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Review

Jing Si Herbal Drink as a prospective adjunctive therapy for COVID-19 treatment: Molecular evidence and mechanisms

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ABSTRACT

Background: SARS-CoV-2 has led to a sharp increase in the number of hospitalizations and deaths from pneumonia and multiorgan disease worldwide; therefore, SARS-CoV-2 has become a global health problem. Supportive therapies remain the mainstay treatments against COVID-19, such as oxygen inhalation, antiviral drugs, and antibiotics. Traditional Chinese medicine (TCM) has been shown clinically to relieve the symptoms of COVID-19 infection, and TCMs can affect the pathogenesis of SARS-CoV-2 infection *in vitro*. Jing Si Herbal Drink (JSHD), an eight herb formula jointly developed by Tzu Chi University and Tzu Chi Hospital, has shown potential as an adjuvant treatment for COVID-19 infection. A randomized controlled trial (RCT) of JSHD as an adjuvant treatment in patients with COVID-19 infection is underway

Objectives: This article aims to explore the efficacy of the herbs in JSHD against COVID-19 infection from a mechanistic standpoint and provide a reference for the rational utilization of JSHD in the treatment of COVID-19.

Method: We compiled evidence of the herbs in JSHD to treat COVID-19 *in vivo* and *in vitro*.

Results: We described the efficacy and mechanism of action of the active ingredients in JSHD to treat COVID-19 based on experimental evidence. JSHD includes 5 antiviral herbs, 7 antioxidant herbs, and 7 anti-inflammatory herbs. In addition, 2 herbs inhibit the overactive immune system, 1 herb reduces cell apoptosis, and 1 herb possesses antithrombotic ability.

Abbreviations: 3CLpro, 3-chymotrypsin-like cysteine protease; AA, Artemisia argyi; ACE2, angiotensin-converting enzyme 2; ADRP, ADP ribose phosphatase; AKT1, AKT serine/threonine kinase 1; ALI, acute lung injury; Ang-II, angiotensin-II; ARDS, acute respiratory distress syndrome; ASC, C-terminal caspase recruitment domain; AT1R, angiotensin II type I receptor; ATF2, activating transcription factor 2; BALF, bronchoalveolar lavage fluid; CCR, CC chemokine receptor; citH3, citrullinated H3; COPD, chronic obstructive pulmonary disease; CoVs, coronaviruses; COX-2, cyclooxygenase-2; CPE, cytopathogenic effect; CSF, colony-stimulating factor; CSFR, colony-stimulating factor receptor; DA, dehydromatricarin A; DAMPs, damage-associated molecular patterns; DIC, disseminated intravascular coagulation; GC-MS, gas chromatography-mass spectrometry; GM-CSF, granulocyte-macrophage colony-stimulating factor; GSK3β, glycogen synthase kinase beta; HIF-1, hypoxia-inducible factor 1; HIV-1, human immunodeficiency virus type 1; HLH, hemophagocytic lymphohistiocytosis; HMGB1, high mobility group box 1; HSP70, heat shock protein 70; ICAM-1, intercellular adhesion molecule 1; IFN, interferon; ILC3, type 3 innate lymphoid cells; iNOS, inducible nitric oxide synthase; JAK2, Janus kinase 2; JSHD, Jing Si herbal drink; LC–MS, liquid chromatography-mass spectrometry; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MMP-9, matrix metallopeptidase 9; MPO, myeloperoxidase; Mpro, main protease; NE, neutrophil elastase; NETs, neutrophil extracellular traps; NEK7, NIMA-related kinase 7; NF-κB, nuclear factor kappa B; NK, natural killer; NLRP3, NLR family pyrin domain-containing 3; NO, nitrogen monoxide; Nrf2, nuclear factor erythroid-related factor 2; Nsps, nonstructural proteins; PD, platycodin D; PG, *Platycodon grandiflorum*; PI3K, phosphoinositide 3-kinase; PLE, perilla leaf extract; PLpro, papain-like protease; PRRs, pattern recognition receptors; PrsDMe, prosapogenin D methyl ester; RA, rosmarinic acid; RBD, receptor-binding domain; RCT, randomized controlled trial; RdRP, RNA-dependent RNA polymerase; RNP, ribonucleoprotein; RORγ, RAR-related orphan receptor γ; ROS, reactive oxygen species; SM, Seomae mugwort; SOD, superoxide dismutase; STAT, signal transducer and activator of transcription; TCM, traditional Chinese medicine; TGF-β, transforming growth factor-β; TLR, Toll-like receptor; TMPRSS2, transmembrane serine protease 2; TNF-α, tumor necrosis factor-α; TXA2, thromboxane A2; VCAM-1, vascular cell adhesion molecule 1; VEGF, vascular endothelial growth factor; VOC, variants of concern; WHO, World Health Organization.

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Conclusion: Although experimental data have confirmed that the ingredients in JSHD are effective against COVID-19, more rigorously designed studies are required to confirm the efficacy and safety of JSHD as a COVID-19 treatment.

Introduction

Coronaviruses (CoVs) were first isolated in 1962 and are known to cause mild respiratory and gastrointestinal infections in humans and animals [1]. Two viruses of zoonotic origin, severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), are causative agents of fatal infections of the lower respiratory tract [2]. The discovery of SARS-CoV-2 in 2019 was regarded as the third jump of coronaviruses from animals to humans [1]. An outbreak of this new type of coronavirus (COVID-19) resulted due to a high infection rate caused by person-to-person transmission through respiratory droplets. COVID-19 has led to a dramatic increase in hospitalizations for pneumonia with multiorgan disease [3] and deaths worldwide; thus, in 2020, the World Health Organization (WHO) announced that COVID-19 had become a global health issue. Through August 2021, WHO statistics reported that COVID-19 had caused more than 200 million cases of infection and the death of at least 4.3 million individuals worldwide.

SARS-CoV-2 invades human cells through the binding of the spike proteins on the virus to the angiotensin-converting enzyme 2 (ACE2) receptor, which is broadly distributed on different tissues and immune cells [4]. COVID-19 infection may be asymptomatic, may cause a wide spectrum of mild clinical manifestations, such as fever, cough, sore throat, fatigue, and myalgia, or may cause life-threatening pneumonia, acute respiratory distress syndrome (ARDS), multiorgan injury, and sepsis [3,4]. Multiple studies have determined that the severity of SARS-CoV-2 infection is correlated with the excessive activation of immune cells and overproduction of inflammatory cytokines, known as a cytokine storm, which is fast-developing and causes life-threatening immunopathological damage. Cytokine storms have been implicated in poor clinical outcomes, including ARDS, disseminated intravascular coagulation (DIC), hemophagocytic lymphohistiocytosis (HLH), multiorgan injury, and even death if no adequate therapies are available [4].

At present, general and rapid global vaccination has been a major strategy against the dramatic physiological imbalance caused by SARS-CoV-2 infection and the most effective method for resolving long-term pandemics worldwide [1]. However, alterations of the spike residues within major epitopes may affect antibody binding and neutralization, which further mitigates the efficiency of antibodies produced by vaccination or natural infection [1]. To date, four globally recognized COVID-19 variants have been labeled “variants of concern” (VOC), including Alpha/B.1.1.7, Beta/B.1.351, Gamma/P.1 and Delta/B.1.617.2, which exhibit higher transmissibility and morbidity/mortality and a significant decrease in the effectiveness of neutralization by antibodies elicited by infection, vaccination, or therapeutic application [1]. Thus, apart from vaccination, it is essential to have adjunctive therapies that could suppress the invasion of SARS-CoV-2 into human cells, obstruct viral replication and prevent the overproduction of inflammatory cytokines triggered by viral infection.

