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Network Pharmacology and Molecular Docking-Based Investigation of the Bioactive Constituents and Therapeutic Mechanisms of Shufeng Jiedu Capsule in COVID-19

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Abstract

This work explores the bioactive constituents and potential therapeutic mechanisms of Shufeng Jiedu Capsules (SFJDC) against the novel coronavirus using an integrated strategy combining network pharmacology and molecular docking approaches. Chemical constituents of SFJDC were collected from the TCMSP, TCMID, and BATMAN-TCM databases. Candidate active compounds were filtered according to ADME (absorption, distribution, metabolism, and excretion) criteria and structurally confirmed using PubChem, Chemical Book, and ChemDraw software, after which ligand structures for molecular docking were prepared. The SARS Coronavirus-2 major protease (SARS-CoV-2-Mpro) and angiotensin-converting enzyme 2 (ACE2) were selected as docking targets, and AutoDock software was applied to evaluate binding interactions. An integrated herbs–active components–targets network was constructed using Cytoscape 3.7.1, while Gene Ontology (GO) functional annotation and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were performed through the DAVID platform.

In total, 1,244 chemical constituents were identified from SFJDC, of which 210 met the criteria for active components. Ninety-seven of these compounds were further subjected to molecular docking with SARS-CoV-2-Mpro and ACE2, yielding 48 components with favorable binding affinity to SARS-CoV-2-Mpro. Ten compounds—including 7-acetoxy-2-methylisoflavone, kaempferol, quercetin, baicalein, glabrene, glucobrassicin, isoglycyrol, wogonin, petunidin, and luteolin—were capable of simultaneously interacting with both SARS-CoV-2-Mpro and ACE2. Among them, kaempferol, wogonin, and baicalein exhibited the strongest binding performance. The constructed network comprised 7 herbs, 10 key active compounds, and 225 predicted targets. GO analysis indicated that these targets participated in 653 biological processes, while KEGG enrichment identified 130 signaling pathways with a false discovery rate ≤ 0.01. Overall, the major active constituents of SFJDC—particularly kaempferol, wogonin, and baicalein—may exert anti–SARS-CoV-2 effects by binding to ACE2 and modulating multiple targets and signaling pathways, thereby contributing to the therapeutic potential of SFJDC against COVID-19.

Keywords: COVID-19, Mechanism of action, Molecular docking, Network pharmacology, Shufeng Jiedu Capsule

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Introduction

In December 2019, a cluster of pneumonia cases caused by a novel coronavirus emerged in Wuhan, China, and subsequently spread worldwide, leading to the disease now known as COVID-19. Owing to its high transmissibility, COVID-19 rapidly escalated into a global public health emergency. By April 30, 2020, more than

80,000 confirmed cases had been reported in China, with global cases exceeding three million. Clinically, infected individuals commonly present with severe acute respiratory manifestations, including fever, cough, dyspnea, fatigue, and pneumonia [1]. Subsequent studies demonstrated that SARS-CoV-2 shares substantial similarities with SARS-like coronaviruses in terms of pathogenic mechanisms and clinical features [2].

The SARS Coronavirus-2 major protease (SARS-CoV-2-Mpro) is a key enzyme responsible for cleaving viral replicase polyproteins into functional units, making it indispensable for viral replication and survival [3]. Due to its functional resemblance to the 3C protease of picornaviruses, this enzyme is also referred to as the 3C-like protease (3CLpro) [3]. In addition, accumulating evidence indicates that SARS-CoV-2 utilizes angiotensin-converting enzyme 2 (ACE2) as its cellular entry receptor, similar to the original SARS coronavirus, although the binding affinity may differ [4]. ACE2 has been definitively confirmed as essential for SARS-CoV-2 infection, underscoring the importance of understanding its expression and tissue distribution for effective disease prevention and control strategies [5].

