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Review

Review on the potential action mechanisms of Chinese medicines in treating Coronavirus Disease 2019 (COVID-19)

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ABSTRACT

The Coronavirus Disease 2019 (COVID-19) has been declared as a global pandemic, but specific medicines and vaccines are still being developed. In China, interventional therapies with traditional Chinese medicine for COVID-19 have achieved significant clinical efficacies, but the underlying pharmacological mechanisms are still unclear. This article reviewed the etiology of COVID-19 and clinical efficacy. Both network pharmacological study and literature search were used to demonstrate the possible action mechanisms of Chinese medicines in treating COVID-19. We found that Chinese medicines played the role of antivirus, anti-inflammation and immunoregulation, and target organs protection in the management of COVID-19 by multiple components acting on multiple targets at multiple pathways. AEC2 and 3CL protein could be the direct targets for inhibiting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Quercetin, kaempferol, luteolin, isorhamnetin, baicalein, naringenin, and wogonin could be the main active ingredients of Chinese medicines for the management of COVID-19 by targeting on AEC2 and 3CL protein and inhibiting inflammatory mediators, regulating immunity, and eliminating free radicals through COX-2, CASP3, IL-6, MAPK1, MAPK14, MAPK8, and REAL in the signaling pathways of IL-17, arachidonic acid, HIF-1, NF-κB, Ras, and TNF. This study may provide meaningful and useful information on further research to investigate the action mechanisms of Chinese medicines against SARS-CoV-2 and also provide a basis for sharing the “China scheme" for COVID-19 treatment.

1. Introduction

World Health Organization has declared the Coronavirus Disease 2019 (COVID-19) as a pandemic on March 14th, 2020. [1] As of May 12th, 2020, there were more than 4,218,000 confirmed cases of COVID-19 in 216 countries, areas, and territories, and over 290,000 people have lost their lives [2]. The number of cases and deaths rises continuously and rapidly every day. Even worse, the biggest challenge is that there are no proven therapies or vaccines against COVID-19, and there are significant research gaps in many other essential research and innovation areas. As one of the earliest affected countries, the outbreak in China has been well controlled, and it is nearing completion. Many countries and international organizations affirmed that China took active and effective measures. Chinese counterattacks can be replicated to fight the epidemic [3]. Among them, traditional Chinese medicine (TCM) has played an irreplaceable role and provided unique advantages in the management of this disease. Nevertheless, the underlying action mechanisms of Chinese medicines (CMs) are still unclear. In this paper, the possible action mechanisms of CMs in controlling COVID-19 were reviewed and analyzed. This outcome will help us to understand this disease more, develop effective methods to treat this disease, and benefit the world to control this disease.

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2. Etiology of COVID-19

COVID-19 is an acute respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and was first reported at the end of 2019 in Wuhan, China. The clinical symptoms are mainly fever, dry cough, and fatigue. A few are accompanied by nasal congestion, runny nose, sore throat, muscle pain, and diarrhea [4]. Severe patients have high levels of cytokines and chemokines in plasma [5], which can easily lead to cytokine storm. Acute respiratory distress syndrome (ARDS), shock, multiple organ dysfunction syndrome (MODS), and fulminant myocarditis appear in severe and death patients of COVID-19 [5–8].

3. Efficacy of CMs in treating COVID-19

TCM has played an essential role in treating epidemic diseases in the long history of China, and its theories and methods have been recorded in many classic medical books of TCM, such as the *Yellow Emperor's Inner Canon* and the *Treatise on Cold Damage*. The efficacies of these methods were confirmed again in combating SARS in 2003 [9]. Therefore, TCM is a valuable resource for drug discovery against COVID-19 [10].

In China, the treatment protocol of COVID-19 emphasizes the combination of TCM with conventional therapy [11]. The current practice has demonstrated that TCM intervention is essential and effective in the management of COVID-19, showing by the improvement of the cure rate, shortened disease course, delayed disease progression, and reduced mortality rate [12,13]. It was reported that the overall effective rate reached over 90 % in 74187 confirmed COVID-19 cases who received TCM treatment [14]. Lou [15] reported that the change of hematology is positive in COVID-19 patients treated with TCM. A prospective multicenter open-label randomized controlled trial also confirmed the efficacy of Lianhua Qingwen capsule in ameliorating the clinical symptoms of COVID-19 patients, including fever, fatigue, and cough [16]. Several retrospective and controlled clinical studies have also reported that TCM treatment effectively improved the fever, sweating, cough, headache, shortness of breath, chest distress, nausea, and diarrhea in COVID-19 patients [17–20]. The chest radiogram has been improved significantly as well [21]. The levels of ESR, CRP, and IL-6 were significantly decreased, and the level of IFN-γ was increased in the group received both TCM and conventional treatments in comparison with the group only received conventional treatment (antibiotics and antiviral therapy) [22]. TCM was also helpful to the elderly [23], children [24], and severe COVID-19 patients [25,26].

TCM is a combination of philosophy and ancient disease control and treatment experiences with proved efficacies for different diseases. The overall concept and treatment methods are based on syndrome differentiation, which is the most significant and essential feature. In China, doctors are recommended to use different CMs and strategies for the prevention, treatment, and recovery of COVID-19 at its different stages. The frequently used CMs for COVID-19 are summarized in Table 1 [27–29]. At the press conference on COVID-19 of the State Council of China, three-medicines and three-decoctions of TCM (TMTD), *i.e.*, Jinhua Qinggan granules, Lianhua Qingwen capsule, Xuebijing injection, and Qingfei Paidu decoction, Huashi Baidu decoction, Xuanfei Baidu decoction were emphasized for their remarkable clinical effects in controlling COVID-19 during this epidemic [15]. Especially, Lianhua Qingwen capsule (granules) and Huashi Baidu granules have been officially approved for reliving the fever, cough, and fatigue of mild and moderate COVID-19 patients by the China State Drug Administration recently [30,31]. According to TCM theories, these medications have five different functions, *i.e.*, treating exterior syndromes, resolving dampness, clearing heat, replenishing deficiency, and resolving phlegm, cough, and asthma [32]. According to the medicinal properties of CMs used at different stages of COVID-19, the possible mechanisms of CMs for mild cases could be antiviral and symptom relief, for moderate cases could be anti-inflammation and immune regulation, and for severe and critical cases could be antiviral, inhibiting cytokine storm, and protecting target organs. However, the exact mechanisms must be predicted, analyzed, and validated by network pharmacology analysis, animal studies, and eventually clinical trials. In this article, we mainly summarized and analyzed the possible action mechanisms predicted by network pharmacology analysis from others and us for these CMs that have been used in clinics with reported efficacies recently, including TMTD and others.