Chinese herbs as remedial measures against different diseases have been accepted because of certain beneficial characteristics, such as fewer side effects, easy availability, and cost-effectiveness [5]. Emerging evidence reports that Chinese herbs have shown remarkable successes in coping with the pathogenic pathways of SARS-CoV-2 infection. For example, curcumin can bind to a receptor-binding domain (RBD) of the spike protein, nucleocapsid protein, and membrane glycoprotein of SARS-CoV-2 to inhibit viral replication through the phosphoinositide 3-kinase (PI3K)/Akt and nuclear factor kappa B (NF-kB) pathways[5]. Glycyrrhizin binds to the ACE2 receptor, inhibits thrombin, and alleviates airway exudates [5]. Lianhua Qingwen capsule was found to suppress SARS-CoV-2 replication in a dose-dependent manner [6,7]. The ingredients of Qingfei Paidu decoction can restrain cytokine release and diminish excessive immune responses and inflammation by modulating AKT serine/threonine kinase 1 (AKT1), mitogen-activated protein kinase (MAPK)−1, MAPK3, MAPK8, MAPK14, interleukin (IL)−6, RELA, signal transducer and activator of transcription (STAT)−1, and JUN; immune-related pathways, including Th17 cell differentiation, T cells, and B cell pathways; and cytokine-related pathways, including tumor necrosis factor (TNF) signaling pathways, NF-κB, MAPK, vascular endothelial growth factor (VEGF), hypoxia-inducible factor 1 (HIF-1) and Toll-like receptor (TLR) signaling pathways [7]. Huoxiang Zhengqi capsules, Jinhua Qinggan granules, and Lianhua Qingwen capsules regulate the arachidonic acid metabolic pathway to control cytokines for the prevention of SARS-CoV-2 infection [7]. In conclusion, Chinese herbs are promising adjunctive therapies for the inhibition of SARS-CoV-2 infection.

However, doctors and scholars are still exploring more effective herb combination prescriptions. Jing Si Herbal Drink (JSHD), a plant-based formula jointly developed by Tzu Chi University and Tzu Chi Hospital to combat COVID-19 infection and regulate immunity [8], has been approved by the Ministry of Health and Welfare of Taiwan (registration number: MOHW-PM-060,635). JSHD originated from an evaluation of the clinical symptoms of COVID-19 infection to select herbs with symptom-related therapeutic efficacy and was previously referred to as an herbal remedy during the SARS epidemic in 2003 [9,10]. A randomized controlled trial (RCT) of JSHD as an adjuvant treatment in patients with COVID-19 infection is underway (NCT04967755) [11]. This RCT considered the medication safety and thus, exclusion criteria include severe pneumonia needing mechanical ventilation, women during pregnancy or lactation, known allergies to the investigational medications, and severe systemic diseases, such as malignancy, autoimmune diseases, liver or renal diseases. JSHD is administered three times daily, each time 200–300 mL. The standard dose of each ingredient in JSHD was shown in Table 1 and clinical trials displayed that JSHD could effectively reduce the expression of COVID-19 in the throat of infected patients.

PubMed, Embase, Cochrane Library, and Clinical Trials (https://clinicaltrials.gov) were searched for basic research on the herbs or active ingredients of JSHD related to COVID-19 published before June 2021. To expand the scope of the search, we used the "related articles" feature of PubMed to further review the included articles and citations. In this study, we will elucidate the regulatory role of the ingredients in JSHD on the pathogenic pathways of SARS-CoV-2.

Pathophysiological pathways of SARS-CoV-2

In the following paragraphs and Figs. 1 and 2, we will depict the possible mechanism of COVID-19 infection in detail. SARS-CoV-2 is a single-stranded positive-sense RNA virus containing four major structural proteins, including spike (S), envelope (E), membrane protein (M), and nucleocapsid (N), all of which are required to constitute a structurally complete viral particle [12]. The RBD on the spike proteins facilitates SARS-CoV-2 access to human lung, heart, and kidney cells by binding to the ACE2 receptor on the host cells [13,14], and neutralizing antibodies against the RBD are important for immunity [15]. SARS-CoV-2 enters human cells by the endocytic pathway, and subsequently, cathepsin B/L mediates cleavage of the S protein in lysosomes [16]. Furthermore, fusion of the viral envelope with the host plasma membrane aids in SARS-CoV-2 access to human cells, where transmembrane serine protease 2 (TMPRSS2) mediates cleavage of the S protein [16]. Cleavage of the S

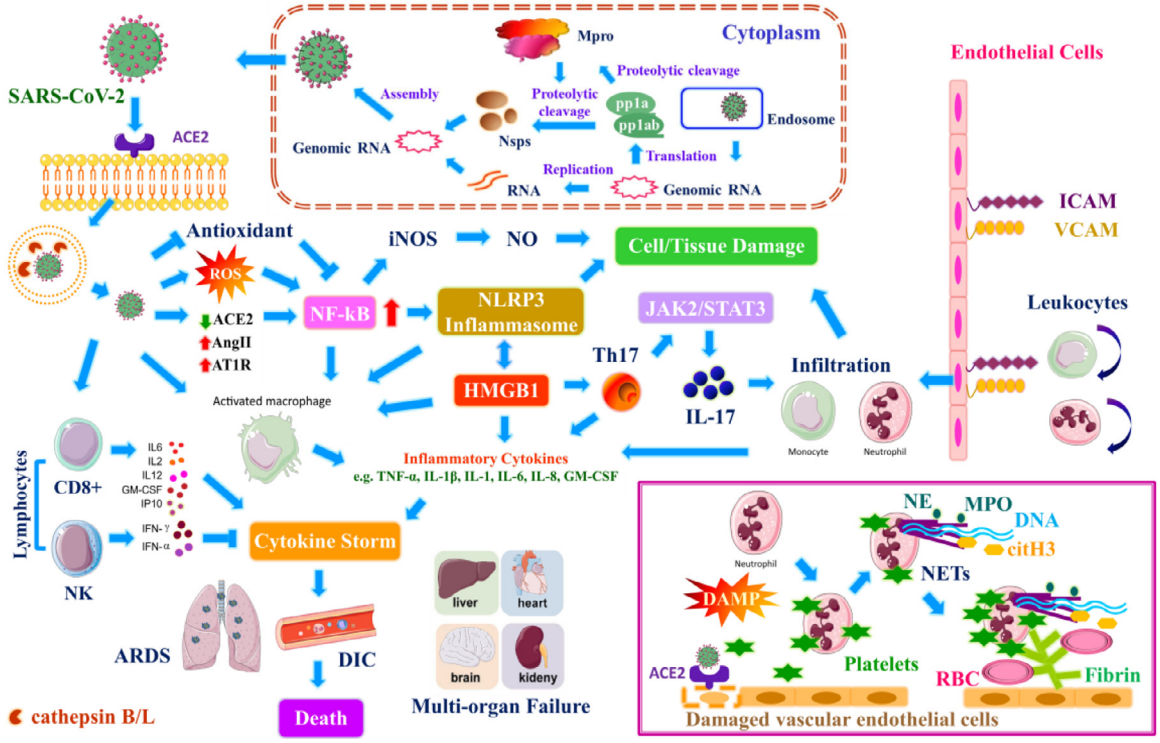

Fig. 1. Pathophysiological pathways of SARS-CoV-2. The Pathophysiological pathways of SARS-CoV-2 include replication and transcription of virus, the entrance of virus into host cells, hyperactivities of immune cells and inflammatory responses, leukocyte infiltration, anti-oxidation and ROS production.

