

Potential therapeutic effect of Shufeng Jiedu capsule and its major herbs on coronavirus disease 2019 (COVID-19): A review

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SUMMARY The outbreak and rapid spread of coronavirus disease 2019 (COVID-19) poses a huge threat to human health and social stability. Shufeng Jiedu capsule (SFJDC), a patented herbal drug composed of eight medicinal plants, is used to treat different viral respiratory tract infectious diseases. Based on its antiviral, anti-inflammatory, and immunoregulatory activities in acute lung injury, SFJDC can be effectively used as a treatment for COVID-19 patients according to the diagnosis and treatment plan issued in China and existing clinical data. SFJDC has been recommended in 15 therapeutic regimens for COVID-19 in China. This review summarizes current data on the ingredients, chemical composition, pharmacological properties, clinical efficacy, and potential therapeutic effect of SFJDC on COVID-19, to provide a theoretical basis for its anti-viral mechanism and the clinical treatment of COVID-19.

Keywords Shufeng Jiedu capsule, coronavirus disease 2019, chemical composition, pharmacological properties, antiviral, anti-inflammatory

1. Introduction

Coronavirus disease 2019 (COVID-19), characterized by a rapid spread and profound impact on public health worldwide, has led to remarkable financial investments in the research and development of new drugs and vaccines (1). Fever, fatigue, and dry cough are the most common clinical presentations of COVID-19. However, few patients may experience nasal congestion, runny nose, and diarrhea (2). The basic clinical treatment for COVID-19 includes anti-infection, anti-inflammatory cytokines, non-specific antiviral drugs, and life support therapy (3-6). Despite increasing understanding of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and COVID-19, no clinical trial has revealed a validated significant effect for the treatment of patients with mild and moderate symptoms.

Traditional Chinese medicine (TCM) has been used for thousands of years in China to treat human diseases. Shufeng Jiedu capsule (SFJDC), a TCM containing eight types of herbal medicines, has a history of more than 30 years as a treatment for acute lung injury (ALI) and respiratory infections in China (7). SFJDC has been recommended by the China Food and Drug

Administration (CFDA) for the treatment of the 2009 influenza A (H1N1)-related upper respiratory tract infections since 2009. According to "Novel Coronavirus Pneumonia Diagnosis and Treatment Program (from the fourth to the eighth edition)" in China, SFJDC is recommended for use during the medical observation period when clinical manifestations of fatigue and fever are displayed.

In this review, we sought to summarize the ingredients, chemical composition, pharmacological properties, clinical efficacy, and potential therapeutic effect on COVID-19 of SFJDC to provide a theoretical basis for its anti-viral mechanism and the clinical treatment of COVID-19.

2. Ingredients of SFJDC

SFJDC is a TCM formula that is composed of eight medicinal herbs, including *Bupleurum chinense*, *Fallopia japonica*, *Forsythia suspensa*, *Glycyrrhiza uralensis*, *Isatis indigotica*, *Patrinia scabiosaefolia*, *Phragmites australis*, and *Verbena officinalis*, that exert a synergistic effect. The herbal composition of SFJDC is summarized in Figure 1.

3. Chemical composition of SFJDC

The primary analytical approach implemented in phytochemical studies includes the separation and identification of active components, which is crucial for the modernization of traditional Chinese medicine. Recently, ultra-performance chromatography (UPLC/Q-TOF) and tandem mass spectrometry (MS) methods have been established to characterize the chemical profile of extracts from SFJDC. A total of 94 compounds, including 1 carbohydrate, 7 amino acids, 1 coumarin, 11 phenylethanoid glycosides, 4 phenolic



Figure 1. Herbal compositions of SFJDC. Every 1000 capsules of SFJDC comprise 360 g *Bupleurum chinense*, 450 g *Fallopia japonica*, 360 g *Forsythia suspensa*, 180 g *Glycyrrhiza uralensis*, 360 g *Isatis indigotica*, 360 g *Patrinia scabiosaefolia*, 270 g *Phragmites australis*, and 360 g *Verbena officinalis* according to data from the Chinese Pharmacopoeia.

acids, 5 plant lignins, 25 flavonoids, 6 anthraquinones, 5 alkaloids, 18 triterpenoid saponins, 1 iridoid, and 7 glycosides were tentatively identified (8). The identification of these components may serve as a foundation for future studies on the pharmacological effects of SFJDC.

4. Chemical composition and pharmacological activities of the constituents of SFJDC

SFJDC is mainly composed of eight Chinese traditional medicinal herbs, each of which produces its own therapeutic effect. The independent pharmacological activity of each constituent jointly and synergistically exerts antiviral, antibacterial, antitumor, and anti-inflammatory activities. The chemical composition and pharmacological activities of each constituent are summarized in Table 1.