4. Possible action mechanisms of CMs in treating COVID-19

Since the accessibility to SARS-CoV-2 is very limited, the current researches mainly utilized virtual simulation technologies, such as network pharmacology, which can predict the potential bioactive components and action mechanism with a high probability as we have done in a classic Chinese medicine formula Gualuo Xiebai decoction [33]. To understand the current status of researches on the mechanisms of CMs in treating COVID-19, we searched several medical databases, including Web of Science, PubMed, and Chinese National Knowledge Infrastructure (CNKI), from 2019 till now with the subjects of Chinese medicines, mechanism, and COVID-19 or SARS-CoV-2. From the retrieved literature, we further screened the literature by selecting computer-simulated or experimental researches, such as network pharmacology, *in vivo* or *in vitro* studies on COVID-19 or SARS-CoV-2 with recommended formulas or Chinese patent medicines in the Diagnosis and Treatment Protocol for COVID-19 of China [4], and excluding duplicates, reviews, case reports, and studies on other viruses or diseases, *etc.* Finally, two *in vitro* study in English, twenty-five network pharmacology studies in Chinese and one in English were selected and analyzed. The result showed that the action mechanisms of CMs in treating COVID-19 were multi-dimensional (Table 1 and Fig. 1); the detailed mechanisms were described below.

4.1. Direct action on SARS-CoV-2

According to the literature [61–63], angiotensin-converting enzyme 2 (ACE2) and 3C-like protease (3CL pro) can be the critical targets for antiviral drug design. CMs could target ACE2 to prevent SARS-CoV-2 from entering into host cells or target 3CL pro to inhibit the replication and assembly of the virus in cells.

Li [46] reported that the Lianhua Qinwen capsule significantly and dose-dependently inhibited the replication of SARS-CoV-2 with an IC_{50} value of 411.2 μg/mL in Vero E6 cells that were infected with 100 $TCID_{50}$ of SARS-CoV-2 using cytopathic effect and plaque reduction assay. The number of virions of cells treated with Lianhua Qinwen capsule at 600 μg/mL was significantly reduced compared with that of control cells under the transmission electron microscope. Wang [47], Ling [48] and Ye [49] speculated that quercetin, kaempferol, luteolin, aloe-emodin, rutin, forsythoside E, and hyperoside in Lianhua Qinwen could be the active ingredients in inhibiting SARS-CoV-2 through JAK-STAT signaling pathway by network pharmacology analysis and computer-aided drug design (CADD) of virtual screening.

Wu [35], Xu [37], and Fan [39] reported that the mechanisms of Qingfei Paidu decoction in the treatment of COVID-19 were to inhibit the invasion and replication of virus directly. Patchouli alcohol (*Pogostemonis Herba*), saikosaponin B (*Bupleuri Radix*), ergosterol (*Polyporus*), shionone (*Asteris Radix et Rhizoma*), 23-acetate alisol B (*Alismatis Rhizoma*) might act directly on the SARS-CoV-2 3CL pro to block virus proliferation. In contrast, patchouli alcohol, tussilagone (*Farfarae Flos*), ergosterol, asarinin (*Asari Radix et Rhizoma*), ephedrine hydrochloride (*Ephedrae Herba*), and shionone (*Asteris Radix et Rhizoma*) might act on host cell ACE2 to block the invasion.

By using molecule docking and network pharmacology analyses, Du [41] and Deng [42] screened out licorice glycoside E, naringenin, robinin, kaempferol, (2R)-7-hydroxy-2-(4-hydroxyphenyl) chroman-4-

Table 1
Summary of studies on the action mechanisms of Chinese medicines recommended in the Diagnosis and Treatment Protocol for COVID-19 of China.