Shufeng Jiedu Capsules (SFJDC) are a traditional Chinese medicine formulation composed of eight herbal ingredients: Polygonum cuspidatum (Huzhang), Forsythia suspensa (Lianqiao), Isatis tinctoria L. (Banlangen), Bupleurum chinense DC. (Chaihu), Patrinia scabiosaefolia Fisch. (Baijiangcao), Verbena officinalis L. (Mabiancao), Phragmites communis (Lugen), and Glycyrrhiza uralensis Fisch. (Gancao). Within this formulation, Polygonum cuspidatum serves as the principal herb and is traditionally used to dispel wind and eliminate dampness; extracts and purified compounds such as resveratrol from this plant have demonstrated inhibitory effects on HIV-1 replication [6, 7]. Forsythia suspensa, regarded as a ministerial herb, promotes blood circulation and alleviates blood stasis, with studies reporting antiviral activity of its major constituent quercetin against human cytomegalovirus and respiratory syncytial virus in vitro [8, 9].

Isatis tinctoria L., another ministerial component, is known for its heat-clearing and detoxifying properties and has been shown to attenuate influenza virus–induced inflammation and repair pathological damage in tracheal and lung tissues [10]. Bupleurum chinense DC., functioning as an adjuvant herb, is reported to mitigate lipopolysaccharide-induced acute lung injury in experimental models [11]. Additional adjuvant herbs, including Patrinia scabiosaefolia Fisch. and Verbena officinalis L., contribute anti-inflammatory and detoxifying effects, while Phragmites communis supports fluid production and thirst relief [12, 13]. Glycyrrhiza uralensis Fisch., acting as the conductant herb, has long been employed in the management of respiratory disorders such as cough, bronchitis, and pneumonia and is recognized for its antiviral activity [14].

Clinically, SFJDC is widely used for its antiviral and antibacterial properties and its capacity to enhance immune function [15]. It has demonstrated efficacy in treating acute viral upper respiratory tract infections characterized by wind-heat syndrome [16], as well as acute exacerbations of chronic obstructive pulmonary disease [17]. Extensive clinical application has confirmed its therapeutic reliability, leading to its inclusion in official diagnostic and treatment guidelines for COVID-19 during the pandemic [18–20].

Despite the established clinical effectiveness of traditional Chinese medicine, the precise active components, molecular targets, and underlying mechanisms often remain insufficiently defined [21]. Network pharmacology offers a systematic framework for elucidating complex drug–disease interactions by integrating multi-component and multi-target information [22]. Molecular docking further complements this approach by simulating intermolecular interactions, enabling the prediction of binding modes and affinities between small-molecule ligands and macromolecular receptors [23, 24].

In the present study, network pharmacology combined with molecular docking was employed to clarify the active constituents of SFJDC and their potential mechanisms against SARS-CoV-2. SARS-CoV-2-Mpro and ACE2 were selected as core targets, and the interactions between these proteins and SFJDC-derived compounds were systematically analyzed. Functional annotation and pathway enrichment of the predicted targets were subsequently performed to elucidate the biological processes and signaling pathways involved. The results of this study may provide a theoretical and experimental foundation for the development of novel therapeutic strategies for COVID-19.

Materials and Methods

Ethical approval

Ethical clearance was not required for this work, as no experiments involving humans or animals (or their tissues) were conducted.

Identification of active constituents in SFJDC

Chemical constituents of Shufeng Jiedu Capsules (SFJDC) were retrieved from the TCMSP database (http://lsp.nwu.edu.cn/tcmsp.php), the Traditional Chinese Medicine Integrated Database (TCMID; http://bionet.ncpid.org/), and BATMAN-TCM (http://bionet.ncpsb.org/batman-tcm/). Candidate compounds were further filtered according to oral bioavailability [25] and drug-likeness indices [26].

Consistent with previously reported criteria [27]. compounds with oral bioavailability ≥ 30% and drug-likeness ≥ 0.18 were considered active and retained for subsequent analyses. Structural information for the selected compounds was verified using the PubChem and Chemical Book databases (https://www.ncbi.nlm.nih.gov/, https://www.chemicalbook.com/). For molecules lacking available structural data, chemical structures were generated using ChemDraw software (version 16.0, https://www.chemdraw.com.cn).

