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Review

Therapeutic mechanisms and impact of traditional Chinese medicine on COVID-19 and other influenza diseases

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ABSTRACT

Coronavirus disease 2019 (COVID-19), first reported in Wuhan, China, has rapidly spread worldwide. Traditional Chinese medicine (TCM) has been used to prevent and treat viral epidemics and plagues for over 2,500 years. In the guidelines on fighting against COVID-19, the National Health Commission of the People's Republic of China has recommended certain TCM formulas, namely Jinhua Qinggan granule (JHQGG), Lianhua Qingwen granule (LHQWG), Qingfei Paidu decoction (QFPDD), Xuanfei Baidu granule (XFBD), Xuebijing injection (XBJ), and Huashi Baidu granule (HSBD) for treating COVID-19 infected individuals. Among these six TCM formulas, JHQGG and LHQWG effectively treated mild/moderate and severe COVID-19 infections. XFBD therapy is recommended for mild COVID-19 infections, while XBJ and HSBD effectively treat severe COVID-19 infections. The internationalization of TCM faces many challenges due to the absence of a clinical efficacy evaluation system, insufficient research evidence, and a lack of customer trust across the globe. Therefore, evidence-based research is crucial in battling this infectious disease. This review summarizes SARS-CoV-2 pathogenesis and the history of TCM used to treat various viral epidemics, with a focus on six TCM formulas. Based on the evidence, we also discuss the composition of various TCM formulas, their underlying therapeutic mechanisms, and their role in curing COVID-19 infections. In addition, we evaluated the roles of six TCM formulas in the treatment and prevention of other influenza diseases, such as influenza A (H1N1), severe acute respiratory syndrome (SARS), and Middle East respiratory syndrome (MERS). Furthermore, we highlighted the efficacy and side effects of single prescriptions used in TCM formulas.

1. Introduction

A novel coronavirus disease 2019 (COVID-19) was first reported in Wuhan in December 2019, caused by the coronavirus SARS-CoV-2. This disease has spread rapidly worldwide because of its prolonged incubation and high pathogenicity [1,2]. COVID-19 has a low fatality rate and a high transmission rate from human to human compared to the severe acute respiratory syndrome (SARS) outbreak in 2003 and the Middle East respiratory syndrome (MERS) outbreak in 2012. The existence of many asymptomatic SARS-CoV-2 human carriers exerts a potential burden on COVID-19 control and prevention programs worldwide [2–4]. SARS-CoV-2 is a single-stranded, non-segmented RNA virus with a 30 kb genome size, isolated from COVID-19 infected patients who shared 79.5% genome sequence similarity with SARS-Co-V [2,5,6]. The long latency, high infectivity, and complex curing features have made COVID-19 a major threat to global health and the economy.

SARS-CoV-2 is transmitted from infected to healthy people via aerosol particles such as sneezing and coughing. Based on the evidence of rising global infection rates, the possibility of virus transmission by asymptomatic human carriers has dramatically increased. The COVID-19 infected individuals showed respiratory disorders ranging from mild to severe, i.e., fever, cough, myalgia, diarrhea, fatigue, loss of smell or taste, muscle pain, body aches, and lung damage [2,7]. In severe infections, complications may occur, i.e., acute myocardial injury, blood clotting, acute respiratory distress syndrome, liver/kidney disorder, septic shock, or death [8,9]. These disorders complicate global COVID-19 prevention and treatment [10]. Oxygen therapy and fluid supply are recommended for treating severe infections. For mild COVID-19 infections, the WHO has recommended guidelines for COVID-19 treatment together with adequate nutritional support to cure pain and fever. Supportive measures and potential antiviral drugs such as remdesivir, hydroxychloroquine, and ribavirin (used to treat other viral infections)

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have been repurposed for treating mild SARS-CoV-2 infected people. However, due to a lack of large-scale randomized clinical trials or potential side effects, effective anti-COVID-19 therapy has not yet been reported [3,11]. Due to the low success rate against the mutant SARS-CoV-2 strain, developing a vaccine for COVID-19 prevention is complex, challenging, and expensive [3,12]. Therefore, despite the vaccine development, scientists are trying to develop new antiviral drugs or restructure existing drugs to neutralize this deadly SARS-CoV-2. Although efforts to combat COVID-19 infections have been made, a lack of safe and effective antiviral drugs remains a critical factor in preventing and treating the global COVID-19 pandemic. Angiotensin-converting enzyme 2 (ACE2) is a cell surface protein found in the gastrointestinal tract, heart, and kidneys that regulates blood pressure and vasoconstriction. In addition, ACE2 serves as a receptor for SARS-CoV-2 attachment and entry into the cell cytoplasm [13,14]. The SARS-CoV-2 spike protein mediates the virus fusion with the host membrane protein (ACE2) to initiate the infection process. Coronavirus adopts two routes for fusion and entry into the host cells. First, SARS-CoV-2 fuses with the target cell membrane with the help of transmembrane protease serine 2 (TMPRSS-2) to release the virus genome into the host cell cytoplasm [15,16]. Second, virus spike protein undergoes conformational changes before binding to the host ACE2 receptor and employs TMPRSS-2 to facilitate virus entry into the cytoplasm [16]. In the absence of the membrane proteases, the coronavirus may use a non-clathrin or clathrin-mediated endocytosis pathway. In this pathway, cathepsin activation influences viral fusion with the host cell. These findings show that the availability of membrane proteases and the target cell membrane govern SARS-CoV-2, SARS-CoV, and MERS-CoV entry into the cell cytoplasm. SARS-CoV-2 releases genomic RNA and takes control of the host replication machinery, allowing it to replicate and spread. The viral mRNA undergoes ribosomal frameshift during translation, resulting in ORF1a and ORF1b, which encode polypeptides pp1a and pp1b. Viral 3-chymotrypsin like protease (3CLpro) further processes these polypeptides to form sixteen non-structural proteins (NSPs). ORF1a encodes the first eleven NSPs, while the remaining four NSPs are encoded by ORF1b. NSP5 (3CLpro) and NSP3 (papain-like protease) are required for virus replication and other cellular processes and thus can be used to detect SARS-CoV-2 in biological samples [17,18]. The virus genomic RNA also translates into four structural proteins, i.e., nucleocapsid protein, envelope protein, membrane protein, and spike protein [19–21], and eight accessory/auxiliary proteins, namely, 7b, 3a, 7a, 3b, 9b, p6, 8b, and ORF14. After post-translational modifications in the Endoplasmic reticulum (E. reticulum), these proteins are transferred to the E. reticulum-Golgi apartment. Once the genome has been translated for virions, it will interact with the nucleocapsid protein to form a nucleocapsid, which will then be transferred to the E. reticulum-Golgi apartment (Fig. 1a). In this complex apartment, the viral nucleocapsid will interact with other structural components to form vesicles that will eventually be released from the infected host cell via exocytosis [15]. The eight accessory proteins are not required for coronavirus replication; however, they may affect viral pathogenesis, stability, and release [22].

Traditional Chinese medicine (TCM) has a long history of treating infectious viral diseases since the Chinese Qin-Han dynasty (221 BCE–220 CE). During the Ming-Qing dynasty (1368–1912 CE), a TCM theory describing infectious diseases caused by toxic qi was developed, i.e., a pathogen from an infected host spreads via aerosol inhalation and infects the lungs [23]. According to TCM theory, an epidemic disease is an acute infection with a sudden onset, rapid transmission, and severe infection [24]. TCM theories of treating pre-disease, such as yin and yang theory, holistic theory, and five elements theory, i.e., visceral meridian theory, etiology and pathogenesis theory, diagnosis and therapy theory, prevention and health care theory, and qi doctrine, were initiated in the Shang and Yin dynasties and took shape in the Yellow Emperor's Inner Classic (Huangdi Neijing: ancient Chinese medical book) [25]. Several studies have shown that the therapeutic effects of TCM are safe, effective, and economical for H1N1, SARS, and MERS infections [7,26,27]. During the H1N1 outbreak in 2009, the Beijing Municipal Government released ten million RMB for a clinical trial to screen and treat H1N1 infections through TCM [26]. In the light of TCM theory, pathogen dampness-toxin and host healthy-qi deficiency characterize COVID-19 disease. China has contributed significantly to the prevention, detection, and treatment of COVID-19. According to China's clinical guidelines and experience in treating SARS and MERS patients, TCM formulas can effectively treat SARS-CoV-2 patients [7,27].

