Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Research paper

Analysis of the mechanism of Shufeng Jiedu capsule prevention and treatment for COVID-19 by network pharmacology tools

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ABSTRACT

Introduction: The novel coronavirus pneumonia that broke out in 2019 has become a global epidemic. According to the diagnosis and treatment plan issued in China and the existing clinical data, Shufeng Jiedu (SFJD) Capsule can be effectively used in the treatment of COVID-19 patients. This study aimed to explore its mechanism of action by network pharmacology and molecular docking technology.

Methods: The Chinese Medicine System Pharmacology Analysis Platform (TCMSP), a Bioinformatics Analysis Tool for Molecular mechANism of Traditional Chinese Medicine (BATMAN-TCM), the Encyclopedia of Traditional Chinese Medicine (ETCM) and related literature records were used to search the composition and main active compounds of SFJD, and to screen out the targets of drug components. Disease-associated genes were obtained by the Human Gene Database (GeneCards), the Human Online Mendelian Inheritance Platform (OMIM) and the DisGeNET database, and the co-targeted genes/proteins as targets of both SFJD and COVID-19 were selected by the Comparative Toxicogenomics Database (CTD). Co-targeted genes/proteins were analyzed by STRING, the Database for Annotation, Visualization and Integrated Discovery (DAVID) and Reactome for proteins to protein interaction (PPI), pathway and GO (gene ontology) enrichment, and predicted by AutoDock for their high-precision docking simulation. In addition, the therapeutic effect for SFJD treatment on COVID-19 was validated by the Chinese medicine anti-novel coronavirus pneumonia drug effect prediction and analysis platform (TCMCOVID).

Results: Screening resulted in 163 compounds and 463 targeted genes. The PPI core network contains 76 co-targeted proteins. The Reactome pathways were enriched in signaling by interleukins, immune system, etc. Finally, 6 key proteins of *TNF, IL-10, IL-2, IL-6, STAT1* and *CCL2* were selected and successfully docked with 4 active ingredients of quercetin, luteolin, wogonin and kaempferol.

Conclusion: SFJD may play a role in the prevention and treatment of COVID-19 through multiple active compounds acting on multiple targets and then multiple pathways.

1. Introduction

Coronavirus disease 2019 (COVID-19) caused by a novel virus strain, 2019-nCoV/*SARS-CoV-2* spread rapidly around the world in the first half of 2020 causing a global pandemic [1], and has posed a serious threat to global public health and economy [2]. COVID-19 is a respiratory illness. Traditional Chinese Medicine (TCM) plays a significant role in the treatment of respiratory diseases in China [3]. The research on antiviral TCM literature in the past 20 years suggests that the antiviral TCM is mainly based on clearing heat and detoxification [4]. SFJD capsule is a typical antibacterial and antiviral compound preparation used for this purpose.

As an ancient system of alternative medicine, TCM played an active role in the prevention and control of COVID-19 in China. It improved the clinical symptoms of patients, reduced the mortality rate, improved the recovery rate, and effectively relieved the operating pressure on the national medical system during a critical time [5]. TCM has its unique advantages for treatment based on syndrome differentiation [6]. TCM can provide more effective and personalized treatment via adjusting the specific medicine for each patient based on the different syndromes. TCM often has different effects on the distinct stages of diseases, contributing to the prevention, treatment and rehabilitation [7]. The analysis of Chinese medical sciences theory and clinical application of TCM shows that TCM contributes a systematic theoretical

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understanding about the pathological evolution and a positive clinical efficacy on novel coronavirus pneumonia [8]. As an indispensable part of TCM, Chinese patent medicines are highly valued and critically acclaimed in their campaign to contain and tackle the epidemic, they can achieve considerable effects for both suspected cases under medical observation period, and confirmed individuals with serious underlying diseases or critical conditions [9]. At present, there is a report that ranks the frequencies of Chinese Patent Medicine recommendations by guidelines and expert consensus for treatment of COVID-19 in China. Among them, the top 10 Chinese Patent Medicines include Shufeng Jiedu (SFJD) Capsule [10].

The Chinese national guideline summarised the opinions and frontline experience of medical experts across the country to provide by far the best management for COVID-19 [11]. According to "Novel Coronavirus Pneumonia Diagnosis and Treatment Program (Trial Seventh Edition)" in China, it is recommended to use Chinese patent medicine Shufeng Jiedu Capsules (granules) during the medical observation period when there are clinical manifestations of fatigue and fever. [12]. According to the clinical trial results of 200 ordinary COVID-19 patients in Wuhan Third Hospital from January 27, 2020 to March 5, 2020, it was found that the combined application of SFJD capsules with Western medicine could significantly improve ordinary COVID-19 patients with clinical symptoms such as cough, expectoration, fatigue, chest tightness and wheezing, improve the effectiveness of the main symptoms, regulate the expression of related peripheral blood inflammation indicators, promote the absorption of lung inflammation, and increase the cure rate [13]. According to the clinical trial results of 200 patients with mild novel coronavirus pneumonia in outpatient clinics of Wuhan Central Hospital from January 24 to January 30, 2020, SFJD capsule combined with Abidol in the treatment of mild novel coronavirus pneumonia can significantly improve the blood composition of patients, the percentage level of white blood cells and lymphocytes, make the chest CT infected foci obvious absorption [14]. According to the clinical trial results of 70 COVID-19 patients diagnosed and treated at the COVID-19 designated hospital Bozhou People's Hospital from January 31, 2020 to February 11, 2020, it was shown that the addition of SFJD capsule can shorten the time for patients to improve their clinical symptoms and the time for SARS-CoV-2 to become negative [15].

SFJD capsule evolved from "Detox Powder"[9], and it is commonly used for clinical treatment of acute upper respiratory tract infection caused by wind-heat syndrome [16]. Modern pharmacological studies have shown that SFJD capsules have a relatively broad inhibitory effect on common fungi, viruses, bacteria, etc. [9], and have a broad-spectrum antiviral effect in vitro [17]. In addition, SFJD and antibiotic combination therapy can reduce the inflammatory response and improve prognosis for septic patients [18]. SFJD is an eight-herb prescription that Hu Zhang (*Polygoni cuspidati* Rhizoma et Radix) is the monarch-ingredient; Ban Lan Gen (*Isatidis* Radix) and Lian Qiao (*Forsythiae* Fructus) are adjutant-ingredients; Lu Gen (*Phragmitis* Rhizoma), Bai Jiang Cao (*Patrinia scabiosifolia* Herba), Ma Bian Cao(*Verbenae* Herba) and Chai Hu(*Bupleuri* Radix) are assistant-ingredients; Gan Cao(*Glycyrrhizae* Radix et Rhizoma) is the envoy-ingredient [9].

The TCM network pharmacology approach provides a new research paradigm for translating TCM from an experience-based medicine to an evidence-based medicine system. It was created to prioritize disease-associated genes, to predict the target profiles and pharmacological actions of herbal compounds, to reveal drug-gene-disease co-module associations, to screen synergistic multi-compounds from herbal formulae in a high-throughput manner, and to interpret the combinatorial rules and network regulation effects of herbal formulae [19]. Therefore, we used network pharmacology tools to study the molecular mechanism of SFJD against COVID-19, aiming to provide a theoretical basis for the clinical application of SFJD and more accurate and effective use in the treatment of clinical COVID-19 patients. As shown in **Fig. 1**, to explore the molecular mechanism for SFJD against COVID-19, we tried to integrate the bioinformatics and network pharmacology tools [20] to predict the target genes and proteins and to analyze the interactions between SFJD ingredients with the targeted genes.

