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Traditional Chinese Medicine (TCM) in the treatment of COVID-19 and other viral infections: Efficacies and mechanisms

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ABSTRACT

COVID-19 has remained an uncontained, worldwide pandemic. While battling for the disease in China, six Traditional Chinese Medicine (TCM) recipes have been shown to be remarkably effective for treating patients with COVID-19. The present review discusses principles of TCM in curing infectious disease, and clinical evidence and mechanisms of the 6 most effective TCM recipes used in treating COVID-19 in 92% of all of the confirmed cases in China. Applications of TCM and specific recipes in the treatment of other viral infections, such as those caused by SARS-CoV, MERS-CoV, hepatitis B virus, hepatitis C virus, influenza A virus (including H1N1 and H7N9), influenza B, dengue virus as well as Ebola virus, are also discussed. Among the 6 TCM recipes, Jinhua Qinggan (JHQG) granules and Lianhua Qingwen (LHQW) capsules are recommended during medical observation; Lung Cleansing and Detoxifying Decoction (LCDD) is recommended for the treatment of both severe and non-severe patients; Xuanfeibaidu (XFBD) granules are recommended for treating moderate cases; while Huashibaidu (HSBD) and Xuebijing (XBJ) have been used in managing severe cases effectively. The common components and the active ingredients of the six TCM recipes have been summarized to reveal most promising drug candidates. The potential molecular mechanisms of the active ingredients in the six TCM recipes that target ACE2, $3CL^{pro}$ and IL-6, revealed by molecular biological studies and/or network pharmacology prediction/molecular docking analysis/visualization analysis, are fully discussed. Therefore, further investigation of these TCM recipes may be of high translational value in enabling novel targeted therapies for COVID-19, potentially via purification and characterization of the active ingredients in the effective TCM recipes.

Abbreviations: $3CL^{pro}$, Coronavirus 3-chymotrypsin-like protease; ACE2, angiotensin converting enzyme 2; AGE-RAGE, Advanced glycation end products-Receptor for AGE; Akt, Protein kinase B; ARDS, Acute respiratory distress syndrome; BCL2, B-cell lymphoma 2; CASP3, Caspase 3; CCL2, C-C Motif Chemokine Ligand 2; COVID, Coronavirus disease; COVID-19, Coronavirus disease 2019; COX-2, Cyclooxygenase-2; CRP, C-reactive protein; CT, computerized tomography; CVA, cough variant asthma; DAVID, Database for Annotation, Visualization, and Integrated Discovery; EGFR, epidermal growth factor receptor; ESR, erythrocyte sedimentation rate; GO, gene ontology; HIF-1, Hypoxia-Inducible Factor-1; HNF4A, hepatocyte nuclear factor 4 alpha; HSBD, Huashibaidu granules; HSP90AA1, Heat shock protein HSP 90-alpha; HSP90AB1, Heat shock protein HSP 90-beta; HXZQ, Huoxiang Zhengqi dropping pills; IC50, 50% inhibitory concentration; ICU, intensive care unit; IFN-γ, Interferon gamma; IL-6, Interleukin-6; IP-10, Interferon gamma-induced protein 10; JHQG, Jinhua Qinggan granules; KEGG, Kyoto Encyclopedia of Genes and Genomes; LCDD, Lung Cleansing and Detoxifying Decoction; LHQW, Lianhua Qingwen capsules; MAPK, Mitogen-activated protein kinase; MCP-1, Monocyte Chemoattractant Protein-1; miRNAs, micro RNAs; NCOA2, Nuclear receptor coactivator 2; NFkB, Nuclear factor kappa B; NOS2, Nitric Oxide Synthase 2 (inducible Nitric Oxide Synthase/iNOS); Nrf2, nuclear factor erythroid 2-related factor 2; PCT, procalcitonin; PI3K, Phosphoinositide 3-kinase; PPARG, peroxisome proliferator-activated receptor gamma; PPI, protein-protein interaction; PTGS1, Prostaglandin-endoperoxide synthase 1; PTGS2, Prostaglandin-endoperoxide synthase 2; RCT, randomized controlled trial; ROS, reactive oxygen species; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; SIRS, systematic inflammatory response syndrome; SOCS1, suppressor of cytokine signaling 1; S protein, SARS-CoV-2 spike (S) glycoprotein; TCM, Traditional Chinese Medicine; TCMID, Traditional Chinese Medicine Integrated Database; TFs, transcription factors; TNF-α, Tumor Necrosis Factor Alpha; TP53, Tumor protein p53; UPLC-DAD-QTOF-MS, Ultra performance liquid chromatography coupled with diode-array detector and quadrupole time-of-flight mass spectrometry; WBC, white blood cell; WHO, World Health Organization; XBJ, Xuebijing; XFBD, Xuanfeibaidu granules.