During the outbreak, Chinese experts explored several TCM formulas to treat COVID-19 patients in clinical trials. Finally, they screened the six most effective TCM formulas, namely Jinhua Qinggan granule (JHQGG), Lianhua Qingwen granule (LHQWG), Qingfei Paidu decoction (QFPDD), also known as lung cleansing and detoxifying decoction, Xuanfei Baidu granule (XFBD), Xuebijing injection (XBJ), and Huashi Baidu granule (HSBD) for COVID-19 treatment. Previous researchers have shown that treating COVID-19 patients with TCM improves cure rates, shortens disease duration, delays disease progression from mild to severe stages, and lowers mortality rates [25,28]. The China National Health Commission declared that TCM combined with conventional medicine effectively treated 92% of COVID-19 patients in China, of which 90% of the patients either recovered or improved their health status [29]. It is also worth noting that COVID-19 has affected over 77,200 people in China, all of whom have recovered after treatment with TCM formulas or TCM combined with conventional medicine [30]. TCM treatment exerts an auxiliary effect, improves blood oxygen saturation, and cures dyspnea in severe/critical COVID-19 patients [7]. Formulated TCM has effectively been used in managing SARS outbreaks in 2003, MERS in 2012, and other seasonal influenza outbreaks [31], which reduced the patient hospitalization period and side effects compared with conventional medicines [32]. After the human swine flu (H1N1) virus outbreak in Mexico in 2009, the Chinese authorities recommended guidelines for diagnosing and treating swine influenza [33]. China's National Health Commission highly recommends JHQG, LHQWG, and XBJI treatments for preventing acute respiratory distress syndrome, lung injury, and kidney damage in COVID-19 infected individuals [25,34].

2. Leading six TCM influential roles in treating COVID-19

Six TCM formulas showed an influential role in curing COVID-19 patients, with JHQGG and LHQWG being recommended for mild/severe COVID-19 cases. XFBD is recommended for curing mild/moderate COVID-19 infections, whereas XBJ and HSBD effectively treat severe COVID-19 patients. During the outbreak, several TCM formulas were included in the Chinese National Health Commission's guidelines for the diagnosis and treatment of COVID-19 [35]. The major constituents of TCM formulas and their potential targets in COVID-19 and other influenza viruses are shown in Table 1. JHQGG and LHQWG are highly effective for treating early COVID-19 infections with clinical manifestations, fatigue, and fever. HSBD and XBJ treatment are recommended for severe COVID-19 infections, XFBD for mild, and QFPDD for severe/mild cases [25,34] (Fig. 1).

2.1. JHQGG formula

JHQGG formula is combining two classical recipes (Maxingshigan decoction and Yinqiao San) of 12 herbal components, i.e., Lianqiao (Forsythiae Fructus; Niubangzi (Arctium Lappa L.), Shigao (Gypsum Fibrosum), Forsythia Suspensa), Jinyinhua (Honeysuckle: Lonicerae Japonicae Flos), Mahuang (Ephedra Herba: Gymnosperm Shrubs), Chaoxingren (Prunus armeniaca), Huangqin (Baikal Skullcap root: Scutellariae Radix), Zhebeimu (Fritillaria Thunbergii Miq), Qinghao (Artemisia Annua; sweet Wormwood herb), Bohe (wild mint herb: Menthae haplocalycis herb), Zhimu (Anemarrhena Asphodeloides Bunge), and Gancao (Licorice: Glycyrrhizae Radix Et Rhizoma) [36]. Ingredients like honeysuckle can clear heat and detoxify the COVID-19 patient lungs [7].