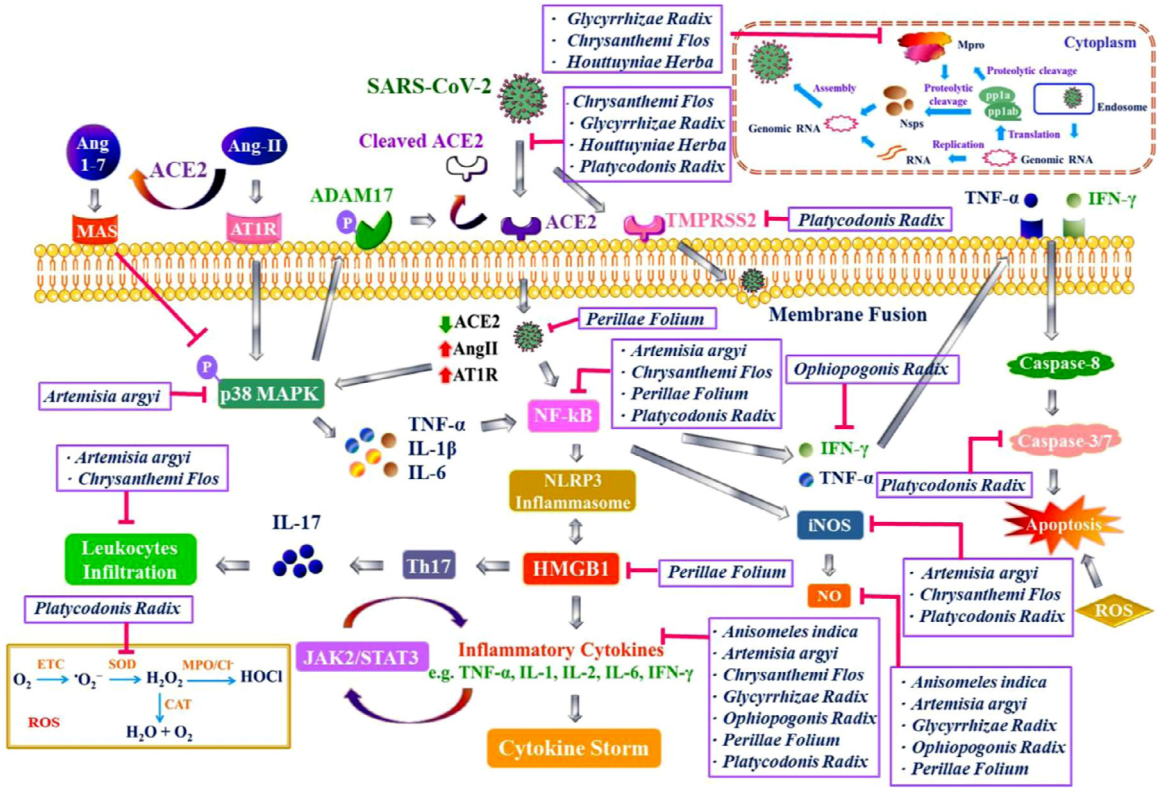

Fig. 2. Regulatory mechanism of eight ingredients of Jing Si Herbal Drink in SARS-CoV-2. The ingredients of JSHD target different pathways involved in replication and transcription of virus, the entrance of virus into host cells, hyperactivities of immune cells and inflammatory responses, leukocytes infiltration, cell apoptosis and production of ROS, for the inhibition of SARS-CoV-2 infection.

Table 1
Overview ingredients of JSHD and the efficacy of each ingredient.

Chinese name	English/ Latin name	Family	Species	Dosage (g)	Prescription functions [84] [72,110]
Yujencao	Indian Epimerdei/ *Anisomeles indica* (L.) Kuntze	Lamiaceae	*Anisomeles indica*	6	Remove heat and detoxification
Ai Ye	Asiatic Wormwood/*Artemisia argyi folium*	Asteraceae	*Artemisia argyi*	6	Stop bleeding and alleviate pain
Juhua	Florists Dendranthema/ *Chrysanthemi Flos*	Asteraceae Compositae	*Chrysanthemum morifolium Ramat*	0.2	Reduce heat in lung, liver and kidney
Clean heat and toxins					
Gancao	Liquorice root/ *Glycyrrhizae radix*	Fabaceae	Glycyrrhiza glabra, inflata and uralensis	2	Clear toxicity and relieve sore throat
Diminish toxicity					
Yuxingcao	Heartleaf Houttuynia Herb/ *Houttuyniae herba cum radice*	Saururaceae	Houttuynia cordata	4	Reduce toxicity, treat clinically lung and intestinal abscesses, superficial sores, pneumonia, bronchiectasis, pulmonary tuberculosis and pelvic inflammation.
Maidong	Dwarf Lilyturf Root Tuber/ *Ophiopogonis radix*	Asparagaceae	Ophiopogon japonicas	4	Clear heat in lung and heart
Zisuye	Cultibated Purple Perilla Leaf/ *Perillae Folium*	Lamiaceae	Perilla frutescens	2	Alleviate abdominal pain and transform Damp-Phlegm
Jiegeng	Balloonflower Root/ *Platycodonis Radix*	Campanulaceae	Platycodon grandiflorus	4	To ascend and disperse the Lung-Qi, to treat cough with phlegm.

protein by cathepsin B/L and/or TMPRSS2 further facilitates the release of viral RNA in the cytosol of host cells [16]. Therefore, host cells are susceptible to SARS-CoV-2 depending on the abundance and availability of the host proteases cathepsin B/L and TMPRSS2 as well as ACE2 receptors. SARS-CoV-2 binding to ACE2 results in a decrease in ACE2 [17], impeding downstream angiotensin-II (Ang-II) metabolism and eventually leading to Ang-II accumulation [13]. This increase in Ang-II causes pulmonary vasoconstriction, acute lung injury, lung edema, and lung fibrosis [13,18–20]

After entry into human cells, SARS-CoV-2 releases genomic RNA. The viral genome encodes two polyproteins, pp1a and pp1ab, which are cleaved into the main protease (Mpro) and 16 nonstructural proteins (Nsps). Mpro plays a crucial role in the production of Nsps. Six Nsps, including NSP3, NSP9, NSP10, NSP12, NSP15, and NSP16, are responsible for the collection of replication transcription complexes (RTCs) to execute RNA replication [21]. N proteins bind to SARS-CoV-2 genomic RNA to form helical ribonucleoprotein (RNP) complexes together with M proteins to facilitate new intact virions [22], which are ultimately released from human cells.

NF-κB regulates immune cell activation and inflammatory responses

NF-κB is a pleiotropic transcription factor that is responsible for the transcriptional activities of various genes involved in immune functions and inflammatory responses. NF-κB mediates the survival, activation, and differentiation of innate immune cells, including macrophages, dendritic cells, neutrophils, and T cells [23]. These innate immune cells express pattern recognition receptors (PRRs) that recognize various pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) released by necrotic cells and damaged tissues [23]. The signaling pathways of PRR-activated innate immune cells are associated with NF-κB regulation, which controls the transcriptional expression of proinflammatory cytokines, chemokines, and additional inflammatory mediators [23]. These inflammatory mediators can elicit inflammation and indirectly activate the differentiation of T cells [23]. Severe COVID-19 causes hypercytokinemia via macrophage activation within the lung and ultimately progresses to organ failure [24]. Upregulated Ang-II binding to the angiotensin II type I receptor (AT1R) promotes NF-κB and macrophage activation, further inducing cytokine release [13,23]. The upregulation of proinflammatory cytokines, such as TNF-α, IL-6, and IL-1β, induced by microphage activation is called a cytokine storm, which contributes to acute respiratory distress syndrome (ARDS) [13]. Moreover, SARS-CoV-2 affects the natural killer (NK) and CD8+ cell populations, leading to reduced production of anti-inflammatory cytokines, including interferon (IFN)-α and IFN-γ, and increased levels of pro-inflammatory cytokines [5].

NLRP3 inflammation regulates HMGB1 for cytokine secretion and immune cell activation and infiltration

NLR family pyrin domain-containing 3 (NLRP3) detects intracellular danger components, a wide range of pathogens, and environmental irritants to subsequently form and activate the NLRP3 inflammasome in the cytosol. The NLRP3 inflammasome is composed of NLRP3, an apoptosis-associated speck-like protein containing a C-terminal caspase recruitment domain (ASC), pro-caspase-1, and NIMA-related kinase 7 (NEK7). The multiprotein complexes prompt caspase-1 cleavage and stimulate the production of the proinflammatory cytokines IL-1β and IL-18 and other DAMPs [25]. High levels of DAMPs are released after hyperactivation of NLRP3 inflammation, triggering the secretion of high mobility group box 1 (HMGB1), pyroptosis, macrophage activation, decreased apoptosis, neutrophil infiltration and considerable cytokine production, leading to the subsequent cytokine storm and lung fibrosis [25].

HMGB1 is one of the major downstream DAMPs in the NLRP3 activation pathway and it was originally found after endotoxin lethality in mice [26]. It is also a late marker of lethal systemic inflammation [27], and infection correlates with epithelial barrier failure, organ dysfunction, vascular leakage, and even death [25,28]. High expression of HMGB1 plays a crucial role in intense inflammatory responses and pathological severity during viral infection [29,30]. Infection or injury elevates the levels of HMGB1 in the lungs in influenza virus and acute lung injury models, which results in pneumonia and even death; however, these phenomena can be inhibited by the administration of HMGB1-specific antibodies [30,31].