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1. Introduction

COVID-19 has remained an uncontained, worldwide pandemic. During the fight against the disease in China, the National Health Commission of the People's Republic of China declared that 92% of the confirmed

Formulated Chinese medicine has been used in managing previous pandemics, such as the two previous coronavirus outbreaks involving SARS-CoV in 2003 and MERS-CoV in 2012, and seasonal epidemics caused by influenza viruses and dengue virus (Li et al., 2020). During the 2002–2003 SARS (Severe Acute Respiratory Syndrome) epidemic in China, TCM was used in the prevention (Lau et al., 2005) and treatment of SARS (Chen & Nakamura, 2004), which had been shown to result in shorter hospitalization, reduced side effects from steroid treatments, and relief from dyspnoea and malaise (WHO, 2004). To date, dozens of Chinese herbs and hundreds of natural TCM ingredients have been reported to possess antiviral activities (Xian et al., 2020). TCM have been shown to possess antiviral activities against various viral strains including herpes simplex virus, influenza virus, human immunodeficiency virus, hepatitis B and C viruses, and SARS-CoV and MERS-CoV (Xian et al., 2020). When the human transmissible swine flu virus (H1N1) was reported in Mexico and the United States in April 2009, the Chinese government rapidly released three editions of documents entitled "Recommended Schemes for Pandemic Influenza A Diagnoses and Treatments" (Ge et al., 2010). Besides the two targeted anti-flu drugs, Oseltamivir and Zanamivir, four anti-flu TCM prescriptions were recommended for the treatment of H1N1 infection in the third edition (Ge et al., 2010). A meta-analysis of 30 studies including 3444 cases indicates that the mean time to defervescence in the TCM treatment group was significantly reduced, and that the duration of viral [Influenza A (H1N1)] shedding in the subgroup of patients receiving integrated treatment of Chinese and Western medicine, was also significantly shortened (Li, Wang, Guo, & Li, 2016).

TCM drugs are traditionally composed of many different herbs/com-

1i-7.9(1N1)-29Q8.6W.31Tf1.59750.23568()Ti-F1.1Tf43.4428]-[011Tf9.4428]c03g(di0(n1(nul9(TCM)]ere)JH)e)-14QG,31Tf43.4428]-103()Tj/F1Tf43.4428

3.1. JHQG recipe

JHQG granules (金花清感颗粒) combine two classical recipes of Maxingshigan decoction (麻杏石甘汤) and Yinqiao San (银翘散), which are composed of Niubangzi (牛蒡子; Great Burdock Achene; Arctii Fructus), Qinghao (青蒿; Sweet Wormwood Herb; Artemisiae Annuae Herba), Bohe (薄□; Wild Mint Herb; Menthae Haplocalycis Herba), Lianqiao (连翘; Forsythiae Fructus; *Forsythia suspensa*), Jinyinhua (金银花, Wild honeysuckle flower; Lonicerae Japonicae Flos), Kuxingren (苦杏仁; Bitter Almond; Armeniacae Semen Amarum), Shigao (石膏; Gypsum; Gypsum fibrosum), Gancao (甘□; Licorice; Glycyrrhizae Radix et Rhizoma), Huangqin (黄芩; Baikal Skullcap Root; Scutellariae Radix), Mahuang (麻黄; Ephedra; Ephedrae Herba), Zhebeimu (浙贝母; Thunberg Fritillary Bulb; Fritillariae Thunbergii Bulbus), and Zhimu (知母; Common Anemarrhena Rhizome;

stages (0−2*h*) of viral infection, suppressed virus-induced NF-kB activation and alleviated virus-induced gene expression of Interleukin-6 (IL-6), IL-8, tumor necrosis factor (TNF)-α, IP-10, and monocyte chemotactic protein 1 (MCP-1) in a dose-dependent manner (1.5-3 mg/mL) (Ding et al., 2017). Additionally, the viral titers and the levels of inflammatory cytokines were both decreased by LHQW administration (1,300 mg/kg/day for 5 days) in the lungs of the mice inoculated with variant of H1N1 influenza virus A/PR/8/34 (H1N1) (H274Y mutuant) (Ding et al., 2017).