4.1. *Bupleurum chinense*

Bupleurum chinense is a perennial herb belonging to the Umbelliferae family (9). *Bupleurum chinense* is widely used in TCM because of its multiple pharmacological effects. In TCM, Radix Bupleuri, the dried root of *Bupleurum chinense*, has been employed for more than two thousand years in China (10). According to modern pharmacological studies, Radix Bupleuri possesses a wide range of bioactive properties, including antipyretic, anti-inflammatory, hepatoprotective, antibacterial, antiviral, immune regulation, and antiplatelet agglutination functions (11). Among the complex constituents of Radix Bupleuri, saikosaponins have been identified as the major biologically active constituents using modern techniques (12).

Table 1. The family, chemical composition, and pharmacological activities of the constituents of SFJDC

Ingredient	Family	Pharmacological properties	Chemical composition
<i>Bupleurum chinense</i>	Umbelliferae	antipyretic, anti-inflammatory, hepatoprotective, antibacterial, anti-virus, immune regulation and antiplatelet agglutination functions	saikosaponins
<i>Fallopia japonica</i>	Polygonaceae	lipid regulating, anti-shock, anti-inflammatory, antioxidant, anticancer, hepatoprotective, antiviral, antibacterial and antifungal	quinones, stilbenes, flavonoids, coumarins and lignans
<i>Forsythia suspensa</i>	Oleaceae	anti-inflammatory, antioxidant, anti-bacterial, anti-cancer, anti-virus, anti-allergy, and neuroprotective	phenylethanoid glycosides, lignans, flavonoids, phenolic acids, terpenoids, cyclohexylethanol derivatives
<i>Glycyrrhiza uralensis</i>	Leguminosae	anti-inflammatory, anti-allergic, antioxidant, antiulcer, hepatoprogenic, and neuroprotective	flavonoids and triterpenoid saponins
<i>Isatis indigotica</i>	Cruciferae	antiviral, anti-inflammatory and anticancer	alkaloids, phenolic compounds, polysaccharides, glucosinolates, carotenoids, volatile constituents, and fatty acids
<i>Patrinia scabiosaefolia</i>	Valerianaceae	anti-cancer, anti-inflammation, anti-pathogenic microorganisms, anti-oxidation, sedation, and hypnosis	triterpenes, iridoids, saponins, sesquiterpenes, flavonoids, coumarins, and lignans
<i>Phragmites australis</i>	Poaceae	antiasthmatic, antiemetic, antipyretic, antitussive, depurative, diuretic, febrifuge, lithontriptic, sedative, sialogogue, and stomachic	terpenoids, flavonoids, coumarins, acetylenes, caffeoylquinic acids, sterols, and amylase
<i>Verbena officinalis</i>	Verbenaceae	antioxidant, antimicrobial, anti-inflammatory, neuroprotective anticancer, analgesic, or anticonvulsant	iridoids, phenylpropanoid glycosides, phenolic acids, flavonoids, terpenoids, and essential oil

4.2. *Fallopia japonica*

Fallopia japonica is a perennial herb belonging to the Polygonaceae family (13). *Fallopia japonica*, a traditional Chinese medicinal herb, is widely distributed in southern China and Japan. According to numerous studies, the root of *Fallopia japonica* has a wide range of pharmacological activities, including lipid-regulating, anti-shock, anti-inflammatory, antioxidant, anticancer, hepatoprotective, antiviral, antibacterial, and antifungal effects (14-16). More than 67 chemical compounds have been isolated from *Fallopia japonica*, and its major components have been determined to be quinones, stilbenes, flavonoids, coumarins, and ligands (13). Among the chemical compounds, resveratrol, piceid, and emodin have been found to exhibit various biological activities. Resveratrol and piceid have been shown to possess antioxidant, anti-inflammatory, anticancer, anti-aging, and cardioprotective properties (17). Emodin has been shown to exert anti-inflammatory, antibacterial, and antineoplastic activities (18-20).

4.3. *Forsythia suspensa*

Forsythia suspensa is a flowering plant belonging to the Oleaceae family (21). *Forsythia suspensa* is widely distributed in China, Southeast Asia, and many European countries (22). Fructus Forsythiae, the seeds of *Forsythia suspensa*, exhibits high pharmacological activity and is documented in every edition of the Chinese Pharmacopoeia. In fact, a total of 114 Chinese medicinal preparations containing Fructus Forsythiae are listed in the 2015 edition of the Chinese Pharmacopoeia. Based on modern pharmacological studies, Fructus Forsythiae exerts anti-inflammatory, antioxidant, anti-bacterial, anti-cancer, anti-viral, anti-allergy, and neuroprotective effects (23). To date, approximately 210 compounds have been identified from *Forsythia suspensa*, including phenylethanoid glycosides, lignans, flavonoids, phenolic acids, terpenoids, cyclohexylethanol derivatives, and others (23). Among them, lignans and phenylethanoid glycosides, such as forsythiaside, phillyrin, rutin, and phillygenin, are considered the characteristic and active constituents of this herb (23).