SARS-CoV-2 induces immune cell infiltration via ICAM-1 and VCAM-1

The N protein of SARS-CoV-2 induces the TLR2/NF-κB and MAPK signaling pathways to activate endothelial cells, contributing to increased levels of intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), inflammatory cytokines, and chemokines [32]. ICAM-1 and VCAM-1 are major adhesive proteins expressed on activated endothelial cells that play crucial roles in mediating the adhesion of leukocytes, such as monocytes and neutrophils, to endothelial cells as well as cell infiltration into tissues [32]. On the other hand, serum levels of ICAM-1 and VCAM-1 are elevated in pa-

tients with mild COVID-19 infection and dramatically increased in patients with severe COVID-19, whereas the serum levels of ICAM-1 and VCAM-1 decrease during the convalescence phase [33]. Patients with both severe COVID-19 infection and lymphopenia frequently have aberrant monocyte/macrophage activation along with elevated levels of neutrophils [34]. Neutrophil extracellular traps (NETs) are networks of extracellular fibers containing chromatin DNA filaments coated with granule proteins. NETs released by neutrophils capture infective pathogens; however, aberrant NETs exacerbate inflammation and further lead to cystic fibrosis, ARDS, thrombosis, and cytokine storms [34–38]. Activated T cells also stimulate inflammatory responses from innate immune cells to trigger cytokine storms. The interaction of expressed IL-1β, colony-stimulating factor receptor (CSF)−1, and CSF2 on T cells with IL-1R and colony-stimulating factor receptor (CSFR) expressed on monocytes could induce the activation of monocytes [39]. Th1 cells activate inflammatory monocytes to produce IL-6 in patients with severe COVID-19. Moreover, the Th17 response causes the release of different types of cytokines, such as TNF-α, IL-1, IL-6, IL-17, and granulocyte-macrophage colony-stimulating factor (GM-CSF) [13,34]. Patients with severe COVID-19 infection have a significantly higher number of CC chemokine receptor (CCR)−6+ Th17 cells in peripheral blood, which further supports Th17 responses in cytokine storms [40]. Taken together, these findings may be associated with the release of proinflammatory cytokines by innate immune cells, further sparking the cytokine storm and eventually organ injury [34,40].

Th17 cells promote IL-17A secretion via the JAK2/STAT3 signaling pathway for immune cell infiltration

Th17 cells are major immune cells that secrete the proinflammatory cytokine IL-17A under the stimulation of transforming growth factor-β (TGF-β). IL-6 and IL-23 originate from phagocytes and other innate immune cells, including NK cells, $\gamma\delta$ T cells, and type 3 innate lymphoid cells (ILC3s) [41,42]. Neutrophils and macrophages can provoke IL-17A production via IL-1β and IL-23[42]. IL-6 induces the differentiation of Th17 cells in an early stage of inflammation through the Janus kinase 2 (JAK2)/STAT3 signaling pathway, which further activates the nuclear receptor and transcriptional regulator RAR-related orphan receptor γ (RORγ) via a STAT3-dependent pathway to promote the secretion of IL-17A, IL-17F, and IL-22 [42,43]. IL-17A participates in both the recruitment of neutrophils and other immune cells to the infection site and immune cell infiltration, which causes tissue destruction and exacerbates SARS-CoV-2 infection [42]. In addition, the upregulation of HMGB1 induces neutrophil infiltration into the lung tissue, which is regulated by Th17-induced IL-17 production [25,41].

iNOS and no production in the NF-κB pathway

NF-κB activation promotes an increase in inflammatory factors and inducible nitric oxide synthase (iNOS). Nitrogen monoxide (NO) derived from iNOS is involved in the regulation of the immune system [44] and is correlated with tissue damage [45]. iNOS has been found in various types of immune cells during inflammation, including macrophages, neutrophils, eosinophils, and airway epithelial cells [46,47]. Moreover, the inhibition of iNOS attenuates neutrophil and macrophage infiltration [48].

In addition to the effects of cytokine storms, the NF-κB pathway correlates with the severity of metabolic syndrome in patients with COVID-19 [49]. High levels of glucose and free fatty acids associated with chronic inflammation lead to diabetes mellitus and obesity. Glucolipotoxicity occurring simultaneously with inflammatory responses stimulates the noncanonical NF-κB pathway [50]. Under the effects of insulin resistance, glycogen synthase kinase beta (GSK3β) is activated, and the NF-κB pathway becomes dynamic, heat shock protein 70 (HSP70) inhibition, which contributes to fierce inflammatory responses [50]. Furthermore, iNOS and NO are predominant downstream factors in the NF-κB pathway that inhibit insulin signaling to further deteriorate the metabolic state [51]. The hyperglycemic phenomenon in patients with COVID-19 stimulates TNF-α to accelerate the activation of the noncanonical NF-κB pathway. In conclusion, patients with COVID-19 with comorbidities, such as an excess of metabolites induced by diabetes, hyperlipidemia, and hyperglycemia, have a significantly increased risk of mortality via hyperactivation of the NF-κB pathway.

The binding of SARS-CoV-2 to ACE2 on damaged vascular endothelial cells stimulates the NET formation

Neutrophils, accompanied by platelets, are upregulated in the blood of patients with severe COVID-19 and exhibit a low-density phenotype [52]. Moreover, patients with severe COVID-19 infection have increased levels of serum or plasma markers, including myeloperoxidase (MPO), cell-free DNA, D-dimers, neutrophil-elastase (NE)-DNA complexes, and citrullinated H3 (citH3), which are the degradation products of fibrin or NETs [53]. The antimicrobial proteins MPO and NE released from activated neutrophils have been discovered in NETs [53]. The aggregation of NETs in clots obstructs lung microvessels and other organs in patients with COVID-19 [53]. Although ACE2 is not expressed on neutrophils, numerous ACE2 receptors are expressed on the vascular endothelial cells that are next to the alveolar epithelial cells in the lung [53]. Vascular endothelial cells damaged by SARS-CoV-2 infection provoke neutrophil attraction and NET formation [53]. On the other hand, SARS-CoV-2 infection suppresses the expression of antioxidative transcription factors, such as nuclear factor erythroid-related factor 2 (Nrf2), for the antioxidant response [54]. In addition, SARS-CoV-2 may cause reactive oxygen species (ROS)-dependent NET formation [53]. Injury to vascular endothelial cells promotes coagulation and the secretion of DAMPs, which in turn lures activated platelets and neutrophils to aggregate on the surface of damaged endothelial cells to ultimately form lytic NETs from neutrophils [53]. Finally, NETs activate platelets and fibrin to accelerate immunothrombus formation to eliminate pathogens and protect endothelial integrity [53].

Possible therapeutic effects of the herbs in jshd for COVID-19 treatment

JSHD, approved by the Taiwan Ministry of Health and Welfare, is formulated to treat the symptoms of COVID-19 infection with reference to its prescription to treat SARS in 2003 [9,10]. JSHD consists of Yu Jen Cao (*Anisomeles indica*), Ai Ye (*Artemisiae argyi folium*), Ju Hua (*Chrysanthemi flos*), Gan Cao (*Glycyrrhizae radix*), Yu Xing Cao (*Houttuyniae herba cum radice*), Mai Men Dong (*Ophiopogonis radix*), Zi Su Ye (*Perillae folium*) and Jie Geng (*Platycodi radix*) [8,11]. After the above herbs are decocted, they are concentrated into an extract and added to microcrystalline cellulose and maltodextrin to generate a powder. Finally, 9 g of this Chinese patented medicine was obtained. In addition, an RCT of JSHD as an adjuvant treatment to patients with COVID-19 infection is ongoing [11]. In Table 1, we list the English name, Latin name, family, species, dosage, and functions according to the TCM patterns of each herb in JSHD. To adults, JSHD was orally administered 3 g (one packet) once to three times a day.

