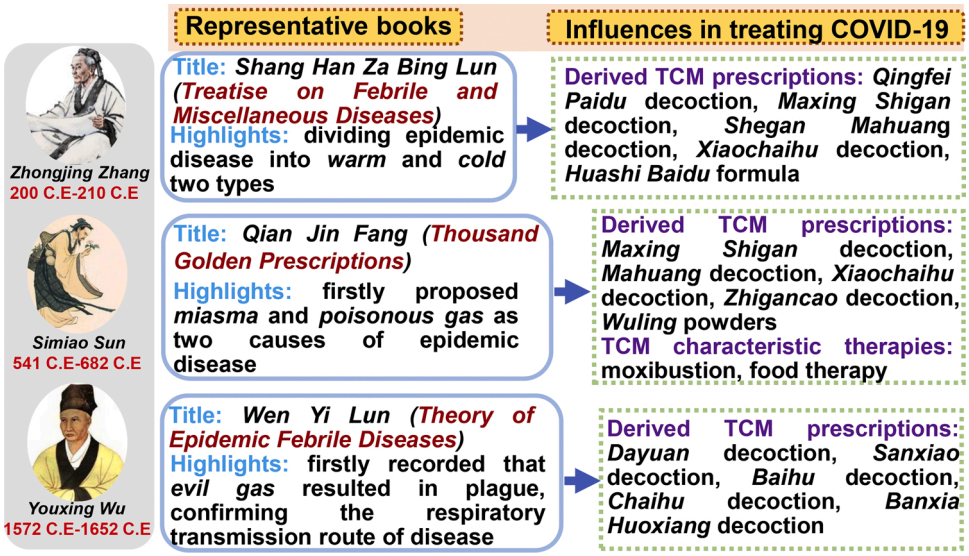

Fig. 2. Influences for current TCM prescriptions and therapies in treating COVID-19 from three ancient books.

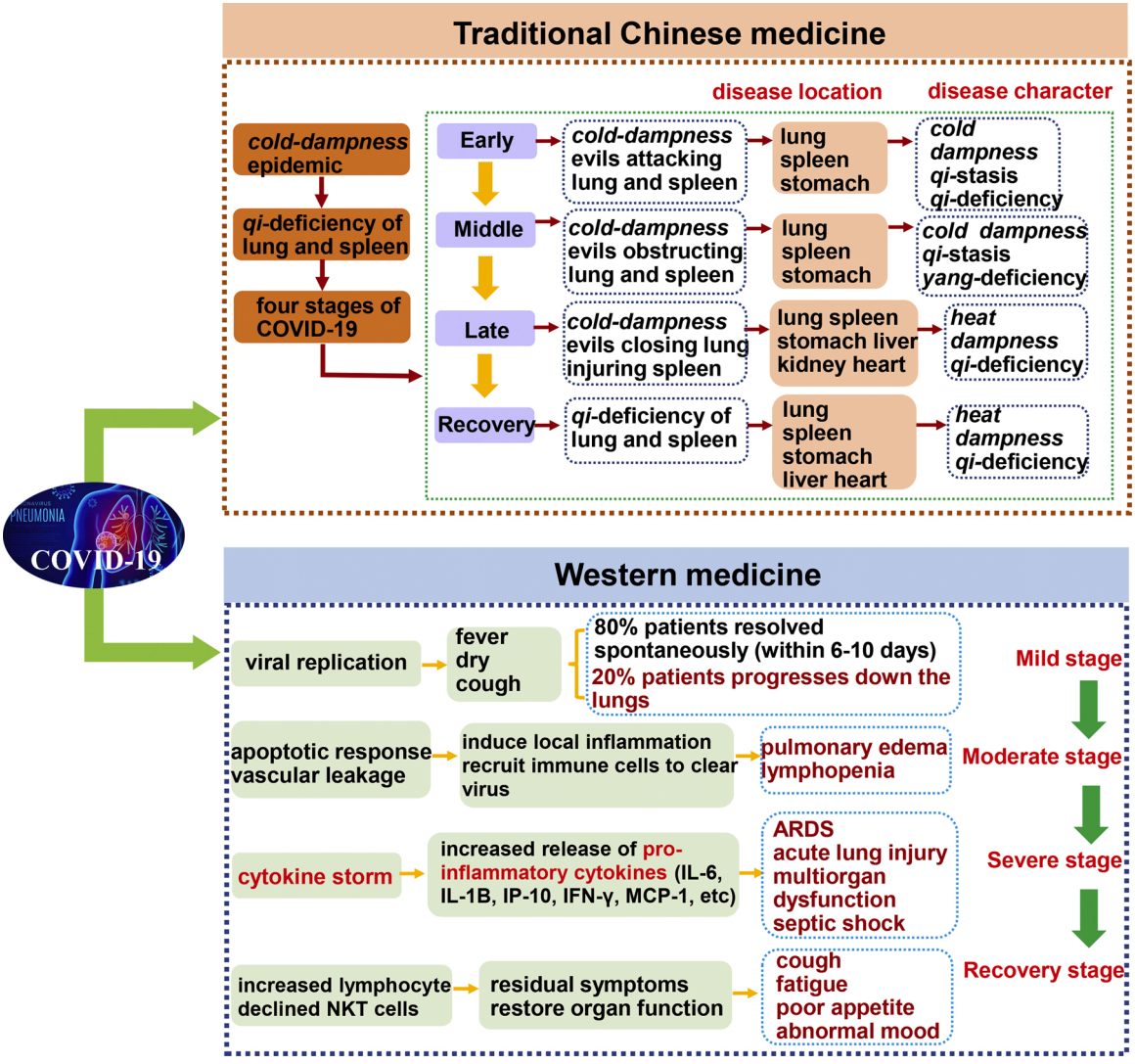

Fig. 3. The compared pathogenesis of COVID-19 from TCM and western medicine.

realized the severity of epidemic diseases and tried to find more accurate understanding. As shown in Fig. 2, *Shang Han Za Bing Lun* (Treatise on Febrile and Miscellaneous Diseases) written by *Zhongjing Zhang*, firstly proposed syndrome differentiation for patients, dividing epidemic diseases into *warm* (A disease type with main symptom of fever caused by warm pathogen) and *cold* (A disease type with main symptom of exogenous fever caused by cold pathogen) types. Combined with the initial symptoms of most patients, such as fear of *cold*, body aches and fatigue, SARS-CoV-2 should belong to the category of typhoid virus, and COVID-19 caused by this virus infection should be dialectical as typhoid fever. Consequently, several TCM prescriptions are derived from this book, such as *Qingfei Paidu* decoction, *Maxing Shigan* decoction, *Shegan Mahuang* decoction, *Xiaochaihu* decoction, etc, which has been widely used to remove cold pathogen of COVID-19 [21]. Besides, *Qian Jin Fang* (Thousand Golden Prescriptions) written by *Simiao Sun*, proposed that *miasma* and *poisonous gas* were two causes of epidemic diseases. Moxibustion and food therapy were firstly developed from *Qian Jin Fang*, providing a theoretical reference for TCM characteristic therapy used in the prevention and recovery of COVID-19 [22,23]. *Wen Yi Lun* (Theory of Epidemic Febrile Diseases) written by *Youxing Wu*, firstly recorded that *evil gas* resulted in plague, confirming the respiratory transmission route of disease [24]. *Dayuan* decoction, *Sanxiao* decoction and *Banxia Huoxiang* decoction were found in *Wen Yi Lun*, which can effectively remove evil *Qi* and lung heat for COVID-19 patients with mild symptoms [25,26]. Therefore, therapies and prescriptions recorded in above ancient books will give us an enlightenment to search new ways in treating COVID-19.