Abbreviations

ACE2	Angiotensin-converting enzyme 2
AKT1	RAC-alpha serine/threonine-protein kinase
BCL2L1	Bcl-2-like protein 1
BDKRB2	B2 bradykinin receptor
CASP3/8	Caspase-3/8
CCL2	C-C Motif Chemokine Ligand 2
CSNK2B	Casein kinase II subunit beta
COMT	Catechol O-methyltransferase
COVID-19	Coronavirus disease 2019
CTD	Comparative Toxicogenomics Database
CXCL8	Interleukin-8
CYP1A1	Cytochrome P450 1A1
CYP3A4	Cytochrome P450 3A4
EGFR	Epidermal growth factor receptor
ESR1	Estrogen receptor
ETCM	Encyclopedia of Traditional Chinese Medicine
FOS	Proto-oncogene c-Fos
FPR2	N-formyl peptide receptor 2
GLA	Alpha-galactosidase A
GO	Gene ontology
GTEx	Genotype-Tissue Expression Portal database
HMOX1	Heme oxygenase 1
HSP90	Heat shock protein HSP 90
IL-2/6/10	interleukin-2/6/10
JUN	Transcription factor AP-1
MAPK	Mitogen-activated protein kinase
MPO	Myeloperoxidase
ORA	Over-representation analysis
PLAT	Tissue-type plasminogen activator
PPARG	Peroxisome proliferator-activated receptor gamma
PPI	Proteins to protein interaction
PRKACA	cAMP-dependent protein kinase catalytic subunit alpha
PTGS2	Prostaglandin G/H synthase 2
RELA	Transcription factor p65
SFJD	Shufeng Jiedu
STAT1/3	Signal transducerand activator of transcription 1/3
TCM	Traditional Chinese Medicine
TCMCOVID	The Chinese medicine anti-new coronavirus pneumonia drug effect prediction and analysis platform
TCMSP	The Chinese Medicine System Pharmacology Analysis Platform
TNF	Tumor Necrosis Factor
TP53	Cellular tumor antigen p53
VEGFA	Vascular endothelial growth factor A

2. Methods

2.1. Meridian tropism and main active compounds analysis

ETCM (http://www.nrc.ac.cn:9090/ETCM/index.php/Home/Index/) is a comprehensive resource database of traditional Chinese medicine, which gathers information on herbal medicines, traditional Chinese medicine compounds, chemical components of traditional Chinese medicines, drug targets and related diseases. The herbal medicine contains information such as origin, medicinal taste, medicinal properties, meridian, indications, ingredients, and quality control standards. TCMSP (http://tcmspw.com/tcmsp.php) is a unique Chinese herbal medicine system pharmacology platform, which contains 499 herbal

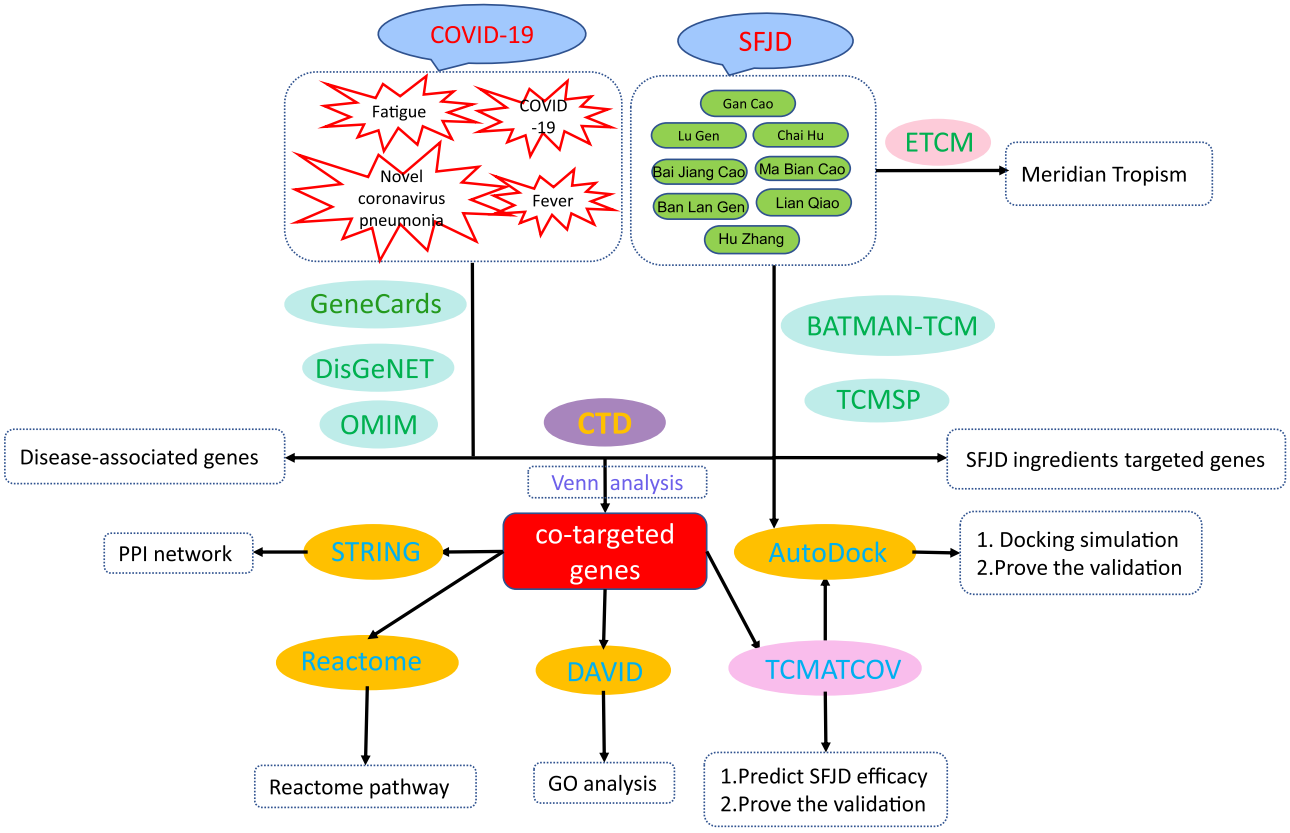


Fig. 1. The flow chart of this whole analysis.

medicines and the compound components of each herbal medicine. It provides comprehensive evaluation data of human absorption, distribution, and metabolism (ADME) properties for each compound. It also provides targets of potentially active molecules and their disease information. BATMAN-TCM (http://bionet.ncpsb.org/batman-tcm/) is the first online bioinformatics analysis tool specifically designed for studying the molecular mechanisms of traditional Chinese medicine, and it can predict the potential target of each query of Chinese medicine components. Choosing the 8 herbs of TCM composed of SFJD as keywords, the ETCM was used to query the meridian and the TCMSP and BATMAN-TCM were used to search the main active compounds of 8 herbs.

2.2. Ingredients targeted genes and Disease-associated genes mining

TCMSP was used to mine the targeted genes information of the main active compounds obtained in 2.1. Ingredients targeted genes of SFJD were made the official name through Uniport (https://www.uniprot.org/). GeneCards (https://www.genecards.org/) is a comprehensive database that can analyze human genetic data. Its main functions include analyzing gene expression, functional pathways, protein-protein interactions, and the relationship between genes and diseases. The DisGeNET (http://www.disgenet.org/) database is one of the largest databases containing human diseases and related gene targets, including 17,549 genes and 24166 diseases. OMIM (http://www.ncbi.nlm.nih.gov/omim) is a database that records the genetic components of all known diseases and predicts their relationship with related genes in the human genome. As SFJD was used to treat symptoms such as fever and fatigue during the medical observation period of novel coronavirus pneumonia, "Novel coronavirus pneumonia", "COVID-19", "Fever" and "Fatigue" were used as keywords to mine disease-associated genes by GeneCards, DisGeNET and OMIM. Through the CTD (http://ctdbase.org/) for Venn analysis, the co-targeted genes were obtained.