4.4. *Glycyrrhiza uralensis*

Glycyrrhiza uralensis is a medicinal herb that belongs to the Leguminaceae family (24). *Glycyrrhiza uralensis* is found in southern Europe (*Glycyrrhiza glabra*) and East Asia (*Glycyrrhiza uralensis*), and has been used for traditional medicinal purposes for almost two thousand years (24). According to phytochemical studies, the main bioactive constituents of *Glycyrrhiza uralensis* are flavonoids and triterpenoid saponins, including licochalcone A, glycyrrhizic acid, isoliquiritigenin, liquiritigenin, and liquiritin, which exhibit a variety of

pharmacological activities, such as anti-inflammatory, anti-allergic, antioxidant, antiulcer, hepatoprogenic, and neuroprotective activities (25-27).

4.5. *Isatis indigotica*

Isatis indigotica is a biennial herbaceous plant belonging to the Cruciferae family (28). *Isatis indigotica* is distributed across China, and Radix Isatidis, the dried roots of *Isatis indigotica*, are widely employed in the prevention and treatment of a wide range of viral infections, including fever, influenza, epidemic hepatitis, and bacterial infection for thousands of years (29). Based on recent clinical data, Radix Isatidis has clinical effects on severe acute respiratory syndrome (SARS) and H1N1-influenza (30,31). Numerous phytochemical studies have led to the isolation of valuable bioactive compounds, such as alkaloids, phenolic compounds, polysaccharides, glucosinolates, carotenoids, volatile constituents, and fatty acids, among which alkaloids are the dominant compounds (29). Owing to numerous studies, these ingredients have been identified to have antiviral, anti-inflammatory, and anticancer effects (32-34).

4.6. *Patrinia scabiosaefolia*

Patrinia scabiosaefolia is a herbaceous perennial plant belonging to the Valerianaceae family. *Patrinia scabiosaefolia* is a Chinese herbal medicine with high nutritional and medicinal value, and is mainly distributed in mainland China (35). Modern pharmacological studies have shown that *Patrinia scabiosaefolia* has various effects, including anti-cancer, anti-inflammatory, anti-pathogenic, anti-oxidation, sedation, and hypnosis (36). According to previous phytochemical investigations, this genus contains a variety of components, including triterpenes, iridoids, saponins, sesquiterpenes, flavonoids, coumarins, and lignans (37). Among them, triterpenoid aglycones and triterpenoid saponins are considered the main active constituents of *Patrinia scabiosaefolia* (36). Typical representatives of triterpenoid aglycones in *Patrinia scabiosaefolia* include ursolic acid, hederagenin, and oleanolic acid.

4.7. *Phragmites australis*

Phragmites australis is a species belonging to the family, Poaceae (38). *Phragmites australis* found in wetlands throughout the temperate and tropical regions of the world. The root of *Phragmites australis* is used as a perennial Chinese herbal medicine (39) and the rhizoma of *Phragmites australis* has been used clinically for patients with pulmonary diseases throughout the long history of TCM use (40). The roots of *Phragmites australis* have been reported to have a

wide range of pharmacological activities, including antiasthmatic, antiemetic, antipyretic, antitussive, depurative, diuretic, febrifuge, lithontriptic, sedative, sialogogue, and stomachic (39). Phytochemical investigations have proven that this genus is rich in terpenoids, flavonoids, coumarins, acetylenes, caffeoylquinic acids, sterols, and amylase (40).

4.8. *Verbena officinalis*

Verbena officinalis is a herbal species of the family, Verbenaceae. Although *Verbena officinalis* is a perennial herb native to Europe, it is now growing worldwide (41). *Verbena officinalis* has traditionally been used to treat melancholia, hysteria, seizures, jaundice, fever, cholecystalgia, anxiety, depression, insomnia, menstrual disorders, abdominal problems, malaria, pharyngitis, edema, cough, asthma, rheumatic, and thyroid problems (42-44). *Verbena officinalis* has been reported to consist of several compounds, including iridoids, phenylpropanoid glycosides, phenolic acids, flavonoids, terpenoids, and essential oils (45,46). Numerous modern pharmacological studies have confirmed the antioxidant, antimicrobial, anti-inflammatory, neuroprotective, anticancer, analgesic, and anticonvulsant effects of *Verbena officinalis* herb extracts (47).