This review intends to discuss the detailed mechanism of JSHD as an adjuvant COVID-19 treatment for future clinical use and experimental reference. The relevant research and mechanism of all of the JSHD herbs or their active ingredients are summarized in Table 2 and Fig. 2 and will be described in detail below.

Anisomeles indica

A. indica, known as Yu Jen Cao in Taiwan, is a traditional anti-inflammatory herb used for the treatment of many diseases, including inflammatory skin diseases, liver disease, gastrointestinal disease, hypertension, and immune system deficiencies [55–57]. Recently, a

Table 2
The potential efficacy of the herbs of JSHD used for the adjunctive therapies of COVID-19 infection.

Ingredient	Refs.	Study design	Subjects	Active ingredients	Mechanism/ Usage
Anisomeles indica (L.) Kuntze	[58]	Animal	Murine	Chloroform and n-butanol fractions of methanol extract	Inhibit NO, TNF-α and IL-12
	[57]	*In vitro*	Peritoneal excluded macrophage cells from mice	Ovatodiolide, pedalitin, scutellarein 7-O-β-D-glucuronide methyl ester, acteoside	Inhibit NO, TNF-α, IL-12
Artemisia argyi	[60]	Animal	Murine	dehydromatricarin A (DA)	Decrease iNOS expression and NF-κB phosphorylation
	[59]	*In vitro*	RAW 264.7	Polyphenolic mixture	Attenuate macrophages activation, Reduce iNOS, TNF-α and IL-1β levels, and MAPK phosphorylation
	[71]	*In vitro*	RAW 264.7	Sesquiterpenoid dimers	Reduce iNOS levels
Chrysanthemi Flos	[75]	Silicon & molecular docking		Luteolin	Inhibit viral-host cell fusion and entry
	[79]	Animal	Rats	Luteolin	Reduce serum levels of IL-1β, IL-6, and TNFα
	[80]	*In vitro* &	Human platelet concentrates	Luteolin and apigenin	Anti-platelet and anti-thrombosis
		Animal	Rats	Casticin	Suppress NF-κB and iNOS. Decrease serum levels of TNF-α, IL-1β, IL-6 and CRP and reduce macrophages, neutrophils, and white blood cells
	[82]	Silicon & molecular docking		Casticin	Bind to 3CLpro, Spike protein, and RdRP of SARS-CoV-2
	[83]	Silicon & molecular docking		Chlorogenic acid	3CLpro inhibitor
Glycyrrhizae Radix et Rhizoma	[92]	In Vero cells		Glycyrrhizin	Induce iNOS in Vero cells
	[88]	Molecular docking		Licorice phenol	Bind Mpro and ACE2
	[85]	Molecule docking & network pharmacology		Licorice glycoside E	3CLpro inhibitors
	[91]	Silicon & molecular docking		Glycyrrhizin	Bind Mpro of SARS-CoV-2
Glycyrrhizae Radix et Rhizoma	[9]	Molecular docking		Glycyrrhizic Acid	Target main replication protein of SARS-CoV-2 and inhibit inflammatory agent release
Houttuyniae herba cum radice	[95]	Molecular docking		6-Hydroxyondansetron & Quercitrin	Inhibit Mpro, PLpro and ADRP
	[96]	Bedside-to-bench (*in vitro* & *in vivo*)	COVID-19 patients	Heartleaf Houttuynia	Block binding between ACE2 and spike protein of SARS-CoV-2
Ophiopogonis radix	[98]	*In vitro*	Human dermal fibroblasts	Methylophiopogonanone A and B Ophiopogonanone A and ophiopogonin B	Downregulate the expression of IL-6 and IL-8
	[99]	*In vitro*	RAW 264.7 mouse macrophage cells	Homoisoflavonoids	Supress LPS-induced NO, IL-6 and IL-1β
	[100]	Animal	Mice	Polysaccharides	Reduce plasma levels of IFN-γ
	[102]	Animal	Mouse & rat	Ethanol extract of O. Radix	Secure endothelial cells from anoxic injury, decrease leukocytes adhesion and inflammation of the vein wall
Perillae folium	[103]	*In vitro*	Human lung epithelial cell line Calu-3	Perilla frutescens leaf extract	Inactivate SARS-CoV-2 spike protein Decrease viral protein/RNA synthesis and TNF-α, IL-1 and IL-6 levels
	[105]	Computer modeling &*In vivo* animal model	Hamsters	Aqueous extracts of Perilla frutescens	Reduce virus load decrease and viral-induced CPE in Vero E6 cells

(*continued on next page*)

Table 2 (*continued*)

Ingredient	Refs.	Study design	Subjects	Active ingredients	Mechanism/ Usage
	[106]	*In vitro*	LPS-stimulated RAW 264.7 cells	Monoterpenoid 4 and alkaloid 5	Inhibit the production of NO, TNF-α and/or IL-6
	[104]	*In vitro* & *in vivo*	Mice	Rosmarinic acid	Inhibit HMGB1 and down-regulating HMGB1-dependent inflammation Hinder HMGB1-mediated leukocyte migration. Decrease CLP-induced HMGB1 release and sepsis-related mortality
di radix	[109]				Block lysosome and TMPRSS2-driven viral entry
	[108]	Animal	Male ICR mice	Prosapogenin D (PrsD) and prosapogenin D methyl ester (PrsDMe) of Platycodin D	Inhibit the expression of LPS-induced iNOS and COX-2 genes by suppressing NF-kB activation
	[107]	Animal	Female BALB/c mice	Platycodin D	Inhibit IL-6 and TNF-α in BALF Inhibit the expressions of NF-κB, Caspase-3 and Bax in lung tissues Restore the expression of Bcl-2 in lungs Improve SOD activity in BALF.
	[107]	*In vitro*	MLE-12 cells	Platycodin D	Reduce the levels of TNF-α and IL-6 Reduce the expressions of NF-κB, Caspase-3 and Bax

ACE2: Angiotensin-converting enzyme 2; ADRP: ADP ribose phosphatase; BALF: Bronchoalveolar lavage fluid; Bax: BCL2 Associated X, Apoptosis Regulator; Bcl-2: B-cell lymphoma-2; CLP: cecal ligation and puncture; 3CLpro: 3-chymotrypsin-like cysteine protease; COX-2: Cyclooxygenase-2; CPE: cytopathogenic effect; E2F1: E2F Transcription Factor 1; ERK: extracellular regulated protein kinases; HMGB1: High Mobility Group Box 1; IFN: Interferon; IL: Interleukin; iNOS: nitric oxide synthase; JSHD: Jing-Si herbal drink; LPS: Lipopolysaccharide; MAPK: mitogen-activated protein kinase; Mpro: main protease; NF-κB: nuclear factor kappa B; NO: Nitric Oxide; PI3K-Akt signaling pathway: PI3K is phosphoinositide 3-kinase; "Ak" in Akt stands for a temporary classification name for a mouse bred. The "t" represents 'Thymoma'; Akt also known as Protein Kinase B (PKB) ; PIK3CG: Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Gamma; PLpro: Papain-like protease; RdRP: RNA dependent RNA polymerase; RNA: ribonucleic acid; SOD: superoxide dismutase; TMPRSS2: transmembrane protease serine 2; TNF: tumor necrosis factor.

study demonstrated that *A. indica* had anti-inflammatory effects against murine peritoneal macrophages [58]. The active compounds of *A. indica* were found in the chloroform and n-butanol fractions of the methanol extract. A total of fourteen compounds were identified, including pedalitin, asigenin, ovatodiolide, methylgallate, 3,4-dihydroxy benzoic acid, scutellarein 7-O-β-D-glucuronide methyl ester, apigenin 7-O-glucuronide, calceolarioside, cistanoside F, betonyoside A, campneoside II, acteoside, isoacteoside and terniflorin. The invading pathogens induce innate immunity via the production of inflammatory mediators, such as NO, TNF-α and IL-12. However, the overproduction of macrophage-derived mediators may cause the injury of normal cells, further leading to inflammatory diseases [58]. All extracts suppressed the production of NO radicals and the secretion of proinflammatory cytokines (TNF-α and IL-12) induced by lipopolysaccharide (LPS)/IFN-γ in a dose-dependent manner [58]. Among these, ovatodiolide most significantly inhibited the enhanced production of NO, TNF-α and IL-12, followed by pedalitin, scutellarein 7-O-β-D-glucuronide methyl ester and acteoside [58]. Moreover, ovatodiolide, pedalitin and scutellarein 7-O-β-D-glucuronide methyl ester most significantly induced G0/G1 stage arrest of mitogen Con-A-stimulated spleen cells, suggesting that the inhibition of these inflammatory mediators was associated with a cell cycle arrest in response to the administration of these compounds [58]. Additionally, other findings showed the potent anti-inflammatory properties of *A. indica*, which may alleviate the uncontrolled release of pro-inflammatory cytokines in response to COVID-19 infection [57].