Molecular docking and preparation of SARS-CoV-2-Mpro receptors

High-resolution crystal structures of SARS-CoV-2 main protease (SARS-CoV-2-Mpro; PDB ID: 6LU7) and angiotensin-converting enzyme 2 (ACE2; PDB ID: 1R42) were processed using AutoTools. Redundant protein chains and co-crystallized ligands were removed, followed by deletion of water molecules and hydrogenation of the protein structures. Gasteiger charges were assigned, and the processed receptors were saved in pdbqt format for docking analysis. Molecular docking between small-molecule ligands and protein receptors was carried out using AutoDock Vina (version 1.2, http://vina.scripps.edu/index.html), after which the optimal binding conformations were evaluated. Docking interaction diagrams were generated with Maestro (Schrödinger) software.

Target prediction and network construction for SFJDC active compounds

Potential molecular targets associated with SFJDC active compounds exhibiting favorable binding energies toward SARS-CoV-2-Mpro and ACE2 were predicted using the TCMSP platform (http://lsp.nwu.edu.cn/tcmsp.php). Target protein names were standardized and converted into corresponding gene symbols via the UniProt database (https://www.uniprot.org/) by restricting the species to Homo sapiens. An integrated herbs–bioactive components–targets (HB–C–T) interaction network for SFJDC was subsequently established using Cytoscape software (version 3.7.1, https://cytoscape.org).

Functional enrichment analysis of SFJDC-related targets

Functional characterization of the predicted targets was conducted using the DAVID 6.8 database (https://david.ncifcrf.gov/). Gene Ontology (GO) annotation was applied to explore associated biological processes, while Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis was performed to identify significantly enriched signaling pathways.

Results and Discussion

Selection of active components in SFJDC

Using the TCMSP, TCMID, and BATMAN-TCM platforms, a total of 1,244 chemical constituents were identified from the eight herbal components of SFJDC **(Table 1)**. Following ADME-based screening, 210 compounds met the predefined criteria and were classified as active constituents. Representative physicochemical and pharmacokinetic characteristics of selected active components are summarized in **Table 2**.

Table 1. Distribution of chemical constituents identified from each herb in Shufeng Jiedu Capsules (SFJDC) across different databases

No.	Herbal component (Chinese name)	TCMID	BATMAN-TCM	TCMSP	Total components
H1	*Polygonum cuspidatum* (Huzhang)	74	0	62	104
H2	*Forsythia suspensa* (Lianqiao)	90	47	150	156
H3	*Isatis tinctoria* L. (Banlangen)	0	33	169	185
H4	*Bupleurum chinense* DC. (Chaihu)	132	0	349	376
H5	*Patrinia scabiosaefolia* Fisch. (Baijiangcao)	0	0	52	52
H6	*Verbena officinalis* L. (Mabiancao)	18	0	58	66
H7	*Phragmites communis* (Lugen)	0	0	31	31
H8	*Glycyrrhiza uralensis* Fisch. (Gancao)	172	125	282	274

Table 2. Active components from SFJDC screened by ADME

No.	Compound ID	OB (%)	Compound name	Source herb(s)	DL
1	MOL000358	36.91	β-Sitosterol	H1, H2, H3, H5, H6	0.75
2	MOL000449	43.83	Stigmasterol	H3, H4, H5, H6, H7	0.76
3	MOL000098	46.43	Quercetin	H1, H2, H4, H5, H6, H8	0.28
4	MOL000422	41.88	Kaempferol	H2, H4, H5, H6, H8	0.24
5	MOL000006	36.16	Luteolin	H1, H2, H5, H6	0.25

