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Analysis of the active components and mechanism of Shufeng Jiedu capsule against COVID-19 based on network pharmacology and molecular docking

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Abstract

This study investigates the active components and mechanism of Shufeng Jiedu Capsules (SFJDC) against novel coronavirus through network pharmacology and molecular docking.

The TCMSP, TCMID, and BATMAN-TCM databases were used to retrieve the components of SFJDC. The active components were screened by ADME (absorption, distribution, metabolism, and excretion) parameters, and identified by Pubchem, Chemical Book, and ChemDraw softwares. The molecular docking ligands were constructed. SARS Coronavirus-2 Major Protease (SARS-CoV-2-M^{pro}) and angiotension converting enzyme 2 (ACE2) were used as molecular docking receptors. AutoDock software was used for molecular docking. Cytoscape 3.7.1 software was used to generate an herbs-active components-targets network. Gene Ontology gene function and Kyoto Encyclopedia of Genes and Genomes signal pathway analysis were performed by DAVID data.

A total of 1244 components were identified from SFJDC, and 210 active components were obtained. Among them, 97 active components were used as docking ligands to dock with SARS-CoV-2-M^{pro} and ACE2. There were 48 components with good binding activity to SARS-CoV-2-M^{pro}. Ten active components (including 7-Acetoxy-2-methylisoflavone, Kaempferol, Quercetin, Baicalein, Glabrene, Glucobrassicin, Isoglycyrol, Wogonin, Petunidin, and Luteolin) combined with SARS-CoV-2-M^{pro} and ACE2 simultaneously. Among them, Kaempferol, Wogonin, and Baicalein showed higher binding activity. The herbs-active components-targets network contained 7 herbs, 10 active components, and 225 targets. The 225 target targets were involved in 653 biological processes of Gene Ontology analysis and 130 signal pathways (false discovery rate $\leq$ 0.01) of Kyoto Encyclopedia of Genes and Genomes analysis.

The active components of SFJDC (such as Kaempferol, Wogonin, and Baicalein) may combine with ACE2 and act on multiple signaling pathways and targets to exert therapeutic effect on novel coronavirus.

Abbreviations: ACE2 = angiotension converting enzyme 2, COVID-19 = novel coronavirus, GO = Gene Ontology, KEGG = Kyoto Encyclopedia of Genes and Genomes, SARS = severe acute respiratory symptoms, SARS-CoV-2-M^{pro} = SARS Coronavirus-2 Major Protease, SFJDC= Shufeng Jiedu Capsules.

Keywords: COVID-19, mechanism of action, molecular docking, network pharmacology, Shufeng Jiedu Capsule

1. Introduction

In December 2019, an outbreak of pneumonia caused by the SARS-CoV-2 occurred in Wuhan, China, which is later named as COVID-19 and has been spreading since. The novel coronavirus (COVID-19) is highly contagious. As of April 30, 2020, more than 80,000 cases have been diagnosed in China, and more than

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3 million have been diagnosed worldwide. Patients have severe acute respiratory symptoms (SARS), including fever, dyspnea, fatigue, cough, and pneumonia.[1] Recent research results showed that SARS-CoV-2 was most similar to a group of SARS-like corona viruses in pathogenesis and clinical manifestations.[2] SARS Coronavirus-2 Major Protease (SARS-CoV-2-M^{pro}), the main proteolytic enzyme of SARS coronavirus, can cut the replicase of SARS coronavirus into functional proteins, thus playing an important role in the life cycle of SARS-coronavirus.[3] Because the hydrolysis specificity of the M^{pro} is similar to that of the 3C protease ($3C^{pro}$) of picornaviruses, M^{pro} is also called 3C-like protease ($3CL^{pro}$).[3] It has been reported that the SARS-CoV-2 may have the same receptor as that of SARS coronavirus (i.e., angiotension converting enzyme 2 [ACE2]), although its binding ability to ACE2 may be weaker than that of SARS coronavirus.[4] ACE2 was further confirmed to be indeed necessary for SARS-CoV-2 to infect cells.[5] Therefore, a deep understanding of the distribution and expression of ACE2 is of great significance for the prevention and control of COVID-19.[5]