In TCM, the disease is the result of unbalanced relationship between human and nature, which means that environmental factors are very significant in the occurrence of diseases. Early COVID-19 cases were occurred in Wuhan, China, which is closely related to the local hot and humid climate in the winter of 2019, causing easier viral infection and transmission [27]. *Nong Tang et, al.* held the view that COVID-19 should be classified into *cold-dampness* epidemic (A disease caused by internal abundance of cold-damp pestilential pathogen). It is proposed that the direct cause of this disease is the invasion of evil *Qi*, and basic cause is the insufficiency of vital *Qi*, as well as the abnormal external environment at the end of 2019 [28]. This epidemic can be divided into four stages: the early stage with symptoms of *cold-dampness* evils attacking lung and spleen, the middle stage with symptoms of *cold-dampness* evils obstructing lung and spleen, the late stage with symptoms of *cold--dampness* evils closing lung and injuring spleen, and the recovery stage with symptoms of *qi*-deficiency of lung and spleen (Fig. 3) [29]. We also summarize the corresponding pathogenesis of SARS-CoV-2 infection from the perspective of western medicine, which is also shown in Fig. 3. Among them, in the mild stage, SARS-CoV-2 replication is occurred in the trachea, which may be incubated for 5–6 days [30]. After that, there is a mild symptom for 80 % infected patients, mainly including fever and dry cough, which disappeared spontaneously within 6–10 days [8]. Nevertheless, about 20 % patients developed viral infection from trachea to lungs [31]. SARS-CoV-2 binds with targets in alveolar epithelial cells such as ACE2 and TMPRSS2 and induces apoptosis response associated with vascular leakage [32]. This leakage causes the first wave of local inflammation and recruits immune cells from the blood into the lungs, thereby eliminating extracellular viruses and destroying infected cells [33]. The increased proinflammatory cytokines is attributed to the recruitment of leukocytes, further accelerating the local inflammatory response in lungs, including IL-6, IL-1β, IFN-γ, etc [34]. In this stage, the disease may rapidly develope into severe illness manifested as ARDS, acute lung injury, multiple organ dysfunction and septic shock [35]. More importantly, the detected levels of G-CSF, IP-10, MCP-1, MIP-1A and TNF-α in the serum of severe patients are higher than that of mild patients, implying a potential cytokine storm related to disease severity [19]. During the recovery stage, it is reported that lymphocyte count is also increased [36]. Besides, a declined number of natural killer T cell (NKT) is observed in patients in this stage, suggesting that the presence of these cells may be used to clear the virus during the initial infection [36]. Some patients still have clinical manifestations such as cough, fatigue, poor appetite, abnormal mood, which needs more time to recovery completely [37]. Taken together, we can acquire a comprehensive understanding of pathogenesis of COVID-19 from both TCM and western medicine, which is contributed to find the optimal treatment in clinic. Further, *Xiaoqian Sun et, al.* concluded four TCM treatment principles and confirmed that *dissipating cold and dispelling dampness*, *ventilating lung and relieving superficies* is mainly used to restore homeostasis and regulate immunity to prevent further evolution of syndromes; *clearing heat and resolving dampness*, *ventilating lung and detoxifying* mainly affects antiviral pathways such as inhibiting virus replication and enhancing immune function; *clearing away heat and toxic materials* is focused on inhibiting inflammation and cell differentiation, anti-apoptotic pathways; *replenishing energy and increasing Yang-qi* exhibits the effects of enhancing immunity and thus being beneficial for recovery [38].

2.2. TCM prescriptions for clinical treatment of COVID-19

TCM has shown obvious effects on treatment of COVID-19, having a preventive role in mild patients, improving the prognosis of severe patients, and reducing the mortality rate [39]. Currently, this disease is divided into five stages on the basis of different severity: mild stage, moderate stage, severe stage, critical stage and recovery stage. There are several TCM prescriptions recommended from the Diagnosis and Treatment Protocol for COVID-19 of China, including *Maxing Shigan* decoction (MXSGD), *Qingfei Paidu* decoction (QFPDD), *Dayuan* decoction (DYD), *Huashi Baidu* formula (HSBD), *Shufeng Jiedu* formula (SFJD), *Lianhua Qingwen* capsules (LHQW), *Huoxiang Zhengqi* capsules (HXZQ), *Jinhua Qinggan* granules (JHQG) and *Toujie Quwen* granules (TJQW), etc (Fig. 4). Among them, during the medical observation period, HXZQ is suggested for patients with fatigue and gastrointestinal discomfort, and JHQG, LHQW and SFJD are used for patients with fatigue and fever. Besides, QFPDD is applied in the treatment of mild, common and severe patients. MXSGD, DYD and TJQW are also recommended for mild patients with symptom of *cold-heat* invading lung and moderate patients with *cold-dampness* impeding lung. The main symptoms in the severe and critical stage are inner blocking causing collapse. *Angong Niuhuang* pills, *Xiyanping* injection, *Xuebijing* injection and *Reduning* injection are suggested to recover *Yang-qi*. Finally, in the recovery stage, symptoms of *qi*-deficiency of lung and spleen are improved by a TCM prescription consisted of *Pinellinae Rhizoma Praeparata*, *Citrus reticulata Blanco*, *Astragali Radix preparata*, *Codonopsis pilosula*, *Atractylodes macrocephala Koidz*, *Poria cocos*, *Pogostemon cablin*, *Glycyrrhiza uralensis Fisch* and *Amomum villosum Lour*.

Here, we summarize the herbal composition, active compounds, potential mechanisms and clinical applications of representative TCM prescriptions for the treatment of COVID-19, which is detailly listed in Table 3. These prescriptions with multi-compounds exhibit different pharmacologic actions on treating COVID-19 via multi-targets and multi-pathways, acquiring satisfactory clinical efficacy.

2.2.1. Maxing Shigan decoction

Maxing Shigan decoction (MXSGD), composed of *Ephedra sinica Stapf*, *Prunus armeniaca L*, *Gypsum Fibrosum* and *Glycyrrhiza glabra L*, is originated from *Treatise on Febrile and Miscellaneous Diseases* in *Han* dynasty, having functions to remove lung-heat and relieve asthma, pungent-cool and ventilate lung. This prescription is applicable to reduce cough and asthma caused by evil heat obstructed in the lung, which is mostly used to treat patients with external *wind-cold*, or wind-heat invading the lungs and internal heat and external *cold* [62]. Previous reports revealed that MXSGD exhibits antiviral effects via inhibiting viral proliferation and absorption, and protecting infected cells, which are more effective than ribavirin [63]. Furthermore, MXSGD has shown obvious improvement on H1N1-induced acute lung injury in mice model, by decreasing lung

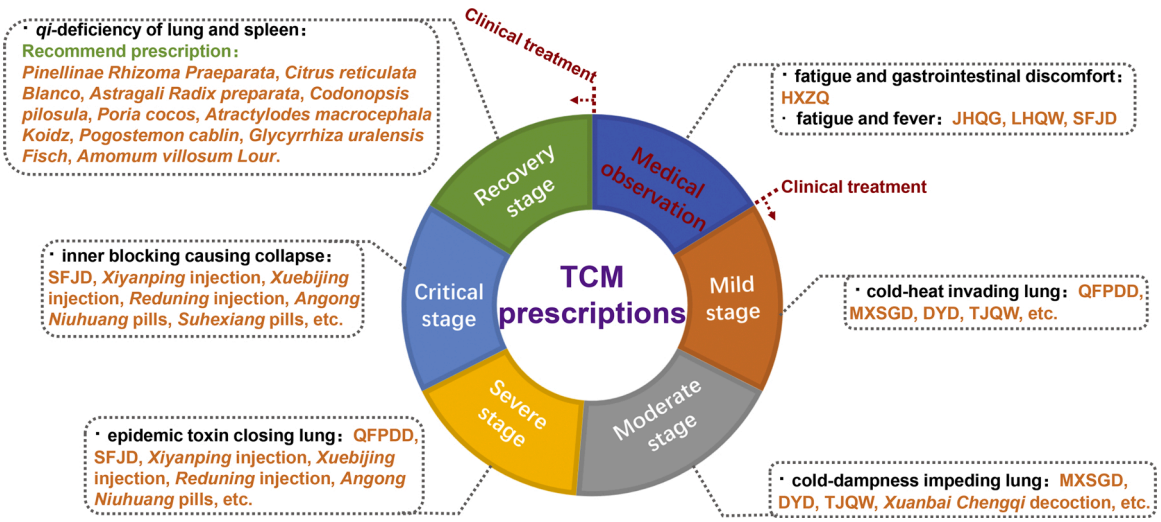

Fig. 4. Clinical stage differentiation and corresponding TCM prescriptions of COVID-19.

Table 3
Composition, active compounds, mechanisms and clinical applications of representative TCM prescriptions.