6	MOL000359	36.91	Sitosterol	H3, H5, H8	0.75
7	MOL001790	39.84	Linarin	H3, H5, H8	0.71
8	MOL001689	34.97	Acacetin	H3, H5	0.24
9	MOL000354	49.60	Isorhamnetin	H4, H8	0.31
10	MOL001697	63.39	Sinoacutine	H3, H5	0.53
11	MOL001792	32.76	Liquiritigenin	H3, H8	0.18
12	MOL002322	31.29	Isovitexin	H3, H5	0.72
13	MOL000211	55.38	Mairin	H2, H8	0.78
14	MOL004856	51.08	Gancaonin A	H8	0.40
15	MOL002844	64.72	Pinocembrin	H8	0.18
16	MOL000392	69.67	Formononetin	H8	0.21
17	MOL004917	37.25	Glycyroside	H8	0.79
18	MOL002311	90.78	Glycyrol	H8	0.67
19	MOL002565	49.22	Medicarpin	H8	0.34
20	MOL001803	50.56	Sinensetin	H3	0.45
21	MOL001750	66.02	Glucobrassicin	H3	0.48
22	MOL001756	33.17	Quindoline	H3	0.22
23	MOL002881	31.14	Diosmetin	H6	0.27
24	MOL005229	49.55	Artemetin	H6	0.48
25	MOL003330	95.04	(–)-Phillygenin	H2	0.57
26	MOL003347	44.03	Hyperforin	H2	0.60
27	MOL003348	44.03	Adhyperforin	H2	0.61
28	MOL000173	30.68	Wogonin	H2	0.23
29	MOL002776	40.12	Baicalin	H4	0.75
30	MOL004991	38.92	7-Acetoxy-2-methylisoflavone	H8	0.26

Molecular docking analysis of key SFJDC active compounds with ACE2 and SARS-CoV-2-Mpro

Molecular docking simulations were conducted using 97 bioactive compounds derived from SFJDC as ligands, with SARS-CoV-2 main protease (SARS-CoV-2-Mpro) and angiotensin-converting enzyme 2 (ACE2) serving as the target receptors. The strength of interaction between each compound and its corresponding protein was assessed based on binding energy, where higher binding energy indicates a more stable ligand–receptor complex [28]. The docking analysis demonstrated that 10 out of the 97 screened compounds displayed favorable binding affinities toward both SARS-CoV-2-Mpro and ACE2, suggesting their potential roles as key active constituents of SFJDC **(Table 3)**.

Table 3. Molecular docking of active components in SFJDC

Active compound	Molecular formula	SARS-CoV-2-Mpro (kcal•mol^{-1})	ACE2 (kcal•mol^{-1})
7-Acetoxy-2-methylisoflavone	$C_{18}H_{14}O_4$	–6.3	–4.1
Kaempferol	$C_{15}H_{10}O_6$	–5.7	–4.3
Quercetin	$C_{15}H_{10}O_7$	–4.9	–3.8
Baicalein	$C_{15}H_{10}O_5$	–5.7	–4.3
Glabrene	$C_{20}H_{18}O_4$	–5.2	–4.1
Glucobrassicin	$C_{16}H_{19}N_2O_9S_2$	–4.9	–4.0
Isoglycyrol	$C_{21}H_{18}O_6$	–4.9	–4.0
Wogonin	$C_{16}H_{12}O_5$	–5.9	–4.3
Petunidin	$C_{16}H_{13}O_7^+$	–5.0	–4.0
Luteolin	$C_{15}H_{10}O_6$	–5.6	–3.9
Remdesivir	$C_{27}H_{35}N_6O_8P$	–4.9	–
Lopinavir	$C_{37}H_{48}N_4S_5$	–4.7	–
Ritonavir	$C_{37}H_{48}N_6O_5S_2$	–3.9	–

The binding affinities of currently recommended clinical antiviral agents, including lopinavir, ritonavir, and remdesivir, were also evaluated for comparison. Among these drugs, remdesivir exhibited the most favorable

interaction with SARS-CoV-2-Mpro, showing the lowest optimal binding energy (–4.9 kcal mol^{-1}) **(Table 3)**. Notably, kaempferol, baicalein, and wogonin demonstrated even lower binding energies with SARS-CoV-2-Mpro than remdesivir, reflecting stronger predicted binding stability. In addition, these three compounds also showed optimal binding affinities toward ACE2. As illustrated in **Figure 1**, kaempferol, baicalein, and wogonin were positioned within the active pocket of the ACE2 protein, where they formed hydrogen bond interactions with two amino acid residues, UNK910 and ALA614. Furthermore, all three compounds docked effectively into the active site of SARS-CoV-2-Mpro, establishing hydrogen bonds with five residues (THR26, ASN140, ASN142, GLU166, and PHE140) and π–π interactions with the VAL3 residue. These interaction patterns indicate that hydrogen bonding is a critical determinant for molecular recognition and binding stability between SFJDC active constituents and ACE2 as well as SARS-CoV-2-Mpro. Collectively, these findings support the notion that the principal bioactive components of SFJDC may exert therapeutic effects against COVID-19 through direct interactions with key viral and host proteins.