Shufeng Jiedu Capsules (SFJDC) is a pure Chinese medicine preparation made from 8 Chinese herbs, including Polygonum cuspidatum (Chinese name Huzhang), Forsythia suspensa (Chinese name Lianqiao), Isatis tinctoria L. (Chinese name Banlangen), Bupleurum chinense DC. (Chinese name Chaihu), Patrinia Scabiosaefolia Fisch (Chinese name Baijiangcao), Verbena officinalis L. (Chinese name Mabiancao), Phragmites communis (Chinese name Lugen), and Glycyrrhiza uralensis Fisch (Chinese name Gancao). Among them, Polygonum cuspidatum (Chinese name Huzhang) has the effect of dispelling wind and eliminating dampness and is the monarch drug in SFJDC. Studies have shown that the Polygonum cuspidatum extract or its purified active ingredients (such as resveratrol) can inhibit HIV-1 virus replication.[6,7] Forsythia suspensa (Chinese name Lianqiao) has the effect of promoting blood circulation and removing blood stasis, and is the ministerial drug in SFJDC. Forsythia suspensa and its main active ingredient quercetin have anti-human cytomegalovirus effects and cytotoxicity in vitro.[8] The effective ingredient of Forsythia suspensa also has anti-respiratory syncytial virus effects in vitro.[9] Isatis tinctoria L. (Chinese name Banlangen) has heat-clearing and detoxicating effects and is the ministerial drug in SFJDC. It can significantly improve the inflammatory response caused by influenza virus FM1, and can repair the pathological damage of trachea and lung tissue.[10] Bupleurum chinense DC. (Chinese name Chaihu) has reconciling superficies and interior effects and is the adjuvant drug in SFJDC. It is reported that Bupleurum chinense DC. (Chinese name Chaihu) could alleviate acute lung injury in mice induced by lipopolysaccharide.[11] As an adjuvant drug in SFJDC, Patrinia Scabiosaefolia Fisch (Chinese name Baijiangcao) can exert heat-clearing and detoxicating effects. Cho et al[12] reported that the methanol extract of Patrinia scabiosaefolia played an anti-inflammatory role in mice with ulcerative colitis. Verbena officinalis L. (Chinese name Mabiancao), another adjuvant drug of SFJDC, can promote blood circulation, remove blood stasis, and has heat-clearing and detoxicating effects. Its extracts have anti-inflammatory activity.[13] Phragmites communis (Chinese name Lugen) can help produce saliva and slake thirst and serves as an adjuvant drug of SFJDC. Glycyrrhiza uralensis Fisch (Chinese name Gancao) is a conductant drug of SFJDC. In traditional Chinese medicine, Glycyrrhiza uralensis Fisch (Chinese name Gancao) is used to treat respiratory diseases such as cough, bronchitis, and pneumonia. It also has anti-viral effects.[14]

SFJDC has functions of anti-viral and anti-bacterial infection, and can enhance immunity.[15] It is often used clinically for the treatment of acute viral upper respiratory infection with wind-heat syndrome.[16] It is also used for treating acute exacerbations of chronic obstructive pulmonary disease.[17] After years of clinical observation, its effect is definite, and it is an ideal drug for anti-viral infection.[18,19] Since the outbreak, SFJDC has been included in the diagnosis and treatment guidelines for COVID-19.[20]

The traditional Chinese medicine plays an important role in the treatment of various diseases and has achieved significant clinical efficacy.[21] However, the potential components, targets and mechanism of the traditional Chinese medicine have not yet been clarified. Network pharmacology is an advanced approach to identify drug components, which can systematically explain the relationship between drugs and diseases.[22] Molecule docking can use chemometric methods to simulate the geometry and intermolecular forces of molecules, and to study the interactions between molecules,[23] which allows us to identify the active sites of small molecules (or ligands) and large molecules (or receptors) of known structure at low energy.[24]

In this paper, active components of SFJDC and its mechanisms against SARS-CoV-2 were investigated. The structure of SARS-CoV-2-M^{pro} was used as a template for network pharmacology and molecular docking. The active components of SFJDC were used as the matching library. SARS-CoV-2-M^{pro} and ACE2 were used as molecular docking receptors. Gene functions and metabolic pathways of components-targets were then analyzed. Our findings may provide experimental evidence for developing new drugs for the treatment of COVID-19.

2. Materials and methods

2.1. Ethical approval

Ethical approval was not necessary because this study did not involve animals or human subjects (tissues).