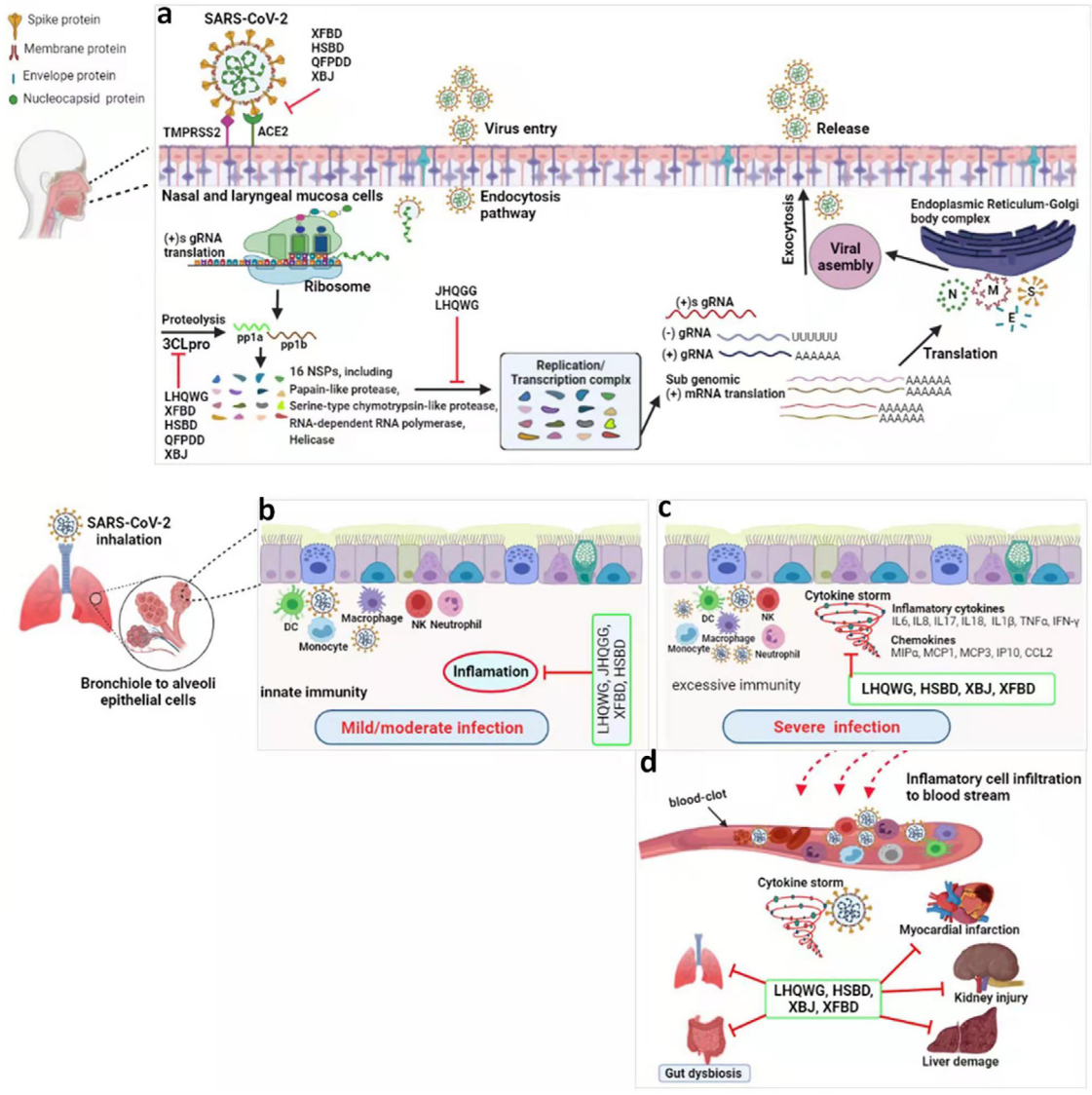

Fig. 1. TCM anti-SARS-CoV-2 mechanisms and virus pathogenesis. (a) replication of SARS-CoV-2 and antiviral mechanisms of TCM formulas. Coronavirus enters the host cell cytoplasm via an endosomal pathway or fuses spike protein to the human membrane ACE2. The viral RNA is unveiled and transcribed into viral 3CLpro in the infected cell cytoplasm. The 3CLpro cleaves the two polypeptides (pp1b and pp1a) into 16 non-structural proteins (NSPs), such as papain-like protease, serine-type chymotrypsin protease, helicase, and RNA-dependent RNA polymerase. The treatment of Xuanfei Baidu granule (XFBD), Huashi Baidu granule (HSBD), Qingfei Paidu decoction (QFPDD), and Xuebijing injection (XBJ) inhibits the proteolysis of the 3CLpro enzyme. The two most important TCM formulas, JHQGG and LHQWG, prevent the 16 NSPs from forming the replication-transcription complex. RNA-dependent RNA polymerase and helicase enzymes are combined for synthesizing negative strand guide RNA (gRNA) and RNAs. These RNAs are important for viral replication and transcription. The newly synthesized viral genome is translated and produces spikes, envelopes, nucleocapsids, and membrane proteins. These structural proteins are then transported to the E. reticulum-Golgi body apartment for assembly (encapsulated viral genomic RNA) to form new viruses. The newly synthesized viruses are released from the cytoplasm of human cells via exocytosis. (b) LHQWG, JHQGG, XFBD, and HSBD therapies have anti-inflammatory, antipyretic, and immunomodulatory effects on COVID-19 infections. (c) Anti-cytokine storm, anti-oxidation, and immune-regulating properties of LHQWG, HSBD, XBJ, and XFBD therapies. TCM treatment regulates the levels of cytokines, chemokines, and MAPKs in COVID-19-infected cells. (d) A cytokine storm can lead to myocardial injury, kidney/liver dysfunction, septic shock, blood clots, acute respiratory distress syndrome, and death in severe cases.

2.1.1. Underlying mechanisms and impact of JHQGG treatment on COVID-19

The JHQGG formula, previously developed for treating influenza H1N1 patients, has therapeutic benefits for COVID-19 patients during medical observation. The host surface protein ACE2 act as a primary receptor for SARS-CoV-2 attachment and entry into the cell cytoplasm to initial infection [13]. According to previous findings, COVID-19 infected patients in China who received JHQGG treatment had a lower fatality rate and relatively better clinical outcomes. The China Food and Drug Administration has recommended a JHQGG prescription for preventing and treating COVID-19 infections [3]. This TCM formula can effectively relieve COVID-19 clinical symptoms, delay disease progression from mild to severe stage, and reduce mortality in patients. JHQGG formula's underlying therapeutic mechanisms primarily reduce SARS-CoV-2 pathogenesis, organ protection, immune regulation, and anti-inflammatory actions [37]. Furthermore, JHQGG treatment showed broad-spectrum antiviral activities, i.e., target and inhibit SARS-CoV-2 life cycle, immune regulation, and anti-inflammation, indicating the

Table 1
Major constituents of TCM formulas and their potential targets in COVID-19 and other influenza viruses.

TCM formula	Active components	Possible targets	Refs
JHQGG			
	Huangqin, zhimu, niubangzi	Inhibit SARS-CoV-2 transcription, replication	[3]
	Luteolin, myricetin, quercetin, rutin, ursolic acid, wogonin	IL6, IFN-γ, immunomodulatory activity	[38, 39]
	Huangqin	Inhibit influenza-A virus life cycle, hemagglutinin, neuraminidase	[45]
	Luteolin, quercetin	Inhibit SARS-CoV 3CLpro	[150]
	Myricetin	Inhibit SARS-CoV helicase	[151]
LHQWG			
	Hyperin, forsythoside E, rutin	SARS-CoV-2 3CLpro	[51]
	Naringenin, β-carotene, luteolin, kaempferol, wogonin, quercetin	Akt1 kinase, reduce tissue damage, eliminate SARS-CoV-2 infection, cure lung fibrosis	[52]
	Quercetin, luteolin, wogonin, kaempferol	IL6, IL-1B, IL10, TNFα, CXCL8, MAPK1, MAPK8, VEGFA, CASP3	[54]
	Glycyrrhetinic acid, stigmasterol, indigo, kaempferol, quercetin	SARS-CoV-2 3CLpro, ACE2, MAPK, PI3K-AKT, NF-κB	[152]
	Luteolin, quercetin	Inhibit SARS-CoV 3CLpro	[150]
QFPDD			
	Baicalein, β-sitosterol, kaempferol, isorhamnetin, luteolin, naringenin, nobiletin, quercetin, stigmasterol, wogonin	MAPK14, NOS2, PPARG, PTGS2, PTGS1	[73]
	Baicalein, kaempferol, luteolin, naringin, quercetin	Anti-inflammation, SARS-CoV-2 proteins	[73]
	Medicarpin, alysifolinone, letrozole, (2S)-ihydrobaicalein, taxifolin, vestitol, leucocyanidol, cyclo(L-Tyr-l-Phe)	SARS-CoV-2N protein, E protein, papain-like protease, Nsp14, 15, 16, helicase, host immunity, signaling transduction pathways	[75]
	Luteolin, quercetin	Inhibit SARS-CoV 3CLpro	[150]
XFBD			
	Quercetin, diosmetin, kaempferol, stigmasterol, rhein, estrone, wogonin, irisolidone, luteolin, isorhamnetin, physovenine, naringenin, ribavirin, ritonavir	SARS-CoV-2 3CLpro, ACE2	[79]
	Pachypodol, axillarin, cumaldehyde, linalool, quercetin-3-methyl ether, sesamin, linalool	anti-SARS-CoV-2	[80]
	Atractylenolide β-pinene, atractylone, β-sitosterol, syringin, cirsiliol, eriodictyol, isoquercitrin, flavoxanthin, ephedroxane, isoquercitrin, scopolin, luteolin, scoparone	anti-SARS-CoV-2, anti-inflammation	[80]
	Luteolin, quercetin	Inhibit SARS-CoV 3CLpro	[150]
XBJ			
	Salvianolic acid-B, hydrosafflor yellow-B, rutin	SARS-CoV-2 proteins, anti-inflammatory, immune regulation	[88]
	Baicalein, kaempferol, luteolin, quercetin	Anti-SARS-CoV-2, ESR1, DPP4, CALM1, AR, kinase 1	[90]
	Hydroxysafflor yellow-A, chlorogenic acid, salvianolic acid-B	Anti-SARS-CoV-2, NF-κB, HIF-1, VEGF	[153]
	Luteolin, quercetin	Inhibit SARS-CoV 3CLpro	[150]
HSBD			
	Baicalein, kaempferol, luteolin, quercetin	SARS-CoV-2 3CLpro, spike protein, ACE2	[102]
	Naringenin, β-sitosterol, aloe-emodin, luteolin, quercetin	SARS-CoV 3CLpro	[99]
	Kaempferol	SARS-CoV 3a protein	[99]
	Luteolin, quercetin	Inhibit SARS-CoV 3CLpro	[150]

JHQGG (Jinhua Qinggan granule), LHQWG (Lianhua Qingwen granule), QFPDD (Qingfei Paidu decoction), XFBD (Xuanfei Baidu granule), XBJ (Xuebijing injection), HSBD (Huashi Baidu granule).

importance of the JHQGG formula [3]. At least three JHQGG ingredients, Baikal Huangqin, Zhimu, and Niubangzi, can stop SARS-CoV-2 transcription and replication, suggesting underlying therapeutic mechanisms of this formula [3]. The most common active components reported in the JHQGG formula were luteolin, myricetin, quercetin, rutin, ursolic acid, and wogonin, which could have a therapeutic effect by targeting and suppressing IL6 production in COVID-19 patients [38]. In another similar study, JHQGG treatment significantly decreased IL6 and increased IFN-γ levels in the plasma of treated individuals, indicating that JHQGG has immunomodulatory activity against COVID-19 infection [39]. Chinese and Western medical experts jointly approved JHQGG treatment for COVID-19 patients due to the presence of hundreds of previous TCM prescriptions for various disease treatments, such as febrile diseases [40]. Clinical studies showed that JHQGG treatment significantly improved mild COVID-19 symptoms, including fever, anxiety, fatigue, cough, and expectoration [25]. It was also reported that seven-day JHQGG treatment increased the viral clearance rate and reduced pneumonia in COVID-19 individuals [40]. Usually, JHQGG treatment is recommended for mild COVID-19 patients with clinical manifestation, body pain, weakness, fever, cough, headache, and sore throat. A case-control trial showed that JHQGG treatment significantly relieved anxiety, cough, fever, and fatigue in 123 mild COVID-19 patients [41].