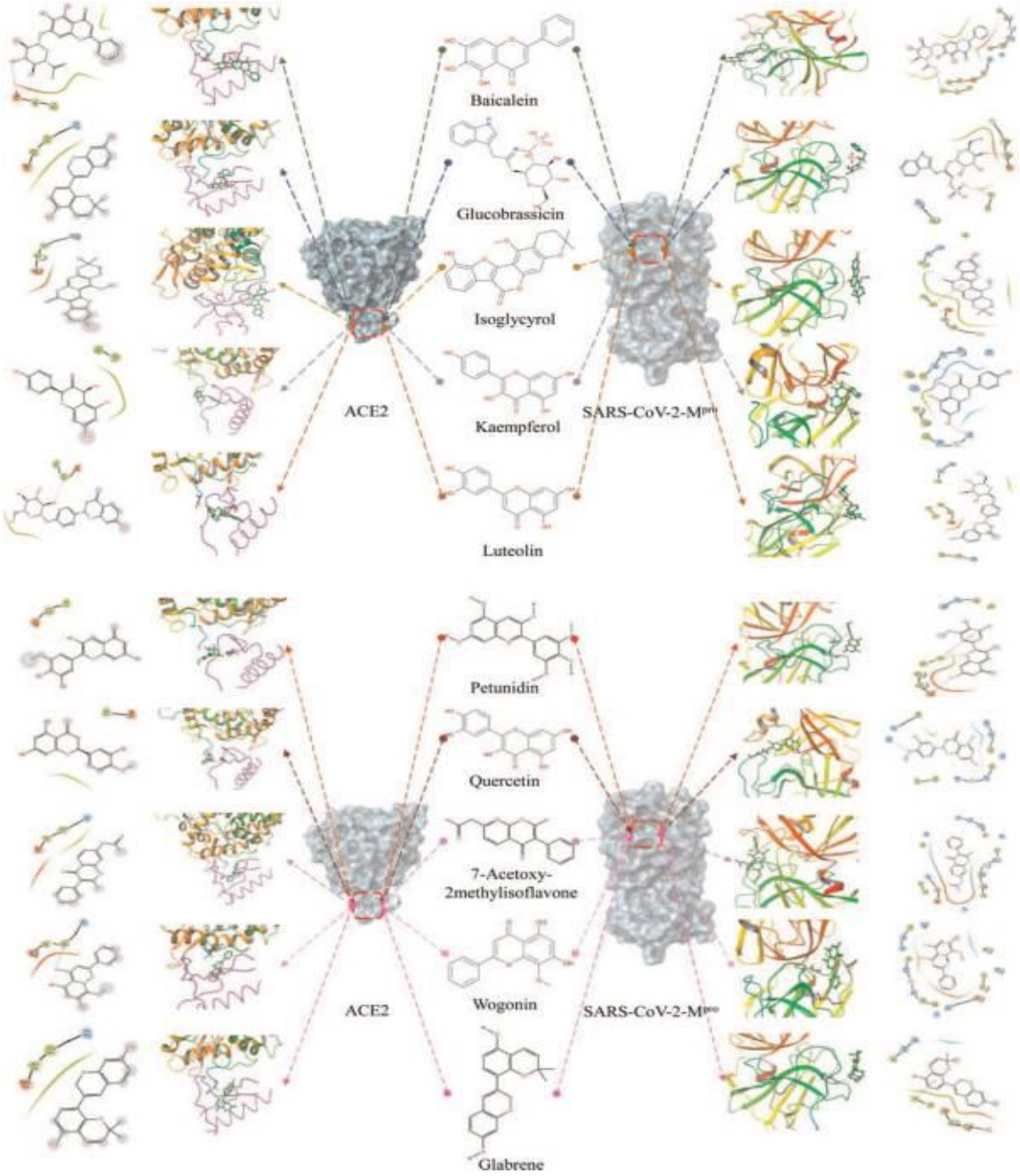

Figure 1. Molecular docking profiles illustrating the interactions between SARS-CoV-2-Mpro and ACE2 with ten representative active compounds. ACE2 denotes angiotensin-converting enzyme 2, and SARS-CoV-2-Mpro refers to the SARS Coronavirus-2 main protease.