2.2. Screening of SFJDC active components

The active components of SFJDC were collected through the TCMSP platform (http://lsp.nwu.edu.cn/tcmsp.php), TCMID (http://bionet.ncpid.org/), and BATMAN-TCM (http://bionet.ncpsb.org/batman-tcm/). These active components were further screened by the oral bioavailability[25] and drug-likeness.[26] As previously described,[27] oral bioavailability $\geq$ 30 and drug-likeness $\geq$ 0.18 were set as the criteria for screening active components in this study. The structures of these components were confirmed by Pubchem and Chemical Book databases (https://www.chemicalbook.com/, https://www.ncbi.nlm.nih.gov/). For components with no available structure, Chemdraw (Version: 16.0, https://www.chemdraw.com.cn) was used to draw the component structure.

2.3. Prediction of SARS-CoV-2-M^{pro} receptor and molecular docking

AutoTools was used to pre-treat high-resolution crystal structure of SARS-CoV-2-M^{pro} (PDB ID: 6LU7) and ACE2 proteins (PDB ID: 1R42). The excess protein chains and ligands were removed. The water molecules were also removed by hydrogenation. The Gasteiger charge was calculated and saved as a pdbqt file for molecular docking. Then Autodock Vina (version: 1.2, http://vina.scripps.edu/index.html) was used for small molecule and

protein docking. Finally, the dominant conformation was analyzed. The Meastro (Schrodinger) software was used for drawing.

2.4. Prediction and screening of Targets for SFJDC active components

TCMSP (http://lsp.nwu.edu.cn/tcmsp.php) was used to predict and screen targets corresponding to the active components with better binding energy to SARS-CoV-2-M^{pro} and ACE2 in molecular docking. Protein names of the targets were converted into gene names based on the Uniprot database (https://www.uniprot.org/) using the keyword "Homo sapiens" (human genera). The herbs-active components-targets network (HB-C-T Network) of SFJDC was constructed using Cytoscape 3.7.1 software (version: 3.7.1, https://cytoscape.org).

2.5. Function analysis of targets for SFJDC active components

The targets of SFJDC active components were analyzed by DAVID6.8 database (https://david.ncifcrf.gov/) using Gene Ontology (GO) analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) signal pathway analysis.

3. Results

3.1. Screening of SFJDC active components

We collected a total of 1244 components from 8 herbs of SFJDC by TCMSP, TCMID, and BATMAN-TCM analysis platform (Table 1). Among them, 210 active components were obtained by screening the components through ADME (absorption, distribution, metabolism, and excretion) parameters. The basic information of some active components of SFJDC is shown in Table 2.

3.2. Molecular docking analysis reveals the interaction of SFJDC main active components with ACE2 and SARS-CoV-2-M^{pro} protein

Molecular docking was performed using 97 active components of SFJDC as ligands, and proteins of SARS-CoV-2-M^{pro} and ACE2 as receptors. The binding between the active component and the target was evaluated by the binding energy. The larger the binding energy, the more stable the ligand is bound to the receptor.[28] The docking results showed that 10 of the 97 active components of SFJDC exhibited good binding activity with SARS-CoV-2-M^{pro} and ACE2 (Table 3).

The binding energy of the current clinically recommended chemical drugs (Lopinavir, Ritonavir, and Remdesivir) was also analyzed. The results showed that the optimal binding energy of Remdesivir was the lowest among the 3 drugs (–4.9 kcal mol^{-1}) (Table 3). The binding energy of Kaempferol, Baicalein, and Wogonin with SARS-CoV-2-M^{pro} was lower than –4.9 kcal mol^{-1}, indicating good binding activity. Kaempferol, Baicalein, and Wogonin also had optimal binding energy with ACE2. As shown in Figure 1, Kaempferol, Baicalein, and Wogonin bound to the active site of the ACE2 protein, respectively. They formed hydrogen bonding interactions with 2 amino acids of UNK910 and ALA614 of ACE2 protein. They also bound to the active sites of SARS-CoV-2-M^{pro} protein and formed hydrogen bonding interactions with 5 amino acids (THR26, ASN140, ASN142, GLU166, and PHE140). They also formed pi-pi interactions with VAL3 amino acids of SARS-CoV-2-M^{pro} protein. The results indicate that hydrogen bonding plays a key role in the recognition and binding stability of active components of SFJDC with ACE2 and SARS-CoV-2-M^{pro} protein. This also suggests that the main active components of SFJDC exert therapeutic effects in the treatment of COVID-19 by interacting with related proteins.