Chinese medicine	Constituent	Predicted active ingredient	Predicted target	Signaling pathway and mechanism			Reference
				Anti- SARS-CoV-2	Anti- inflammation and immunoregulation	Target organs Protection	
Huashi Baidu decoction	14 herbs, including *Ephedrae Herba, Armeniacae Semen Amarum, Glycyrrhizae Radix et Rhizoma, Pogostemonis Herba, etc.*	baicalein, licorice phenol, *etc.*	IL6, MAPK3, MAPK8, CASP3, IL10, MAPK1, CCL2, IL2	inhibiting the virus replication	IL-17 signaling pathway, NF-κB signaling pathway, Toll-like receptor signaling pathway, renin-angiotensin system		SUN, et al. [31]
Qingfei Paidu decoction	21 herbs, including *Pogostemonis Herba, Glycyrrhizae Radix et Rhizoma, Ephedrae Herba, Armeniacae Semen Amarum, Scutellariae Radix, Asteris Radix et Rhizoma,* and *Polyporus, etc*	quercetin, luteolin, kaempferol, beta-sitosterol, naringenin, isorhamnetin, patchouli alcohol, ergosterol, shionone, tussilagone, 3,4-dicaffeoylquinic acid, 4,5-dicaffeoylquinic acid, baicalein, glycyrrhizic acid, *etc*	MAPK8, IL-6, COX-2, mPGES-1, AKT1, MAPK1, JUN, TNF, EGFR, CASP3, IL1B, PTGS2, NOS2, MAPK14, *etc*	inhibiting the virus adsorption and replication	arachidonic acid metabolism pathway, TNF, NF-κB, MAPK, non-small cell lung cancer, small cell lung cancer, IL17, tuberculosis, Th17, pertussis signal pathway, TLR, *etc*	TNF, NF-κB signaling pathways, PI3K-Akt pathway, MAPK pathway, T-cell pathway, B cell pathway, Ras, apoptosis, *etc*	REN, et al. [34] et al. [35] ZHAO, et al. [36] XU, et al. [7] XU, et al. [8] FAN, et al. [9] YANG, et al. [40]
Huoxiang Zhengqi capsule	11 herbs, including *Pogostemonis Herba, Magnoliae officinalis Cortex, Poria, Arecae Pericarpium, etc*	quercetin, wogonin, isorhamnetin, irisolidone, robinin, stigmasterol, kaempferol, licorice glycoside E, *etc*	PTGS2, HSP90AB1, mPGES-1, LTA4H, NOS2, PTGS2, *etc*	inhibiting the virus invasion and replication	arachidonic acid metabolic pathway, small cell lung cancer, non-small cell lung cancer, T-cell, PI3K-Akt, *etc*		DU, et al [41] DENG, et al. [42] REN, et al. [34]
Jinhua Qinggan granules	12 herbs, including *Lonicerae Japonicae Flos, Gypsum Fibrosum, Ephedrae Herba, Armeniacae Semen Amarum, Fritillariae Thunbergii Bulbus, Forsythiae Fructus, etc*	quercetin, lonicerin, naringenin, lappaol D, baicalein, isorhamnetin, β-sitosterol, stigmasterol, coptisine, wogonin, kaempferol, oroxylin A, formononetin, glabridin, licochalcone A, licochalcone B, *etc*	COX-2, sEH, 5-LOX, PTGS2, AKTI, HSP90AA1, RELA, MAPK1, CASP3, TP53, ALB, TNF, IL6, MAPK8, MAPK14, *etc*	inhibiting the virus invasion by Kaposi sarcoma-associated herpesvirus infection, hepatitis C, *etc.*	arachidonic acid metabolism, IL17, TNF, AGE-RAGE, PI3K-Akt, HIF-1, TNF, Toll-like receptor, MAPK, NF-κB signaling pathways	Ras signaling pathway	SIMAYI, et al. [43] REN, et al. [34] SHEN, et al. [44] MAO, et al. [45]
Lianhua Qingwen capsule (granules)	13 herbs, including *Pogostemonis Herba, Forsythiae Fructus, Lonicerae Japonicae Flos, Ephedrae Herba, Armeniacae Semen Amarum, Isatidis Radix,* and *Rhei Radix et Rhizoma, etc*	quercetin, luteolin, kaempferol, rutin, naringenin, β-sitosterol, wogonin, lonicerin, lappaol D. aloe-emodin, 18β-glycyrrhetinic acid, indigo, forsythoside E, hyperoside, formononetin, loganic acid, salidroside, *etc*	MAPK8, IL 6, COX-2, sEH, RELA, cPLA2α, mPGES-1, TNF, DPP4, IL1B, CASP3, MAPK1, EGFR, BAX, BCL2, JUN, PIK3CG, *etc*	inhibiting the virus infection and replication by JAK-STAT signaling pathway	arachidonic acid metabolism, Toll-like receptor, JAK-STAT, T cell receptor, TNF, VEGF, Fc epsilon RI, B cell receptor, ErbB, MAPK, natural killer cell mediated cytotoxicity, AGE-RAGE, Kaposi, IL-17, hepatitis B, *etc.*	renin-angiotensin system	LI, et al. [46] REN, et al. [34] WANG, et al. [47] LING, et al. [48] Ye, et al. [49] WANG, et al. [50]
Xuebijing injection	5 herbs, including *Carthami Flos, Paeoniae Radix Rubra, Chuanxiong Rhizoma, Salviae Miltiorrhizae Radix et Rhizoma,* and *Angelicae Sinensis Radix*	quercetin, rutin, kaempferol, ferulic acid, apigenin, luteolin, gallic acid, hydroxysafflor yellow A, senkyunolide I, salvianolic acid B, rosmarinic acid, *etc*	LTA4H, 12-LOX, IL2, cPLA2, IL6, RELA, TNF, PTGS2, IL10, NOS2α, CASP3, MAPK1, *etc.*	inhibiting the virus replication through PI3K-Akt signal pathway	arachidonic acid metabolism pathway, HIF-1, PI3K-Akt, VEGF, influenza A, NF-κB, hepatitis B, hepatitis C, inflammatory bowel disease, IL17, *etc.*	NF-κB signaling pathway	REN, et al. [34] SHI, et al. [51] HE, et al. [52] KONG, et al. [53]
Reduning injection	3 herbs, including *Lonicerae Japonicae Flos, Artemisiae Annuae Herba,* and *Gardeniae Fructus*	quercetin, luteolin, lonicerin, isorhamnetin, salicylic acid	COX-2, sEH, IL6, CCL2, CASP3, IL4, MAPK1, RELA, FOS, NOS2, IL1B, CXCL10, MAPK14, EGFR, *etc.*		arachidonic acid metabolism pathway, IL-17 signaling pathway, C-type lectin receptor signaling pathway, HIF-1 signaling pathway and NF-κB signaling pathway, *etc.*	IL-17 signaling pathway	REN, et al. [34] SUN, et al. [54]

(*continued on next page*)

Table 1 (*continued*)