5. Clinical efficacy of SFJDC

SFJDC is mainly used to treat fever, parotitis, amygdalitis, plague, and other diseases (48). Recent

studies have shown that SFJDC has been widely used in the clinical treatment of viral diseases, such as Middle East Respiratory Syndrome (MERS), influenza, human infection with H7N9 avian influenza, and respiratory diseases (such as acute upper respiratory illness, acute exacerbation of chronic obstructive pulmonary disease, and pneumonia) (7). Based on clinical data, SFJDC might be a promising candidate for the treatment of COVID-19. The combination of SFJDC with conventional antiviral drugs for the treatment of COVID-19 patients can effectively improve clinical symptoms, including dry cough, fever, and systemic fatigue (48,49). In particular, the combination of arbidol, a synthetic broad-spectrum antiviral drug, and SFJDC to treat common-type COVID-19 reduces the duration of symptoms and increases the clinical effectiveness without causing significant adverse reactions (50). Similarly, another clinical study showed that SFJDC, added to standard antiviral therapy, significantly reduced the clinical recovery time of COVID-19, fatigue, and cough days compared to AVD alone (51). SFJDC therapy was also found to be significantly more effective when administered within the first 8 days after symptom onset (51). Based on case reports, four patients with mild or severe 2019-nCoV pneumonia were cured or had significant improvement in their respiratory symptoms after treatment with combined lopinavir/ritonavir, arbidol, and SFJDC on the basis of supportive care (52). The recommended diagnosis and treatment schemes for SFJDC are summarized in Figure 2.

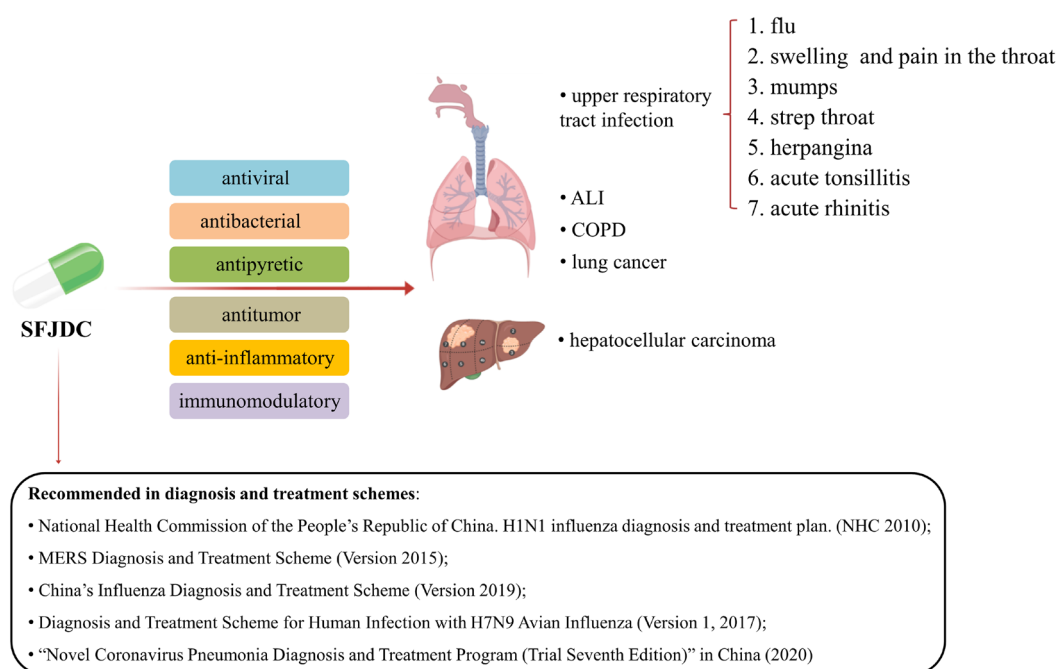


Figure 2. The pharmacological properties and clinical efficacy of SFJDC. SFJDC exerts antiviral, antibacterial, antitumor, and anti-inflammatory activities and is used to treat different upper respiratory tract infections, ALI, COPD, lung cancer, and hepatocellular carcinoma. SFJDC has been recommended in several diagnosis and treatment schemes.