3.3. Prediction and screening of active targets corresponding to active components

The active targets of these 10 active components were screened through the TCMSP analysis platform. The gene name-protein name conversion of targets was conducted through the Uniprot database. Totally, 384 targets were identified. After deleting the duplicate target names, 225 target targets were obtained. An HB-C-T network was constructed through network analysis to clarify the relationship between herbs, active components, and target targets (Fig. 2). The average Degree of the entire constructed network was 3.18. For the components, there were 9 components with Degree greater than 3.18. About 70% of the components had more than 20 targets on average, indicating that there may be a few key components in the network that can act on most of the SFJDC targets. Among them, Quercetin (Degree = 153), Kaempferol (Degree = 61), Luteolin (Degree = 58), Baicalein (Degree = 27), 7-Acetoxy-2-methylisoflavone (C1, Degree = 26), and Glabrene (Degree = 20), Liquiritigenin (Degree = 20) had the most targets. For the targets, the more components a single target is affected by, the more likely SFJDC can act on this target. There were 29 targets with Degree greater than 3.18. Among them, AR (Degree = 7), PRSS1 (Degree = 7), NCOA2 (Degree = 7), PPARG (Degree = 6), PTGS2 (Degree = 6), and HSP90AA1 (Degree = 6) were affected by more than 6 components. Therefore, multiple

Table 1

The number of components each herb of SFJDC.

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

SFJDC = Shufeng Jiedu Capsules.

Table 2

Active components from SFJDC screened by ADME.

No.	Components	OB (%)	DL	Herb
MOL000358	Beta-sitosterol	36.91	0.75	H1, H5, H6, H3, H2
MOL000449	Stigmasterol	43.83	0.76	H4, H5, H6, H7, H3
MOL000098	Quercetin	46.43	0.28	H1, H4, H5, H6, H2, H8
MOL000422	Kaempferol	41.88	0.24	H4, H5, H6, H2, H8
MOL000006	Luteolin	36.16	0.25	H1, H5, H6, H2
MOL000359	Sitosterol	36.91	0.75	H5, H3, H8
MOL001790	Linarin	39.84	0.71	H5, H3, H8
MOL001689	Acacetin	34.97	0.24	H5, H3
MOL000354	Isorhamnetin	49.6	0.31	H4, H8
MOL001697	Sinoacutine	63.39	0.53	H5, H3
MOL001792	Liquiritigenin	32.76	0.18	H3, H8
MOL002322	Isovitexin	31.29	0.72	H5, H3
MOL000211	Mairin	55.38	0.78	H2, H8
MOL004856	Gancaonin A	51.08	0.4	H8
MOL002844	Pinocembrin	64.72	0.18	H8
MOL000392	Formononetin	69.67	0.21	H8
MOL004917	Glycyroside	37.25	0.79	H8
MOL002311	Glycyrol	90.78	0.67	H8
MOL002565	Medicarpin	49.22	0.34	H8
MOL001803	Sinensetin	50.56	0.45	H3
MOL001750	Glucobrassicin	66.02	0.48	H3
MOL001756	Quindoline	33.17	0.22	H3
MOL002881	Diosmetin	31.14	0.27	H6
MOL005229	Artemetin	49.55	0.48	H6
MOL003330	(–)-Phillygenin	95.04	0.57	H2
MOL003347	Hyperforin	44.03	0.6	H2
MOL003348	Adhyperforin	44.03	0.61	H2
MOL000173	Wogonin	30.68	0.23	H2
MOL002776	Baicalin	40.12	0.75	H4
MOL004991	7-Acetoxy-2-methylisoflavone	38.92	0.26	H8

H1 to H8 = as indicated in Table 1.

ADME = absorption, distribution, metabolism, and excretion, DL = drug-likeness, OB = oral bioavailability, SFJDC = Shufeng Jiedu Capsules.

components of SFJDC can act on 1 target at the same time and a single component of SFJDC can act on multiple targets.