3.2.2. LHQW recipe in the treatment of COVID-19

LHQW has been recommended by the Evidence-Based Medicine Chapter of the China International Exchange and Promotive Association for Medical and Health Care (CPAM) and the Chinese Research Hospital Association (CRHA) to treat patients with mild or moderate COVID-19 in combination with conventional therapy, which refers to respiratory support, symptomatic treatment, antiviral treatment, and antibacterial treatment if needed (Jin et al., 2020). A retrospective analysis of clinical records showed that fever was better resolved and fever duration was shortened in patients treated with LHQW plus conventional therapy (21 confirmed COVID-19 patients), compared to conventional therapy alone (21 confirmed COVID-19 patients) (Yao, Liu, Li, Huang, & Cai, 2020). Results from a retrospective analysis of 54 COVID-19 patients indicate that LHQW is effective in significantly relieving symptoms of fever, cough and weakness, and in shortening duration of having these symptoms (Cheng & Li, 2020). Another RCT of mild COVID-19 patients showed that, compared with Arbidol (anti-influenza drug) treatment group of 148 patients, the total effective rate and the TCM syndrome scores (based on the TCM syndrome rating scale) were significantly improved after 7 day treatment with LHQW (6 g each time, three times daily) plus Arbidol in 147 patients (Yu, Li, Wan, & Wang, 2020). LHQW combined with Arbidol more effectively alleviated clinical symptoms and improved treatment efficacy in patients with mild COVID-19 (Yu et al., 2020). Besides, a study of 151 severe COVID-19 patients indicated that quadruple combination therapy of LHQW, Ribavirin, Lopinavir/ritonavir and Umifenovir may serve as a preferred protocol for treating severe COVID-19 patients (Li et al., 2020). This combination of LHQW with three drugs may result in maximal suppression of viral replication and infection through different mechanisms of action (Li, Yang, Liu, Yang, et al., 2020). Additionally, a study of 283 COVID-19 patients indicated that LHQW combined with Huoxiang Zhengqi dropping pills (HXZQ, 藿香正气滴丸) have advantages in the treatment of nausea, vomiting and limb soreness (Xiao et al., 2020). The combination of LHQW with HXZQ reduced the use of macrolides antibiotics and the number of diagnosed patients progressing into severe disease (Xiao et al., 2020). A prospective multicenter RCT of 284 COVID-19 patients indicate that clinical cure rate and the rate of recovery of chest CT manifestations were markedly higher in the patient group treated with LHQW (4 capsules thrice daily for 14 days) (Hu et al., 2020). Results from a recent meta-analysis of 154 COVID-19 patients indicate that the main clinical symptoms of fever, cough and fatigue disappeared faster in LHQW treated group; and that other symptoms of runny nose, sputum, nasal congestion, muscle pain, difficulty breathing, chest tightness, nausea and vomiting, and loss of appetite also disappeared faster while the duration of fever was significantly reduced by LHQW treatment (Zeng, Li, & Wu, 2020). In addition, Hu et al. evaluated the efficacy of LHQW in the treatment of common pneumonia and COVID-19 pneumonia by meta analysis of 42 studies involving 3793 subjects, in which LHQW treatment was found associated with improvements in flu-like symptoms and conversion of severe cases (Hu et al., 2020). Ultra performance liquid chromatography coupled with diode-array detector and quadrupole time-of-flight mass spectrometry (UPLC-DAD-QTOF-MS) was employed for qualitative and quantitative analyses of the major ingredients of LHQW, among which a total of 61 ingredients including flavonoids, phenylpropanoids, anthraquinones, triterpenoids, iridoids, and other types of compounds were unambiguously or tentatively identified by comparing the retention times and the accurate mass measurements with reference compounds and/or data in the literatures (Jia et al., 2015). Among them, twelve representative ingredients, including salidroside, chlorogenic acid, forsythoside E, cryptochlorogenic acid, amygdalin, sweroside, hyperin, rutin, forsythoside A, phillyrin, rhein, and glycyrrhizic acid were further quantified (Jia et al., 2015). In another study, the primary active ingredients of LHQW were identified by network pharmacology analysis, with a focus on 61 candidate ingredients to further identify their related targets (Wang et al., 2016). The main effective ingredient-target (MECT) network was constructed to reveal the main effective ingredients and their key targets for LHQW (Wang et al., 2016). It has been shown that the docking scores to $3CL^{pro}$ of SARS-CoV-2 of three ingredients in LHQW, rutin, forsythoside E, and hyperoside, are better than that of Lopinavir (anti-viral drug) (Ye et al., 2020). In addition, at molecular levels, Li et al. observed that LHQW significantly inhibited SARS-CoV-2 replication in Vero E6 cells, and markedly reduced mRNA expression of pro-inflammatory cytokines of TNF-α, IL-6, CCL-2/MCP-1 and CXCL-10/IP-10 (Li et al., 2020). Recently, network pharmacology and molecular docking analyses performed by Xia et al. indicated that the six active ingredi81.3088TD[(10)fa15(t)20.13.9(a)0(l).4593159 edin