2.3. PPI and GO analysis

With STRING (search tool for the retrival of interacting genes/proteins) (https://string-db.org), we analyzed the co-targeted proteins that are encoded by disease-associated genes that interact with SFJD ingredient-targeted genes to explore their relationship within a PPI network. DAVID (https://david.ncifcrf.gov/) is a biological information database that provides systematic and comprehensive biological function annotation information for large-scale gene or protein lists. Entered the above targets into DAVID, and selected the species as "homo sapiens", set the threshold value $P \leq 0.05$ for GO enrichment analysis, and used Graphpad software to draw the results into histograms.

2.4. Reactome pathways enrichment

The Reactome Knowledgebase (https://reactome.org) provides molecular details of pathways and reactions in human biology. Reactome Knowledgebase is a new tool for studying biological pathways at a holistic level, and it can simplify data search and research related to biological pathways. We used it to draw two pathways that co-targeted genes set enriched.

2.5. Classic anti-COVID-19 prescription validation

The Chinese medicine anti-novel coronavirus pneumonia drug effect prediction and analysis platform (TCMAntiCOVID-19 V1.0, http://tcmatcov.bbtcml.com/) can realize the rapid prediction and analysis of the potential drug effect of traditional Chinese medicine or prescriptions and provide a reference for the evaluation of drug efficacy

Table 1
Four properties, five flavors and meridians.

Herb name	Herb Property	Herb Flavor	Herb Meridian Tropism
Hu Zhang (*Polygoni cuspidati* Rhizoma et Radix)	Mildly cold	Mildly bitter	Gallbladder meridian, Lung meridian, Liver meridian
Lian Qiao (*Forsythiae* Fructus)	Mildly cold	Bitter	Lung meridian, Small intestine meridian, Heart meridian
Ban Lan Gen (*Isatidis* Radix)	Cold	Bitter	Stomach meridian, Heart meridian
Chai Hu (*Bupleuri* Radix)	Mildly cold	Bitter, Pungent	Gallbladder meridian, Lung meridian, Liver meridian
Bai Jiang Cao (*Patrinia scabiosifolia* Herba)	Mildly cold	Bitter, Pungent	Stomach meridian, Large intestine meridian, Liver meridian
Ma Bian Cao (*Verbenae* Herba)	Cold	Bitter, Pungent	Liver meridian, Spleen meridian
Lu Gen (*Phragmitis* Rhizoma)	Cold	Sweet	Bladder meridian, Lung meridian, Stomach meridian
Gan Cao (*Glycyrrhizae* Radix et Rhizoma)	Even	Sweet	Lung meridian, Spleen meridian, Stomach meridian, Heart meridian

[21]. It compares the changes of network topological characteristics before and after drug intervention, and uses the disturbance rate to evaluate the effect of drugs on disease. Based on the TCMATCOV platform, SFJD was calculated and predicted to have a high disturbance score and to account for a high proportion of the classic anti-COVID-19 prescriptions used by clinicians. We built a component-drug target-disease protein interaction network on the TCMATCOV platform.

2.6. Molecular docking

Combining the targets analyzed by the PPI and the TCMATCOV platform, the overlapping targets were selected as the core target genes, and then the compound with high frequency corresponding to the core target genes were used as the core compounds. Selected core compounds and download the sdf structure of the compound from the PubChem (https://pubchem.ncbi.nlm.nih.gov/) database. The files were imported into AutoDock software to add charge and display rotatable keys and then saved in pdbqt format. The protein crystal structures corresponding to the core target genes were downloaded from the PDB database, imported into PyMOL software to remove water molecules and hetero molecules, imported into AutoDock software to add hydrogen atoms and charge operations, saved to pdbqt format. The above core compounds were used as ligands, and the proteins corresponding to the core target genes were used as receptors for molecular docking. From the 50 results, the one with the largest binding energy and the largest number of hydrogen bonds was selected as the final result. The results were analyzed and interpreted by PyMOL software.

3. Results

3.1. Meridian tropism and main active compounds analysis

The results of ETCM and literature search are shown in **Table 1**. The seven other herbs except for Gan Cao are all categorized as bitter cold, mainly in the lung, stomach and liver meridians.

A total of 163 active ingredients of SFJD were retrieved through the TCMSP and BATMAN-TCM. In addition to Gan Cao, 43 compounds were excavated with oral bioavailability (OB) ≥50% and drug-likeness (DL) ≥0.18 as parameters. The remaining 7 herbs were excavated with OB ≥30% and DL ≥0.18 as parameters. There are 10 effective compounds in Hu Zhang, 26 in Lian Qiao, 42 in Ban Lan Gen, 17 in Chai Hu, 12 in Bai Jiang Cao, 12 in Ma Bian Cao, and 1 in Lu Gen. Sorted by DL value, **Table 2** showed the top 20 active ingredients (more details showed in supplement material 1).

3.2. Disease-associated genes targeted by SFJD

According to GeneCards, OMIM and DisGeNET search, 429 "Novel coronavirus pneumonia" target genes, 324 "COVID-19" target genes, 7385 "Fever" target genes, and 7384 "Fatigue" target genes were obtained. 383 disease-associated genes were obtained by Venn analysis, as shown in **Fig. 2(A)**. Through TCMSP and BATMAN-TCM (score≥20; $P<0.05$) mining, 463 ingredients targeted genes of SFJD were obtained, which were subjected to Venn analysis with disease-associated genes to obtain 76 co-targeted genes of SFJD for preventing COVID-19, as shown in **FIG. 2(B)**.

3.3. The PPI networks of SFJD targeted proteins

Using STRING, we analyzed the interactions of 76 proteins that are disease-associated genes interaction with SFJD ingredient-targeted genes on the condition of highest confidence of 0.900, and the multiple PPI enrichment were obvious (P <1.0e−16). As shown in **Fig. 3**, the circular nodes represent the genes, and the straight line between the nodes represents the connection between the two genes, The darker the line, the stronger the correlation. We abandoned the above proteins with no effect relationship, imported the results into the Cytoscape software as a TSV format file for target relationship mining, and arranged them in the order of Degree, Closeness, Betweenness and Topological Coefficient, and selected the targets with a Degree greater than or equal to 10 as the " important targets" ", the results were shown in **Table 3** (more details showed in supplement material 3).

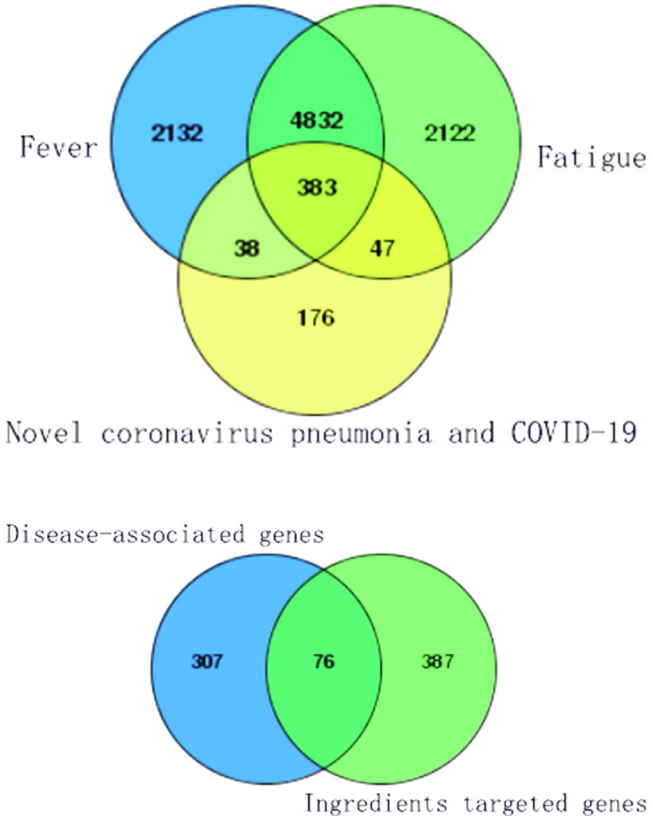


Fig. 2. Venn analysis of genes. (A) Disease-associated genes; (B) Co-targeted genes. NOTE: The original data showed in supplementary material 2.