3.4. GO gene function and KEGG pathway analysis

To further understand the effect of SFJDC, we used GO gene biological processes and KEGG signal pathway analysis to analyze the 225 targets through the DAVID database. Our results showed that the 225 targets were related to 653 biological processes and 130 signal pathways (Fig. 3). The biological processes were mainly focused on the RNA polymerase II promoter and apoptosis, as well as positive regulation of gene expression, signal transduction, protein phosphorylation, proteolysis, immune response, inflammatory response, drug response, and response to viruses. The main

Table 3

Molecular docking of active components in SFJDC.

Active components	Molecular formula	Binding energy (kcal mol^{-1})	
		SARS-CoV-2-M^{pro}	ACE2
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	–

ACE2 = angiotension converting enzyme 2, SARS-CoV-2-M^{pro} = SARS Coronavirus-2 Major Protease, SFJDC = Shufeng Jiedu Capsules.

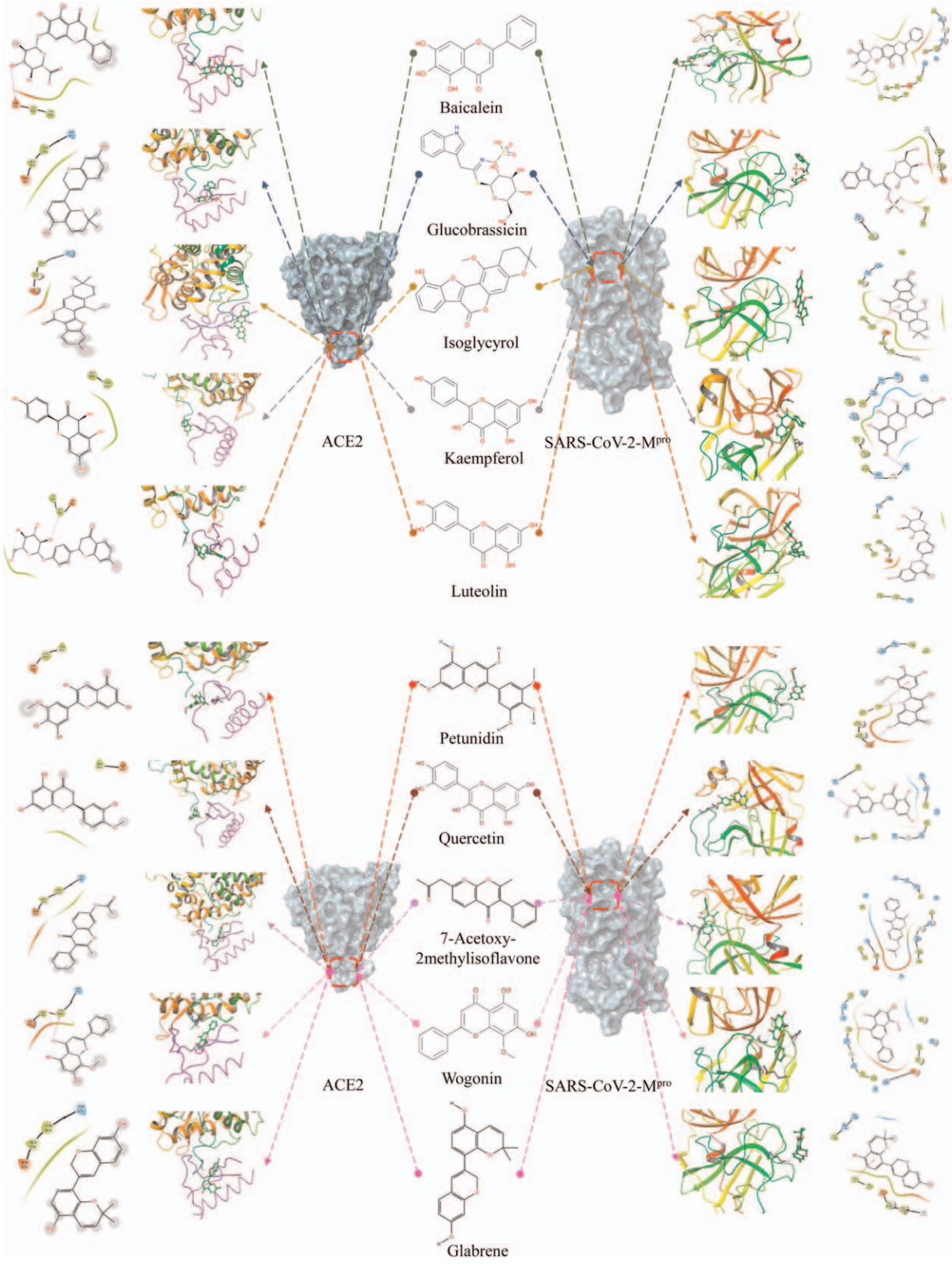

Figure 1. Molecular docking diagram of SARS-CoV-2-M^{pro} and ACE2 with 10 active compounds. ACE2 = angiotension converting enzyme 2, SARS-CoV-2-M^{pro} = SARS Coronavirus-2 Major Protease.