2.1.2. Underlying mechanisms and impact of JHQGG treatment on influenza

The *3CLpro* gene mediates SARS-CoV-2, SARS-CoV, and MERS-CoV replication and is a potential therapeutic target [42,43]. Since all the six TCM formulas described here are commonly used to treat influenza infections in China; therefore, we investigate their roles in preventing influenza virus attachment and entry into the cell cytoplasm. A tripolymer, hemagglutinin on the influenza virus surface promotes virus attachment and penetration into the host cell cytoplasm. On the other hand, neuraminidase is essential for influenza virus detachment and release from infected cells [3,44]. JHQGG active compound, Baikal Skullcap root (Huangqin), targets the hemagglutinin and neuraminidase of the influenza virus, inhibiting its life cycle. In 2009, TCM experts formulated a JHQGG recipe to control the influenza A (H1N1) outbreak in Mexico [25]. This prescription was found effective for curing H1N1-infected animals and humans [45]. In a clinical trial [39], JHQGG decreased mortality rate, improved survival rate, and reduced pulmonary lesion in H1N1-infected mice. According to Wang et al. (2011), combining JHQGG with oseltamivir significantly reduced fever duration (19%) in H1N1 patients compared to oseltamivir treatment alone, demonstrating the importance of JHQGG therapy against influenza infections [46]. JHQGG five-day treatment (5 g orally three times a day) significantly reduced serum cytokine IFN-γ levels and improved immune regulation

in 174 influenza patients in a double-blind, randomized trial [47]. In addition, the same amount of JHQGG treatment accelerated the recovery of 136 influenza patients [48].

2.2. LHQWG formula

The TCM formula, LHQWG, comprises 13 herbs, namely Lianqiao (Forsythia Suspensa), Jinyinhua (Honeysuckle flower; Lonicerae Japonicae, Mahuang (Ephedra Herba: Gymnosperm Shrubs), Banlangen (Isatis Indigotica root), Guanghuoxiang (Patchouli: Pogostemon cablin Benth), Dahuang (Rheum Palmatum), Gancao (Licorice: Glycyrrhizae Radix Et Rhizoma), Mianmaguanzhong (Dryopteris Crassirhizoma), Hongjingtian (Rhodiola Crenulata), Yuxingcao (Houttuynia Cordata), Prunus Sibirica, Shigao (Gypsum Fibrosum) and Bohenao (Menthol) [25,49]. UPLC-DAD-QTOF-MS analysis revealed 61 ingredients in LHQWG, including flavonoids, phenylpropanoids, anthraquinones, and triterpenoids. The twelve active components, i.e., salidroside, glycyrrhizic acid, chlorogenic acid, forsythoside A, forsythoside E, hyperin, phillyrin, rhein rutin, sweroside, cryptochlorogenic acid, and amygdalin were quantified as chemical markers [50].

2.2.1. Underlying mechanisms and impact of LHQWG treatment on COVID-19

Analyses revealed Rheum palmatum (Dahuang) and Houttuynia cordata (Yuxingcao) in LHQWG inhibit 3CLpro to stop SARS-CoV-2 transcription and replication, suggesting underlying mechanisms of LHQWG treatment on COVID-19 [3]. It has been shown that the docking scores of three ingredients in LHQWG, i.e., hyperin, forsythoside E, and rutin for targeting SARS-CoV-2 3CLpro, are more effective than lopinavir antiretroviral medicine. Furthermore, LHQWG inhibited or reduced SARS-CoV-2 replication in infected Vero-E6 cells and increased pro-inflammatory cytokine levels, including interleukin-6 (IL6), IP10, MCP1, and tumor necrosis factor-alpha (TNFα) in a dose-dependent manner [51]. Network pharmacology and molecular docking analyses revealed six additional anti-SARS-CoV-2 active components in LHQWG, namely naringenin, β-carotene, luteolin, kaempferol, wogonin, and quercetin. These components inhibit Akt1 kinase, reducing tissue damage (e.g., lung fibrosis) and aiding in eliminating SARS-CoV-2 infection [52]. In another study, network pharmacology and molecular docking technology revealed 160 active components in LHQWG, including MOL003006, MOL003014, MOL003283, MOL003365, and MOL000522, that produce therapeutic effects against SARS-CoV-2 via targeting 57 different targets, including TLR-signaling pathway, IL6, TNFα, MAPK1, HSP90AA1, CCL2, etc., indicating that LHQWG contains multiple active components to cure COVID-19 infection [53]. In addition, components in LHQWG, such as quercetin, luteolin, wogonin, and kaempferol, demonstrated high affinity for nine targets in COVID-19 patients, including IL6, IL-1B, IL10, TNFα, CXCL8, MAPK1, MAPK8, VEGFA, and CASP3. Moreover, these four ingredients were docked successfully to the viral 3CL pro receptor [54].

A retrospective study showed that LHQWG treatment effectively relieved symptoms like body weakness, cough, and fever and reduced infection in 54 COVID-19 patients [55]. A multicenter, randomized controlled trial indicated that the clinical recovery rates of chest computed tomography (CT) findings were higher in 284 COVID-19 patients after treatment with LHQWG (four capsules thrice a day for 14 days) [49]. Studies have recommended that LHQWG, combined with conventional medicine, is an adequate treatment to cure mild COVID-19 patients [56]. A retrospective clinical study showed that LHQWG combined with conventional medicine effectively reduced fever duration in 21 COVID-19 patients compared to conventional medicine alone [57]. For example, LHQWG combined with arbidol (an anti-influenza drug) effectively relieved mild COVID-19 symptoms than arbidol alone [58]. Besides this, combined treatment of LHQWG with lopinavir/ritonavir/umifenovir (antiretroviral protease inhibitor drugs), ribavirin (inhibit viral transcription and replication, as well as induce mutation in the viral genome), and umifenovir (arbidol: inhibit virus-host fusion) effectively reduced diseased symptoms in 151 severe COVID-19 patients, indicating the effectiveness of LHQWG combined with conventional drugs [59]. In another study, the simultaneous administration of LHQWG and Huoxiang Zhengqi improved symptoms, nausea, vomiting, and limb soreness in 283 COVID-19 patients. These two drug combinations reduced the progression of mild/moderate COVID-19 into the severe stage [60]. A meta-analysis of the randomized controlled trial indicates that the COVID-19 symptoms, such as chest tightness, difficulty in breathing, loss of appetite, dry cough, fatigue, fever, muscle pain, nasal congestion, nausea, runny nose, and vomiting, quickly disappeared in 154 patients after treatment with LHQWG [61].

2.2.2. Impact of LHQWG treatment on influenza infections

Influenza is a highly contagious virus that causes respiratory problems and spreads through aerosol droplets from infected to healthy people [62]. During viral infection, the macrophages and epithelial cells in the upper respiratory tract produce pro-inflammatory cytokines (IL6, IL18, and IL1β), TNFα, and chemokines (MIPα, MCP1, MCP3, and IP10). Therefore, cytokine/chemokine expression control can inhibit their storms, reducing disease severity and patient mortality [63,64]. LHQWG has anti-inflammatory [36], antipyretic [65], and anti-influenza viral effects [66]. Pharmacodynamics studies have confirmed that LHQWG treatment can cure respiratory disorders caused by the influenza virus. In an experimental study, LHQWG treatment effectively reduced SARS pathogenesis in African green monkey Vero-E6 kidney cells [67]. This treatment was also effective at inhibiting the proliferation and pathogenesis of several influenza viruses, including the H1N1 virus [68], the H3N2 virus [69], and the avian influenza H7N9 virus [66]. In 2010, LHQWG treatment was declared safer than the conventional antiviral oseltamivir drug in treating severe H1N1-infected children [70]. However, in a clinical trial, LHQWG and conventional medicines such as potassium succinate, azithromycin, and tanreqing produced good therapeutic effects in H1N1-infected individuals [71].