reduced CRP and erythrocyte sedimentation rate (ESR) (Xiong, Wang, Du, & Ai, 2020). In a study of 280 patients with COVID-19 who were treated with XFBD, no case transformed into severe and critical conditions (ChinaDaily, 2020a). Approximately 326 out of the 1224 putative XFBD targets have been linked to the pathological mediators of COVID-19, among which 109 targets are enriched in the disease pathways of viral infection and lung injury (Wang et al., 2020). The primary biological pathways regulated by the key XFBD targets include those involved in viral infection, and parasites and bacterial infections (Wang, Li, et al., 2020). Network pharmacology and molecular docking analyses indicate that XFBD inhibits viral invasion and viral replication mainly by binding to ACE2 and $3CL^{pro}$ of SARS-CoV-2 through flavonoids and phytosterols (more discussion in Section 3), and may play a role in the treatment of COVID-19 by regulating key targets such as IL6, MAPK3, MAPK1, IL1β, CCL2, EGFR, and NOS2 (Wang, Song, et al., 2020).

3.4. HSBD recipe

Similar to XFBD above, HSBD (化湿败毒颗粒) was also specifically formulated for treating COVID-19 (Pan et al., 2020), and not previously used to treat other viral infections. It is derived with modifications from classic recipes of MXSG (麻杏石甘汤), Huoxiang Zhengqi San (藿香正气散), Xuanbai Chengqi Decoction (宣白承气汤), and TLDZXF (葶苈大枣泻肺汤) (Lai, Liang, He, Huang, & Wu, 2020). The components in HSBD include Caoguo (▫果; Caoguo; Tsaoko Fructus), Fabanxia (法半夏; Pinellia Tuber; Rhizoma Pinelliae), Dahuang (大黄; Rhubarb Tangute Rhubarb; Rhei Radix Et Rhizoma), Shenghuangqi (生黄芪; Milkvetch Root; Astragali Radix), Chishao (赤芍; Red Paeoniae Trichocarpae; Paeoniae Radix Rubra), Kuxingren (苦杏仁; Bitter Almond; Armeniacae Semen Amarum), Fuling (▫苓; Poria; Indian Buead Tuckahoe), Huoxiang (藿香; Ageratum; Herba Agastachis), Mahuang (麻黄; Ephedra; Ephedrae Herba), Shigao (石膏; Gypsum; Gypsum fibrosum), Tinglizi (葶苈子; Pepperweed Seed; Descurainiae Semen), Gancao (甘▫; Licorice; Glycyrrhizae Radix et Rhizoma), Houpo (厚朴; Officinal magnolia bark; Magnoliae Officinalis Cortex), and Cangshu (苍术; Atractylodes; Rhizoma Atractylodis) (Yang, 2020).

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3.5.2. XBJ recipe in the treatment of COVID-19