Prescriptions	Composition	Active compounds	Pharmacologic actions	Potential targets	Cases	Improved symptoms	Effective rate	Reference
MXSGD	4 herbs, including *Ephedra sinica Stapf*, *Prunus armeniaca L*, *Gypsum Fibrosum* and *Glycyrrhiza glabra L.*	quercetin, kaempferol, isorhamnetin, naringenin, wogonin	inhibiting SARS-CoV-2 replication, reducing cytokine storm	AKT1, MAPK3, IL-6, TP53, TNF, CASP3, EGFR, MAPK1, etc.	40	fever, fatigue, cough	96.8 %	[40,41,42]
QFPDD	21 herbs, including *Ephedra sinica Stapf, Glycyrrhiza glabra L, Prunus armeniaca L, Gypsum Fibrosum, etc.*	quercetin, luteolin, kaempferol, isorhamnetin, naringenin, beta-sitosterol, etc.	anti-inflammatory, protecting lung injury, inhibiting virus adsorption and replication	AKT1, MAPK1, MAPK14, IL-6, TNF, CASP3, DPP4, etc.	701	fever, cough, lung CT	94.3 %	[43,44,45]
DYD	7 herbs, including *Areca catechu L, Magnolia officinalis, Paeonia lactiflora Pall, Scutellaria albida L, etc.*	kaempferol, quercetin, naringenin, formononetin	anti-inflammatory, antiviral, immunomodulatory	PTGS2, IL-6, CCL2, IL-1B, etc.	2	cough, asthma, dry throat	100 %	[46,47]
HSBD	14 herbs, including *Ephedra sinica Stapf, Prunus armeniaca L, Gypsum Fibrosum, Glycyrrhiza glabra L, etc.*	quercetin, luteolin, kaempferol, baicalein, etc.	anti-inflammatory, inhibiting SARS-CoV-2 replication	IL-6, MAPK8, MAPK1, IL-1B, etc.	146	fever, cough, lung CT	74.7 %	[48,49]
SFJD	8 herbs, including *Reynoutria japonica Houtt, Forsythia suspensa, Isatis indigotica Fort, Bupleurum abchasicum Manden, Patrinia heterophylla Bunge, etc.*	quercetin, wogonin, polydatin, etc.	anti-inflammatory, anti-SARS-CoV-2	MAPK14, TNF, IL-6, IL-10, PTGS2, etc.	100	fever, dry cough, fatigue, lung CT	88.0 %	[50,51,52]
LHQW	13 herbs, including *Forsythia suspensa, Lonicera japonica, Ephedra sinica Stapf, Prunus armeniaca L, Isatis indigotica Fort, etc.*	neochlorogenic acid, amygdalin, prunasin, forsythoside I, rutin, forsythoside A, etc	anti-SARS-CoV-2, anti-inflammatory,	IL-6, TNF, MAPK1, IL-1B, MAPK8	122	fever, cough, sputum, polypnea, fatigue, anorexia	98.0 %	[53,54]
HXZQ	10 herbs, including *Areca catechu L, Angelica dahurica, Perilla frutescens, Pinellia ternata, Atractylodes macrocephala, etc.*	quercetin, isorhamnetin, pueraria aglycone, etc	Inhibiting SARS-CoV-2 replication, improving immune, anti-inflammatory	IL-6, IL-1β, TNF, IL-10, PTGS2, AR, etc.	11	fever, cough, fatigue, diarrhea	100 %	[55,56]
JHQG	12 herbs, including *Lonicera japonica Thunb., Fritillaria thunbergii Miq., Scutellaria baicalensis Georgi, Arctium lappa L., etc.*	kaempferol, baicalein, oroxylin A	anti-inflammatory, anti-SARS-CoV-2	IL-6, IL-1β, CXCL8, CCL-2, IL-2, IL-4, ICAM1, IL-10, IL-1, etc.	82	fever, cough, expectoration, psychological anxiety	80.3 %	[57,58]
TJQW	16 herbs, including *Forsythia suspensa, Gremastra appendiculata, Lonicera japonica, Scutellaria baicalensis Georgi, etc.*	quercetin, isoquercitrin, astragaloside IV, rutin, kaempferol, luteolin, isorhamnetin, etc.	anti-inflammatory, anti-SARS-CoV-2, improving immune	PTGS2, IL-6, TNF, etc.	37	fever, cough, fatigue, chest tightness, panting, lung CT	89.2 %	[59,60,61]

cell apoptosis and reducing TNF-α concentration in serum [64]. *Shiying Zhang et, al.* found that MXSGD can control disease progression by regulating multiple targets, including AKT1, MAPK3, IL-6, TP53, TNF, CASP3, EGFR and MAPK1, which interacted with ACE2 that closely related to disease development [40]. Animal experiments have confirmed that the anti-inflammatory effects of MXSGD are mediated via thrombin and Toll-like receptor signaling pathway [62]. The network analysis also showed that the predicated five active compounds including quercetin, kaempferol, isorhamnetin, naringenin and wogonin are effective in inhibiting SARS-CoV-2 replication and reducing cytokine storm [42,65]. According to analysis of clinical medication of 225 patients with COVID-19 in *Wanzhou, Chongqing city*, it is found that intervention therapy with TCM is about 87 % (n = 195 cases), 20.29 % of which is attributed to MXSGD [66]. Additionally, after the combined application of conventional western medicine and MXSGD in 40 common cases for 7 d, the disappearance rates of fever, fatigue and cough are 96.8 %, 100 % and 81.8 %, respectively. The levels of IL-6 and CRP in serum are significantly decreased, reflecting a weakened inflammation [41]. Based on both network pharmacology and bioinformatics technology analysis, researchers speculate that MXSGD blocks the conversion of patients with COVID-19 from mild to severe stage by inhibiting cytokine storm [67].

2.2.2. Qingfei Paidu decoction

Qingfei Paidu decoction (QFPDD) is firstly approved as a general prescription for treatment of COVID-19, consisted of 21 herbs, including *Ephedra sinica Stapf*, *Glycyrrhiza glabra L*, *Prunus armeniaca L*, *Gypsum Fibrosum*, *Cinnamomum cassia Presl*, *Alisma plantago-aquatica Linn*, *Polyporus*, *Atractylodes macrocephala Koidz*, *Poria cocos (Schw.) Wolf*, *Bupleurum abchasicum Manden*, *Scutellaria albida L*, *Pinellia Ternata*, *Zingiber officinale Roscoe*, *Aster tataricus* L. *f*, *Tussilago farfara L*, *Belamcanda chinensis* (L.) *DC*, *Asarum sieboldii Miq*, *Dioscorea oppositifolia L*, *Citrus aurantium L*, *Citrus reticulata Blanco*, *Agastache rugosa (Fisch.&C.A. Mey.) Kuntze*. This prescription is a combination of several classical prescriptions from *Treatise on Febrile and Miscellaneous Diseases* for the treatment of exogenous febrile disease caused by pathogenic *cold*, including *MXSGD* (removing lung fever), *Shegan Mahuang* decoction (relieving cough and asthma), *Chaihu* decoction (clearing away gallbladder-heat and regulating the stomach) and *Wuling* powders (warming *Yang* and activating *Qi*). In addition, *Dioscorea oppositifolia L*, *Agastache rugosa (Fisch. & C.A.Mey.) Kuntze*, *Citrus reticulata Blanco* and *Citrus aurantium L* used in the QFPDD prescription have effects of strengthening the spleen and regulating *Qi*. As of February 5 in 2020, about 214 confirmed cases in four pilot provinces were treated with the QFPDD, for which the total effective rate was over 90 %, including 60 % of patients with improved symptoms and imaging manifestations and keeping 30 % of cases with stable symptoms [68]. Subsequently, QFPDD was recommended to treat COVID-19 around China, acquiring ideal clinical response. 98 confirmed cases (54 mild, 33 common and 11 severe cases) in *Sichuan* Province were treated with QFPDD for 3 days as a course of treatment. The total effective rate is 84.22 % after 3 days of treatment, 90.15 % after 6 days of treatment, and 92.09 % after 9 days of treatment [43]. In general, as of February 17 in 2020, QFPDD has been used to treat 701 confirmed patients in 57 hospitals of 10 provinces. As a result, 130 cases were cured with asymptomatic, 51 cases with disappeared symptoms, 268 cases with improved symptoms, 212 cases with stable symptoms, which reached to the effective rate of 94.29 % [69]. The curative rate of 22 confirmed cases treated with the combination of QFPDD and interferon α-1b was about 100 %, suggesting satisfactory application of integrated TCM and western medicine treatment [70]. Besides, investigated by network pharmacology, *Jing Zhao et, al.* reports the multi-components and multi-targets of QFPDD for the treatment of COVID-19. There are 16 herbs targeted to lung meridian, suggesting specific therapy to lung diseases. Similar to SARS-CoV, the 232 of 790 potential targets were also targeted to ACE2 receptor, which indicates that QFPDD could improve symptoms caused by disordered ACE2 receptor expression in SARS-CoV-2 infection. The multiple targets of QFPDD act in inhibiting activated cytokines, alleviating excessive immune response and thereby eliminating inflammation [71]. Detailly, SARS-CoV-2 adsorption and replication were inhibited by QFPDD that regulates NF-κB pathway, TNF pathway, PI3K-Akt pathway and MAPK pathway. *Tianfu Xu et, al.* reported that the active ingredients (quercetin, luteolin, kaempferol, isorhamnetin, naringenin and beta-sitosterol, etc) in QFPDD prescription could inhibit cytokines release, reduce excessive immune response and eliminate inflammation by targeting to AKT1, MAPK1, MAPK14, IL-6 and TNF [45]. Functional units of network pharmacology analysis showed that QFPDD has a protective effect on COVID-19 by regulating a complex molecular network with safety and efficacy, which is closely connected with anti-viral, anti-inflammatory activity and metabolic programming [72].