Table 2
Information of some active ingredients of SFJD.

Herbs	Mol ID	Molecule Name	CAS	OB (%)	DL
Ban Lan Gen	MOL001810	6-(3-oxoindolin-2-ylidene)indolo[2,1-b]quinazolin-12-one	97457-31-3	45.28	0.89
Lian Qiao	MOL000791	bicuculline	485-49-4	69.67	0.88
Gan Cao	MOL005018	Xambioona	N/A	54.85	0.87
Lian Qiao	MOL003305	PHILLYRIN	487-41-2	36.4	0.86
Lian Qiao	MOL003365	Lactucasterol	N/A	40.99	0.85
Lian Qiao	MOL000522	arctiin	20362-31-6	34.45	0.84
Ma Bian Cao	MOL008752	Dihydroverticillatine	N/A	42.69	0.84
Ban Lan Gen	MOL001806	Stigmasta-5,22-diene-3beta,7beta-diol	N/A	42.56	0.83
Ban Lan Gen	MOL001804	Stigmasta-5,22-diene-3beta,7alpha-diol	N/A	43.04	0.82
Lian Qiao	MOL003281	20(S)-dammar-24-ene-3β,20-diol-3-acetate	N/A	40.23	0.82
Lian Qiao	MOL003315	3beta-Acetyl-20,25-epoxydammarane-24alpha-ol	N/A	33.07	0.79
Lian Qiao	MOL000211	Mairin	472-15-1	55.38	0.78
Lian Qiao	MOL000211	Betulinic Acid	472-15-1	55.38	0.78
Gan Cao	MOL000211	Mairin	472-15-1	55.38	0.78
Gan Cao	MOL005001	Gancaonin H	126716-35-6	50.1	0.78
Ban Lan Gen	MOL001755	24-Ethylcholest-4-en-3-one	67392-96-5	36.08	0.76
Ban Lan Gen	MOL000449	Stigmasterol	83-48-7	43.83	0.76
Chai Hu	MOL000449	Stigmasterol	83-48-7	43.83	0.76
Chai Hu	MOL004718	α-spinasterol	481-18-5	42.98	0.76
Bai Jiang Cao	MOL000449	Stigmasterol	83-48-7	43.83	0.76

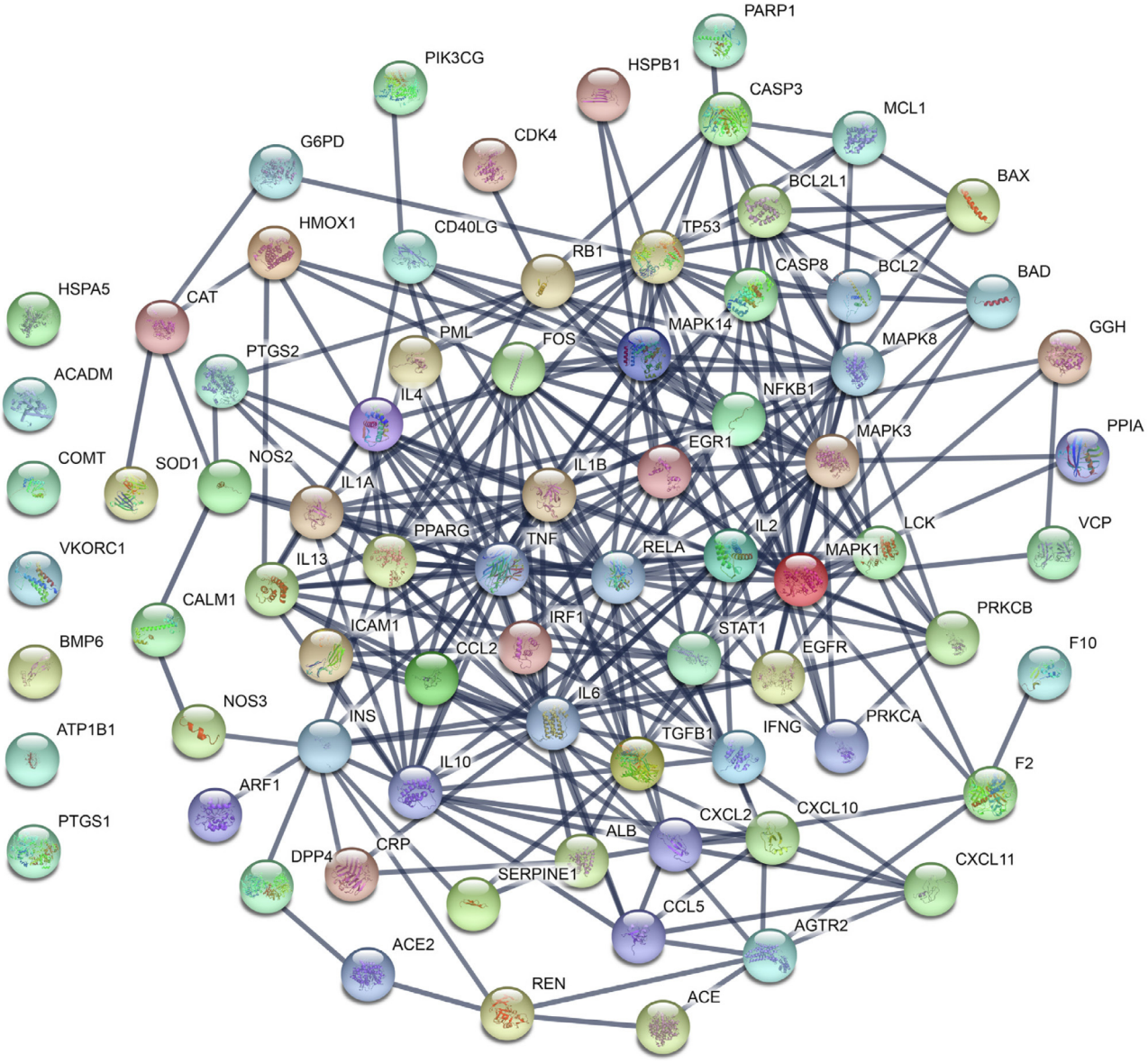


Fig. 3. PPI network.

Table 3
Analysis of interaction topology parameters of important targets.

Targets	Degree	Topological Coefficient	Betweenness Centrality	Closeness Centrality
RELA	24	0.23065476	0.09948818	0.544
MAPK1	24	0.19791667	0.12555263	0.53968254
IL6	23	0.23510467	0.11059687	0.52713178
MAPK3	23	0.21661491	0.08636058	0.53543307
TNF	23	0.21510297	0.11857879	0.544
TP53	19	0.22105263	0.10271104	0.4822695
MAPK8	17	0.27566321	0.0445486	0.48920863
MAPK14	17	0.25860155	0.06081331	0.5
IL1B	16	0.29211957	0.0161661	0.46896552
IL2	15	0.32533333	0.01679801	0.47887324
NFKB1	15	0.30068027	0.02367776	0.47552448
FOS	15	0.28148148	0.03306335	0.49635036
IL10	13	0.33679834	0.00804039	0.42236025
IL4	13	0.32915921	0.01284505	0.45033113
STAT1	12	0.29411765	0.02445102	0.47552448
IFNG	11	0.35909091	0.01944479	0.425
CCL2	11	0.35698448	0.00735614	0.43312102
INS	11	0.17748918	0.15055889	0.45637584
IL13	10	0.4	0.00565501	0.41212121
LCK	10	0.375	0.00134214	0.44444444
CASP8	10	0.35102041	0.01572466	0.45945946
BCL2L1	10	0.34324324	0.00764597	0.40718563
EGFR	10	0.27454545	0.03172251	0.4822695

We used DAVID to perform GO enrichment analysis on the above 76 proteins. Taking "Homo sapiens, $p \leq 0.05$" as the screening condition, the top 20 were drawn as histograms, as shown in Fig. 4 (more details showed in supplement material 4). Among them, biological processes involve inflammatory response, positive regulation of transcription from RNA polymerase II promoter, immune response, etc.; molecular functions include ATP binding, cytokine activity and metal ion binding are the most significant; among the cellular components, extracellular space, extracellular exosome and nucleus are enriched more.