Based on the clinical evidence on XBJ treatment of sepsis, bacterial pneumonia and acute respiratory distress syndrome (ARDS), XBJ was recommended by China's National Health Commission to treat severe and critical cases of COVID-19, especially during systematic inflammatory response syndrome (SIRS) and/or multi-organ failure (Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7), 2020; Song et al., 2020). XBJ was used more frequently in severe/critical patients with significant benefits for earlier discharge (Huang et al., 2020). XBJ (100 mL, twice per day) combined with routine treatment resulted in significantly reduced IL-6 levels and body temperature in a group of 42 COVID-19 patients (Guo et al., 2020). In a retrospective study of 44 COVID-19 patients, XBJ (50 mL XBJ in 100 mL saline, i.v. for 7 days) treatment group ($n = 22$) showed reduced lung inflammation by CT imaging although nucleic acid yet turned negative (Zhang, Li, Zhang, Wang, & Jiang, 2020). In a randomized study of 60 severe COVID-19 patients, low dose (50 mL, twice per day for 7 days) and high dose (100 mL, twice per day for 7 days) of XBJ decreased levels of CRP and ESR compared to routine treatment group while only 100 mL XBJ increased white blood cell count (WBC) (Wen, Zhou, Jiang, & Huang, 2020). Besides, the APACHE II score after treatment was significantly lower in high dose XBJ group than those in low dose XBJ group and the group with routine treatment (Wen et al., 2020). By increasing Th1/Th2 ratio, XBJ injection has been shown to increase the number of Th1 cells in septic rats (Zhang, Sun, Wen, & Yin, 2006). Chen and colleagues reported that XBJ (18 mL/kg, i.p. twice at 0 h and 24 h.) improves survival in response to septic shock in a murine model of polymicrobial sepsis, partially through preventing cytokine storm, inhibiting inflammation and regulating the balance of Tregs and Th17 cells (Chen et al., 2018). In addition, XBJ has been shown to protect against SARS-CoV-2-induced cell death in virus infected Vero E6 cells, and to reduce the average size and the number of the plaque in a dose dependent fashion (12.5–50 mg/mL) (Ma et al., 2020). XBJ was also predicted to treat SARS-CoV-2 infection via modulation of arachidonic acid metabolic pathway (principally used to synthesize inflammatory cytokines, such as MCP-1, TNF, IL, IFN, etc.) by pharmacophore models (Ren et al., 2020). Kong et al. reported that quercetin, gallic acid, luteolin, rosmarinic acid, rutin, kaempferol hlorogenic acid, tanshinone II A, hydroxysafflor yellow A, and paeoniflorin are the primary active ingredients of XBJ, identified by network pharmacology to be responsible for the treatment effects of XBJ on COVID-19 (Kong et al., 2020). Hydroxysafflor yellow A, chlorogenic acid and salvianolic acid B were identified as major compositions in XBJ by molecular docking, through "multi-component, multi-target, multi-pathway" pattern to exert protective effects on inflammation and vascular endothelial cell injury (He, Duan, Li, & Zhang, 2020).

3.6. LCDD recipe

LCDD (清肺排毒汤) is composed of 4 classic TCM recipes: MSXG (麻杏石甘汤), She Gan Ma Huang decoction (SGMH, 射干麻黄汤), Xiao Chai Hu (XCH, 小柴胡), and Wu Ling San (WLS, 五苓散) that were all initially described in *Treatise on Cold Damage Diseases* (*Shanghan Lun*,伤寒论). Out of the 4 recipes, MXSG is the most important constitute shared among the 3 effective TCM decoctions found effective in treating COVID-19 as described here and above (LCDD, XFBD, HSBD) (Chen et al., 2020). MXSG (components: Mahuang, 麻黄; Gancao, 甘□; Kuxingren, 苦杏仁; Shigao, 石膏) has been used for the treatment of influenza by disrupting viral surface structure and inhibiting viral entry (Hsieh et al., 2012). Overall, LCDD is a recipe of 21 Chinese herbs/components, which include Xixin (细辛; Manchurian Wildginger Herb; Asari Radix Et Rhizoma), Shegan (射干; Blackberrglily Rhizome; Belamcandae Rhizoma), Shanyao (山□; Common Yam Rhizome; Dioscoreae Rhizoma), Kuandonghua (冬花; Common Coltsfoot Flower; Farfarae Flos), Zhishi (枳实; Immature Bitter Orange; Aurantii Fructus Immaturus), Ziyuan (紫苑; Tatarian Aster Root; Asteris Radix et Rhizoma), Kuxingren (苦杏仁; Bitter Almond; Armeniacae Semen Amarum), Chenpi (陈皮; Tangerine Peel; Citri Reticulatae Pericarpium), Shengjiang (生姜; Fresh Ginger; Zingiberis Rhizoma Recens), Huangqin (黄芩; Baikal Skullcap Root; Scutellariae Radix), Guizhi (桂枝; Ramulus cinnamomi; Cinnamomi Ramulus), Mahuang (麻黄; Ephedra; Ephedrae Herba), Jiangbanxia (姜半夏; Pinelliaternata processed with ginger; Pinelliae Rhizoma), Fuling (□苓; Poria; Indian Buead Tuckahoe), Huoxiang (藿香; Ageratum; Herba Agastachis), and Zhigancao (炙甘□; Prepared Liquorice Root; Glycyrrhizae Praeparata cum Melle Radix et Rhizoma) (Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7), 2020).