Identification and screening of targets associated with key active components

Putative molecular targets corresponding to the ten selected bioactive compounds were predicted using the TCMSP analysis platform. Target protein identifiers were subsequently standardized and converted to gene symbols through the UniProt database. In total, 384 potential targets were initially retrieved, and after removal of redundant entries, 225 unique targets were retained for further analysis. To elucidate the interactions among herbs, active compounds, and their corresponding targets, an herbs–bioactive components–targets (HB–C–T) interaction network was generated **(Figure 2)**.

The overall average degree value of the constructed network was 3.18. With respect to the component nodes, nine compounds exhibited degree values exceeding the network average, and approximately 70% of the components were linked to more than 20 targets on average, suggesting the presence of several core constituents capable of regulating a large proportion of SFJDC-related targets. Among these, quercetin (Degree = 153), kaempferol (Degree = 61), luteolin (Degree = 58), baicalein (Degree = 27), 7-acetoxy-2-methylisoflavone (C1, Degree = 26), glabrene (Degree = 20), and liquiritigenin (Degree = 20) were associated with the highest number of targets.

From the target perspective, those influenced by a greater number of compounds are more likely to represent key regulatory nodes for SFJDC activity. A total of 29 targets displayed degree values above 3.18, among which AR (Degree = 7), PRSS1 (Degree = 7), NCOA2 (Degree = 7), PPARG (Degree = 6), PTGS2 (Degree = 6), and HSP90AA1 (Degree = 6) were modulated by more than six compounds. These findings indicate that SFJDC exerts its pharmacological effects through a multi-component, multi-target mode of action, whereby several active constituents converge on the same targets while individual compounds simultaneously regulate multiple molecular targets.