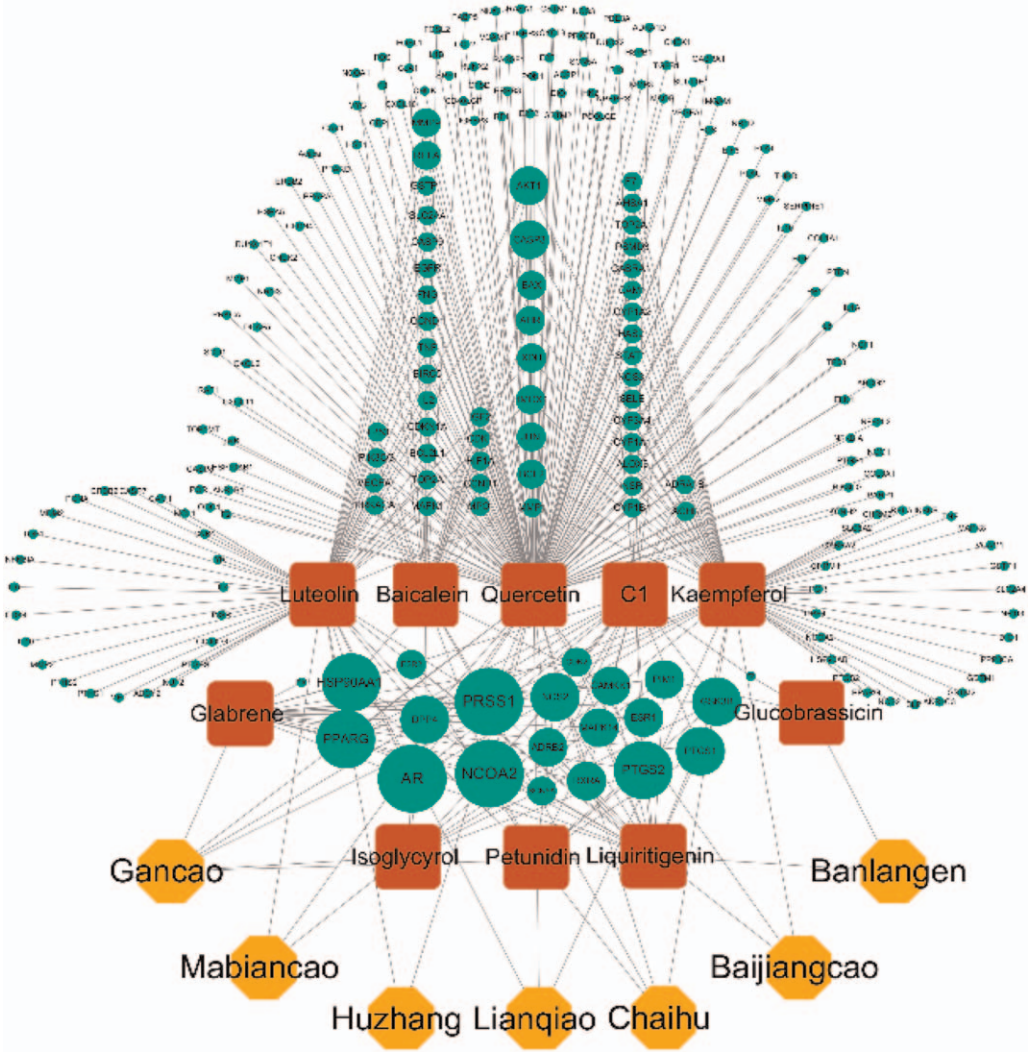

Figure 2. Herbal-active component-action target network. The network consists of 242 nodes (7 herbs, 10 active components, and 225 active targets) and 385 edges. The edges between HB (yellow octagon), C (red quadrilateral), and T (green circle) represent interactions. A degree of node (Degree) represents the number of nodes that directly interact with the node in the protein interaction network. The size of the node is proportional to the degree. The greater the degree of a node, the more biological functions it participates in, and the stronger its biological significance.