2.3. QFPDD formula

A multicomponent TCM formula, QFPDD, comprising 21 herbs, namely Mahuang (Ephedra Herba: Gymnosperm Shrubs), Zhigancao (Radix Glycyrrhizae Preparata), Xingren (Semen Armeniacae Amarum), Chaihu (Bupleuri Radix: Bupleurum Scorzonerifolium and Bupleurum Chinense Roots), Shigao (Gypsum Fibrosum), Guanghuoxiang (Patchouli: Pogostemon cablin Benth), Guizhi (Ramulus Cinnamomi), Zexie (Rhizoma Alismatis Oriental Rhizome), Zhuling (Grifola Umbellata Pilat), Ziwan (Radix Asteris Tatarici), Xixin (Chinese Ginger; Herba Cum Radix Asari), Baizhu (Atractylodes macrocephala), Shegan (Rhizoma Belamcandae), Fuling (Poria cocos), Shengjiang (Zingiber officinale Roscoe rhizoma), Shanyao (Dioscorea Polystachya Rhizoma), Kuandonghua (Farfarae Flos), Huangqin (Scutellaria Baicalensis Rhizome), Chenpi (Dried Tangerine Peel) Jiangbanxia (Pinellinae Rhizoma Praeparatum), and Zhishi (Aurantium Rhizome) [72].

2.3.1. Underlying mechanisms and impact of QFPDD treatment on COVID-19

After adequate treatment in multi-provincial clinical trials in China, QFPDD was recommended for patient treatment in the seventh edition of the COVID-19 guideline [72]. Due to the multi-herbal formula (21 herbs), the complex mechanism of the QFPDD formula in the treatment of COVID-19 needs further investigation. Several researchers have used molecular docking scores, network pharmacology technology, and computer-aided drug design programs to study the SARS-CoV-2 structure and the therapeutic mechanism of the QFPDD formula. Network pharmacology technology screened 148 related SARS-CoV-2 targets, including ACE2 and 3CLpro for 302 active components in QFPDD. GeneCards (a database), keywords, such as COVID-19, SARS-CoV-2, and novel coronavirus pneumonia, identified 362 SARS-CoV-2 related

targets for the active components in this TCM formula. In addition, Venn diagram analysis revealed 23 targets for this TCM. The network topology of the ten most effective active components, namely baicalein, β-sitosterol, kaempferol, isorhamnetin, luteolin, naringenin, nobiletin, quercetin, stigmasterol, and wogonin, and five key targets, MAPK14, NOS2, PPARG, PTGS2, and PTGS1 were identified through Cytoscape software [73]. The molecular docking result showed that quercetin had the most potent binding and interaction ability with the target PTGS2. The GO and enriched KEGG pathway revealed baicalein, kaempferol, luteolin, naringin, and quercetin to be anti-inflammatory and anti-SARS-CoV-2 agents. Most active components target 144 signaling pathways, including MAPK, TNFα, IL17, phosphatase, regulating metabolism, the immune response, and lung inflammation [73]. Another study discovered 200 SARS-CoV-2 specific targets and 51 common targets for 186 active components in QFPDD. The GO and enriched KEGG pathway analysis identified IL17, NF-B, TNFα, MAPK, and Th17 involved in anti-inflammation, immune regulation, and neuroprotection [74]. Furthermore, for targeting the SARS-CoV-2 structure and non-structure proteins, such as N protein, E protein, papain-like protease, Nsp14, 15, 16, and helicase, QFPDD four common ingredients, M3, S1, O2, and X2, demonstrated excellent docking with papain-like protease, E and M viral proteins. In addition, five specific ingredients, WO1, MX16, MS1, XO1, and SX1, showed docking with N, nsp12, nsp16, nsp15, nsp14, nsp12, nsp14, and nsp15 viral proteins. These four common and five specific QFPDD ingredients can prevent COVID-19 infection by targeting virus proteins and regulating the host immune response [75].

In a retrospective study, 782 COVID-19 patients from 54 hospitals in nine Chinese provinces were administered QFPDD. The results show that early treatment with QFPDD was associated with better disease control, faster patient recovery, reduced viral transmission, and hospital duration [76]. Clinical trials evaluated the efficacy and safety of QFPDD after administering it to 11,237 COVID-19 patients in China. Combining QFPDD treatment with conventional medicine reduced virus replication, hospital stay, and faster recovery of COVID-19 patients. It was also found that there were no severe side effects observed after the administration of this combination, emphasizing the importance of QFPDD in treating COVID-19 infections [77].

2.4. XFBD formula

XFBD formula comprises 13 herbs, namely Mahuang (Ephedra Herba: Gymnosperm Shrubs), Xingren (Armeniacae Semen Amarum), Sheng Yiyiren (Coicis Semen), Maocangshu (sword-like Atractylodes rhizome), Guanghuoxiang (Patchouli: Pogostemon cablin Benth), Qinghao (Artemisia Annua), Huzhang (Polygonum cuspidatum), Mabiancao (Verbena Officinalis L.), Lugen (Reed rhizome), Gancao (Licorice: Glycyrrhizae Radix Et Rhizoma), Tinglizi (Lepidium Seed), Shigao (Gypsum Fibrosum), and Huajuhong (Pummelo peel). Chinese Academician Professor Zhang Boli and his team proposed XFBD prescriptions for the retention of damp-toxin in patients with lung syndrome.

2.4.1. Underlying mechanisms and impact of XFBD treatment on COVID-19

A network pharmacology study found that XFBD therapy regulates the levels of inflammatory cytokine IL6, chemokine CXC ligand-8, suppresses cytokine storm, and excessive immune activation, as well as related T lymphocytes (Th1, Th2, and Th17) in COVID-19 patients [78]. During the early viral infection, the inflammatory response in the host is reduced, which then increases the immune response at the late stage. This bidirectional immune regulation may improve clinical symptoms in COVID-19 patients. Treatment with XFBD was highly influential in hastening the mild/moderate COVID-19 patient recovery and preventing them from progressing to the severe stage [34]. The XFBD key components targets were primarily enriched in the lung injury and viral infection pathways, which explains their efficacy in accelerating moderate patient's recovery and preventing their progression to severe/critical stages. In another study, molecular docking revealed that XFBD treatment inhibits SARS-CoV-2 3CLpro binding with ACE2 via quercetin, kaempferol, stigmasterol, estrone, wogonin, irisolidone, luteolin, isorhamnetin, physovenine, rhein, diosmetin, naringenin, ribavirin, ritonavir, etc., exerting anti-cytokine storm, anti-oxidation, and regulating the host immune response. More specifically, XFBD treatment plays a role in curing COVID-19 patients by regulating cytokines, IL6, IL1β, chemokine (CCL2), MAP kinases (MAPK1, and MAPK3), nitric oxide synthase 2, and estimated glomerular filtration rate in infected host cells [79]. Using a reverse finding target technique, Wang and his team identified several anti-SARS-CoV-2 and anti-inflammatory components in XFBD, including rutin, pachypodol, axillarin, cumaldehyde, ephedroxane, isoquercitrin, cirsiliol, luteolin, syringin, etc. [80], indicating the effectiveness of this TCM formula in the treatment of COVID-19 patients.