3.6.1. LCDD recipe in the treatment of previous infectious diseases

A prospective RCT of 410 patients with H1N1 influenza indicate that MXSG (麻杏石甘汤)–Yin Qiao San (银翘散) combination can serve as an alternative treatment for H1N1 infection (Wang et al., 2011). Time to fever resolution was reduced by 19% with Oseltamivir plus MXSG–Yin Qiao San treatment, compared to Oseltamivir treatment alone (Wang et al., 2011). In an experimental study, the transcriptomic analysis of lung tissues of LPS induced pneumonic rats revealed that MXSG regulates multiple complement and coagulation cascades as well as thrombin system to interfere with infection (Yang et al., 2020). Mechanistically, MXSG has been shown to attenuate host cell entry of influenza virus by regulating PI3K/AKT signaling pathway (Hsieh et al., 2012). The second recipe in LCDD, SGMH (射干麻黄汤), is composed of Mahuang (麻黄), Jiangbanxia (姜半夏), Shengjiang (生姜), Ziyuan (紫苑), Kuandonghua (冬花), Shegan (射干), and Xixin (细辛); and is a classical prescription for the treatment of flu-like symptoms, tonsillitis, and asthma (Lin et al., 2020). It has been used to treat patients with cough variant asthma (CVA) (Wang et al., 2012), and shown to downregulate production of Th2/Th17 cells while upregulating CD4 + FoxP3+ Tregs cells in asthmatic airway hyperresponsiveness in mice (Lin et al., 2020). The third recipe in LCDD, XCH (小柴胡), is composed of Radix Gancao (甘□), Chai Hu (柴胡), Huangqin (黄芩), Banxia (半夏), Shengjiang (生姜), and has been shown to possess antiviral and various anticarcinogenic properties (Cheng, Ng, & Lin, 2006; Zheng et al., 2013). XCH has been used to treat chronic hepatitis B (Kong et al., 2019), and found to attenuate liver fibrosis by activating Nrf2 pathway (Li et al., 2017). The forth recipe in LCDD, WLS (五苓散), is composed of Guizhi (桂枝)ZZexiapLiCD4v

of multi-organ impairment (Xin et al., 2020). In a retrospective study of 98 patients with COVID-19, LCDD treatment relieved symptoms such as fever and cough, normalized laboratory indexes including LYMPH%, CPR, ESR, and reversed pulmonary CT imaging characteristics showing obvious absorption of inflammation, only 6 days after initiation of the treatment (Wang et al., 2020). Four provincial hospitals in China used

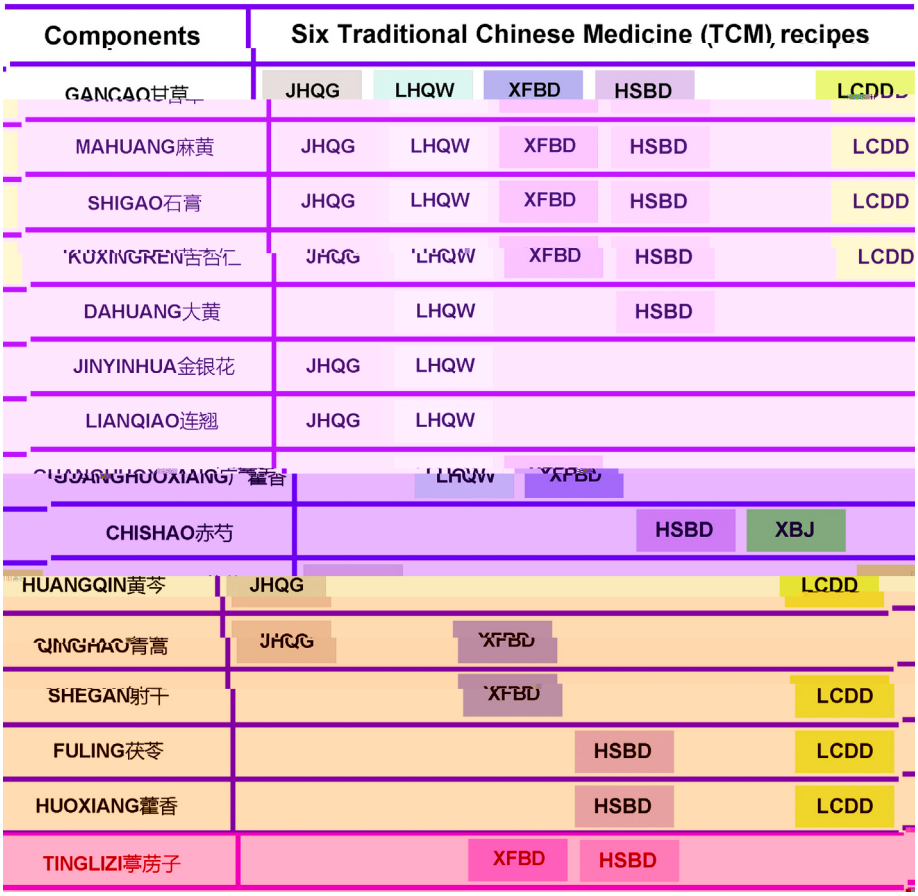

Fig. 2. The common components of the six TCMs (JHQG, LHQW, XFBD, HSBD, XBJ and LCDD). All of the components in JHQG, LHQW, XFBD, HSBD, XBJ and LCDD were compared and the common components of the six TCM recipes are presented.