2.2.3. Dayuan decoction

Dayuan decoction (DYD) is composed of *Areca catechu L*, *Magnolia officinalis Rehder & E.H.Wilson*, *Atractylodes macrocephala Koidz*, *Citrus reticulata Blanco*, *Amomum tsao-ko Crevost et Lemaire*, *Ephedra sinica Stapf*, *Zingiber officinale Rosc*, *Citrus × aurantium L*, *Pogostemon cablin (Blanco) Benth*, *Hansenia weberbaueriana (Fedde ex H.Wolff) Pimenov & Kljuykov* that are present in the mass ratio of 10: 10: 15: 10: 6: 6: 10: 10: 10 [73]. Eight of them are aromatic Chinese herbs, having functions of dissolving the turbid with aromatics, and clearing heat and nourishing *Yin*. Experimental studies have shown that DYD has obvious antipyretic effects, the mechanism of which is related to decreasing prostaglandin E2 level in the cerebrospinal fluid, thereby reducing the excitatory stimulation to the body temperature center [74]. During January to April 2003, a total of 112 confirmed SARS cases were treated with DYD, with over 93.7 % of the patients experiencing noticeable symptoms reduction and recovery [73]. This prescription is quite consistent with the treatment principle for COVID-19 in terms of etiology, pathogenesis, efficacy and indications, thus being used for mild and common cases during the clinical treatment period. In clinic, it is found that DYD can relieve symptoms of cough, asthma and dry throat, improve prognosis of COVID-19 patients, and shorten disease progression, making it worthy of clinical application and promotion [46,75]. In the treatment of COVID-19, DYD also decreases the severity of ARDS by acting on cytokine storm [73]. Furthermore, by using network pharmacology and molecular docking method, *Yang Zong et, al.* found that active compounds in DYD prescription may act on PTGS2, IL-6, IL-1β, CCL2 and other targets by combining with ACE2 to regulate multiple signaling pathways, having a therapeutic effect on COVID-19 [47]. *Xiaofeng Ruan* reported that there was a high affinity between the key compounds (kaempferol, quercetin, naringenin and formononetin) and key targets (IL-6, IL-1β, CCL2) through molecular docking analysis. Finally, DYD was demonstrated to reduce the level of IL-6 in COVID-19 patients, exerting anti-inflammatory and immune regulation activities [26].

2.2.4. Huashi Baidu

Huashi Baidu formula (HSBD) consists of *Ephedra sinica Stapf*, *Prunus armeniaca L*, *Gypsum Fibrosum*, *Glycyrrhiza glabra L*, *Agastache rugosa (Fisch.&C.A.Mey.) Kuntze*, *Magnolia officinalis Rehder&E.H.Wilson*, *Atractylodes lancea (Thunb.) DC*, *Amomum tsaoko Crevost et Lemarie*, *Pinellia pedatisecta Schott*, *Poria cocos(Schw.)Wolf*, *Rheum officinale Bail*, *Astragalus mongholicus Bunge*, *Eruca sativa Mill*, *Radix Paeoniae Rubra*, which is added or subtracted from MXSGD, HXZQ powders, *Xuanbai Chengqi* decoction. *Ephedra sinica Stapf*, *Agastache rugosa* and *Gypsum Fibrosum* are monarch drugs of HSBD formula, having effects of relieving exterior and suppressing asthma, and removing dampness for regulating stomach. In addition, *Prunus armeniaca L*, *Pinellia pedatisecta Schott*, *Magnolia officinalis*, *Atractylodes lancea*, *Amomum tsaoko* and *Poria cocos* are minister drugs, to assist monarch drugs to remove damp and strengthen spleen, and excrete evils from texture of skin and muscle [76]. *Lizhu Han et, al.* proposed a systematic program to evaluate the efficacy and safety of HSBD formula combined with antiviral drugs in

the treatment of COVID-19 via meta-analysis, providing references for clinical diagnosis and treatment [77]. HSBD formula is suitable for severe cases with pestilence poison closing lung syndrome, significantly shortening nucleic acid negative conversion time, and improving results of biochemical criterion and lung CT [78]. By March 20, a total of 146 cases have been admitted to *Jinyintan* Hospital, of which 109 cases are cured and discharged, with a discharge rate of 74.7 % [49]. Moreover, HSBD are applied in 124 moderate cases of *Dongxihu Fangcang* Hospital, and 894 mild and moderate cases of *Jiangjunlu* Street Health Center, respectively, with no adverse events or liver and kidney damage [79]. The molecular docking results showed that quercetin, luteolin, kaempferol in HSBD prescription have a good combination with 3CL hydrolase and ACE2, associated to key targets such as IL-6, MAPK8, MAPK1 and IL-1β [48]. *Quyuan Tao et, al.* confirmed that baicalein and quercetin are the top two compounds in HSBD formula, which may regulate multiple signaling pathways such as TNF, PI3K-Akt, NOD-like receptor, MAPK, and HIF-1 [80].

2.2.5. Shufeng Jiedu

The main herbs in *Shufeng Jiedu* (SFJD) formula are *Reynoutria japonica Houtt*, *Forsythia suspensa (Thunb.) Vahl*, *Isatis indigotica Fort*, *Bupleurum abchasicum Manden*, *Patrinia heterophylla Bunge*, *Verbena officinalis L*, *Glycyrrhiza glabra L*, etc. SFJD aims to the early stage of disease with dampness-evils depressed in lung and obstruction of cardinalate, having functions of resolving damp and detoxification, and diffusing lung to remove evils [81]. *Reynoutria japonica Houtt* is the monarch drug of this prescription that dispels wind, removes dampness, relieves surface and attacks various swellings. *Forsythia suspensa* can penetrate muscles and relieve surface, clear away heat and dispel wind [82]. Clinical symptoms (fever, dry cough, fatigue) of 100 mild cases were effectively controlled after combination therapy of SFJD capsules and Arbidol. At the same time, hemameba and lymphocytes were significantly increased, and the chest CT was obvious absorbed, indicating that SFJD capsules can be effectively used in the treatment of patients with mild COVID-19 [51]. Another report showed that 100 common cases treated with regimen of SFJD capsules combined with Arbidol for 14 days have significantly decreased CRP and IL-6 levels, suggesting that inflammatory response is weakened [83]. The network pharmacology and molecular docking results revealed that there are 18 active compounds with inhibitory effect on SARS-CoV-2 3CL, 158 active compounds with inhibitory activity on ACE2 receptor, and 11 of 155 pathways related to viral, bacterial and parasitic infections, indicating multi-components, multi-targets and multi-pathways of SFJD against COVID-19 [84]. *Xiao Chen et, al.* reported that RELA, MAPK1, MAPK14, CASP3, CASP8 and IL-6 are the key targets, involving in multiple signaling pathways of MAPK and NF-κB [85]. *Zhengang Tao et, al.* found that 94 compounds from SFJD prescription are screened as candidate compounds and their 80 corresponding targets are mostly associated with immunomodulation and inflammation. In a HCoV-229E mouse model, *Lu Xia et, al.* confirmed that SFJD significantly reduces the virus load in the lung from 1109.29 ± 696.75 to 0 ± 0 copies/mL, decreases levels of inflammatory factors (IL-6, IL-10, TNF-α, and IFN-γ), and increases amount of CD4+ and CD8+ cells in the blood, compared to the model group. Importantly, Quercetin, wogonin, and polydatin could directly bind to the key protease of SARS-CoV-2 [52].