Artemisiae argyi folium

A. argyi folium is a therapeutic herb that is widely distributed in the Northern Hemisphere [59]. It has been used to treat patients with abdominal pain, dysmenorrhea, and inflammation [60]. Previous research has demonstrated that *A. argyi folium* not only has antioxidant [61], antidiabetic [62], anticancer [63,64], antimicrobial [65], and antiulcer activities [66] but also has anti-inflammatory [67] and antiallergic properties [68]. Although there have been no studies on the effectiveness of *A. argyi folium* to treat COVID-19, a previous study reported that *A. argyi folium* strongly inhibits inflammation [67].

It was shown that *A. argyi folium* and its active compound, dehydromatricarin A (DA), attenuated airway inflammation in an LPS-induced acute lung injury (ALI) murine model. In comparison with ALI-induced mice, the decreases in tumor necrosis factor (TNF)-α and IL-6 in bronchoalveolar lavage fluid (BALF) of mice after treatment with *A. argyi folium* and DA was remarkable. In addition, the administration of *A. argyi folium* and DA significantly decreased NF-κB phosphorylation and iNOS expression. Histological examination of the lung tissues proved that the mice treated with *A. argyi folium* and DA had less inflammatory cell infiltration into the peribronchial and alveolar lesions induced by LPS instillation [60]. On the other hand, *A. argyi folium* and DA were also demonstrated to reduce inflammatory cell counts, levels of IL-4, IL-5, and IL-13, and ovalbumin-specific IgE in asthmatic animals [69]. Asthmatic animals had extensive inflammatory cell accumulation in perivascular and peribronchial and mucus hypersecretion, which was diminished by *A. argyi folium* and DA treatment [69]. The study reported that Erk mediated cytokines expression, such as IL-5, for the regulation of IgE switching and eosinophil activation [69]. Erk was phosphorylated during inflammatory responses and subsequently phosphorylated Erk induced various inflammatory mediators, such as matrix metallopeptidase 9 (MMP-9) secreted by inflammatory cells [69]. MMP-9 not only destroyed normal alveolar structure but also degraded collagen to exacerbate airway inflammation [69]. The study revealed that *A. argyi folium* and DA treatment significantly reduced Erk phosphorylation and the expression of MMP-9 in asthmatic animals [69].

Another study displayed that the essential oil from *A. arg*nents, including monoterpenes, sesquiterpenes, alcohols, and aromatic compounds, and among which, the major components were cineole, camphor, α-(-)-thujone, and borneol [70]. AAEO inhibited the release of proinflammatory mediators in a dose-dependent manner, such as NO, PGE2, and ROS, and various cytokines, including TNF-α, IL-6, IFN-β, and MCP-1 in LPS-induced RAW264.7 macrophages [70]. Moreover, AAEO decreased the phosphorylation of JAK2 and STAT1/3, indicating that AAEO had anti-inflammatory activity through the inhibition of JAK2 and STAT1/3 pathways [70].

Xue et al. revealed that the dimeric sesquiterpenoids of *A. argyi folium* inhibited NO production [71]. They also suggested that Compound 2, a new guaianolide sesquiterpenoid dimer, had an inhibitory effect on the expression of iNOS via the activation of NF-κB and phosphorylation of MAPKs [71]. In Korea, there is a native Korean variety of *Artemisia argyi* H. called Seomae mugwort (SM). A polyphenolic mixture composed of 14 polyphenols, including five hydroxycinnamates, eight flavonoids, and one lignin, was extracted from SM by aqueous 70% methanol followed by the elution of ethyl acetate over a silica gel column. Polyphenols isolated from SM exhibited anti-inflammatory properties in lipopolysaccharide-treated RAW 264.7 macrophages. Additionally, SM polyphenols inhibited the production of nitric oxide, activation of NF-κB, mRNA expression of iNOS synthase, TNF-α and IL-1β, and phosphorylation of MAPK, further suppressing macrophage activation [59]. Given the anti-inflammatory properties of *A. argyi folium* caused by blocking the NF-κB pathway, *A. argyi folium* may have therapeutic potential to attenuate COVID-19-induced inflammatory-related conditions.

Chrysanthemi flos

C. flos, documented as Ju Hua, has been widely used in TCM for its benefits to the lungs, liver, and kidneys [72], heat and toxin cleaning, and eyesight improvements [8]. Modern pharmacological studies have reported its bioactivities, which include anti-inflammatory, antioxidant, anticancer, antihepatotoxic, antiangiogenic, and immunomodulatory effects, and have identified important types of bioactive components, namely, flavonoids, volatile oils, organic acids, and other minor components, such as vitamin C [72–74].

Luteolin

Luteolin, a key flavonoid contained in *C. flos,* has been identified as a potent blocker of SARS-CoV-2 cell entry. Recent studies conducted via computational methods, including molecular docking, have suggested that luteolin shows a high affinity for human ACE2 and can bind to various SARS-CoV-2 target proteins, which prevents viral-host cell fusion. The binding of luteolin weakens the recognition and interaction of the RBD of SARS-CoV-2 spike protein with human ACE2. Previous studies have also confirmed that luteolin can inhibit SARS-CoV-2 from entering cells, which implies the possible strong antiviral activity of luteolin [75,76]. As a natural immunosuppressant and an anti-inflammatory agent, luteolin has been reported to possess pharmacological effects to combat cytokine storms. [77,78]. A study investigated the protective effects of luteolin in injury-induced inflammation in rats and found that after treatment with luteolin, serum levels of IL-1β, IL-6, and TNFα, *i.e.*, proinflammatory cytokines, were significantly reduced [79]. Moreover, flavonoids are widely recognized as inhibitors of platelet function. Luteolin and another flavonoid, apigenin, found in *C. flos*, have been identified to have antithrombotic efficacy. An *in vitro* human platelet aggregation study revealed that these two compounds efficiently inhibited thromboxane A2 (TXA2) synthesis and collagen-induced platelet aggregation, exerting positive effects to treat or prevent thrombotic events [80].

Casticin

Casticin, a polymethylflavone, exhibits a wide range of bioactivities, such as anti-inflammatory, antioxidative, and anticancer activities. An *in vitro* study demonstrated the lung-protecting effects of casticin against chronic obstructive pulmonary disease (COPD) in rats. The results revealed that casticin significantly suppressed the NF-κB and iNOS pathways, restored proinflammatory cytokine (TNF-α, IL-1β, and IL-6) and C-reactive protein levels in serum to near normal and ameliorated the increased levels of macrophages, neutrophils, and white blood cells [81]. Taken together, these results indicate the potential of casticin to suppress possible tissue damage and cytokine storms during COVID-19 infection. Moreover, as a popular bioactive compound in molecular docking studies to explore potential agents against SARS-CoV-2, casticin has been reported to have increased binding affinity to three therapeutic targets of coronavirus, including 3-chymotrypsin-like cysteine protease (3CLpro), spike protein, and RNA-dependent RNA polymerase (RdRP) [82].

Chlorogenic acid

Chlorogenic acid, a phytocompound, was identified in silico as a powerful 3CLpro inhibitor to tackle COVID-19 infection. Abundant research has also described the bioactivities of chlorogenic acid to modulate NF-κB, the TNF pathway, IL-17, and Th17 cell differentiation [83]. Furthermore, many components of *C. flos* have been recorded to possess a high affinity for SARS-CoV-2 target proteins and other bioactivities, including anti-inflammatory and antioxidative activities, which makes this herb a potential agent to treat COVID-19.