in HSBD may regulate multiple signaling pathways through ACE2, which in turn exert therapeutic effects on COVID-19 (Tao et al., 2020). The results of molecular docking analyses indicate that quercetin has a high affinity for $3CL^{pro}$ and ACE2. Sekiou et al. also reported that quercetin exhibits better inhibitory effects on $3CL^{pro}$ and ACE2 than Hydroxy-Chloroquine using in-silico identification (Sekiou et al., 2020). Therefore, quercetin may represent one of the most important TCM ingredients that have played a major role in mechanistically inhibiting pathophysiological pathways of COVID-19.

4.3. TCM regulation of ACE2 for the treatment of COVID-19

Binding to ACE2 is a critical initial step for SARS-CoV-2 to enter into target cells (Hoffmann et al., 2020; Lan et al., 2020). Therefore, ACE2 is an important therapeutic target for COVID-19 (Monteil et al., 2020). Several active ingredients of TCM as discussed above, including quercetin, glabridin, and gallic acid, have been shown to downregulate ACE2 expression by regulating the aforementioned transcription factors (TFs) or miRNAs (Niu et al., 2020). The TFs and miRNAs include hepatocyte nuclear factor 4 alpha (HNF4A), peroxisome proliferator-activated receptor gamma (PPARG), hsa-miR-2113, and hsa-miR-421 (Niu et al., 2020). Network pharmacology analyses and high throughput molecular docking analyses showed that 3-methoxy-glycerol, crude-glycerin and glycyrrhizin B, the active ingredients of JHQG, have strong binding activity for ACE2 (Shen et al., 2020). Notably, these analyses revealed that the action mechanism of JHQG might be attributed to its active ingredients of kaempferol, baicalein and oroxylin A, which regulate multiple signaling pathways (such as PTGS1, PTGS2, BCL2, HSP90AB1, HSP90AA1, NCOA2 and CASP3) by binding to ACE2, thereby exerting therapeutic effects on COVID-19 (Gong et al., 2020; Jimilihan et al., 2020). Additional network pharmacology and molecular docking analyses indicate that XFBD inhibits viral invasion and viral replication mainly by binding to ACE2 through flavonoids and phytosterols (Wang, Song, et al., 2020). Baicalein and quercetin, the two major active ingredients of HSBD, were predicted by network pharmacology and molecular docking analyses to treat COVID-19 by binding ACE2 (Tao et al., 2020). The results of molecular docking predict that quercetin, luteolin, kaempferol, active ingredients from HSBD, physically bind to ACE2 (Lai et al., 2020). These findings demonstrate that HSBD exerts therapeutic effects on COVID-19 through ACE2 (Lai et al., 2020). In-silico identification results indicated that quercetin, hispidulin, cirsimaritin, sulfasalazine, artemisin and curcumin exhibit potential inhibitory effects on ACE2 (Sekiou et al., 2020). Besides, network pharmacology study showed that ACE2 was also targeted by patchouli alcohol from Huoxiang (藿香), shionone from Ziwan (紫▫), and ergosterol from Zhuling (猪苓) (Wu, Wang, et al., 2020). Therefore, ACE2 appears to be one of the major targets for TCM to exert therapeutic effects on COVID-19.

4.4. TCM regulation of $3CL^{pro}$ for the treatment of COVID-19

Coronavirus 3-chymotrypsin-like protease (known as Mpro, 3CL hydrolase or $3CL^{pro}$) is a three-domain (domains I to III) cysteine protease that is highly conserved among coronaviruses and required for proteolytic maturation of the coronaviruses (Dai et al., 2020; Elmezayen, Al-Obaidi, Sahin, & Yelekci, 2020; Zhang et al., 2020). Besides, $3CL^{pro}$ has no human homolog (Dai et al., 2020). Therefore, $3CL^{pro}$ is an attractive drug target for coronaviruses including SARS-CoV-2 (Dai et al., 2020; Elmezayen et al., 2020; Zhang, Lin, et al., 2020). Su et al. found that baicalin and baicalein, active ingredients of Huangqin (黄芩), were the first identified non-covalent, non-peptidomimetic inhibitors of SARS-