6. Potential therapeutic effect of SFJDC on COVID-19

Currently, SARS-CoV-2 infection and immune dysfunction are believed to be the two main factors driving the pathogenesis of COVID-19 (53). In the early course of infection, the manifestation of the disease is primarily driven by the replication cycle of SARS-CoV-2. In the late course of infection, the severity of the disease is driven by a remarkable inflammatory/immune response to the virus. Thus, the anti-viral and anti-inflammatory/anti-oxidative capabilities and properties of SFJDC might act in tandem to improve the outcomes of infected patients. The potential therapeutic effects of SFJDC on SARS-CoV-2 are summarized in Figure 3.

6.1. Potential inhibitory effect of SFJDC on the replication cycle of COVID-19

6.1.1. Antiviral activity of SFJDC

Based on clinical investigations and basic research, SFJDC alone or in combination with other chemotherapeutic drugs exhibits antiviral effects. Modern clinical studies have shown that SFJDC has therapeutic effects on viral diseases, including MERS, influenza, and human infection with H7N9 avian influenza (48). Moreover, pre-clinical studies have shown that treatment with SFJDC and/or oseltamivir could decrease the elevated levels of NLRP3-inflammasome-associated components in human bronchial epithelial cells inoculated with the influenza A virus (IAV) (54). The combination of SFJDC and oseltamivir improved survival rates, alleviated lung damage, and reduced viral titers in lung homogenates from IAV-infected chronic obstructive pulmonary disease (COPD) rats (54). Furthermore, SFJDC significantly reduced the viral load in the lungs of HCoV-229E mice (51). Clinical data have shown that the addition of SFJDC to standard antiviral therapy significantly reduces the clinical recovery time of COVID-19 (50,51).