2.2.6. Lianhua Qingwen

Lianhua Qingwen (LHQW) has been widely concerned and recognized for its unique theoretical composition and previous remarkable efficacy in combating SARS and influenza epidemics, becoming a representative Chinese patent medicine for public health events in the respiratory system [86,87]. This prescription is composed of *Forsythia suspensa (Thunb.) Vahl*, *Lonicera japonica Thunb*, *Rheum officinale Baill*, *Prunus armeniaca L*, *Gypsum Fibrosum*, *Isatis indigotica Fort*, *Dryopteris crassirhizoma Nakai*, *Heartleaf houttuynia herb*, *Pogostemon cablin (Blanco) Benth*, *Rheum officinale Baill*, *Rhodiola rosea L*, *Menthol*, *Glycyrrhiza glabra L*, which is a added formula on the basis of MXSGD and *Yinqiao* powders [86]. Among them, the main efficacy of MXSGD is to relieve lung-heat and collateral toxic-heat, *Yinqiao* powders to dispel toxin and dissolving turbidity, *Rheum officinale Baill* to dredge intestines and clear lung, *Agastache rugosa* to eliminate dampness and *Rhodiola rosea L* to supply *Qi* and nourish *Yin*, fully reflecting characteristics of truncating the etiological factors, overall regulation and multi-targets therapy. *Zheng Li et, al.* concluded that LHQW is reliable for providing the desired efficacy in COVID-19 management because of its property of heat-clearing and lung-freeing, and multifunctionality in coping with virus infection and inflammatory response [88]. *Nanshan Zhong* reported that LHQW could significantly inhibit the SARS-CoV-2 replication in Vero E6 cells and reduce generation of pro-inflammatory cytokines such as IL-6, TNF-α, CCL-2/MCP-1 and CXCL-10/IP-10, helping to protect from viral infection [89]. Actually, clinical research of 42 mild cases with COVID-19 in *Wuhan* showed that LHQW has positive effects on improving symptoms of fever, cough, sputum and polypnea, effectively decreasing 1.5 days of fever reduction time and proportion turning to severe cases [90,91]. Besides, clinical trial in 142 confirmed cases were evaluated on LHQW capsules for 14 days, with 91.5 % of recovery rate, 83.8 % of improved chest computed tomographic manifestations and 78.9 % of clinical cure rate [92]. *Suliman Khan et, al.* reported that the combination therapy of LHQW with Arbidol Hydrochloride for 5–7 days in 122 patients with mild symptoms has shown 98 % recovery rate [93]. Further, *Lin Wang et, al.* found that the key targets in LHQW prescription include IL-6, TNF, MAPK1, IL-1β and MAPK8, the mechanism of which may be related to broad-spectrum antiviral, antipyretic, and regulating immunity [54]. A total of 8 components including neochlorogenic acid, amygdalin, prunasin, forsythoside I, rutin, forsythoside A, glycyrrhizin and rhein exhibited good binding affinity to ACE2, mainly via influencing the binding between ACE2 and S protein [94]. *Facai Wang et, al.* indicated that quercetin, luteolin, kaempferol and sitosterol in LHQW prescriptions have the most potential targets for treating COVID-19 through network pharmacology [95].

2.2.7. Huoxiang Zhengqi

Yunfei Lu et, al. analyzed the clinical characteristics of 50 COVID-19 patients and found that 56 % of them are accompanied by diarrhea [96]. On the basis of removing *cold* and *dampness*, *Huoxiang Zhengqi* (HXZQ) also improves gastrointestinal function and enhances cellular immunity, which is recommended to treat COVID-19 patients with fatigue and diarrhea during the medical observation period. The basic prescription is composed of *Areca catechu L*, *Angelica dahurica* var. *formosana (Boissieu) Yen*, *Perilla frutescens* (L.) *Britt*, *Poria cocos (Schw.) Wolf (Schw.) Wolf*, *Pinellia ternata (Thunb.) Makino*, *Atractylodes macrocephala Koidz*, *Citrus reticulata Blanco*, *Magnolia officinalis Rehder&E.H.Wilson*, *Platycodon grandiflorus (Jacq.) A. DC*, *Agastache rugosa (Fisch.&C.A.Mey.) Kuntze* and *Gypsum Fibrosum*. It is applied to relieve the abdominal distention and pain, vomiting and diarrhea induced by exogenous *wind-cold* and endogenous damp stagnation, showing good effects of relieving the exterior and dispersing dampness, and regulating *Qi*. Because of similar replication cycle between animal virus infection, HXZQ has therapeutic effects on a variety of virus infections (H5N1 avian influenza virus, Rotavirus, Norovirus, etc), suggesting possible inhibitory effects on SARS−COV-2 [97]. Actually, from molecular docking results, 3CLpro of SARS-CoV-2 is well combined with five compounds (Elicorice glycoside E, naringenin, robinin, kaempferol and (2R)-7-hydroxy-2-(4-hydroxyphenyl)chroman-4-one) in HXZQ, which is better than that of remdesivir, implying anti-SARS-CoV-2 activity by directly inhibiting virus replication [98]. Network pharmacology preliminarily predicted that this process may be affected via PI3K-Akt signaling pathway. Besides, quercetin, isorhamnetin and pueraria aglycone in HXZQ have the strongest binding affinity to ACE2, and act on targets such as PTGS2, HSP90AB1, AR and CAMSAP2 to regulate multiple signal pathways [55]. Cytokine storm has been confirmed in severe COVID-19 patients, especially the existence of IL-6 [99]. HXZQ

has an obvious anti-inflammatory effects, including decreasing levels of various pro-inflammatory cytokines (IL-6, IL-1β, TNF-α, IL-2) and increasing level of IL-10 as well as regulating NF-κB pathways, indicating that HXZQ may have therapeutical effects for COVID-19 patients [100]. Clinically, HXZQ combined with western medicine significantly reduced clinical symptoms (fever, cough, fatigue, white and greasy tongue fur) in 11 confirmed cases with lung stagnation, prevented the transition from mild to severe, and increased the clinical cure rate, which is worthy of popularization and application [56].

2.2.8. Jinhua Qinggan

Jinhua Qinggan (JHQG) granule with functions of heat-clearing and detoxification, was the first TCM prescription in treating H1N1 infection, consisted of *Lonicera japonica Thunb., Fritillaria thunbergii Miq., Scutellaria baicalensis Georgi, Arctium lappa* L., *Artemisia annua* L., *etc*. Among them, *Lonicera japonica*, the monarch drug in JHQG prescription, has obvious antiviral effects that associated with inhibiting viral adsorption and protein replication [101]. The damaged viral pneumonia tissue can be repaired by *Scutellaria baicalensis Georgi* via reducing levels of TNF-α, IL-1 and IL-6 [102]. Modern pharmacological studies have shown that JHQG granule can reduce serum CRP and IFN-γ levels in patients with viral pneumonia, improve inflammatory symptoms and regulate immunity [103]. *Guoqin Li et, al.* reported that JHQG has good efficacy and clinical safety for the syndrome of wind-heat invading the lungs of influenza [104]. In clinic, JHQG granule has shown a significant effect on the treatment of mild and common COVID-19 (n = 82), reflected in the reduction of symptoms (fever, cough, expectoration) and remission of psychological anxiety in patients [58]. Additionally, *Zengli Liu et, al.* found that JHQG granule can effectively shorten the nucleic acid detection time and promote the absorption of pneumonia inflammatory exudate, with no noticeably adverse events [105]. *Hao Chen et, al.* performed a protocol of systematic review and meta-analysis, providing high-quality evidence of JHQG granules for COVID-19 [106]. The network pharmacology study discovers that JHQG exerts antiviral effects and regulation in immune inflammation and apoptosis via PI3K-Akt, HIF-1, TNF, MAPK and NF-κB signaling pathway on the treatment of COVID-19 [107]. In addition, it can effectively reduce the serum levels of various cytokines and enhance immune function, which mainly acted on IL-6, IL-1β, CXCL8, CCL2, IL-2, IL-4, ICAM1, IL-10, IFNG and IL-1A [108]. Another report indicated that the affinity of kaempferol, baicalein and oroxylin A in JHQG granule with ACE2 is similar to that of clinically recommended compounds, mainly involves the regulation of PI3K-Akt signaling pathway, TNF signaling pathway, and Toll-like receptor signaling pathway [109].