Chinese medicine	Constituent	Predicted active ingredient	Predicted target	Signaling pathway and mechanism			Reference
				Anti- SARS-CoV-2	Anti- inflammation and immunoregulation	Target organs Protection	
Tanreqing injection	5 herbs, including *Lonicerae Japonicae Flos, Forsythiae Fructus,* and *Scutellariae Radix, etc*	lonicerin, quercetin, kaempferol, luteolin, baicalein, wogonin, *etc.*	COX-2, sEH, LTA4H, IL6, IL1B, IL10, MAPK1, IL4, CXCL8, MAPK14, EGFR, CXCL10, *etc.*	inhibiting the virus replication	arachidonic acid metabolism pathway, Th 17 cell differentiation, MAPK, EGFR, TNF signal pathway, *etc.*		REN, et al. [34] KONG, et al. [55]
Shufeng Jiedu capsule	8 herbs, including *Polygoni Cuspidati Rhizoma et Radix, Forsythiae Fructus, Isatidis Radix,Bupleuri Radix, Patrinia Herb, Verbenae Herb, Phragmits Rhizoma, Glycyrrhizae Radix et Rhizoma.*	quercetin, luteolin, wogonin, kaempferol, β-sitosterol, acacetin, puerarin, licochalcone A, isorhamnetin, 5,7,4′-trihydroxy-8-methoxyflavone, β-sitosterol, 6-(3-oxoindolin-2-ylidene) indolo [2,1-b] quinazolin-12-one, bicuculline, licoisoflavanone, *etc.*	IL6, IL1B, CCL2, IL2, MAPK8, MAPK1, MAPK14, CASP3, FOS, ALB, IL4, IL1B, EGFR, FOS, AR, BCL2L, NOS2, F10, PTGS2, PTGS1, ESR1, DPP4, *etc.*		HIF-1, NF-κB, IL-17, EGFR, MAPK, endocrine resistance, tyrosine kinase resistance, platinum drug resistance, antifolate resistance, arginine biosynthesis, sphingolipid, human cytomegalovirus infection, Kaposi's sarcoma, small cell lung cancer, *etc.*	endocrine resistance	XU, et al. [56] SHEN, et al. [57] CAO, et al. [58]
Xuanfei Baidu decoction	13 herbs, including *Ephedrae Herba, Armeniacae Semen Amarum, Coicis Semen, Glycyrrhizae Radix et Rhizoma, Pogostemonis Herba, etc.*	artemisinin, glycyrrhizic acid, pogostone, amygdalin, emodin, naringenin, gentisic acid, atractylodin, ephedrine, descurainolide A, verbenalin, *etc.*	TNF, IL6, IFNG, JAK1, STAT1, TP53, CASP, ICAM1, ITGB2, IL10		tuberculosis, TNF, toxoplasmosis, IL-17, salmonella infection, pertussis, malaria, leishmaniasis, influenza A, *etc.*		WANG, et al. [59]
Shenmai injection	2 herbs, including *Ginseng Radix et Rhizome Rubra, Ophiopogonis Radix*	ophiopogonin D′, ophiopogonin D, ginsenoside Rg2, ginsenoside Rb2, phiopogon A, sanchinoside Rd, ginsenoside Re, *etc.*	IL6, GAPDH, ALB, TNF, MAPK1, MAPK3, TP53, EGFR, CASP3, *etc.*		HIF-1, TNF, sphingolipid, Toll-like receptor, neurotrophin, VEGF, apoptosis, Ras, PI3K-Akt, prolactin signaling pathway		HAN, et al. [60]

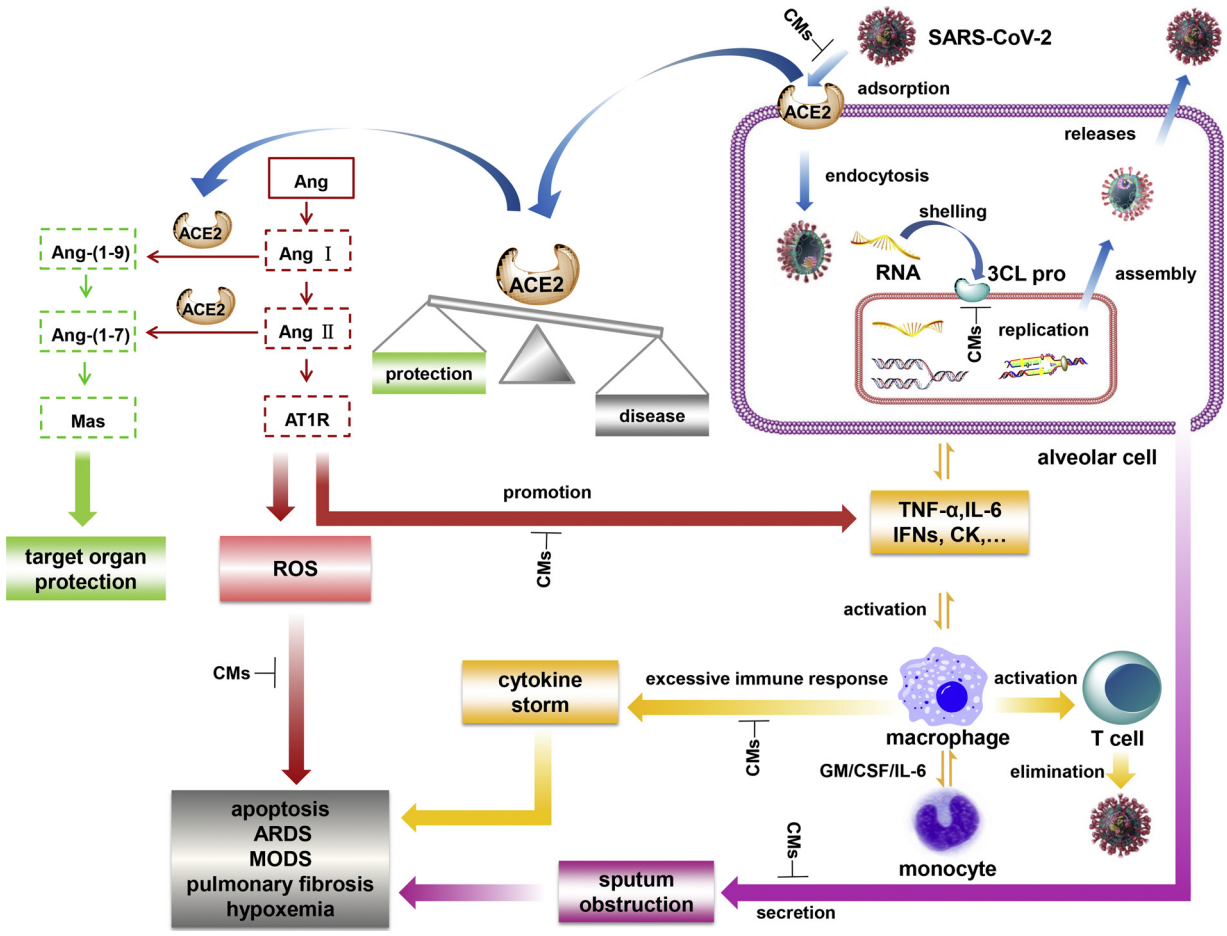

Fig. 1. The potential action mechanisms of Chinese medicines in treating COVID-19. Blue arrows: Chinese medicines (CMs) might directly inhibit SRAS-CoV-2 adsorption and replication by interfering virus's binding to ACE2 and 3CL pro. CMs can also indirectly protect target organs by inhibiting the binding of SRAS-CoV-2 to ACE2, regulating the balance of ACE2 in the body through the Ang / Mas pathway. **Red arrows**: CMs might reduce the production of inflammatory mediators, protect target organs, and relieve the deterioration of COVID-19 by anti-inflammatory and anti-oxidant effects through affecting the Ang / AT1R pathway. **Yellow arrows**: CMs might play an anti-inflammatory and immune regulatory role to prevent cytokine storm. **Purple arrows**: CMs also has an expectorant effect of relieving airway obstruction.