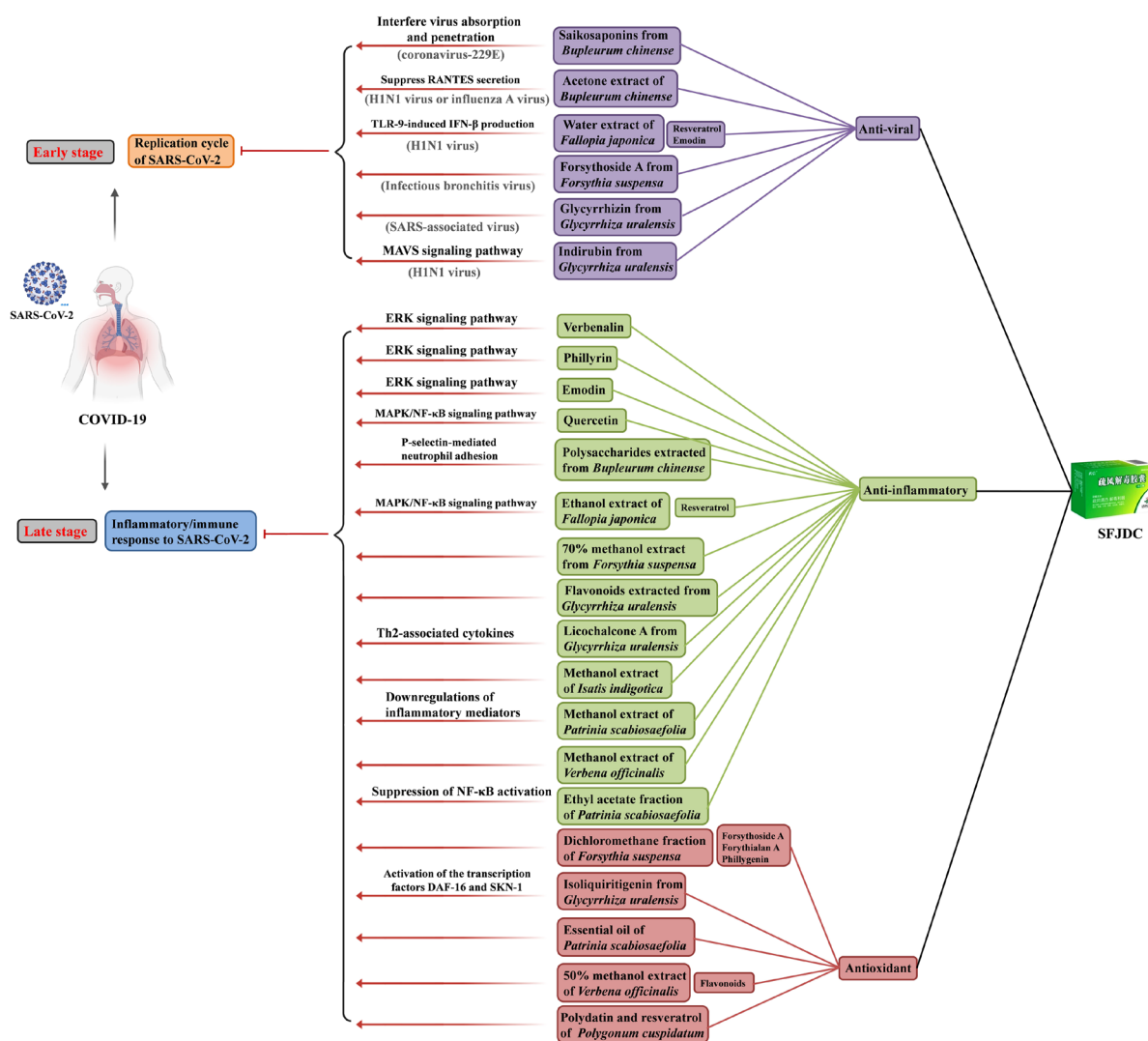


Figure 3. The potential therapeutic effect of SFJDC on SARS-CoV-2. The replication cycle of SARS-CoV-2 in the early course and immunity dysfunction in the late course of infection are the two main factors driving the pathogenesis of COVID-19; the anti-viral and anti-inflammatory/anti-oxidative capabilities and properties of SFJDC and its bioactive components might act in tandem to improve the outcomes of infected patients.

6.1.2. Active ingredients of SFJDC with antiviral activity

The acetone extract of Radix Bupleuri (the dried roots of *Bupleurum chinense*) has been reported to exhibit a significant antiviral effect on acute respiratory tract infections with H1N1 virus infection, the mechanism of which may be related to its suppression of influenza A virus-induced regulation of activation normal T cell expressed and secreted (RANTES) secretion (55). Moreover, saikosaponins (a, b₂, c, and d), the main active ingredient of Radix Bupleuri, exerted definitive antiviral activity against human coronavirus-229E by interfering with the early stage of viral replication, including absorption and penetration of the virus (56). These results suggest that Radix Bupleuri may have therapeutic benefits for the treatment of viral infection-associated diseases.

Fallopia japonica and its active components, resveratrol and emodin, have been shown to suppress influenza virus replication in A549 cells (57). Moreover, they preferentially inhibit the replication of multiple subtypes of influenza A virus. Mechanistically, *Fallopia japonica*, emodin, and resveratrol could upregulate the expression of interferon beta (IFN- β) through Toll-like receptor 9 (TLR9) and downregulate the expression of hemagglutinin and neuraminidase (57). Additionally, the anti-viral activity of resveratrol was abolished when supplemented with neutralizing anti-IFN- β antibodies or a TLR9 inhibitor in A549 cells, indicating that resveratrol may inhibit influenza virus replication by acting synergistically with IFN- β .

Forsythoside A is a major active constituent of *Forsythia suspensa* fruits. The antiviral activity of forsythoside A was confirmed by infecting primary chicken embryo kidney cells with infectious bronchitis virus (IBV) infection. The results indicate that forsythoside A inhibited the replication of avian IBV infection *in vitro* in a dose-dependent manner (58).

Glycyrrhizin is an active component of *Glycyrrhiza uralensis*. High concentrations of glycyrrhizin (4,000 mg/L) have been demonstrated to completely block SARS-CoV-2 replication (59,60). Glycyrrhizin can also inhibit the adsorption and penetration of the virus (59).

Indirubin, a bisindole alkaloid, is the main active ingredient in *Isatis indigotica*. A previous study demonstrated that indirubin significantly decreased the susceptibility of restrained mice to influenza H1N1 virus owing to the lowered mortality and reduced viral replication in the lungs (31). Mechanistically, indirubin maintained the morphology and function of mitochondria following influenza A virus infection and enhanced IFN- β production by promoting the mitochondrial antiviral signaling pathway (31).

6.2. Potential anti-inflammatory and anti-oxidative activities of SFJDC on the inflammatory/immune response to SARS-CoV-2

6.2.1. Anti-inflammatory and anti-oxidative activities of SFJDC

The anti-inflammatory and immunomodulatory properties of SFJDC have been demonstrated in several studies. Some active compounds of SFJDC, including forsythiaside (61), vitexin (62), and emodin (63), have been reported to possess anti-inflammatory effects. Tao *et al.* used an LPS-induced ALI rat model to investigate the anti-inflammatory effect of SFJDC (64). Based on the results, SFJDC can alleviate LPS-induced stress injury and inhibit inflammation in lung tissue by suppressing the mitogen-activated protein kinase (MAPK)/nuclear factor kappa-B (NF- κ B) signaling pathway (64). Recently, target prediction and RNA sequencing (RNA-Seq) based on transcriptome analysis have been used to clarify the inflammation-eliminating mechanism of SFJDC (65). According to the results, various ingredients of SFJDC, especially verbenalin, phillyrin, and emodin, could ameliorate *Pseudomonas aeruginosa*-induced acute lung injury, among which the extracellular regulated protein kinases (ERK) pathway was identified as a key pathway related to its anti-inflammatory effect (65). Similarly, airway inflammation and lung injury in IAV-infected rats could be controlled by the combination of SFJDC and oseltamivir by modulating the nucleotide-binding oligomerization domain (NOD)-like receptors containing pyrin domain 3 (NLRP3) inflammasome and subsequently downregulating interleukin-1 β (IL-1 β) and IL-18 levels (54).