2.2.9. Toujie Quwen

Most of the patients found in *Guangzhou*, China had symptoms of lung-heat in the early stage, accumulation of damp and heat in the middle stage, and lack of *Yin-qi* in the later stage [110]. Under the guidance of *Warm pestilence* theory, *Toujie Quwen* (TJQW) granules (formerly known as "Pneumonia No.1 Prescription") were formulated by the Eighth People's Hospital of *Guangzhou*, with effects of clearing away heat and detoxification, dispelling wind and penetrating surface, replenishing *Qi* and nourishing *Yin*. This prescription is composed of 16 Chinese herbs such as *Forsythia suspensa (Thunb.) Vahl, Gremastra appendiculata (D.Don) Makino, Lonicera japonica Thunb., Scutellaria baicalensis Georgi, Poria cocos (Schw.) Wolf, Fritillaria thunbergii Miq., Scrophularia ningpoensis Hemsl, Prunus mume (Sieb.) et Zucc, Pseudostellaria heterophylla, Astragalus membranaceus,* etc [60]. A large amount of *Forsythia suspensa* and *Gremastra appendiculata* used in TJQW prescription have functions of clearing lung-heat, dissipating phlegm and resolving masses. *Scrophularia ningpoensis Hemsl* and *Prunus mume* are used to protect from viral infection of uninfected parts in the lungs. Additionally, in the early stage of COVID-19, *Pseudostellaria heterophylla* and *Astragalus membranaceus* are applied in removing evil *Qi* and retaining healthy *Qi*, which can effectively prevent deficiency of *Qi* and *Yin* at the later stage. *Miaobo Ye* et, al. reported that the common key targets between TJQW and COVID-19 are PTGS2, TNF and IL-6 enriched in IL-17 signaling pathway and TNF signaling pathway. The molecular docking results showed that quercetin, isoquercetin, astragaloside IV and rutin exhibited the most affinity scores than that of other compounds. Importantly, quercetin and isoquercitrin could combine with S protein while astragaloside IV and rutin combine with ACE2 [61]. Besides, 30 active compounds and 22 core targets, 10 signaling pathways were obtained in TJQW according to another systematic pharmacological investigation, further revealing the therapeutic mechanism of TJQW for COVID-19 by regulating viral infection, immune and inflammation, in the way of multiple components, multiple targets and multiple pathways [60]. Clinically, TJQW granules in combination with Arbidol have positive effects on the early treatment of COVID-19 with a total effective rate of 89.2 % (n = 37), including improving symptoms of patients, regulating inflammation indicators of peripheral blood, and preventing aggravation of the disease [59]. Besides, it is effective for 2 common cases treated with TJQW granules based on differentiating syndrome on time at the early stage [111].

2.3. Analysis of medication characteristics and mechanisms of TCM prescriptions in treating COVID-19

Tiantian Fan et, al. concluded the 17 most commonly used Chinese herbs in the treatment of COVID-19 via frequency analysis of TCM prescriptions, including *Glycyrrhiza glabra L*, *Scutellaria baicalensis Georgi*, *Prunus armeniaca L*, *Gypsum fibrosum*, *Forsythia suspensa*, *Ephedra sinica Stapf*, *Lonicera japonica*, *Pogostemon cablin*, *Platycodon grandifloras*, *Poria cocos*, *Pinellia ternate*, *Rheum palmatum L*, *Atractylodes macrocephala*, *Gardenia jasminoides*, *Magnolia officinalis*, *PanaxginsengC.A.Mey.* and *Citrus reticulata Blanco*. These herbs have effects of invigorating spleen-*qi*, clearing heat and detoxifying, dispelling phlegm and relieving cough, helping to relieve damp-heat symptom of COVID-19. For example, several herbs with functions of clearing lung and relieving superficies are used to improve symptoms of fever, chill and muscle soreness in COVID-19 patients at the early stage, including *Ephedra sinica Stapf*, *Lonicera japonica*, *Forsythia suspensa*, *Pogostemon cablin*, *Platycodon grandifloras* and *Glycyrrhiza glabra L*. Subsequently, for patients with the lung obstructed by pathogenic heat and depressed lung-*qi*, *Scutellaria baicalensis Georgi*, *Ephedra sinica Stapf*, *Prunus armeniaca L*, *Rheum palmatum L* and *Gardenia jasminoides Ellis* are applied to clear lung heat and purge phlegm toxin. Besides, for patients with turbid dampness, there are also some herbs for regulating *Qi*, and removing dampness and turbidity, such as *Poria cocos*, *Pinellia ternate*, *Magnolia officinalis* and *Citrus reticulata Blanco*. Moreover, herbs-pair and triple-herbs are the basic forms of herbal compatibility. There are 24 herbal combinations with high frequency of more than 70 times from above prescriptions. *Ephedra sinica Stapf & Prunus armeniaca L* is the most commonly used in high frequency herbal combination, which is originated from MXSGD, QFPDD, HSBD and LHQW prescription. Both *Ephedra sinica Stapf* and *Prunus armeniaca L* are two frequently used herbs ascribed to the lung meridian, and have the effects of freeing lung, relieving asthma, discharging depressed lung heat, which is often used to heat syndrome caused by SARS-CoV-2. Above herbs and their combinations illustrated that the principles of TCM are strengthening resistance and eliminating pathogenic factors to achieve the treatment of both symptoms and root causes [112]. *Yufeng Huang et, al.* summarized that the active compounds and possible mechanisms from several TCM prescriptions researches. Among them, quercetin, kaempferol, luteolin, isorhamnetin, baicalein, naringenin, wogonin, ergosterol, lonicerin and tussilagone are considered as the top ten active compounds. AEC2 and 3CL proteins may be two direct targets for the inhibition of SARS-CoV-2 replication [4]. *Boyu Pan et, al.* reported that quercetin not only has a receptor blocking effect, but also has a virus-neutralizing effect on SARS-CoV-2, suggesting a promising candidate against COVID-19 [113]. Additionally, the top ten targets such as

Table 4
The high frequency herbs, active compounds, targets and pathways concluded from TCM prescriptions [4,113].

Herbs	Herbal combination	Active compounds	Targets	Signaling pathways
Glycyrrhiza glabra L	*Ephedra sinica Stapf & Prunus armeniaca L*	quercetin	ACE2	IL-17
Scutellaria baicalensis Georgi	*Forsythia suspensa & Glycyrrhiza glabra L*	kaempferol	3CL pro	HIF-1
Prunus armeniaca L	*Glycyrrhiza glabra L & Prunus armeniaca L*	luteolin	COX-2	NF-κB
Gypsum fibrosum	*Gypsum fibrosum & Ephedra sinica Stapf*	isorhamnetin	CASP3	Ras
Forsythia suspensa	*Glycyrrhiza glabra L & Ephedra sinica Stapf*	baicalein	IL-6	TNF
Ephedra sinica Stapf	*Gypsum fibrosum & Prunus armeniaca L*	naringenin	MAPK1	MAPK
Lonicera japonica Thunb	*Gypsum fibrosum & Glycyrrhiza glabra L*	wogonin	MAPK14	PI3K-Akt
Pogostemon cablinBlanco (Benth)	*Glycyrrhiza glabra L & Ephedra sinica Stapf & Prunus armeniaca L*	ergosterol	MAPK8	Toll-like receptor
Platycodon grandiflorus	*Glycyrrhiza glabra L & Ephedra sinica Stapf & Prunus armeniaca L*	lonicerin	EGFR	Th17 cell differentiation
Poria cocos	*Scutellaria baicalensis Georgi & Forsythia suspens*	tussilagone	IL-2	
Pinellia ternata(Thunb.)Breit	*Lonicera japonica Thunb & Forsythia suspensa*	β-sitosterol	TNF	
Rheum palmatum L	*Gypsum fibrosum & Glycyrrhiza glabra L & Ephedra sinica Stapf*	rutin	CCL-2	
Atractylodes macrocephala Koidz	*Scutellaria baicalensis Georgi & Glycyrrhiza glabra L*	stigmasterol	IL-10	
Gardenia jasminoides Ellis	*Forsythia suspensa & Ephedra sinica Stapf*	7-methoxy-2-methyl	IL-1B	
Magnolia officinalis	*Forsythia suspensa & Prunus armeniaca L*	isoflavone	IL-4	
PanaxginsengC.A.Mey.	*Gypsum fibrosum & Glycyrrhiza glabra L & Prunus armeniaca L*	acacetin	STAT1	
Citrus reticulata Blanco	*Gypsum fibrosum & Forsythia suspensa*	chlorogenic acid	TP53	
	Glycyrrhiza glabra L & Platycodon grandiflorus	formononetin	AKT1	
	Pinellia ternate (Thunb.) Breit & Poria cocos	hydroxysafflor yellow A	ALB	
	Gypsum fibrosum & Rheum palmatum L	licochalcone A	ICAM1	
	Gypsum fibrosum & Glycyrrhiza glabra L & Ephedra sinica Stapf & Prunus armeniaca L	licorice glycoside E	MAPK3	
	Scutellaria baicalensis Georgi & Gardenia jasminoides Ellis			
	Scutellaria baicalensis Georgi & Prunus armeniaca L			
	Scutellaria baicalensis & Lonicera japonica Thunb.			