ketone, quercetin, isorhamnetin and irisolidone from Huoxiang Zhengqi as potential 3CL pro inhibitors, which could inhibit SARS-CoV-2 replication by targeting on PIK3CG and E2F1 through PI3K-Akt signaling pathway. Besides, based on traditional Chinese medicine systems pharmacology database and analysis platform (TCMSP) and literatures, SHI [51] constructed and analyzed the mechanisms of Xuebijing injection and found rosmarinic acid in this injection could inhibit the virus replication through PI3K-Akt signal pathway as well.

Simayi [43] and Shen [44] predicted the active ingredients of Jinhua Qinggan granules based on network pharmacology and molecular docking. Kaempferol, quercetin, luteolin, baicalein, oroxylin A, licochalcone B, and glyasperin C were proposed to bind with ACE2 and regulate multiple signal pathways, such as PTGS2, BCL2, CASP3, Kaposi sarcoma-associated herpesvirus infection, hepatitis C, human cytomegalovirus infection, Epstein-Barr virus infection, and measles.

Kong [55] showed the results of Tanreqing injection against SARS-Cov-2 by molecular docking. Kaempferol, quercetin, baicalein, luteolin, and rhubarb wogonin had a good affinity with SARS-CoV-2 3CL hydrolase.

By using molecular docking, Sun [31] found baicalein, licorice phenol, and other twelve main active ingredients in Huashi Baidu decoction could bind to Mpro and ACE2, which could inhibit SARS-CoV-2 replication and block the virus binding sites.

4.2. Anti-inflammation and immunoregulation

Virus-infected alveolar cells release signals to recruit and activate immune cells. These immune cells secrete a variety of cytokines and chemokines to recruit more immune cells to the lesion site. The activated immune cells destroy the virus by releasing inflammatory mediators and phagocytosis. However, the excessive immune responses initiate a "cytokine storm", which causes many immune cells and secretions in the lungs of COVID-19 patients. Cytokine storm alters vascular permeability, blocks airways, causes edema, hypoxia, and target organ damage, *etc.* The occurrence of cytokine storm in patients with COVID-19 is an essential cause of exacerbation and even death [64,65]. CMs can play a regulatory role in the causes, processes, and other aspects of the cytokine storm by modulating the release of cytokines, the functions of macrophages, monocytes and neutrophils, the permeability of pulmonary vessels, and the activities of T cells [67].

Wu [35], Zhao [36], Xu [37], Xu [38] and Fan [39] applied network pharmacology to analyze Qingfei Paidu decoction and found that quercetin, luteolin, kaempferol, naringenin, beta-sitosterol, isorhamnetin, baicalein, and tussilagone could be the main active ingredients. These ingredients could suppress cytokines release, alleviate excessive immune responses and eliminate inflammation by regulating AKT1, MAPK1, MAPK3, MAPK8, MAPK14, IL-6, RELA, STAT1, JUN, and immune-related pathways, such as Th17 cell differentiation pathway, T cells, and B cells pathway, and the function of the cytokines

related pathways, such as TNF signaling pathways, NF-κB, MAPK signal pathway, VEGF signaling pathways, HIF-1 signaling pathway and TLRs signaling pathways. Yang [40] also verified that the therapeutic effects of Qingfei Paidu decoction might result from glycyrrhizic acid mediated anti-inflammatory effects by suppressing IL-6 production in macrophage.

Basing on the pharmacophore models, Ren [34] reported that Huoxiang Zhengqi capsules, Jinhua Qinggan granules, Lianhua Qingwen capsules, Qingfei Paidu decoction, Xuebijing injection, Reduning injection, and Tanreqing injection could prevent SARS-CoV-2 *via* regulating cytokines through the arachidonic acid metabolic pathway.

Shen [44] and Mao [45] showed that kaempferol, naringenin, wogonin, neobaicalein in Jinhua Qinggan granules well docked with specific target proteins of SARS-CoV-2. The core target proteins such as AKTI, HSP90AA1, ELA, IL6, TNF, and MAPKs are mainly related to inflammation and immunoregulation.

Li [46] reported that Lianhua Qinwen markedly reduced pro-inflammatory cytokines (TNF-α, IL-6, CCL-2/MCP-1, and CXCL-10/IP-10) production in a concentration-dependent manner in SARS-CoV-2 infected Huh-7 cells at the mRNA levels by real-time quantitative PCR assays. Wang [47] Ling [48] and Wang [50] speculated that quercetin, luteolin, and kaempferol in Lianhua Qinwen could be involved in immune regulation on the targets of COX-2, ILs, CASP3, EGFR, DPP4, CALM1, RELA, and MAPKs through the signaling pathways of Chagas disease (American trypanosomiasis), Toll-like receptor, JAK-STAT, T cell receptor, TNF, AGE-RAGE, Kaposi, IL-17, human cytomegalovirus infection, and hepatitis B. From the constructed component-target-pathway network, Ye [49] showed that formononetin, rutin, emodin 8-O-β-D-glucoside, hyperoside, loganic acid and salidroside in Lianhua Qinwen could improve human immunity through T cell and B cell receptor signaling, natural killer cell mediated cytotoxicity, and anti-inflammatory pathways including Fc epsilon RI, ErbB, and MAPK signaling pathways.