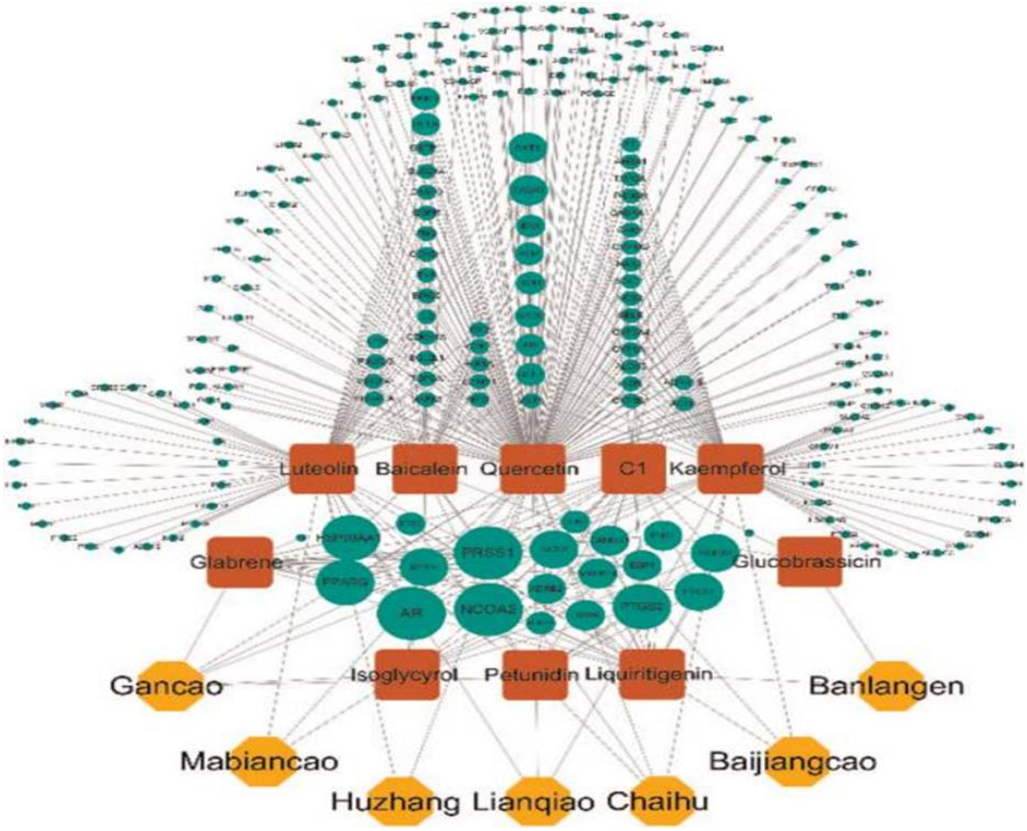

Figure 2. Herbs–active components–targets (HB–C–T) network. The network comprises 242 nodes (7 herbs, 10 active compounds, and 225 targets) and 385 edges. Edges connecting herbs (yellow octagons), compounds (red quadrilaterals), and targets (green circles) represent predicted interactions. Node degree reflects the number of direct interactions in the network, and node size is proportional to its degree; nodes with higher degrees are involved in more biological processes and are considered more biologically significant.

GO functional enrichment and KEGG pathway analysis

To explore the potential mechanisms of SFJDC, the 225 identified targets were subjected to Gene Ontology (GO) biological process analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment using the DAVID database. A total of 653 biological processes and 130 signaling pathways were associated with these

targets **(Figure 3)**. Key biological processes included regulation of RNA polymerase II promoter activity, apoptosis, positive regulation of gene expression, signal transduction, protein phosphorylation, proteolysis, immune and inflammatory responses, drug responses, and antiviral responses. The primary enriched pathways encompassed host pathogen recognition and inflammatory immune signaling (e.g., PI3K-Akt, apoptosis, TNF, HIF-1, p53, NOD-like receptor, T cell receptor, Toll-like receptor, NF-κB, and B cell receptor pathways), pathways linked to microbial infections (e.g., HTLV-I infection, influenza A, virus carcinogenesis), as well as the Ras signaling pathway. These results suggest that SFJDC may exert therapeutic effects by modulating multiple immune, inflammatory, and antiviral pathways.

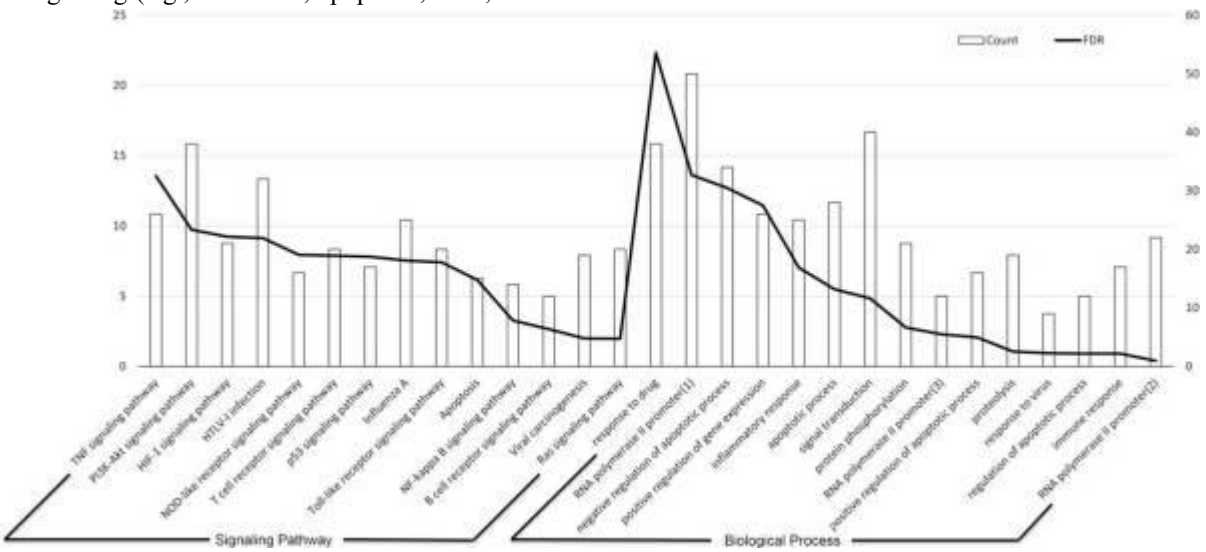

Figure 3. GO and KEGG enrichment analysis of the targets of SFJDC active compounds. FDR (false discovery rate, ≤ 0.01) indicates statistical significance; lower FDR values correspond to higher enrichment. GO = Gene Ontology, KEGG = Kyoto Encyclopedia of Genes and Genomes, SFJDC = Shufeng Jiedu Capsules.