According to TCM theory, XFBD contains heat-clearing and toxin-removing ingredients to clear viruses, transform thick phlegm into thin or clear, cleanse the lungs, soothe the trachea, and relieve breath, cough, and fever in infected people. Another distinguishing feature of XFBD treatment is that it dissipates stasis, providing a moderate anticoagulant effect. Before the widespread use of XFBD in China, 10% of mild/moderate treated cases were evaluated for their progression to severe cases, and it was found that only 2–5% of treated patients experienced disease severity. Overall, XFBD treatment was safe and effective in improving COVID-19 symptoms [81]. These clinical findings were confirmed when Pan and colleagues reported that XFBD treatment significantly reduced COVID-19 symptoms, i.e., fever, fatigue, cough, and conversion of mild disease to the severe stage [82]. Randomized controlled trials also confirmed the efficacy and safety of XFBD therapy for COVID-19. This treatment improved the conversion time of negative nucleic acid tests to positive, the duration of hospital stay, disease symptoms, and lung CT imaging in COVID-19 patients [83]. Another clinical trial compared a single conventional drug and its combination with XFBD and discovered that the combined treatment significantly reduced symptoms like fever, fatigue, and cough, and loss of appetite in 42 COVID-19 patients. In addition, the number of lymphocytes was increased, and the patients returned to normal after the combined treatment. Moreover, this treatment significantly reduced C-reactive protein (CRP) level and erythrocyte sedimentation rate (ESR) in treated patients [84], indicating that XFBD combined with conventional medicine may be an effective strategy to improve clinical symptoms, return blood parameters to normal, and improve host immunity.

2.5. XBJ formula

XBJ injection comprises five herbal extracts, namely Honghua (Carthami Flos: Safflower flower), Danshen (Salvia miltiorrhiza Bunge), Chuanxiong (Ligusticum dry rhizome), Danggui (Radix Angelica Sinensis), and Chishao (Paeoniae Radix Rubra) [25,85]. The National Health Commission and the National Administration of TCM have added the XBJ prescription to the "diagnosis and treatment plan for COVID-19″ (seventh edition).

2.5.1. Underlying mechanisms and impact of XBJ treatment on COVID-19

Network pharmacology and molecular docking studies revealed the underlying therapeutic mechanisms and impact of XBJ injection on COVID-19. Network pharmacology technology constructs interaction networks (drug-target, drug-disease, and target-disease) from XBJ active components, genes, and disease databases to reveal its mechanisms and target sites [86]. Network pharmacology concepts are similar to the holistic TCM view in the sense that they treat complex human diseases using systemic methods. A network pharmacology study is based on the idea that viral pathogenesis-associated proteins correspond to the human subnetwork. The findings show that SARS-CoV-2 regulates several pathways in the infected cell for pathogenesis; therefore, inhibiting these pathways can prevent virus replication/transcription in hosts

[87]. The XBJ injection has been shown to play an essential role in treating COVID-19, providing new hope for disease control [88]. According to molecular docking technology, 45 active components of XBJ were docked with SARS-CoV-2 3CLpro, spike protein, and host ACE2 receptor. In addition, XBJ active components such as apigenin, luteolin, and quercetin may affect TNFα, IL6, and MAPK1 regulation; meanwhile, hydrosafflor yellow B, rutin, and salvianolic acid B may bind to SARS-CoV-2 proteins and exert anti-inflammatory, antiviral, and immune regulatory actions in COVID-19 patients. These various active components in XBJ and their numerous viral targets and pathways in COVID-19 patients, providing a novel perspective of XBJ [88]. In addition, network pharmacology discovered chlorogenic acid, gallic acid, kaempferol, luteolin, paeoniflorin, quercetin, rosmarinic acid, and tanshinone components in XBJ targeting multiple sites in SARS-CoV-2 [89]. Moreover, network pharmacology and molecular docking technologies screened eight essential components, including baicalein, kaempferol, luteolin, and quercetin, for 15 targets, including ESR1 and DPP4 CALM1, AR, and kinase 1. The underlying XBJ mechanisms in the COVID-19 patient treatment require further investigation because their essential compounds regulate the expression of key targets such as B lymphocytes, kinase 1, TNFα, and vascular endothelial growth factor-A, which alleviate the drug target site (ACE2) in SARS-CoV-2 patient, and hypoxia-inducible factor-1 as well as multiple inflammatory signaling pathways (PI3K-Akt, and NF-kB) [90].

A total of 42 COVID-19 patients administered XBJ injection combined with routine treatment in China showed improved levels of IL6, TNFα, and body temperature compared to control. The reduction in body temperature of severe COVID-19 patients was more significant in the treated group than in the control. In addition, treated patients had improved lung CT imagings and a shorter time to covert negative nucleic acid tests, implying that XBJ combined with routine treatment can improve COVID-19 clinical outcomes [91]. In a comparative study, WBC and lymphocyte counts increased in routine XBJ-treated groups (50 mL group; 100 mL group; 20 cases in each group), while CRP and ESR levels decreased. The WBC counts increased significantly after XBJ administration in the 100 mL group compared to the routine treatment group, while CRP and ESR levels decreased significantly in the same groups. The COVID-19 patient's conditions improved, and nucleic acid tests converted negative in all treatment groups (9, 8, and 9 cases in the routine groups, XBJ 50 mL, and 100 mL treatment groups, respectively). The routine treatment group (8 cases) recovered completely, and the 100 mL treatment group improved symptoms more effectively than the 50 mL treatment group, indicating the efficacy of XBJ treatment in reducing inflammation and improving prognosis in severe COVID-19 cases [92]. In a prospective randomized study, XBJ 14-day treatment significantly reduced IL6, IL8, TNFα, and CRP levels while increasing lymphocyte counts compared to controls. An observational study, 11 severe COVID-19 patients, showed reduced TNFα, IFNγ-inducible protein-10, and macrophage inflammatory protein-1β (CCL4) levels after 7–8 days of XBJ treatment. In addition, XBJ treatment prevents monkey Vero-E6 kidney cell death from SARS-CoV-2 infection [93]. XBJ treatment significantly reduced septic shock, symptom duration, and hospital stay time in severely infected COVID-19 patients compared to controls. There were no severe side effects in the treated group, indicating that XBJ treatment may suppress the pro-inflammatory cytokine storm (IL6, IL8, and TNFα) patients and reduce the mortality rate in critical COVID-19 [94]. Clinical trials have shown that combining XBJ with a conventional drug has therapeutic effects on MERS and avian influenza H7N9-infected humans [36]. In addition, XBJ treatment has effectively reduced multiple organ damage caused by influenza virus infections by enhancing anti-inflammatory mediators and immune function. Further, XBJ treatment may be responsible for endotoxin antagonism, anti-inflammation, improved immune function, microcirculation, and regulation of coagulation disorders [95,96]. In a study, XBJ treatment decreased the pro-inflammatory cytokines IL6 and TNFα levels while also alleviating lung injury in H1N1-infected pneumonia mice [97]. In 2004, China approved the sale of the XBJ injection, which has since been used to treat various influenza H1N1, H7N9, dengue, MERS, and ebola diseases.

2.6. HSBD formula

HSBD comprises 14 herbs, namely Dahuang (Radix Rhei Et Rhizome), Mahuang (Ephedra Herba: Gymnosperm Shrubs), Shigao (Gypsum Fibrosum), Guanghuoxiang (Patchouli: Pogostemon cablin Benth), Houpo (Magnolia Officinalis), Tinglizi (Descurainiea Semen; Lepidii Semen), Chishao (Radix Paeoniae Rubra), Fabanxia (Rhizoma Pinelliae Praeparatum), Gancao (Licorice: Glycyrrhizae Radix Et Rhizoma), Fuling (Poria cocos), Xingren (Semen Armeniacae Amarum), Cangzhu (Atractylodes Lancea (Thunb. DC.), Caoguo (Amomum Tsaoko: Chinese Cardamom Seeds), Shenghuangqi (Hedysarum Multijugum Maxim: Astragalus Carthamus) [25,98].