CoV-2 $3CL^{pro}$, effective in decreasing the replication of coronaviruses in a cell-based system, by interacting with two catalytic residues (the crucial S1/S2 subsites and the oxyanion loop) of the $3CL^{pro}$ to ensconce in the core of the substrate-binding pocket (Su et al., 2020). $3CL^{pro}$ was predicted to be the target of the active ingredients of JHQG (3-methoxy-glycerol, crude-glycerin and glycyrrhizin B,3-methoxy-glycerol, crude-glycerin and glycyrrhizin B) by network pharmacology prediction and high throughput molecular docking analyses (Shen et al., 2020). Chlorogenic acid, forsythoside A, and ephedrine were found to be the core active ingredients of JHQG that have strong affinity for $3CL^{pro}$ by visualization analysis, thereby inhibiting viral replication (Ren, Yin, et al., 2020). Network pharmacology and molecular docking analyses indicated that flavonoids and phytosterols are the two ingredients in XFBD that inhibit SARS-CoV-2 invasion and replication mainly by binding to $3CL^{pro}$, thereby exerting therapeutic effects on COVID-19 (Wang, Song, et al., 2020). Quercetin, luteolin, kaempferol as the active ingredients of HSBD, were predicted to have high affinity for $3CL^{pro}$, indicating effects of HSBD on viral replication and maturation. Liu and colleagues found that baicalein and ethanol extract of Huangqin (黄芩), inhibit $3CL^{pro}$ activity in vitro with activity assay using a peptide substrate (Thr-Ser-Ala-Val-Leu-Gln-pNA) according to the published procedure of SARS-CoV $3CL^{pro}$ assay (Liu et al., 2021). Besides, the docking model verified that baicalein binds well to the substrate binding site of $3CL^{pro}$ (Liu et al., 2021). The carbonyl group of baicalein was hydrogen bonded with the E166 backbone amide group of $3CL^{pro}$, while catalytic residues H41 and C145 of $3CL^{pro}$ were well covered by baicalein, accounting for baicalein's inhibitory effect on SARS-CoV-2 via $3CL^{pro}$ (Liu et al., 2021). In addition, patchouli alcohol, shionone,

and several other mediators, which represents one of the major pathological features of COVID-19 (Sinha, Matthay, & Calfee, 2020). IL-6, a proinflammatory cytokine, is a key mediator of the acute inflammatory response and the cytokine storm (Sinha et al., 2020; Turnquist, Ryan, Horikawa, Harris, & Harris, 2020; Zhang et al., 2020). Elevation in serum IL-6 levels correlates with ARDS, multi-organ failure, and other adverse clinical outcomes in COVID-19 (Moore & June, 2020). IL-6 has been shown to be a good biomarker for earlier detection of COVID-19 progression (Wang, Fei, Li, Zhao, & Yu, 2020), and a promising target for the treatment of COVID-19 (Montesarchio et al., 2020; Sinha et al., 2020). In addition to targeting ACE2 and $3CL^{pro}$, TCM has also been shown to modulate IL-6 to relieve COVID-19 symptoms. Network pharmacology was used by Niu et al. to identify the phytochemicals in TCM for the treatment of COVID-19 that regulates IL-6 (Liang et al., 2020). Quercetin, ursolic acid, luteolin, and rutin, active ingredients of the six recipes discussed in Section 2, have been shown to decrease IL-6 levels (Liang et al., 2020). Network pharmacology and molecular docking analyses indicate that XFBD may play a role in the treatment of COVID-19 by regulating IL-6 after viral infection of host cells, exerting anti-cytokine storm and anti-oxidation effects (Wang, Song, et al., 2020). Analyses applied to identification of molecular targets and mechanisms of HSBD in the treatment of COVID-19 indicate that compound–target network mainly contains 178 compounds and 272 corresponding targets, among which IL-6 is a key target (Tao et al., 2020).

5. Conclusion

TCM has a well-documented history for treating infectious disease. During the fight against COVID-19 in China, six TCM recipes of JHQG, LHQW, XFBD, HSBD, XBJ and LCDD have been shown to be most effective in treating patients with COVID-19. We have systematically reviewed the components, active ingredients, and the potential molecular mechanisms of the 6 TCM recipes in treating COVID-19 and infections by other viruses. The common components/active ingredients among the 6 recipes were also identified to represent most promising drug candidates, characterization of which may result in rapid development of novel therapeutics for the treatment of COVID-19. These ingredients may exert therapeutic effects on COVID-19 via targeting of ACE2, $3CL^{pro}$ and IL-6. Therefore, the key active ingredients of TCM recipes and their molecular mechanisms driving therapeutic efficacies on COVID-19, warrant in-depth and immediate investigation to help better manage the devastating disease of COVID-19.

Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

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