6.2.2. Active ingredients of SFJDC with anti-inflammatory and anti-oxidative activities

Recently, the anti-inflammatory effects and possible mechanisms of water-soluble polysaccharides (BCPs) extracted from *Bupleurum chinense* were investigated. According to the results, BCPs could significantly ameliorate lung injury in an LPS-induced acute pneumonia model by inhibiting P-selectin-mediated recruitment of neutrophils (66). As P-selectin, which mediates adhesion between endothelium and neutrophils, is a promising target for inflammation-related diseases, it provides a new therapeutic strategy for improving inflammation-related disease processes with polysaccharides.

Another study investigated the effects of licorice flavonoids (LF) extracted from the roots of *Glycyrrhiza uralensis* on LPS-induced acute pulmonary inflammation in mice. Treatment with LF significantly decreased LPS-induced inflammatory cells and tumor necrosis factor- α (TNF- α) and IL-1 β mRNA expression in lung tissues, suggesting that LF effectively attenuates LPS-induced pulmonary inflammation (67). Licochalcone A, isolated from *Glycyrrhiza uralensis*, has been reported to have anti-inflammatory effects. According to *in vitro* studies, licochalcone A significantly inhibited reactive

oxygen species, eotaxin, and proinflammatory cytokines in inflammatory human tracheal epithelial (BEAS-2B) cells (68). Consistently, *in vivo* studies revealed that licochalcone A significantly decreased oxidative responses, reduced malondialdehyde levels, and increased glutathione levels in the lungs of ovalbumin (OVA)-sensitized mice (68). These findings suggest that licochalcone A has excellent potential to ameliorate asthmatic inflammation and oxidative stress.

The antinociceptive, anti-inflammatory, and antipyretic effects of *Isatis indigotica* were previously demonstrated. The root extract of *Isatis indigotica* was revealed to significantly inhibit the writhing responses of mice and decrease the licking time in the early and late phases of the formalin test (69). Moreover, carrageenan-induced paw edema in rats and pyrexia induced by LPS were attenuated by treatment with the root extract of *Isatis indigotica* (69).

Patrinia scabiosaefolia is usually used to treat anti-inflammatory diseases, especially colonic inflammation, viral infections, hepatitis, and uteritis in Asia. Numerous studies have shown that oleanonic acid and ursolic acid from *Patrinia scabiosaefolia* have good anti-inflammatory effects (70-72). More recently, the anti-inflammatory effect of the methanol extract of the roots of *Patrinia scabiosaefolia* in a dextran sulfate sodium-induced colitis mouse model was investigated. According to the results, *Patrinia scabiosaefolia* can not only significantly attenuate tissue myeloperoxidase accumulation, but also inhibit the abnormal secretion and mRNA expression of pro-inflammatory cytokines, such as TNF- α , IL-1 β , and IL-6 (73). Similarly, the ethyl acetate fraction of *Patrinia scabiosaefolia* suppressed LPS-induced nitric oxide (NO) and IL-6 production in RAW 264.7 cells, and inhibited the production of IL-6 and TNF- α in LPS-stimulated splenocytes from BALB/c mice. Mechanistically, the ethyl acetate fraction of *Patrinia scabiosaefolia* could downregulate the LPS-induced increase in NF- κ B activity. Therefore, *Patrinia scabiosaefolia* may be a potential therapeutic candidate for the treatment of inflammatory diseases.

Verbena officinalis has traditionally been used for the treatment of topical inflammation. Recently, the anti-inflammatory and gastroprotective activities of *Verbena officinalis* were evaluated in an acute gastric ulcer model induced by ethanol in rats. All extracts obtained with different solvents (methanol, enriched flavonoids, and supercritical CO₂) of *Verbena officinalis* exerted anti-inflammatory activity and decreased the area of ethanol-induced gastric damage in rats (74).