pathways were signal pathways related to human body recognition of pathogens and inflammatory immune response (such as PI3K-Akt signal pathway, apoptosis, TNF signal pathway, HIF-1 signal pathway, p53 signal pathway, NOD-like receptor signal pathway, T cell receptor signal pathway, Toll-like receptor signal pathway, NF-κB signal pathway, B cell receptor signal pathway), pathways related to pathogenic microorganisms (such as HTLV-I infection, influenza A infection, and virus carcinogenesis), as well as the Ras signal pathway.

4. Discussion

This study investigated the active components and mechanism of SFJDC against COVID-19 by network pharmacology and molecular docking. When performing molecular docking, it is generally believed that lower binding energy indicates higher binding ability.[28] In this paper, Redoxivir had a binding energy of $-4.9\,kcal\,mol^{-1}$ with SARS-CoV-2-M^{pro}, which was the lowest among the 3 chemical drugs. Thus, this binding energy may be used as the screening standard for the components of SFJDC. There were 48 components with good binding activity (lower than $-4.9\,kcal\,mol^{-1}$) with SARS-CoV-2-M^{pro}. Among them, there were 30 components from Glycyrrhiza uralensis Fisch (Chinese name Gancao), 7 from Forsythia suspensa (Chinese name Lianqiao) and Isatis tinctoria L (Chinese name Banlangen), 5 from Patrinia Scabiosaefolia Fisch (Chinese name Baijiangcao) and Verbena officinalis L. (Chinese name Mabiancao), 3 from Bupleurum chinense DC (Chinese name Chaihu), and 1 from Polygonum cuspidatum (Chinese name Huzhang). The results indicate that these components may directly act on the SARS-CoV-2-M^{pro}, thereby blocking the virus' proliferation. Meanwhile, 10 active components had good binding activity with ACE2. Among them, Kaempferol, Baicalein, and Wogonin had good binding activity with both SARS-CoV-2-M^{pro} and ACE2. The 3 of them are all flavonoids, and have various pharmacological activities against virus and bacteria.[29–31]

The HB-C-T network analysis showed that, Kaempferol, Wogonin, and Baicalein had the highest node degrees, indicating