COX-2, CASP3, IL-6, MAPK1, EGFR, IL-2, TNF and CCL-2 are closely linked to the top ten signaling pathway of IL-17, HIF-1, NF-κB, Ras, TNF, MAPK, PI3K-Akt, Toll-like receptor and Th17 cell differentiation [4]. The detailed herbal combination, active compounds and mechanisms are illustrated in Table 4. Therefore, the mechanism of TCM prescriptions to treat COVID-19 is mainly involved in antiviral, anti-inflammatory, immunomodulatory and organ-protective effects of multi-components acting on multi-pathways. Future research can focus on above compounds, targets and signaling pathways to further develop anti-SARS-CoV-2 drugs.

2.4. TCM characteristic therapy for the prevention and recovery of COVID-19

Currently, because of the long time to develop vaccines, it is particularly important to prevent viral infection and improve body immunity. The *Preventive treatment of disease* concept from TCM theory has unique advantages in the practical application of COVID-19, including moxibustion, TCM aromatherapy, TCM functional exercise, food therapy, TCM tea replacement and TCM foot bath [114]. Here, as illustrated in Table 5, we summarize the commonly used TCM characteristic therapy for the prevention and treatment of COVID-19, including body parts of action, method, frequency of use, therapeutic effects and applicable population. Moxibustion found in *Huang Di Nei Jing* and *Bian Que Xin Shu*, is associated with the acupoints or specific sites on the surface of the body stimulated by burning moxa, inspiring self-regulating function in human body to achieve prevention and treatment of disease [115]. *Xihua Fu et, al.* confirmed that moxibustion acted at *Guanyuan*, *Taichong* and *Zusanli* acupoints has definite efficacy in treating chronic hepatitis B with liver depression and spleen deficiency combined with CFS, which may alleviate symptoms and regulate the body's immune system [116]. *Ping Liu et, al.* reported that moxibustion could increase the total number of T cells [117]. In COVID-19 therapy, moxibustion has functions of anti-inflammatory, antiviral, and immune response adjustment, which has been applied in SARS infection [118]. *Xianbao Huang et, al.* found that heat-sensitive moxibustion used as adjuvant treatment can effectively relieve symptoms of COVID-19 (n = 42), including chest oppression, poor appetite and lassitude, negative emotions [119]. As shown in Table 5, for suspected cases, moxibustion performed on *Zusanli*, *Qihai* and *Zhongwan* acupoints are suggested to regulate immunity and improve symptoms; for mild and common cases, moxibustion at *Hegu*, *Taichong*, *Shenque* and *Zusanli* acupoints are recommended to improve symptoms, shorten the course of illness, and relieve mood; for patients at the recovery stage, moxibustion at *Dazhui*, *Feiyu* and *Zusanli* acupoints are used to restore the function of lung and spleen and enhance the body's vital *Qi*.

Besides, the use of TCM aromatherapy has a long history for epidemic prevention, mainly including TCM sachets and TCM aroma. During COVID-19 outbreak, this special therapy is widely applied among seven provinces and one city, helping to prevent viral infection and improve immunity. For example, a prescription of TCM sachet suggested by the government of *Heilongjiang*, China, is mainly composed of *Pogostemon cablin*, *Eupatorium fortune*, *Cinnamomum camphora*, *Realgar*, *Angelica dahurica*, *Artemisia argyi* [120]. Above herbs are made in bulk, packed into compact bags and carried every day, which is effective in strengthening the body resistance, resolving dampness and repelling foulness. Besides, several herbs are decocted to fumigate the whole body, including *Perilla frutescens*, *Artemisia argyi*, *Acorus tatarinowii*, *ValerianajatamansiJones*, *Mentha haplocalyx*, etc. Aromatherapy herbs are acted on the mouth and nose, the *Xuanfu* and the meridians to prevent and treat diseases, having functions of anti-inflammatory, anti-allergic, promoting metabolism, enhancing immunity [121]. However, the anti-epidemic effect and mechanism of TCM aromatherapy for different physiques still need to be thoroughly and systematically studied.

The core concept of TCM functional exercise is adjusting the functions of viscera and channels and enriching the essence-*qi* to achieve the purpose of prevention and rehabilitation [122]. Compared with modern functional exercise, it emphasizes the combination of movement and static, preventing illness before occurring, and preventing recovery after illness [123]. TCM functional exercise has difficulty to directly treat COVID-19, or cut off the transmission path, however, many studies showed that TCM functional exercise has received satisfactory clinical response on the basis of conventional treatment, which can effectively

Table 5
TCM characteristic therapy used in the prevention and treatment of COVID-19.