2.6.1. Underlying mechanisms and impact of HSBD treatment on COVID-19

Integrating network pharmacology techniques, active compounds, target sites, and key signal pathways revealed HSBD's potential therapeutic mechanisms in severe COVID-19 cases. In a study, the therapeutic effect of HSBD was attributed to 11 active components, i.e., aloe-emodin, baicalein, β-sitosterol, catechin, delphinidin, isorhamnetin, irisolidone, kaempferol, luteolin, naringenin, and quercetin targeting 45 different genes, including TNFα, MAPK1, MAPK8, IL1B, IL6, IL4, CASP8, CXCL8, MAPK3, MAPK14, RELA, TP53 and STAT1 in SARS-CoV-2-infected patients. Among these 11 components, β-sitosterol, luteolin, naringenin, aloe-emodin, and quercetin inhibited SARS-CoV 3CLpro, whereas kaempferol actively inhibited SARS-CoV 3a protein [99]. In another study, various databases searched yielded 223 active components in HSBD attributed to 358 targets. Network pharmacology and molecular docking revealed targets ACE2, ADRA1A, ESR1, and HDAC1 for key components in HSBD. The enriched KEGG analysis screened vital signaling pathways, renin-angiotensin and secretion, NF-kB, AMP-activated protein kinase, and arachidonic acid metabolism in COVID-19 patients after treatment [98], revealing that HSBD may inhibit SARS-CoV-2 via multiple sites and pathways. Modulations of signaling pathways, such as AGE-RAGE, NF-kB, RIG-I-like receptor, and TNFα, might mediate HSBD therapeutic effects on severe COVID-19 patients [100]. In a study, network pharmacology and molecular docking revealed 138 active components in HSBD, with baicalein having the highest affinity for SARS-CoV-2 3CLpro and licorice phenol for ACE2 receptors in COVID-19 patients [101]. Two additional components, baicalein, and quercetin showed the strongest affinity for the ACE2 receptor, indicating the therapeutic efficacy of HSBD via ACE2 inhibition [102]. Furthermore, kaempferol, luteolin, and quercetin have the highest affinity for SARS-CoV-2 3CLpro, spike protein, and the host ACE2 receptor [100]. In brief, HSBD clinical research, network pharmacology, and molecular docking studies show a good curative effect in treating severe COVID-19 patients [102].

HSBF treatment is recommended for severe COVID-19 patients with symptoms such as blood in the sputum, cough, dry/sticky mouth, fatigue, fever, nausea, red urine, shortness of breath, and yellow/sticky sputum [103,104]. A meta-analysis and review evaluated the HSBD therapy efficacy and safety for COVID-19 patients [105]. HSBD therapy is safe and has been shown to effectively treat mild, moderate, and severe COVID-19 cases, resulting in lower mortality rates. A retrospective study from Wuhan, China, looked at 55 severe COVID-19 patients, 23 of whom were treated with HSBD combined with XBJ and other TCM, and 32 were given Western antiviral drugs (abidor and lopinavir-ritonavir), antibiotics (cefoperazone and moxifloxacin), or corticosteroids (methylprednisolone succinate sodium and prednisone). The average time for SARS-CoV-2 RNA clearance in TCM and Western medicine treatment patients was 12 days and 15.5 days, respectively, while the nucleic acid negative test conversion ratio was significantly higher in the TCM treatment group than in the Western medicine group. Chest CT findings

revealed that TCM treatment had more widely absorbed lung lesion opacity when compared to western medicine. Furthermore, decreased CRP and serum ferritin levels were observed in COVID-19 patients after TCM treatment. No severe liver and renal function complications were observed in the treatment groups, implying that TCM therapy has improved anti-inflammation, virus clearance, and lung lesion effects in COVID-19 patients [106]. Other clinical trials also investigated and found the effectiveness of HSBD treatment for curing severe COVID-19 patients [107,108]. In COVID-19 patients, HSBD treatment reduced nucleic acid test negative conversion time [59], shortened hospital stay duration, improved lung CT imaging [109], and reduced mild/moderate disease conversion to severe stage, and a low mortality rate [82].

2.6.2. Underlying mechanisms and impact of HSBD on influenza infections

According to network pharmacology and molecular docking analysis, the therapeutic mechanisms of HSBD in the treatment of COVID-19 were attributed to its eight main active components, namely baicalein, β-sitosterol, formononetin, isorhamnetin, kaempferol, naringenin, stigmasterol, and quercetin [102]. The currently recommended treatment options for curing COVID-19 clinical symptoms are HSBD and conventional antiviral drugs like lopinavir, ritonavir, chloroquine, and remdesivir [110–112]. Baicalein had a high affinity for SARS-CoV-2 3CLpro, and quercetin had a high affinity for both SARS-CoV-2 3CLpro and ACE2 receptor [102], indicating that baicalein and quercetin may be effective therapies for COVID-19 treatment. In addition, both baicalein and quercetin reduce H1N1-induced lung endothelial barrier disruption by inhibiting the NOX4/NF-kB/MLCK pathway, suggesting that these components could effectively treat H1N1 patients and prevent pulmonary endothelial barrier dysfunction [113]. According to a study, baicalein inhibited the over-activation of the complement system in vivo and improved acute lung injury caused by H1N1 infection [114]. Both SARS and SARS-CoV-2 spike proteins attach to the host membrane (ACE2) to penetrate the cytoplasm and initiate infection [115,116]. According to a study, quercetin acted as a competitive antagonist to prevent virus attachment and COVID-19 progression. In COVID-19 patients, quercetin can also inhibit capillary brittleness, antioxidant activity, detoxification, angiogenesis, cell cycle, and cell apoptosis [117].

3. Application and efficacy of single prescriptions used in TCM formulas

The preceding discussion has confirmed that five components, namely Shigao, Patchouli, Gancao, Xingren, and Mahuang were the most frequently used items among the TCM formulas. According to the TCM theory, the Mahuang in the TCM formulas (JHQGG, LHQWG, QFPDD, XFBD, and HSBD) aids in the removal of invading pathogens and dampness to improve lung ventilation. Shigao, another important TCM component in JHQGG, LHQWG, QFPDD, XFBD, and HSBD formulas, aids in the clearance of invading pathogens and the detoxification of toxic compounds, whereas Gancao regulates functions of multiple herbal components in these TCM formulas apart from maintaining healthy gastrointestinal tract functions. The clinical symptoms-relieving, immune regulatory, toxic antiviral effects of these components are discussed in TCM theory. According to pharmacodynamic studies, LHQWG treatment has broad-spectrum antipyretic, anti-inflammatory, cough-relieving, immunoregulation, antiviral, and antibacterial effects. Clinically, it has achieved remarkable curative effects in treating respiratory diseases, including COVID-19, influenza A, colds, nasal congestion, and pulmonary infections, demonstrating the importance of the TCM [118]. Shigao may have an antipyretic effect due to the combined action of various trace minerals in TCM formulas. The antipyretic effect of TCM treatment is probably related to infection control by selenium, copper, iron, and other trace elements that regulate the host immune response against viral infections [119].

Mahuang (Ephedra Herba: Gymnosperm Shrubs), a member of the *Ephedraceae* family, is native to southwest and central Asia, including China. Some species of this plant are used in TCM to treat asthma, colds, coughs, headaches, flu, fever, and nasal congestion. The use of Ephedra plant species in TCM formulas dates back to 5000 BCE, with Mahuang being mentioned for the treatment of flu-like symptoms such as asthma, bronchospasm, chills, cough, headache, fever, and nasal congestion [120]. According to the national guidelines, Mahuang is the sixth most commonly used herb in China to treat COVID-19 and relieve asthma symptoms in humans [120]. The alkaloids ephedrine and pseudoephedrine in the Mahuang stem may be responsible for their toxicity. Because the use of ephedra-containing dietary products resulted in several complications and deaths among consumers, the FDA banned the sale of these products in 2002 [120]. This prescription has a strong effect, so it should only be used under the supervision of a qualified physician.

The Xingren herb (Semen Armeniacae Amarum) is commonly used to treat asthma-like symptoms, coughing, and chest wheezing [121]. Due to its effectiveness in curing coughing and chest wheezing, Xingren is one of China's most widely used herbal remedies for combatting COVID-19 infections [122,123]. The previously mentioned Chinese and Korean government guidelines recommended Xingren-containing remedies over 70 times [122], and a study reported that 32% of COVID-19 patients improved clinical complications after treatment with a TCM formula supplemented with this herb [124]. Xingren [123,125] is the common name for bitter apricot seeds, a contentious agent that has gained popularity as anti-cancer therapy. The amygdalin compound, which occurs naturally in apple, apricot, peach, almond, and plum seeds, is responsible for its toxicity [120]. Before the FDA banned them in 1978, these were used as an anti-cancer therapy [126] due to the amygdalin being metabolized to hydrocyanic acid/cyanide by the enzyme β-glucosidase [127].