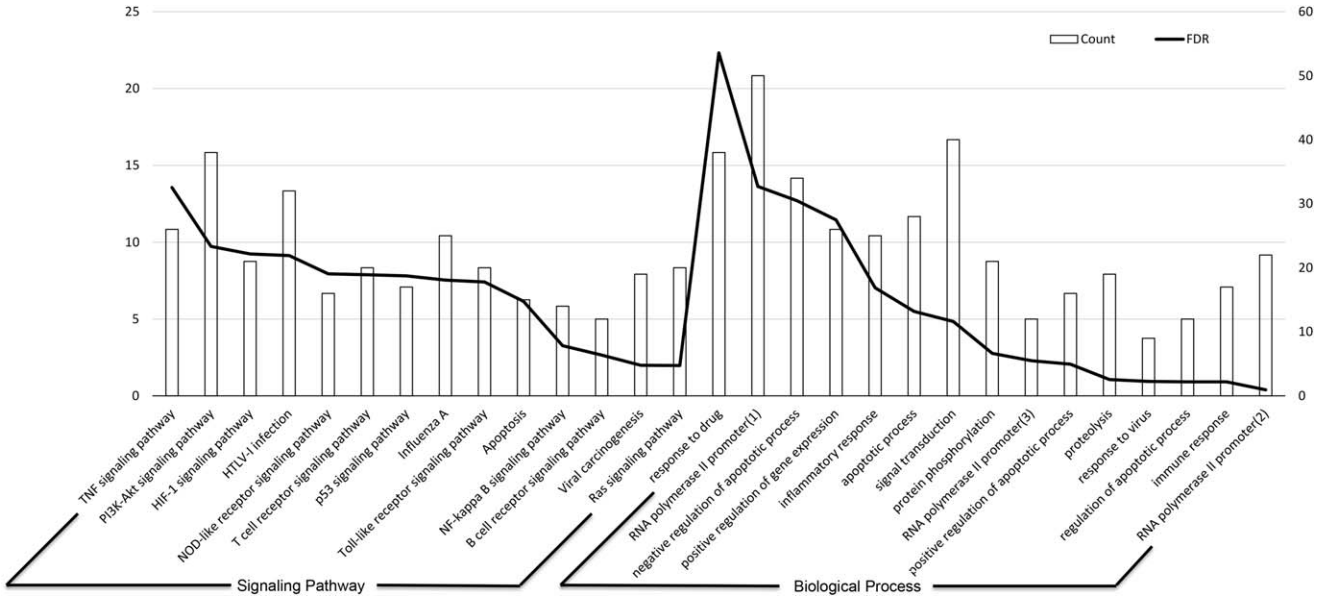

Figure 3. GO and KEGG analysis of the targets of SFJDC active components. FDR (false discovery rate, ≤ 0.01). The smaller the FDR, the smaller the enrichment analysis, the higher the degree of enrichment. GO = Gene Ontology, KEGG = Kyoto Encyclopedia of Genes and Genomes, SFJDC = Shufeng Jiedu Capsules.

that they may participate in many biological functions. It has been reported that Kaempferol inhibits the NF-κB signaling pathway by reducing oxidative stress and TNF-α, IL-6, and IL-1β inflammatory factors in bronchoalveolar lavage fluid.[32] It can inhibit the excessive activation of the complement system in the body and improve the acute lung injury induced by influenza A virus.[33,34] Wogonin reduces inflammatory pathological damage of lung tissue by inhibiting the expression of TNF-α and IL1-1β.[35] Baicalein can inhibit systemic allergic reactions by inhibiting the release of inflammatory mediators and mast cell degranulation.[36] Baicalein can also inhibit vascular remodeling and improve rat pulmonary arterial hypertension induced by crocin and the mechanism may be related to its inhibition of mitogen-activated protein kinase and NF-κB signaling pathway.[37] The recent studies on COVID-19 also reported the anti-COVID-19 potential of flavonoids such as Kaempferol and Baicalein,[38,39] which is consistent with our results. Therefore, Kaempferol, Wogonin, and Baicalein are main active components of SFJDC in treating COVID-19.

We further performed GO and KEGG analysis on the identified targets of SFJDC. The GO biological processes mainly included the RNA polymerase II promoter and apoptosis, as well as positive regulation of gene expression, signal transduction, protein phosphorylation, proteolysis, immune response, inflammatory response, drug response, and response to viruses. The main virus-relevant pathways obtained by KEGG analysis were the PI3K-Akt signaling pathway, as well as the signaling pathways related to the virus' natural immune response, such as the NOD-like receptor signaling pathway and the Toll-like receptor signaling pathway. Many viruses can regulate the host cell PI3K-Akt signaling pathway during infection to complete virus replication.[40] Targets that are involved in these 3 signaling pathways included MAPK1, RELA, IL6, and IKBKB. Chen et al[41] reported that RELA, MAPK1, and IL6 were important targets of SFJDC in treating COVID-19. Zhuang et al[42] also found that RELA and CASP9 were key targets of SFJDC in treating COVID-19. These findings further confirm the accuracy of the prediction results of this study. Among them, RELA was the target of Kaempferol, Baicalein, and Wogonin. However, whether the main active components in SFJDC regulate the PI3K-Akt signaling pathway, the NOD-like receptor signaling pathway, and the Toll-like receptor signaling pathway by acting on MAPK1, RELA, IL6, and IKBKB targets needs further study.

5. Conclusions

In conclusion, our results show that SFJDC may exert therapeutic effects on COVID-19 through the synergistic effect of multiple components and multiple targets. However, due to the limitations of network pharmacology and molecular docking, more experiments are needed to provide theoretical and experimental basis for SFJDC treatment of COVID-19 and later drug development.

Author contributions

Wenting Zhou, Jimilihan Simayi, and Maimaitiming Nuermaimaiti participated in the conception and design of the study. Wenting Zhou, Jimilihan Simayi, Maimaitiming Nuermaimaiti, Ainiwaer Wumaier, Maierdan Yusufu, Muhadaisi Nuer, Nulibiya Maihemuti, Bayinsang, and Kaysar Adurusul acquired and analyzed the data. Jimilihan Simayi, Maimaitiming Nuermaimaiti, and Nawaz Khan drafted and revised the manuscript. All authors have read and approved the final submitted manuscript.

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