Besides, Shi [51], He [52], and Kong [53] speculated that Xuebijing injection played an anti-inflammatory effect by NF-κB, VEGF, HIF-1, IL17, and PI3K-Akt signal pathway. The active ingredients of Xuebijing injection, such as rosmarinic acid, quercetin, apigenin, luteolin, hydroxysafflor yellow A, chlorogenic acid, and salvianolic acid B, well targeted RELA, TNF, PTGS2, NOS2, PTGS2, MAPK1, and IL6.

Sun [54] reported that quercetin, luteolin, rutin, and isorhamnetin in Reduning injection played the effects of anti-inflammation, antivirus, and immunomodulation for the treatment of lung injury in COVID-19. It could act on CASP3, IL6, MAPK1, CCL2, and other targets through IL-17, C-type lectin receptor, and HIF-1 signaling pathways.

Through enrichment analysis of KEGG signaling pathway, Kong [55] revealed that multiple targets of Tanreqing injection could play a role in reducing overproduced cytokines, alleviating the excessive immune response and eliminating inflammation by regulating immune-related signaling pathways, such as Th17 cell differentiation, MAPK, EGFR, and TNF.

In Shufeng Jiedu capsule, Xu [56], Shen [57], and Cao [58] reported that quercetin, luteolin, wogonin, kaempferol, acacetin, isorhamnetin, 5,7,4'-trihydroxy-8-methoxyflavone, β-sitosterol, and licochalcone A could be the active ingredients. These ingredients might target on IL6, IL1B, CCL2, MAPK8, MAPK1, MAPK14, CASP3, FOS, ALB, CALM1, NOS2, PTGS2, DPP4, and PTGS2 through endocrine resistance, EGFR tyrosine kinase resistance, platinum drug resistance, antifolate resistance, arginine biosynthesis, HIF-1, NF-κB, MAPK, IL-17, and small cell lung cancer signaling pathways.

In addition, Wang [59] screened artemisinin, glycyrrhizic acid, pogostone, and amygdalin as the potential active ingredients of Xuanfei Baidu decoction from the databases of TCM-PTD, ETCM, TCMSP, and SymMap. TNF signaling pathway, IL-17 signaling pathway, and tuberculosis related pathway could be the key for treating COVID-19.

Sun [31] speculated that the anti-inflammatory effect of Huashi Baidu decoction in treating COVID-19 could involve IL6, MAPK3 and MAPK8, IL-17, NF-κB, Toll-like receptor signaling pathway, and the renin-angiotensin system.

By molecular docking and network analysis, Han [60] showed that ophiopogonins, ginsenosides, and sanchinoside Rd might be the main ingredient of Shenmai injection to treat COVID-19 by targeting on IL-6, IL-2, and TNF.

4.3. Target organs protection

ACE2 can catalyze the splitting of angiotensin (Ang) I and Ang II into Ang (1-9) and Ang (1-7), respectively, and regulate ACE2-Ang (1-7)-Mas axis to protect the acute lung injury [66]. However, ACE2 is also a cell receptor of SARS-CoV-2 in the human body [68]. The combination of SARS-CoV-2 and ACE2 [69] disrupts the balance between Ang I/ Ang II and Ang (1-9)/Ang (1-7), thereby generate many free radicals, which can change the permeability of cell membranes and lead to the organ damages. ZHOU [70] speculated that SARS-CoV-2 could infect type II alveolar epithelial cells through ACE2, thus destroying the lung tissue and air-blood barrier. Then, the virus continued to infect other organs through ACE2, such as the heart, kidneys, and liver by blood circulation. It further triggered an excessive immune response, such as the imbalance of T-helper-1 (Th1) and Th2 cells, which produced numerous inflammatory cytokines, causing a cytokine storm and leading to MODS ultimately. CMs can play a direct or indirect role in protecting target organs by inhibiting the binding of the virus to ACE2 to produce anti-inflammation, anti-oxidation, anti-fibrosis, and expectorant action [71].

Qingfei Paidu decoction targeted lungs [36] and protected multiple organs. Wu [35], Xu [38], and Fan [39] speculated that Qingfei Paidu decoction might protect the lung from injury by regulating TNF, PI3K-Akt, Ras, MAPK, B cell receptor, and apoptosis signaling pathways. Mao [45] found that Jinhua Qinggan granules played a role in regulating apoptosis *via* PI3K-Akt, MAPK, and Ras pathways. Ling [48] reported that 18β-glycyrrhetinic acid, stigmasterol, indigo, β-sitosterol, luteolin, quercetin and naringenin in Lianhua Qingwen Prescription might target on ACE2 and protect the target organs of COVID-19 through the renin-angiotensin pathway. Xu [56] predicted that MAPK8, MAPK1, MAPK14, FOS, CASP3, endocrine resistance, EGFR tyrosine kinase resistance, platinum drug resistance, antifolate resistance, arginine biosynthesis, and MAPK signaling pathways could be involved in the inhibition of cell apoptosis and pulmonary fibrosis by Shufeng Jiedu capsule.

4.4. Common potential active ingredients and action mechanisms of CMs for treating COVID-19

From the above-reviewed researches, we can see that there are some ingredients and action mechanisms in common for these CMs used for treating COVID-19, which could be important for these CMs to exert their effect and drug development. Therefore, we further calculate the frequencies of these ingredients and action mechanisms that appeared in these reports. The results (Table 2) show that quercetin, kaempferol, luteolin, isorhamnetin, baicalein, naringenin, wogonin (the last three are in the same rank) are the top five ingredients; AEC2 and 3CL protein could be the potential direct targets for anti-SARS-CoV-2; COX-2, CASP3, IL-6, MAPK1, MAPK14, MAPK8 and RELA (the last three are in the same rank) are the top five targets; and IL-17, arachidonic acid metabolic pathway, HIF-1, NF-κB, Ras, and TNF (the last four are in the same rank) are the top five signaling pathways. These ingredients, targets, and signaling pathways could be the major players in the management of COVID-19 by using TCM and should be focused on in future research and drug development.

Although the currently available researches have covered the major formulae and medications recommended in the Diagnosis and Treatment Protocol for COVID-19 of China and generated some useful

Table 2
Frequency analysis of the medications recommended in the Diagnosis and Treatment Protocol for COVID-19 of China.