Gancao, also known as licorice, is a flowering plant that has been used in TCM formulations to treat symptoms like coughing and phlegm production in humans. The extract of Gancao roots inhibited SARS replication in clinical isolates [128,129], demonstrating that this herb might be effective against COVID-19. Later on, the Chinese and Korean governments recommended Gancao supplementation in different herbal preparations for COVID-19 treatment [122]. According to a report, 48.39% of COVID-19 patients were effectively treated with TCM formulas supplemented with Gancao [123]. Gancao and Glycyrrhizin sweeteners are found in the roots of the licorice plant (found in South Asia and Europe) [130] and are commonly used in soft drinks and food products. Gancao was thought to be a healthy natural substance for centuries, but its increased consumption sometimes causes toxic effects. It is worth noting that the main issue with Gancao dosing is that it comes in different forms, each with a different concentration. The daily Gancao consumption limit varies, but it is usually between 100 and 200 mg/day. Gancao root toxicity can lead to apparent mineralocorticoid excess syndrome, which is caused by inhibition of the 11-β-hydroxysteroid dehydrogenase and increased cortisol activity [130,131]. Gancao contains 200–800 mg of glycyrrhizin per 2–4 mL of root extract [130], which may inhibit liver aldosterone metabolism via suppression of 5-β-reductase activity [130]. Overconsumption of Gancao root causes clinical manifestations such as hyperaldosteronism, with hypertension, muscle weakness, hypokalemia, and hypernatremia being the most common among consumers [130,131].

Patchouli, also known as Pogostemon cablin Benth, is a *Lamiaceae* family flowering plant used in TCM formulations since the Han dynasty to treat colds, diarrhea, fever, headache, and nausea. The patchouli herb contains several bioactive compounds, including terpenoids and others, the most important of which are β-patchoulene, patchoulene epoxide, and patchouli alcohol, all of which have anti-peptic ulcer, anti-inflammatory, anti-microbial, anti-tumor, anti-diabetic, anti-oxidative, anti-hypertensive, and immune regulatory properties [132]. Patchouli extracts have been shown to protect against bacterial infections [133], other than *H. pylori*-induced gastric ulcers, and suppress adipogenesis and fat accumulation in adipose tissues [132]. Patchouli oil has also

been shown to have in vitro antiviral activity against adenovirus, coxsackievirus, H1N1, and respiratory syncytial viruses [134]. Based on previous research, β-patchoulene, patchouli epoxide, and patchouli alcohol are the materials that enhance patchouli's therapeutic effects.

We reviewed TCM formulations and the underlying mechanisms of six TCM formulas and their impacts on COVID-19 patients. We also discuss the role of TCM in treating SARS, MERS, and other influenza infections. Furthermore, we highlighted the application and efficacy of some single prescriptions used in TCM formulas. The information provided in this review may help to alleviate the current COVID-19 pandemic around the world.

4. Conclusions and future perspectives

This review discussed the TCM formulations and the underlying mechanisms of six TCM formulas, namely JHQGG, LHQWG, QFPDD, XFBD, XBJ, HSBD, and their impacts on COVID-19, SARS, MERS, and other influenza diseases in detail. The common ingredients used in these TCM formulas may play anti-inflammatory, antiviral, and immunomodulatory roles in COVID-19 patients. Recently, COVID-19 prevention and control have improved in China; however, the resumption of industries, shopping malls, transportation, personnel cross-flow, and people's close contact has increased asymptomatic COVID-19 cases. Prevention and control measures at the national level should be strengthened with the possibility of increasing local and imported COVID-19 cases. In addition to strict control measures, the human immune system should be boosted to resist different SARS-CoV-2 strains via immunization. Furthermore, frequent hand washing, mask wear, social distancing, locking down cities, and other preventive measures, e.g., using TCM sachets in face respirators, can prevent COVID-19 transmission.

The concept of the TCM theory of treating pre-disease was first reported in the Yellow Emperor's Inner Classic medical book [135]. In previous Chinese dynasties, doctors prioritized disease prevention and treatment, especially infectious diseases [136]. Wearing TCM sachets containing TCM (Dayuan-yin or Xiangpei) can prevent COVID-19 or other respiratory diseases [137–139]. According to modern medicine, the aromatic TCM sachet stimulates mucosa in the respiratory tract to promote immunoglobulin secretion and kills invading viruses [139]. TCM prevents disease progression in clinical practice and relieves symptoms through administration, moxibustion, and external fumigation [138,140]. Since the COVID-19 outbreak, Chinese local health committees and medicine administration bureaus have actively promoted TCM to prevent SARS-CoV-2 infection and transmission [137]. By summarizing the accumulated clinical evidence, we hope the pharmacological effects of six TCM formulas (i.e., JHQGG, LHQWG, QFPDD, XFBD, XBJ, and HSBD) might be effective therapies against COVID-19 infection. However, each TCM formula has multiple ingredients and links to various disease treatments, so explaining their exact anti-SARS-CoV-2 mechanism is complex. TCM adds or subtracts dosage based on the disease symptoms of each patient, reflecting the personalized treatment principle so that each infected person receives the most appropriate treatment.

In addition to its beneficial effects, the widespread use of Xingren herb in QFPDD, XFBD, and HSBD and Mahuang herb used in LHQWG, QFPDD, XFBD, and HSBD formulas resulted in severe disability and multiple deaths among consumers [120,126]. Excessive LHQWG administration in clinical trials resulted in mild adverse effects, including gastrointestinal disturbance (73.9%), with the most common complications diarrhea, nausea, skin rashes, and vomiting in treated individuals [141]. The Chinese FDA has approved LHQWG treatment for mild COVID-19 patients, benefiting severe cases requiring extensive clinical trials. In the light of COVID-19 treatment, the LHQWG formula may be a potent and effective treatment against unknown viral infections [58,142,143]. Some herbal components used in TCM formulas may be toxic, especially when prepared by untrained practitioners, misused, or self-prescribed. Therefore, healthcare workers should be aware of the toxic effects of each ingredient used in TCM formulas. Components in TCM formulas and their underlying molecular therapeutic effect against COVID-19 demand immediate and thorough investigation to manage this pandemic. Based on previous evidence, TCM monitoring guidelines should be strengthened to encourage their application while ensuring people's safety and avoiding adverse reactions.

According to network pharmacology and molecular docking analyses, Patchouli alcohol from Pogostemon cablin Benth, Tussilagone from Kuandonghua (Farfarae Flos), and Ephedrine hydrochloride from Ephedrae Herba can bind to the ACE2 receptor and inhibit SARS-CoV-2 attachment and entry into the host cell cytoplasm [144]. However, ACE2 down-regulation may increase the degree of lung injury, acute lung failure, and other pulmonary diseases [145]. Therefore, direct blocking of the ACE2 receptor may not be an effective TCM strategy for inhibiting SARS-CoV-2 attachment to the host surface. Instead of computer-based analyses, more clinical-based evidence is needed to explore each TCM therapeutic effect on the patient's blood parameters. In addition, SARS-CoV-2 genomic RNA and ACE2-expressing intestinal epithelial cells were found in the feces of COVID-19 patients, indicating the importance of the intestinal microbiota in COVID-19 disease [146]. Furthermore, a clinical trial reported a difference in the composition of gut microbiota in COVID-19 and H1N1 patients compared with healthy individuals [147]. Prebiotics, probiotics, and herbal nutrition can alleviate COVID-19 clinical symptoms in patients by modifying their gut-lung axis [148,149]. Based on the evidence presented above, we concluded that TCM treatment improves immune regulation, reduces endotoxin levels, gut-lung mucosal barriers, and intestinal microbiota composition in SARS-CoV-2 infected individuals.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable

Author contributions

Z.B conceived and designed the study and is responsible for study coordination. T.S, X.K, and Z.S wrote the first draft. All authors read and approved the manuscript for publication.

Declaration of Competing interest

The authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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