In recent years, several studies have shown that extracts from *Forsythia suspensa* exhibit remarkable antioxidant activity. Previously, phillyrin and forsythoside were found to be the major components of *Forsythia suspensa*, which are responsible for its antioxidant activities (75). Subsequently, forsythialan A, forsythialan B, phillygenin, and 8-hydroxypinoresinol,

extracted from the fruits of *Forsythia suspensa*, also exerted potent protective effects against peroxynitrite-induced oxidative stress in LLC-PK1 cells (76). Additionally, the dichloromethane (CH₂Cl₂) fraction of *Forsythia suspensa* exerted the strongest scavenging activity in a 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical scavenging experiment (77). These results indicate that *Forsythia suspensa* exerts protective effects against oxidative stress.

7. Network pharmacology tools to analyze the mechanism of SFJDC prevention and treatment of COVID-19

More recently, to identify new candidates with potential activity against SARS-CoV-2 viral targets, several studies employed computer modeling to explore the mechanism of SFJDC using network pharmacology and molecular docking technology. In this section, the active ingredients of SFJDC for the treatment of COVID-19 were predicted by network pharmacology methods, including quercetin, resveratrol, emodin, and phillyrin.

Among the viral proteins of SARS-CoV-2, 3C-like protease (3CLpro), a protease highly conserved among coronaviruses, is an attractive target for antiviral inhibitors owing to its indispensable role in viral replication and gene expression of viral proteins (78). Thus, molecules that can inhibit SARS-CoV-2 3CLpro would hinder viral replication and represent appropriate candidates for the development of low-toxicity drugs against this devastating pathogen. Quercetin has been reported to interact with 3CLpro using biophysical techniques and bind to the active site in molecular simulations (79). In particular, the study revealed a significant inhibition by quercetin of 3CLpro with a docking binding energy corresponding to -6.25 kcal/mol (79). Consistently, protein-chemical interactions suggest quercetin is a promising drug candidate against COVID-19 and other SARS-like viral infections (80).

Recently, network pharmacology and bioinformatics analysis were conducted to uncover the pharmacological mechanisms of resveratrol against COVID-19 (81). A significant overlap in geneontology (GO) terms and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways was found between SFJDC targets and SARS-CoV-2 differentially expressed genes (DEGs) (81). The shared targets were highly enriched in inflammation-related pathways, including the IL-17 signaling pathway, NF- κ B signaling pathway, and TNF signaling pathway (81). Resveratrol has also been suggested to be a promising drug candidate against COVID-19 through protein-chemical interactions (80). Collectively, these studies revealed that resveratrol is a promising therapeutic candidate for COVID-19 and highlighted the probable key targets and pathways involved.

Another study screened and harvested the candidate genes or targets of emodin and COVID-19 using

bioinformatics databases (82). According to the results, the core targets of emodin for the treatment of COVID-19 include MAPK1, tumor protein (TP53), and TNF. GO analysis of emodin against COVID-19 mainly highlighted the cytokine-mediated signaling pathway, response to LPS, and response to molecules of bacterial origin. KEGG analysis revealed that the molecular pathways mainly included the IL-17 signaling pathway, advanced glycation end-product (AGE)-advanced glycation end-product receptor (RAGE) signaling pathway in diabetic complications, and TNF signaling pathway (82). Molecular docking results revealed the docking capability of emodin and COVID-19 (82). Taken together, the current bioinformatic findings revealed the targets and pharmacological mechanisms of emodin in the treatment of COVID-19.

A research strategy combining network pharmacological analysis, protein docking, and molecular docking virtual computation was adopted to identify potential inhibitors of COVID-19 from active compounds in Mongolian medicine (83). Phillyrin was found to block the combination of SARS-CoV-2 S-protein and angiotensin-converting enzyme 2 (ACE2) at the molecular level (83). ACE2 is a functional receptor on the cell surface through which SARS-CoV-2 enters host cells (84). Therefore, phillyrin can be used as a potential inhibitor of the ACE2 receptor of SARS-CoV-2 in further research and development.

8. Conclusions

The global outbreak of COVID-19 has had a catastrophic impact on the global economy and human health. However, no specific therapeutic drugs are available to treat COVID-19. SFJDC is a commonly used Chinese medical preparation for the treatment of viral influenza due to its good clinical efficacy and few side effects. According to modern pharmacological studies, SFJDC, composed of eight traditional Chinese medicines, contains a variety of active ingredients. These ingredients exhibit a wide range of biological activities and pharmacological effects, including antiviral, antibacterial, antitumor, and anti-inflammatory properties, making SFJDC an adjuvant therapy for COVID-19. Nevertheless, further studies are required to elucidate the unconfirmed effects, regulatory mechanisms, and adverse reactions of SFJDC in the treatment of COVID-19.

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