Decoction piece	Frequency*	Active ingredient	Frequency*	Target	Frequency*	Signaling pathway	Frequency*
Glycyrrhizae Radix et Rhizoma	7	quercetin	9	ACE2	13	IL-17	8
Armeniacae Semen Amarum	5	kaempferol	8	3CL pro	13	arachidonic acid metabolic pathway	7
Ephedrae Herba	5	luteolin	7	COX-2	11	HIF-1	6
Gypsum Fibrosum	5	isorhamnetin	6	CASP3	10	NF-κB	6
Pogostemonis Herba	5	baicalein	5	IL6	10	Ras	6
Forsythiae Fructus	4	naringenin	5	MAPK1	9	TNF	6
Lonicerae Japonicae Flos	4	wogonin	5	MAPK14	6	MAPK	5
Artemisiae annuae Herba	3	ergosterol	4	MAPK8	6	PI3K-Akt	5
Atractylodes Rhizoma	3	lonicerin	4	RELA	6	Toll-like receptor	5
Pinelliae Rhizoma	3	tussilagone	4	EGFR	5	hepatitis B related	4
Poria	3	β-sitosterol	4	IL2	5	small cell lung cancer related	4
Scutellariae Radix	3	rutin	3	LTA4H	5	T cell receptor signaling pathway	4
Bupleuri Radix	2	stigmasterol	3	NOS2	5	apoptosis	3
Citri reticulatae Pericarpium	2	7-methoxy-2-methyl isoflavone	2	TNF	5	human cytomegalovirus infection related	3
Descurainiae Semen, Lepidii Semen	2	acacetin	2	12-LOX	4	influenza A related	3
Isatidis Radix	2	chlorogenic acid	2	CCL2	4	non-small cell lung cancer related	3
Magnoliae officinalis Cortex	2	formononetin	2	COX-1	4	AGE-RAGE	2
Menthae haplocalycis Herba	2	hydroxysafflor yellow A	2	IL10	4	B cell receptor	2
Paeoniae Radix Rubra	2	licochalcone A	2	IL1B	4	Chagas disease (American trypanosomiasis)	2
Phragmitis Rhizoma	2	licorice glycoside E	2	IL4	4	EGFR tyrosine kinase resistance	2
Polygonum cuspidatum Rhizoma et Radix	2			PPARG	4	hepatitis C related	2
Rhei Radix et Rhizoma	2			sEH	4	Kaposi sarcoma-associated herpesvirus infection	2
Verbenae Herba	2			STAT1	4	pertussis related	2
Zingiberis Rhizoma	2			TP53	4	Th17 cell differentiation	2
				AKT1	3		
				ALB	3		
				ICAM1	3		
				MAPK3	3		
				mPGES-1	3		

Note: listed only if frequency ≥ 2 for decoction piece, active ingredient, and signaling pathway and ≥ 3 for target.

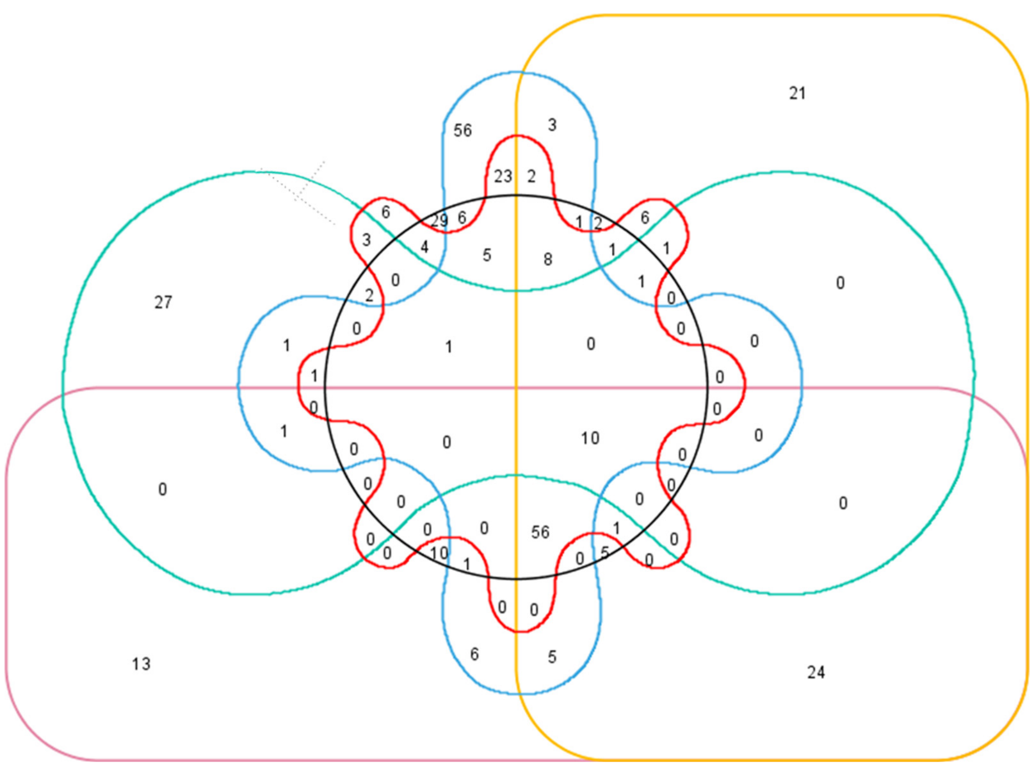

Fig. 2. The Venn diagram analysis of the three-medicines and three-decoctions. Pink route: Jinhua Qinggan granules; **Green route**: Xuebijing injection; **Blue route**: Qingfei Paidu decoction; **Red route**: Haushi Baidu decoction; **Black route**: Xuanfei Baidu decoction; **Yellow route**: Liianhua Qingwen capsule.