Glycyrrhizae radix

G. radix, also known as licorice in English and Gan Cao in Chinese, is commonly used not only in TCM prescriptions but also in food preparation for desserts and cuisines [84]. A study has shown that licorice is surprisingly one of the top 10 main ingredients used in TCM prescriptions for COVID-19 [84]. According to the Chinese Pharmacopeia, licorice has been categorized in the Qi reinforcement segment. It can replenish Qi (crucial energy that moves within the body to sustain one's health), tonify the spleen, eliminate heat, diminish toxicity, eradicate phlegm, relieve coughs, spasms, and pain, and harmonize other herbs in a single prescription [85]. Experimental and clinical studies have demonstrated that licorice or *G. radix* possesses antiviral, anti-inflammatory, immunomodulatory, antimicrobial, antitussive, and expectorant activities [84–86].

Licorice has been reported to attack SARS-CoV-2 directly by blocking its entry [86]. For example, the molecular docking and network pharmacology approach confirmed that licorice glycoside E can inhibit 3CLpro to block SARS-CoV-2 replication by targeting phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit gamma (PIK3CG) and E2F transcription factor 1 (E2F1) through the PI3K-Akt signaling pathway [87,88]. Furthermore, licorice phenol in Huashi Baidu decoction can bind to Mpro and ACE2, which could hinder SARS-CoV-2 replication and block viral binding sites [89]. Glycyrrhizin, a main compound of licorice, has been reported to have antiviral effects on SARS-associated coronaviruses (CoVs), human immunodeficiency virus type 1 (HIV-1), and chronic hepatitis C virus [90,91]. This study revealed that the key antiviral mechanism of glycyrrhizin is the induction of nitrous oxide synthase in Vero cells [92]. Given that COVID-19 belongs to the SARS-type coronavirus family, glycyrrhizin has potential in SARS-CoV-2 therapy. Through in silico and molecular docking analyzes, a study suggested that glycyrrhizin could be a potential drug candidate for SARS-CoV-2 treatment. Glycyrrhizin shows a higher possibility of binding to Mpro of SARS-CoV-2 and thus inhibits virus replication [91]. Nevertheless, *in vivo* studies are warranted to further verify these promising findings. A recent study revealed that glycyrrhizic acid, the key ingredient in licorice, effectively hinders the entry and replication of the SARS virus.

Additionally, glycyrrhizic acid can obstruct SARS-CoV-2 entry, replication, and inflammation by regulating steroid metabolism, targeting the main protein of SARS-CoV-2, inhibiting inflammatory agent release, and eventually diminishing virus-induced cytokine storms [9]. The coronavirus invades host cells through attaching to lipid raft on the plasma membrane of host cells. Gycyrrhizic acid reduced the size of the lipid raft domain to suppress the invasion of COVID-19 [93]. Additionally, COVID-19 patients with comorbidities, such as hypertension, may have severe or fatal risk because cholesterol can assist the invasion of COVID-19. Gycyrrhizic acid was found to decrease cholesterol domain on vascular endothelial cell membrane and meanwhile suppress platelet aggregation and thrombus formation [93]. The metabolic syndrome patients often have high levels of lipopolysaccharide (LPS) in the blood [93]. The combination of COVID-19 and LPS promotes NF-κB and cytokine activation, further inducing inflammation and even ARDS [93]. The study showed that gycyrrhizic acid regulated NF-κB to attenuate inflammatory response induced by LPS [93]. On the other hand, SARS-CoV-2 could infect intestinal epithelial cells and patients accompanied with inflammatory bowel disease (IBD) had poor recovery [93]. Gycyrrhizic acid was also found to suppress TNF-α activity to mitigate intestinal inflammation and improve IBD [93].

We have known that SARS-CoV-2 infection may damage brain nerves. The study showed that gycyrrhizic acid had a powerful neuroprotective effect in neuroinflammation and ischemic brain damage through activating anti-apoptotic mechanisms, regulating PI3K/Akt signaling, and inhibiting HMGB1 activity [93].

SARS-CoV-2 infection promotes the expression of activating transcription factor 2 (ATF2), resulting in activating pro-inflammatory genes and increasing inflammatory pain [93]. Gycyrrhizic acid was reported to exert anti-inflammatory activity to alleviate inflammatory pain by suppressing the expression of P38, and subsequently reducing downstream ATF2 activity [93].

Glycyrrhizin derivatives could inhibit SARS-CoV replication in Vero cells [94]. The glycyrrhizin derivatives with N-acetylgycosamine introduced into the glycoside chain had elevated anti-SARS-CoV activities [94]. SARS-CoV viruses are highly glycosylated in spike proteins (S-protein), and the viruses enter host cells through S-protein binding to cellular receptors [94]. In this study, they found that the binding of N-acetylgycosamine to the carbohydrates of the S-proteins could impede viral entry [94].

Houttuyniae herba cum radice

H. herba cum radice, also named Heartleaf Houttuynia, belongs to the family Saururaceae. Traditionally, this plant is acknowledged as a treatment for various diseases, including pneumonia, cough, severe acute respiratory syndrome, uteritis, acne, eczema, stomach ulcers, and leukorrhea. *H. herba cum radice* is known for its power to constrain the replication of a variety of viruses, such as SARS coronavirus, influenza neuraminidase, dengue virus serotype 2, and herpes simplex. Its key ingredients, such as alkaloids and flavonoids, have made *H. herba cum radice* for possible treatment due to its anti-inflammatory, anticancer, antioxidative, antiobesity, and antimicrobial activities [95].

Tsai et al. designed an innovative traditional Chinese medicine formula, NRICM101, as a COVID-19 treatment for a bench-to-bedside study. Heartleaf Houttuynia, one of the ingredients in NRICM101, has been demonstrated to have the potential to inhibit TNF-α production and block the binding of the SARS-CoV-2 spike RBD protein to ACE2 [96]. Das et al. found that *H. herba cum radice* could significantly inhibit three SARS-CoV-2 replication proteins, *i.e.*, Mpro, papain-like protease (PLpro), and ADP ribose phosphatase (ADRP). This study used gas chromatography-mass spectrometry (GC–MS) and liquid chromatography-mass spectrometry (LC–MS) and screened out two phytocompounds from *H. herba cum radice, i.e.*, 6-hydroxyondansetron and quercetin, and then docked these compounds into three SARS-CoV-2 receptor proteins. Their results indicate that 6-hydroxyondansetron shows a higher binding affinity to Mpro and PLpro and passes all the required drug discovery rules while quercetin binds to ADRP but shows less drug-like properties [95].

Ophiopogonis radix

O. Radix, the root of *Ophiopogon japonicus*, is known as Mai Men Dong in traditional Chinese medicine. According to the pharmacological principles of TCM, *O. Radix* has the effects of nourishing yin, moisturizing the lung, tonifying the stomach, and promoting fluid and therefore can be used to treat lung dryness and dry cough. In modern studies, the components of *O. Radix,* including steroidal saponins, polysaccharides, and homoisoflavonoids, have displayed numerous pharmacological properties, such as anti-inflammatory, antioxidative, and immunomodulatory activities [97].

A study conducted on human dermal fibroblasts reported that *O. Radix* could significantly reduce the expression of IL-6 and IL-8 and downregulate the production of IL-6 by the ELISA method in a powerful, concentration-dependent manner. Four main compounds extracted from *O. Radix* by methanol included two homoisoflavonoids and two steroidal saponins. They showed the anti-inflammatory activities against hydrogen peroxide-induced senescence of human dermal fibroblasts through *in vitro* experiments [98]. Another study aimed to identify the anti-inflammatory compounds from *O. Radix* and elucidated that several compounds could significantly repress the formulation of NO in LPS-induced RAW 264.7 mouse macrophage cells; in particular, some of these compounds could strongly reduce the formation of IL-6 and IL-1β. The isolated compounds were mainly homoisoflavonoids [99]. According to research on Sjogren's syndrome in an autoallergic mouse model, *O. Radix* polysaccharides reduced the plasma level of IFN-γ and IFN-γ/IL-4 ratio [100]. In patients with COVID-19, thrombotic complications ranging from venous thromboembolic disease, pulmonary embolism, and stroke are associated with multiorgan failure and are central to the high mortality rate [101]. A recent study highlighted the remarkable inhibitory effects of *O. Radix* on venous thrombosis. The ethanol extract of *O. Radix* protected endothelial cells from anoxic injury, decreased leukocyte-endothelial cell adhesion, and alleviate inflammation of the vein wall in rat and mouse models, further supporting its therapeutic applications for COVID-19 [102].