3.4. Reactome pathways enrichment

We used the Reactome knowledgebase as the enrichment tool with co-targeted genes for Reactome pathways enrichment. As shown in Table 4 (more details showed in supplement material 5), the results indicated that the pathways were enriched in interleukin-10 signaling, interleukin-4 and interleukin-13 signaling, signaling by interleukins, cytokine signaling in the immune system, the immune system and other pathways. These pathways are important in storms caused by COVID-19. With the Reactome knowledgebase, we draw the simulation diagrams for SFJD treatment during *SARS-CoV-2* infection in the immune system (Fig. 5**A**), cytokine signaling in immune system (HSA-1280215, Fig. 5**B**), signaling by interleukins (R-HSA-449147, Fig. 5**C**) which showed the possible targets for SFJD and *SARS-CoV-2* with hit gene numbers and false discovery rate (FDR) scores. These simulation diagrams have vividly illustrated the mechanism of SFJD treatment for COVID-19.

3.5. Prediction of SFJD–COVID-19 disease treatment by TCMATCOV

As shown in Fig. 6, we built a component-drug target-disease protein interaction network on the TCMATCOV platform, which included the component-drug target relationship (from BATMAN-TCM, with a confidence score of 20), and protein interactions between drug targets and disease proteins relationship (from STRING with a confidence score of 0.5). The data showed that the SFJD therapeutic effect on COVID-19 was very close to the positive control (HSZF), which had been reported to be useful in clinical. We also validated the herbs in SFJD prescription, and the data showed in Table 5. TCMATCOV is a COVID-19 severe disease network based on SARS simulation. We used it to predict 126

Table 4
The co-targeted genes Reactome pathways enrichment analysis (top10).

Pathway identifier	Pathway name	Entities found	Entities total	Entities ratio	Entities pValue	Entities FDR	Reactions found	Reactions total	Reactions ratio
R-HSA-6783783	Interleukin-10 signaling	22	86	0.005861	1.11E-16	2.04E-14	13	15	0.001157
R-HSA-6785807	Interleukin-4 and Interleukin-13 signaling	36	211	0.01438	1.11E-16	2.04E-14	35	46	0.003549
R-HSA-449147	Signaling by Interleukins	62	639	0.043549	1.11E-16	2.04E-14	171	490	0.037803
R-HSA-1280215	Cytokine Signaling in Immune system	73	1312	0.089416	1.11E-16	2.04E-14	239	735	0.056704
R-HSA-168256	Immune System	84	2869	0.195529	1.11E-16	2.04E-14	330	1634	0.126061
R-HSA-109606	Intrinsic Pathway for Apoptosis	12	61	0.004157	4.88E-13	7.52E-11	27	62	0.004783
R-HSA-5660668	CLEC7A/inflammasome pathway	6	8	5.45E-04	1.48E-10	1.95E-08	4	4	3.09E-04
R-HSA-447115	Interleukin-12 family signaling	11	96	0.006543	1.34E-09	1.47E-07	22	114	0.008795
R-HSA-8950505	Gene and protein expression by JAK-STAT signaling after Interleukin-12 stimulation	10	73	0.004975	1.44E-09	1.47E-07	5	36	0.002777
R-HSA-2559583	Cellular Senescence	14	200	0.01363	3.80E-09	3.50E-07	39	90	0.006943

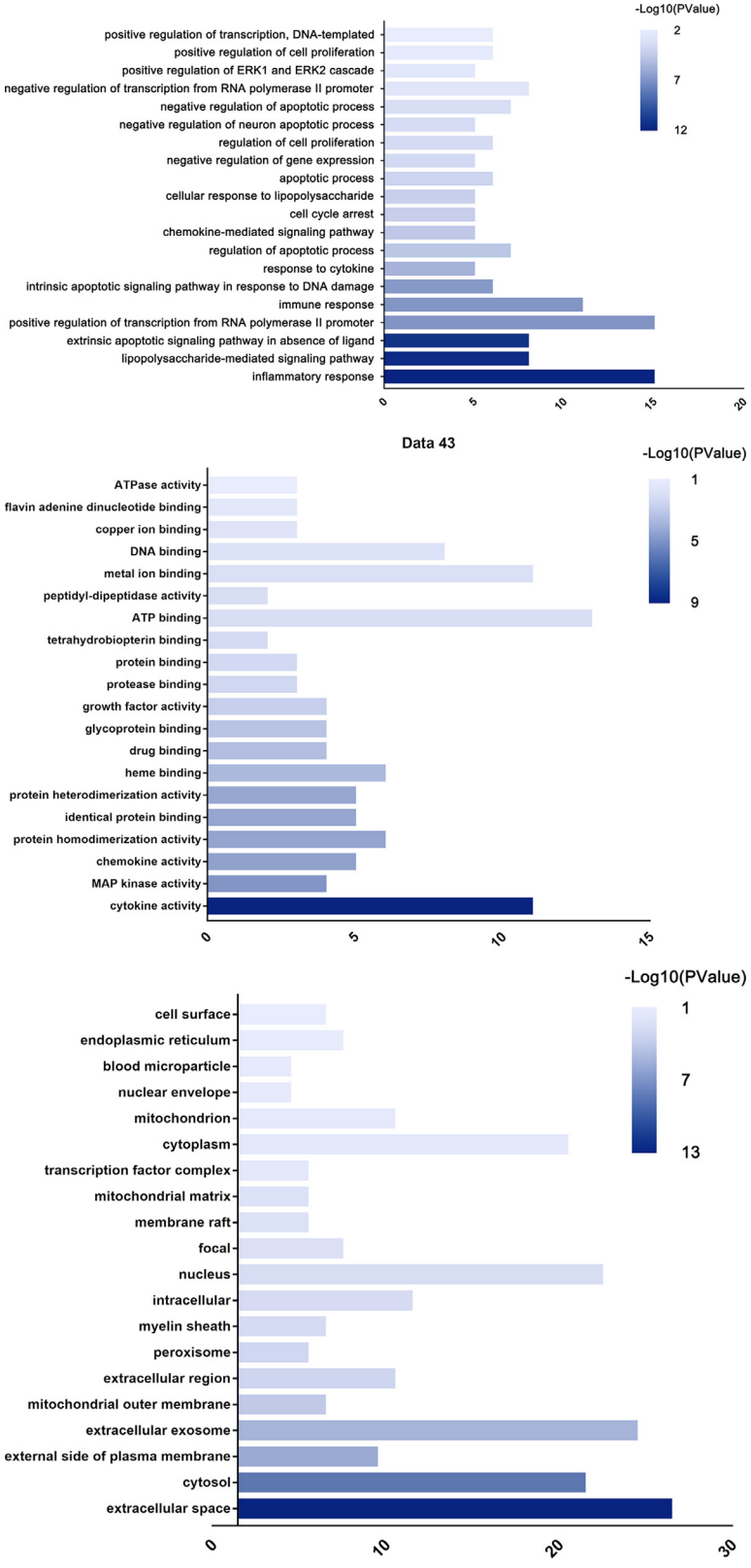


Fig. 4. GO enrichment analysis. (A) Biological process analysis; (B) Molecular function analysis; (C) Cell composition analysis.

Table 5
SFJD (herbs) and related TCM prescriptions validation results by TCMATCOV platform.