This study explored the active constituents and underlying mechanisms of SFJDC against COVID-19 using network pharmacology and molecular docking approaches. In molecular docking, lower binding energy generally reflects stronger ligand–protein interaction [28]. Among the clinically recommended antiviral drugs, remdesivir exhibited a binding energy of –4.9 kcal·mol^{-1} with SARS-CoV-2-Mpro, which served as a reference threshold for evaluating SFJDC components. A total of 48 compounds from SFJDC showed stronger binding to SARS-CoV-2-Mpro than this threshold, including 30 from Glycyrrhiza uralensis Fisch (Gancao), seven from Forsythia suspensa (Lianqiao) and Isatis tinctoria L. (Banlangen), five from Patrinia Scabiosaefolia Fisch (Baijiangcao) and Verbena officinalis L. (Mabiancao), three from Bupleurum chinense DC. (Chaihu), and one from Polygonum cuspidatum (Huzhang). These findings suggest that these compounds may inhibit viral proliferation by directly interacting with SARS-CoV-2-Mpro.

Among the ten compounds exhibiting favorable ACE2 binding, kaempferol, baicalein, and wogonin demonstrated strong binding to both SARS-CoV-2-Mpro and ACE2. All three are flavonoids with documented antiviral and antibacterial activities [29–31]. HB–C–T network analysis showed that these flavonoids had the highest node degrees, indicating involvement in multiple biological functions. Kaempferol has been reported to inhibit the NF-κB pathway by reducing oxidative stress and inflammatory cytokines (TNF-α, IL-6, IL-1β) in bronchoalveolar lavage fluid [32], and to mitigate complement system overactivation, improving influenza A–induced acute lung injury [33, 34] Wogonin reduces inflammatory lung damage by downregulating TNF-α and IL-1β expression [35], while baicalein suppresses systemic allergic reactions, mast cell degranulation [36], and vascular remodeling in pulmonary hypertension via inhibition of MAPK and NF-κB pathways [37]. Recent studies also highlight the anti-COVID-19 potential of flavonoids such as kaempferol and baicalein [38, 39], supporting our findings. Hence, kaempferol, wogonin, and baicalein are likely key active compounds in SFJDC for COVID-19 treatment.

GO and KEGG enrichment analysis revealed that SFJDC targets are involved in 653 biological processes, including regulation of RNA polymerase II promoter activity, apoptosis, gene expression, signal transduction, protein phosphorylation, proteolysis, immune and inflammatory responses, drug response, and antiviral responses. Key KEGG pathways included PI3K-Akt signaling and virus-related innate immune pathways, such as NOD-like receptor and Toll-like receptor signaling. Viral infection often modulates the PI3K-Akt pathway to facilitate replication [40], and the targets associated with these pathways included MAPK1, RELA, IL6, and IKBKB.

Previous studies confirmed that RELA, MAPK1, and IL6 are important SFJDC targets in COVID-19 therapy [41, 42], with RELA being targeted by kaempferol, baicalein, and wogonin. Nevertheless, whether these flavonoids regulate PI3K-Akt, NOD-like receptor, and Toll-like receptor pathways via MAPK1, RELA, IL6, and IKBKB requires further investigation.

Conclusion

SFJDC may exert therapeutic effects against COVID-19 through the synergistic action of multiple compounds on multiple targets. However, given the limitations of network pharmacology and molecular docking, further experimental validation is necessary to support the theoretical and practical application of SFJDC in COVID-19 treatment and drug development.

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Conflict of interest: None

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Ethics statement: None

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