Perillae folium

P. folium, also called perilla, Shisoin Japan, Zi Su Ye in China, Korean perilla, tia to in Vietnam, perilla mint, beefsteak plant, purple mint, and Chinese basil, is an aromatic plant with a unique odor. The whole plant of *P. folium* can be utilized for a variety of remedial functions. Thus, it is frequently used as a TCM and kitchen herb in meals or desserts. For example, its seeds can eradicate phlegm, reduce Qi, comfort cough, and mitigate constipation. The leaves are good at boosting Qi, expelling heat, and tonifying stomach function [103,104].

A recent *in vitro* study of the human lung epithelial cell line Calu-3 indicated that perilla leaf extract (PLE) can reduce virus-induced cytokines such as TNF-α, IL-1, IL-6, and viral protein/RNA synthesis. PLE also manages to impede viral entry by turning off the SARS-CoV-2 virion, *i.e.*, spike protein. It is worth mentioning that PLE together with remdesivir achieves synergistic effectiveness against SARS-CoV-2 [103]. In addition, computational modeling and an *in vivo* study suggested that *P. folium* was efficacious against SARS-CoV-2 infection by decreasing the viral-induced cytopathogenic effect (CPE) of SARS-CoV-2 in Vero E6 cells and reducing the viral load, thus showing a good antiviral effect as a potential herbal candidate against SARS-CoV-2 [105]. It has been demonstrated that *P. folium* can effectively inhibit the inflammatory response by inactivating the HMGB1 signaling pathway through *in vivo* and *in vitro* studies [104]. There also is evidence that rosmarinic acid (RA), a primary compound of *P. folium*, has antimicrobial, antioxidant, and anticancer effects by impeding HMGB1 release, downregu-

Table 3
A comprehensive comparison of the mechanism of the herb in JSHD to treat COVID-19.

Ingredients/Action	Anisomeles indica (L.) Kuntze	Artemisia argyi	Chrysanthemi flos	Glycyrrhizae Radix et Rhizoma	Houttuyniae herba cum radice	Ophiopogonis radix	Perillae folium	Platycodonis radix
Antivirus								
Inhibit viral replication			✔	✔	✔		✔	
Inhibit viral transcription				✔				
Block ACE2 binding			✔	✔	✔			✔
Block membrane fusion							✔	✔
Antioxidation								
Reduce iNOS expression		✔	✔					✔
Reduce NO production	✔	✔		✔		✔	✔	
Promote N_2O production				✔				
Improve ROS reaction								✔
Inhibit overactivated immune								
Block leukocytes infiltration		✔	✔					
Reduce macrophage activation		✔						
Anti-inflammation								
Inhibit p38 MAPK activation		✔						
Block HMGB1 release							✔	
Inhibit NF-κB activation		✔	✔				✔	✔
Inhibit cytokines secretion	✔	✔	✔	✔		✔	✔	✔
Attenuate organ injury								
Reduce cell apoptosis								✔
Promote anti-thrombosis						✔		

ACE2: Angiotensin-converting enzyme 2; HMGB1: High Mobility Group Box 1; iNOS: nitric oxide synthase; MAPK: mitogen-activated protein kinase; N2O: Nitrous oxide; NF-κB: nuclear factor kappa B; NO: Nitric Oxide; ROS: Reactive oxygen species.

lating HMGB1-dependent inflammatory responses in human endothelial cells, hindering HMGB1-mediated hyperpermeability and leukocyte movement in mice, and decreasing sepsis-related mortality and cecal ligation and puncture (CLP)-induced HMGB1 release [104]. Furthermore, in LPS-stimulated RAW 264.7 cells, Wang found that *P. folium*, containing 4 monoterpenoids and 15 alkaloids, could significantly inhibit the production of the cytokines like TNF-α and/or IL-6 and inflammatory-related mediator NO [106].

Platycodi radix

P. radix, the root of *Platycodon grandiflorum* (PG), has been identified as a traditional medicine for lung and throat diseases, such as bronchitis, laryngitis, and tonsillitis, in East Asia for a long time [107]. A recent study showed that platycodin D (PD), a glycosylated triterpenoid saponin that is the major active natural component of *Platycodi radix* [108], exhibits a variety of pharmacological activities, including anti-inflammatory, anticancer, antidiabetic, and antinociceptive properties [107].

A novel study demonstrated that PD could redistribute the membrane cholesterol to block two routes of SARS-CoV-2 entry, including lysosome- and TMPRSS2-driven SARS-CoV-2 entry, which are the main infection routes [109]. Prosapogenin D methyl ester (PrsDMe) contained within PD inhibited the expression of the iNOS and cyclooxygenase-2 (COX-2) genes by suppressing NF-κB activation without considerable cytotoxic effects [107,108]. In another study, PD significantly inhibited the expression of NF-κB, and this result was also found in previous studies. In addition, the expression of the apoptosis-related proteins caspase-3 and Bax was downregulated, while the expression of bcl-2 was significantly restored [107]. Considering the pharmacological effects mentioned above, PG has great potential as a treatment to prevent and improve the clinical outcomes of COVID-19. However, due to the lack of research on human subjects, more clinical trials focusing on patient populations, efficacy and dosing are needed.

A comprehensive evaluation of the functions of the herbs in JSHD

We summarized the description of JSHD and plotted the efficacy of each of its constituent herbs against COVID-19 in Fig. 2 and compiled these data in Table 3. In Table 3, we divided the efficacies against COVID-19 into the following 5 categories: antiviral, antioxidation, suppression of the overactivated immune system, anti-inflammation, and attenuation of organ injury, and further subdivided these 5 categories into their detailed mechanisms. We analyzed each ingredient in JSHD mentioned above according to their detailed mechanisms.

Limitation

Although the results of our study suggest that JSHD is a potential multi-target drug candidate for the inhibition and treatment of COVID-19, our study has some limitations. First, there is no evaluation of interactions of herbal ingredients in JSHD in different pathways and pharmacokinetics changes. Second, JSHD is dissolved in water, but the herbal components of JSHD we report in this review article are extracted by different solvents, which may have differences in efficacy.

Conclusion

The COVID-19 epidemic is still severe, and currently, the spread of COVID-19 cannot be effectively controlled; furthermore, there is no medicine for its treatment. There is much evidence that traditional Chinese medicine can improve the symptoms of patients with COVID-19, delay the deterioration of the disease, and reduce the mortality of severe all-cause mortality. However, different combinations of Chinese medicines may bring better curative effects. JSHD is a formula based on traditional Chinese medicine theories and experiments. We provided evidence of the herbs in JSHD to treat COVID-19 *in vivo* and *in vitro*. The herbs in JSHD showed antiviral and antioxidative effects, suppressed the overactivated immune system, exerted anti-inflammatory effects, and attenuated organ injury. However, the global epidemic is getting worse. It is therefore hoped that in addition to conventional medical therapy, JSHD can be considered an adjunctive therapy for patients with COVID-19. And further rigorously designed studies are needed to prove the efficacy and safety of JSHD against COVID-19 infection.

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Data availability

The data utilized to support the findings of this study are included in the article.

Declaration of Competing Interest

The authors declare no conflicts of interest regarding the publication of this article.

CRediT authorship contribution statement

Ping-Hsun Lu: Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **Jing-Ling Lee:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **En-Yu Lee:** Data curation, Writing – original draft. **Yu-Ping Lin:** Data curation, Writing – original draft. **I-Hsin Lin:** Data curation, Writing – original draft. **Min-Chien Yu:** Data curation, Writing – original draft. **Kuo-Cheng Lu:** Data curation, Writing – original draft. **Ko-Lin Kuo:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing, Supervision, Funding acquisition.

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