TCM herbs	Sum score	Average Degree	Average shortest path	Degree centrality	Closeness centrality
Negative Control (BXTM)	12.59	-1.84	3.53	-0.76	-6.46
Positive Control (HSZF)	20.85	-4.09	9.01	-1.12	-6.63
SFJD	20.84	-4.05	9.28	-1.19	-6.33
Hu Zhang	16.36	-4.65	2.87	-4.89	-3.95
Lian Qiao	8.79	-2.10	-0.21	-0.45	-6.45
Ban Lan Gen	18.04	-4.81	5.94	-1.09	-6.21
Chai Hu	16.88	-2.60	7.47	-1.13	-5.68

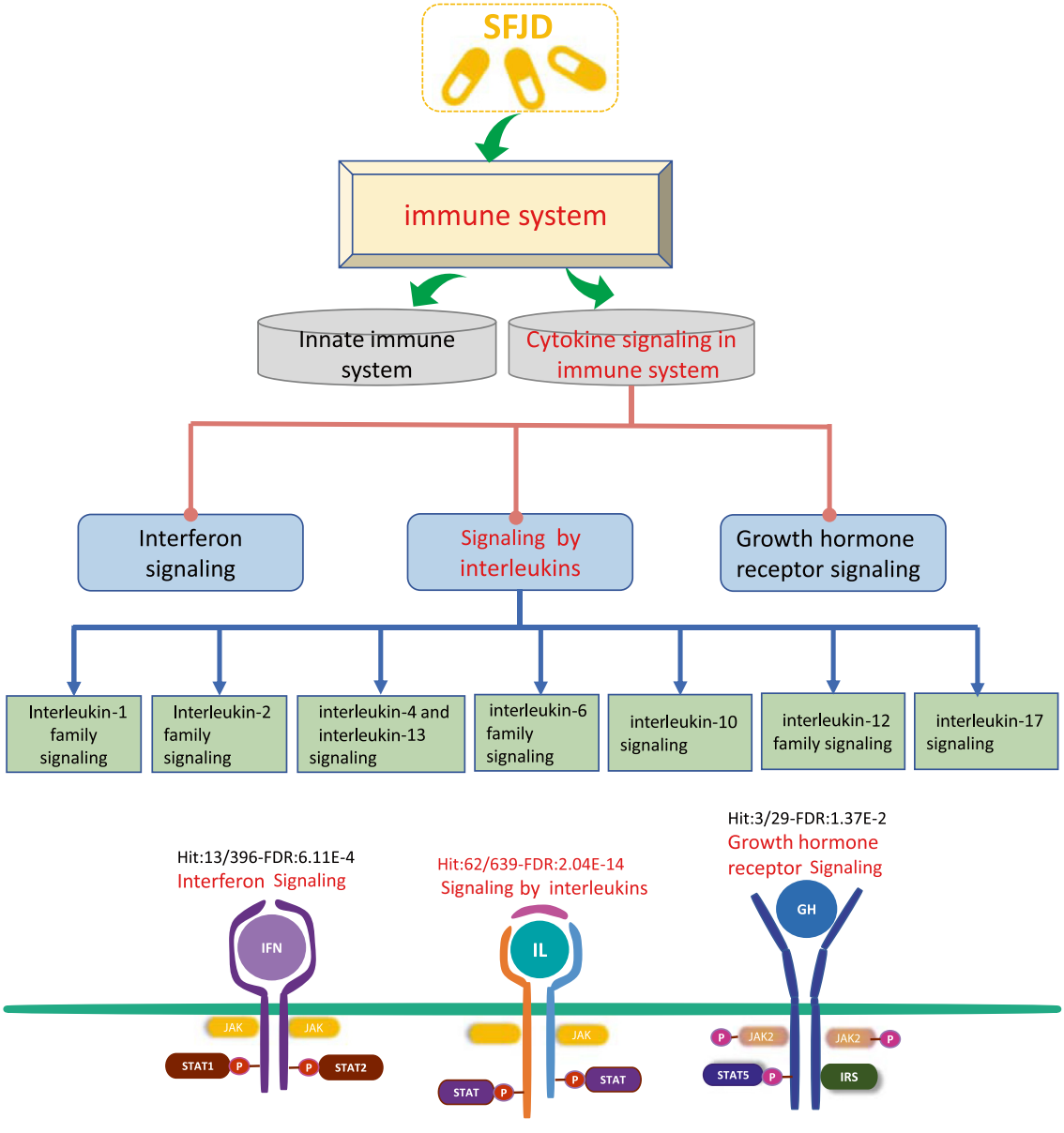


Fig. 5. Simulation diagram for SFJD treatment. (A) SFJD treatment in the immune system; (B) Cytokine signaling in the immune system (HSA-1280215); (C) Signaling by interleukins (HSA-449147). NOTE: FDR: false discovery rate. Acknowledgment: These pictures were drawn based on the database of Reactome.

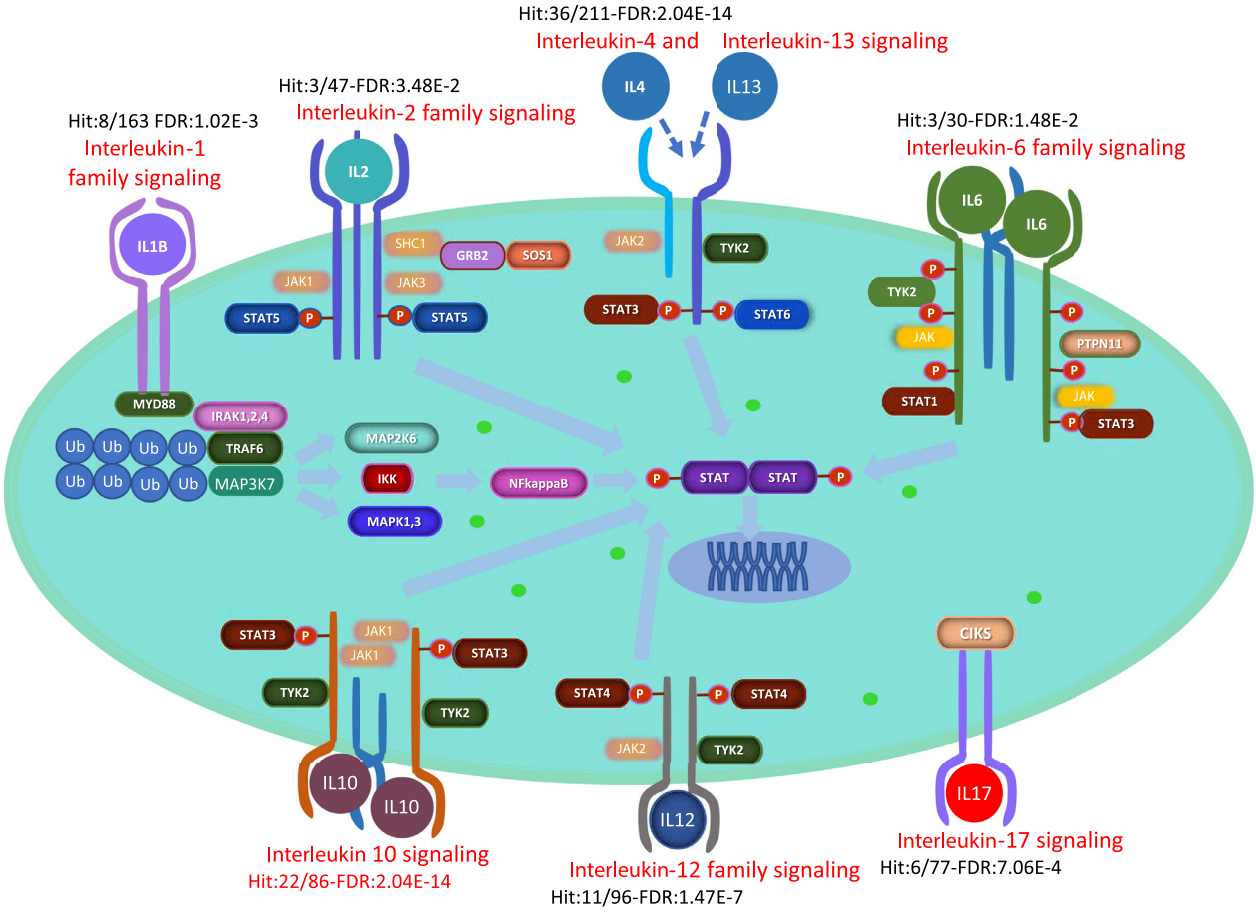


Fig. 5. Continued

Table 6
Information of core target genes.