information, these researches only analyzed these formulae and medications individually. The results of these researches could reflect more on the unique features of individual formula and medication and less on the general features of these formulae and medications. To understand the general features of these formulae and medications, we selected TMTD to screen the common components and then analyzed the targets and signaling pathways that these components may act on using networking analysis. The common components of TMTD were generated by using the SymMap database (https://www.symmap.org/) and TBtools software (V0.665). The results (Fig. 2) shows that there are total 401 compounds in TMTD, of which ten compounds are shared by the six formulae of TMTD, they are ursolic acid, thymol, sucrose, rutin, physcion, oleanolic acid, caffeic acid, β-terpinene, β-sitosterol, and β-elemene. We believe that the common action mechanisms of TMTD may exist in these ten compounds. Therefore, we further predicted the possible targets and signaling pathways that the ten compounds may act on by network pharmacology analysis. The results show that the potential targets were FGF2, BCL2L1, MAPK8, IL6, SRC, JUN, PTGS2, IL1B, FOS, CASP3, REAL, VEGFA, CDK2, TP53, NFKBIA, CDKN1A, CSF2, CASP9, CAT, STAT3, CCND1, CASP1, FASLG, CASP8, and INS and the possible signaling pathways are apoptosis, NOD-like receptor, FoxO, Toll-like receptor, p53, MAPK, cytosolic DNA-sensing, RIG-I-like receptor, VEGF, and Jak-STAT signaling pathways. We also constructed a network to demonstrate the relationship among formulae, component Chinese medicines, active compounds, possible targets, possible signaling pathways, and possible action mechanisms with Cytoscape3.8.0 software (Fig. 3). The network shows that the common action mechanisms of TMTD in the treatment of COVID-19 could be related to signal transduction, immune system, and cell growth and death.

By comparing the results of above two strategies of network pharmacology analysis on the useful formulae and medications of TCM in treating COVID-19, we found that although the common compounds are different, the possible action mechanisms are overlapped with each other, implying that different compounds may act on same or similar targets or pathways. This gives TCM redundant mechanisms to treat diseases and also explains why different TCM formulae with different composition can treat the same disease.

5. Conclusion and prospect

Taken together, the practice in controlling the outbreak in China has proved the clinical efficacy and advantage of integrated TCM and Western medicine in treating COVID-19. Existing clinical data, *in silico* study, and literature analysis confirmed that the possible mechanisms of CMs were antivirus, anti-inflammation, immune regulation, and organ protection through multiple components acting on multiple targets at multiply pathways for the treatment of COVID-19. Nevertheless, the current understanding of the mechanisms of CMs is mainly produced from virtual simulation through molecular docking and network pharmacology analysis. The focus and strategy in different research are somehow different; the ingredients, targets, and pathways predicted in these researches might have certain limitations. To confirm these predicted mechanisms, well designed *in vitro* cell experiments and *in vivo* animal studies based on these predictions are needed. Importantly, the multiple omic technologies, such as proteomics, metabolomics, genomics, should be applied to analyze the biofluid and tissue samples collected from COVID-19 patients who received TCM treatment in well designed and controlled clinical trials to verify these mechanisms [72].

Author contributions

HZ and YX supervised all research and revised the manuscript. YFH and FH collected information. CB performed networking analysis. YFH and HZ analyzed the data and prepared the manuscript.

Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

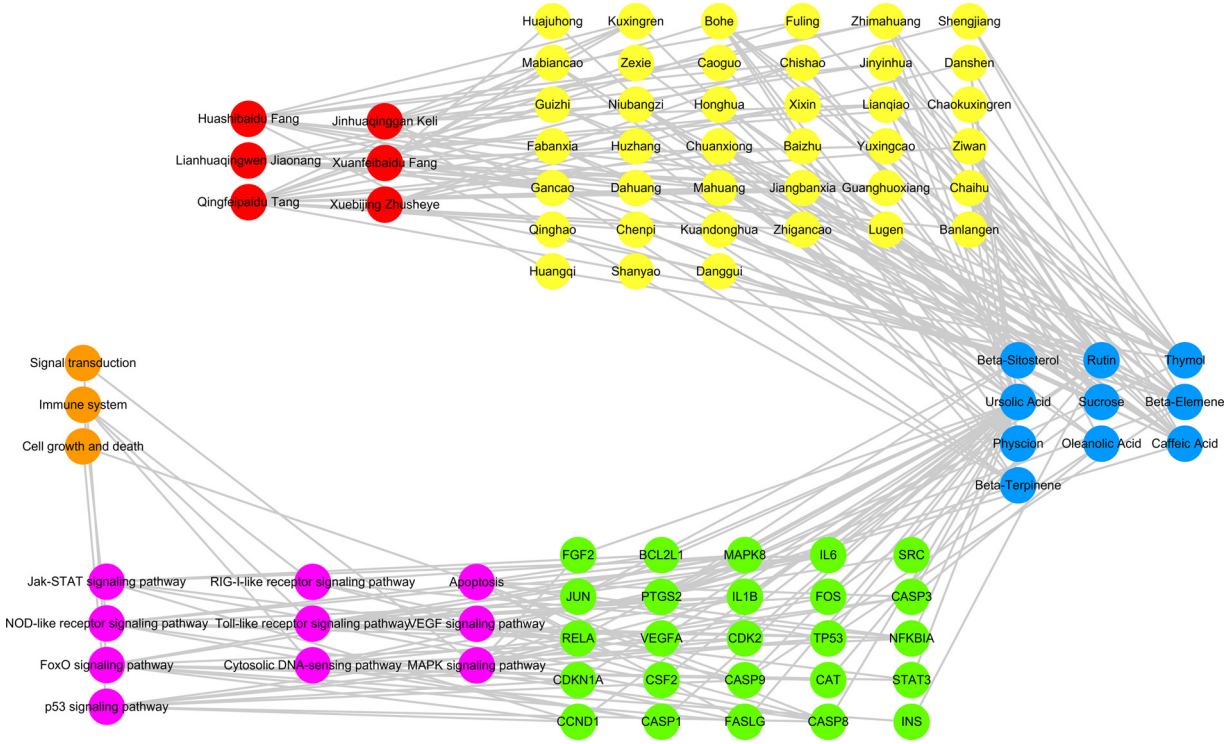

Fig. 3. The network of three-medicines and three-decoctions in treating COVID-19. Red pies: the node group of three-medicines and three-decoctions. **Yellow pies**: the node group of Chinese medicines. **Blue pies**: the node group of active ingredients. **Green pies**: the node group of targets. **Purple pies**: the node group of signal pathways. **Orange pies**: the node group of mechanism classifications.

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