Therapy	Body parts of action	Method/prescription	Frequency of use	Therapeutic effects	Applicable population
moxibustion	*Zusanli acupoint* (lateral crural region), *Qihai acupoint* (hypogastrium), *Zhongwan acupoint* (epigastrium)	*Zusanli*: moxibustion with moxa sticks for 15 min per time; *Qihai* and *Zhongwan*: moxibustion with moxa sticks for 10 min per time.	once a day after lunch or before dinner	regulate immunity and improve symptoms	suspected cases
	Hegu acupoint (opisthenar), *Taichong acupoint* (acrotarsium), *Shenque acupoint* (navel), *Zusanli acupoint* (lateral crural region)	*Hegu* and *Taichong*: moxibustion with moxa sticks for 15 min per time; *Zusanli*: moxibustion with moxa sticks for 10 min per time; *Shenque*: a warm moxibustion box for 10 min per time.	once in the morning and once in the afternoon	improve symptoms, shorten the course of illness, and relieve mood	mild, common cases
	Dazhui acupoint (vertebra), *Feiyu acupoint* (back), *Zusanli acupoint* (lateral crural region), *Kongzui acupoint* (radial side of the forearm)	*Dazhui* and *Feiyu*: a warm moxibustion box for 30 min per time; *Zusanli* and *Kongzui*: moxibustion with moxa sticks for 10 min per time.	once a day	restore the function of lung and spleen and enhance the body's vital *Qi*	recovery stage
TCM sachets	the whole body	prescription: *Pogostemon cablin*, *Eupatorium fortune*, *Cinnamomum camphora*, *realgar*, *Angelica dahurica*, *Artemisia argyi*. Herbs are made in bulk, packed in compact bags and taken along.	every day	strengthen the body resistance, resolve dampness and repel foulness	prevention
TCM aroma	the whole body	prescription: *Perilla frutescens*, *Artemisia argyi*, *Acorus tatarinowii*, *Pogostemon cablin*, *ValerianajatamansiJones*, *Mentha haplocalyx*, *Atractylodes lancea*, *Dryopteris crassirhizoma*, etc. All herbs are decocted to fumigate for 15−20 minutes per time.	once every three days	regulate the body and recover balance between *Yin* and *Yang*	prevention
TCM functional exercise	chest, lung, spleen and heart	*Eight-Section Brocade*: to form a horse step by bending the legs, straighten the left and right arms in turn, and form a claw posture with the palms of the hands; to stretch the triple energizer by holding hands; to raise the head with one hand in turn through the exchange of left and right hands, and then slightly bend the knees with the legs; *Tai Chi*	twice a day, six times per style	relieve respiratory symptoms, improve function of lung and spleen	mild, common cases
	lung, heart and brain	*Eight-Section Brocade* combined with breathing exercises; *Five-animal exercises*: relax the tension of the nervous system by simulating the joyful mood of ape picking peaches; *Tai Chi*	twice a day, six times per style	enhance the recovery of lung function, relieve negative emotions such as fear, anxiety and depression	severe cases
Food therapy	lung and spleen	*Six-character formula*, *Eight-Section Brocade* and *Tai Chi*	twice a day, six times per style	strengthen lung and spleen, and promote healthy *Qi*	recovery stage
	lung, spleen and stomach	prescription: *Soybean*, *Black soya bean*, *peach kernel*, *lean meat*, *Zingiber officinale Rosc*, *perilla leaf*, a party of three.	every day	dissipate *cold*, strengthen spleen and dissolve dampness	population with moderate body
	lung, spleen and stomach	prescription: *Soybean*, *Black soya bean*, *Perilla leaf*, *Zingiber officinale Rosc*, *Citrus reticulata Blanco*, *Red dates*, *Glycyrrhiza uralensis*, a party of three.	every day	supplement spleen and stomach	population with weak body
	lung, spleen and stomach	prescription: *Soybean*, *peach kernel*, *Zingiber officinale Rosc*, *semen coicis*, *Platycodon*、*grandiflorum*, *Citrus reticulata Blanco*, *Phragmites communis*, *TaraxacummongolicumHand*, *Glycyrrhiza uralensis*, a party of three.	every day	remove heat to promote salivation	population with strong body
	lung, spleen and stomach	prescription: Chinese chestnut, lean meat, *Semen coicis*, *Codonopsis pilosula*, *Citrus reticulata Blanco*, *Fermented soya beans*.	every day	replenish vital *Qi*, promote blood circulation	close contacts
	lung and stomach	prescription: *Cralaegus pinnatifida*, *Citrus reticulata Blanco*, *Sterculia lychnophora Hance*	every day	clear throat, promote digestion	population with cough, sore throat, abdominal distension, fatigue
TCM Tea replacement	lung, spleen and stomach	prescription: *Zingiber officinale Rosc*, *red dates*, *Astragalus membranaceus*, *Atractylodes macrocephala*	every day	replenish and restore lung *Qi*, strengthen the spleen and stomach	population with weak body
	lung	prescription: *Phragmites communis*, *Lonicera japonica*, *Platycodon grandiflorum*	every day	remove heat to promote salivation	population with strong body
TCM foot bath	foot	prescription: *Angelica sinensis*, *Astragalus membranaceus*, *Pogostemon cablin*, *Eupatorium fortune*, *Zingiber officinale Rosc*. All herbs are decocted with 1000 mL water for 45 min and taken the juice to bath foot.	once a day	warm meridians and promote blood circulation	general population
	foot	prescription: *Artemisia argyi*, *Artemisia annua L*, *Zingiber officinale Rosc*, *Atractylodes lancea*, water.	once a day	warm *Yang* and freeze *cold*	population with cold hands and feet

improve the patient's cardiopulmonary function, increase immunity, correct negative emotions and accelerate rehabilitation. Importantly, there is also a positive effect for elderly patients with previous underlying diseases to keep healthy [124]. *Lulu Zha et, al.* reported that a lower remission rate in productive cough and expectoration was observed after modified *Eight-Section Brocade* among 60 mild cases with a median age of 54 years old, confirming the adjuvant therapeutic effect of TCM functional exercise in mild patients [125]. Moreover, for mild and common patients with dry cough and fever, *Eight-Section Brocade* combined with *Six-character formula* is recommended to enhance the function of lung, spleen and stomach, with a practice of twice a day and six times per style. During the recovery stage, this combined exercise is focused on promoting healthy *Qi*. Besides, *Eight-Section Brocade* and *Five-animal exercises* may help severe patients to recover lung function and relieve negative emotions such as fear, anxiety and depression [126]. *Yu Shi et, al.* proved that *Tai Chi* is effective and safe for COVID-19 in recovery period via meta-analysis [127]. Actually, it is also suitable for mild, common and severe cases to improve lung function.

Furthermore, food therapy, TCM tea replacement and TCM foot bath are also considered as the non-drug treatment aimed at population with different body to replenish and restore lung-*qi*, strengthen the spleen and stomach, helping to prevent and recovery from infection, which is detailly listed in Table 5 [123].

3. Discussions

On February 24, the Chinese method in the treatment of COVID-19 was recognized by Bruce Elwald, a senior adviser to the director general of WHO [128]. In TCM theory, COVID-19 is a highly pathogenic *cold-dampness* disease and evil *Qi* in this disease plays the leading role in the disease at this time, causing fever and dry cough after entering into lung guard. TCM therapy emphasizes the holistic view and syndrome differentiation, following the basic principle of *strengthening the body and eliminating evils* before identifying pathogen. It is difficult and delayed to find targeted and effective drugs against COVID-19 from modern medicine. Another advantage of TCM for COVID-19 treatment is the lower relapse rate than that of western medicine. Statistically, the total relapse rate is approximately 0.1 % of 8000 cases. To date, there is no relapse cases occurred in many hospitals [128]. Previous mentioned TCM prescriptions and characteristic therapies mainly focus on resolving phlegm and relieving cough, clearing away heat and eliminating dampness, which help to enhance vital *Qi* and improve immunity. *Nannan Shi et, al.* conducted a non-randomised controlled trial to confirm superiority of a combination of HSBD and TCM injection to treat COVID-19 [129]. *Yuanyuan Wang et, al.* summarized a single-center, retrospective study on patients with severe COVID-19 and found that the use of TCM granules reduced the 28-day mortality rate and the time to fever alleviation [130]. Extensive data have shown to support the therapeutic effects of TCM treatment, however, there are no large-scale clinical studies in China using TCM alone, most of which are in combination with other medical approaches, including antiviral drugs, nutritional support, antimicrobial agents and symptomatic support systems. Because of the suddenness of this outbreak and urgency of developing appropriate treatment strategy, long-term studies on the efficacy and safety of TCM have not yet been conducted. Actually, long-term multi-center randomized controlled trials are needed to provide more clinical evidences of TCM therapeutic efficacy. Importantly, the underlying mechanisms of TCM prescriptions has been briefly evaluated by network pharmacology and molecular docking analysis while the in-depth mechanisms remain unclear, such as antiviral effect in viral infection model, the immune regulatory response and inhibitory cytokine storm by host cells. For multi-components, multi-targets, multi-pathways of TCM, the exact mechanism and efficacy still need to be confirmed by combining molecular biological techniques in clinical trials, including genomics, proteomics and metabolomics. Besides, to screen candidate natural components from TCM and further develop the novel compatibility with active components, reasonably designed both *in vitro* and *in vivo* model studies should be performed on the basis of the exploration of material basis and clarification of pharmacological mechanism.

4. Conclusions and prospects

At present, over 200 countries and regions experienced COVID-19 outbreak have received global concerns. As an emergent infectious disease, there is no specific drug to treat COVID-19 worldwide, which will consume long time to develop vaccines against this virus. The practice in controlling this outbreak in China has demonstrated the clinical responses and superiorities of TCM. A great deal of prescriptions and characteristic therapies concluded from ancient TCM provide us with valuable references in fighting against COVID-19. Among them, the underlying mechanisms of TCM are mainly involved in anti-SARS-CoV-2, anti-inflammatory, immunomodulatory and organ-protective effects of multi-components acting on multi-targets at multi-pathways, which has been confirmed by clinical practice, fundamental research and bioinformatic analysis. It is our hope that the global outbreak will be effectively controlled and treated by the contribution of TCM.

Funding source

This work was supported by National Administration of Traditional Chinese Medicine (Grant NO. 2020ZYLCYJ02-3); Sichuan Administration of traditional Chinese Medicine (Grant NO. 2020yj018) and (Grant NO. 2020yj024); the National Traditional Chinese Medicine Clinical Research Base (Grant NO. [2020]33). The authors are sincerely thankful to all individuals who were involved in this study.

Author's contributions

Wei Ren and *Pan Liang* collected literature and prepared the manuscript. *Yue Ma*, *Qin Sun*, *Qingrong Pu*, *Li Dong*, *Gang Luo*, *Maryam Mazhar* and *Jiali Liu* edited and reviewed the manuscript. Furthermore, as guarantors of this work, *Sijin Yang* and *Raoqiong Wang* designed and supervised the overall study and prepared the manuscript. All authors have read, revised and approved the final manuscript.

Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

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