Core target genes	Gene description	Predicted ingredients	TCM Herbs
IL-10	Interleukin 10	Quercetin; Luteolin;	Hu Zhang, Lian Qiao, Chai Hu, Ma Bian Cao, Bai Jiang Cao; Hu Zhang, Chai Hu, Ma Bian Cao, Bai Jiang Cao
TNF	Tumor Necrosis Factor	Quercetin; Luteolin; Kaempferol; Wogonin; Isovitexin;	Hu Zhang, Lian Qiao, Chai Hu, Ma Bian Cao, Bai Jiang Cao; Hu Zhang, Chai Hu, Ma Bian Cao, Bai Jiang Cao; Lian Qiao, Chai Hu, Ma Bian Cao, Bai Jiang Cao; Lian Qiao; Bai Jiang Cao
IL-6	Interleukin 6	Quercetin; Luteolin; Wogonin;	Hu Zhang, Lian Qiao, Chai Hu, Ma Bian Cao, Bai Jiang Cao; Hu Zhang, Chai Hu, Ma Bian Cao, Bai Jiang Cao; Lian Qiao
IL-2	Interleukin 2	Quercetin; Luteolin;	Hu Zhang, Lian Qiao, Chai Hu, Ma Bian Cao, Bai Jiang Cao; Hu Zhang, Chai Hu, Ma Bian Cao, Bai Jiang Cao
CCL2	C-C Motif Chemokine Ligand 2	Quercetin; Wogonin;	Hu Zhang, Lian Qiao, Chai Hu, Ma Bian Cao, Bai Jiang Cao; Lian Qiao
STAT1	Signal transducer and activator of transcription 1-alpha/beta	Quercetin; Kaempferol;	Hu Zhang, Lian Qiao, Chai Hu, Ma Bian Cao, Bai Jiang Cao; Lian Qiao, Chai Hu, Ma Bian Cao, Bai Jiang Cao;
IFNG	Interferon gamma	Quercetin; Luteolin;	Hu Zhang, Lian Qiao, Chai Hu, Ma Bian Cao, Bai Jiang Cao; Hu Zhang, Chai Hu, Ma Bian Cao, Bai Jiang Cao;
CXCL10	C-X-C motif chemokine 10	Quercetin;	Hu Zhang, Lian Qiao, Chai Hu, Ma Bian Cao, Bai Jiang Cao;

anti-COVID-19 target genes. However, we used GeneGards, DisGeNET, OMIM and other databases to select 76 co-targeted genes based on the clinical symptoms of fever and fatigue during the medical observation period. As shown in Table 6, the targets predicted by these two methods were subjected to Venn analysis, and the eight genes obtained were used as core target genes for the prevention and treatment of COVID-19, and the corresponding high-frequency compounds were used as core compounds.

3.6. Molecular docking verification of core compounds and core target genes

According to the binding energy and the number of hydrogen bonds, especially the greater the absolute value of the binding energy, the better the molecular docking result. The two proteins most related to the four core compounds were selected, as shown in Fig. 7 and Table 7 (original data showed in supplement material 7). Quercetin has the largest relationship with *TNF* and *STAT1*. Luteolin has the largest relationship

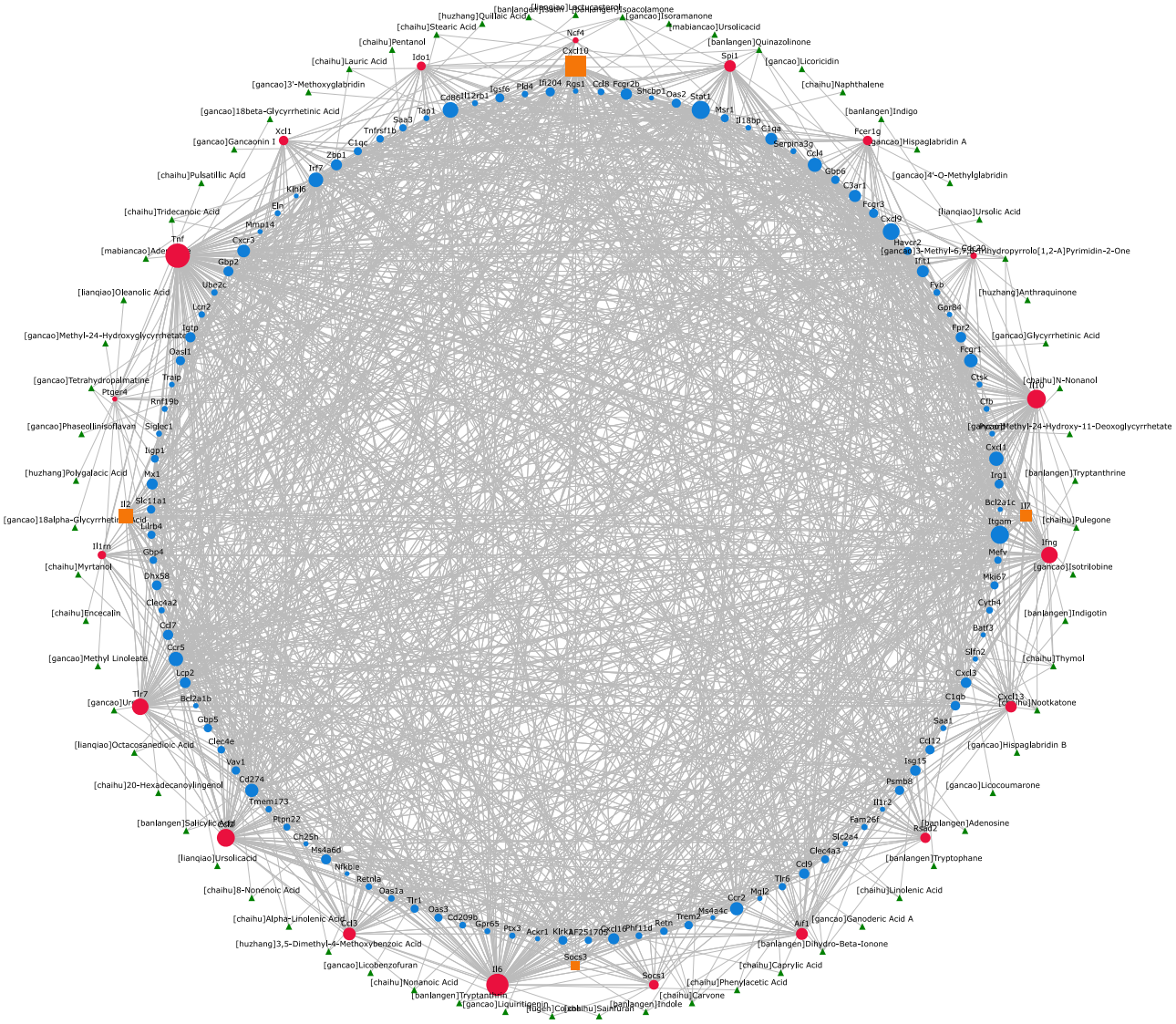


Fig. 6. TCMATCOV network of ingredient-drug target- disease protein. NOTES: Node size represents the size of the degree (original data showed in supplement material 6). Blue dots indicate Disease Protein, red dots indicate Drug Target, orange boxes indicate Disease specific cytokine, and green triangles indicate Ingredient. NOTES: BXTM: Ban Xia Tian Ma Bai Zhu Tang; HSZF: Han Shi Zu Fei Tang.

Table 7

Compounds	Target genes (ID)	Binding energy	The number of hydrogen bonds
Quercetin	TNF (5M2J)	-4.82	5
Quercetin	STAT1 (2KA6)	-4.6	2
Luteolin	IL2 (5LQB)	-5.2	4
Luteolin	STAT1 (2KA6)	-5.55	1
Wogonin	TNF (5M2J)	-4.9	1
Wogonin	CCL2 (4R8I)	-5.26	3
Kaempferol	IL10 (1LK3)	-5.48	4
Kaempferol	IL6 (5FUC)	-5.32	3

with *IL-2* and *STAT1*. Wogonin has the largest relationship with *TNF* and *CCL2*. Kaempferol has the largest relationship with *IL-10* and *IL-6*. These results can prove that SFJD ingredients work with COVID-19 targeted proteins in molecular docking simulation.

4. Discussion

Interleukin-6 (*IL-6*) plays an important role in cytokine release syndrome [22]. Some research has found that cytokines play an important role in the pathogenesis of COVID-19. Also, *IL-6* seems more relevant in the evaluation of the condition of COVID-19 patients [23]. In addition to the core proteins such as *IL-6*, which are involved in molecular docking simulation, the T-helper 1 cytokines (*IL1B, IFN-γ, IP10*, and *MCP1*) increase in patients infected by *SARS-COV-2* [24] and other co-targeted genes such as *IFNG* and MAPK are also involved. *IFNG* is generally considered to be an inflammatory cytokine that plays a key role in antitumor immunity. Studies have found that high levels of *IFNG* activate the JAK1-STAT1-caspase pathway and induce apoptosis in non-small cell lung cancer [25]. MAPK can regulate many important cell physiological/pathological processes such as cell growth, differentiation, stress adaptation to the environment, and inflammatory response [26]. Thus, combined with the enrichment analysis results of GO and Reactome pathway, cytokines and other molecules involved in immune response and inflammation are conceivable therapeutic targets for SFJD.

Table 8
Comparison of network pharmacological analysis of different traditional Chinese medicines for COVID-19.

TCM	Tools	Results	Ref
ShuFeng JieDu capsule	TCMSP; GeneCards; DAVID; R software	Key targets: RELA, MAPK1, MAPK14, CASP3, CASP8 and IL6. KEGG signaling pathways: Kaposi sarcoma-associated herpesvirus infection, AGE-RAGE signaling pathway in diabetic complications, Human cytomegalovirus infection, IL-17 signaling pathway and Hepatitis B, etc.	[53]
Huashi Baidu formula	TCMSP; GeneCards; Cytoscape; STRING	Key targets: MAPK3, MAPK8, TP53, CASP3, IL6, TNF, MAPK1, CCL2, PTGS2, etc. KEGG signaling pathways: TNF signaling pathway, PI3K-Akt signaling pathway, NOD-like receptor signaling pathway, MAPK signaling pathway, and HIF-1 signaling pathway. Molecular docking: Baicalein+ACE2; Quercetin+ACE2.	[54]
Toujie Quwen granule	TCMSP; Swiss Target Prediction; STRING; R software; Cytoscape	Key active ingredients: umbelliprenin, quercetin, kaempferol, luteolin, praeruptorin E, stigmasterol, and oroxylin A. Key targets: EGFR, CASP3, STAT3, ESR1, FPR2, F2, BCL2L1, BDKRB2, MPO, and ACE. Signaling pathways: regulation of inflammatory response, viral process, neutrophil mediated immunity, PI3K-Akt signaling pathway, MAPK signaling pathway, Jak-STAT signaling pathway, Complement and coagulation cascades, and HIF-1 signaling pathway.	[55]
Ma Xing Shi Gan Decoction	TCMSP; PharmMapper; Swiss Target Prediction; STITCH; Cytoscape; STRING R software	Key targets: HSP90, AKT1, JUN, MAPK1, TP53, ESR1, VEGFA, and TNF. KEGG signaling pathways: inflammation-related pathways, immunomodulation-related pathways, and viral infection-related pathways. Mechanisms: reducing inflammation, suppressing cytokine storm, protecting pulmonary alveolar-capillary barrier, alleviating pulmonary edema, regulating immune response, and decreasing fever.	[56]
Qing-Fei-Pai-Du decoction	UHPLC-Q-Orbitrap HRMS; DrugBank; PubChem; STITCH; ETCM; GTEx; STRING; Cytoscape	Key active ingredients: baicalin, glycyrrhizic acid, hesperidin, and hyperoside. Key targets: AKT1, TNF-α, IL6, PTGS2, HMOX1, IL10, and TP53. Molecular docking: Baicalin+ HMOX1/ PRKACA/ COMT/ CSNK2B; Ephedrine+ COMT/ PLAT; Hesperidin+ HMOX1; Hyperoside+ HMOX1/ PRKACA/ COMT/ CSNK2B; Isochlorogenic acid A+ HMOX1; Pseudoephedrine+ GLA; Glycyrrhizic acid+ HMOX1. In intro experiments: inhibiting IL6, CCL2, TNF-α, NF-κB, PTGS1/2, CYP1A1, CYP3A4 activity, the up-regulation of IL10 expression, and repressing platelet aggregation.	[57]
Lian Hua Qing Wen	TCMSP; ETCM; STRING; Cytoscape	KEGG signaling pathways: cancer, immune system-, and viral infection diseases. Mechanisms: modulating the inflammatory process, exerting antiviral effects, repairing lung injury, relieving the “cytokine storm” and improving ACE2-expression-disorder-caused symptoms.	[58]
Maxingyigan Decoction	TCMSP; STRING; Cytoscape	Molecular docking: Quercetin/Formononetin/Luteolin+ IL6/ CASP3/ IL4/ SARS-CoV-2. Mechanisms: anti-inflammatory and immunity-based actions involving activation of T cells, lymphocytes, and leukocytes, as well as cytokine-cytokine-receptor interaction, and chemokine signaling pathways.	[59]
Cold-Damp Plague Formula	TCMSP; TCMID; Swiss ADME; STITCH; GeneCards; STRING; Cytoscape;	Key targets: IL6, TNF, IL10, MAPK8, MAPK3, CXCL8, CASP3, PTGS2, TP53, and MAPK1. KEGG signaling pathways: TNF signaling pathway, MAPK signaling pathway, Fc epsilon RI signaling pathway, toxoplasmosis, leishmaniasis, and so on. Molecular docking: Quercetin/Luteolin+IL6; L-tyrosine/L-phenylalanine+ACE2.	[60]
Respiratory Detox Shot	TCMSP; TCMID; ETCM; Swiss Target Prediction; SEA; TargetNet; HINT; Cytoscape; CPDB; DAVID; STRING	Molecular docking: One-hundred and eighteen candidate constituents showed a high binding affinity with SARS-coronavirus-2 3-chymotrypsin-like protease (3CLpro). Key active ingredients in vitro experiments: Luteolin, Licoisoflavone B, Fisetin, Quercetin, Glyasperin F, Isolicoflavonol, Semilicoisoflavone-B.	[61]
Rhizoma Polygonati	TCMSP; Swiss Target Prediction; GenCLiP3; NCBI; GeneCard; STRING; DAVID; Cytoscape	Key active ingredients: diosgenin, 3′-Methoxydaidzein, 4′,5-Dihydroxyflavone, (2R)-7-hydroxy-2-(4-hydroxyphenyl)chroman-4-one, , DFV, Lopinavir, Remdesivir, (+)-Syringaresinol-O-beta-D-glucoside, beta-sitosterol, sitosterol, baicalein, methylprotodioscin_qt. Key targets: CASP3, TP53, MAPK14, PTGS2, CAT, FOS, PPARG, CASP8, BCL2L1, IL2, RELA. KEGG signaling pathways: tuberculosis, p53 signaling, AGE-RAGE in diabetic complications, IL-17 cytokine, apoptosis, and viral infection. Molecular docking: Diosgenin/ (+)-Syringaresinol-O-beta-D-glucoside+ ACE2/3CL/ Spike protein S1/ RNA-dependent RNA polymerase.	[62]

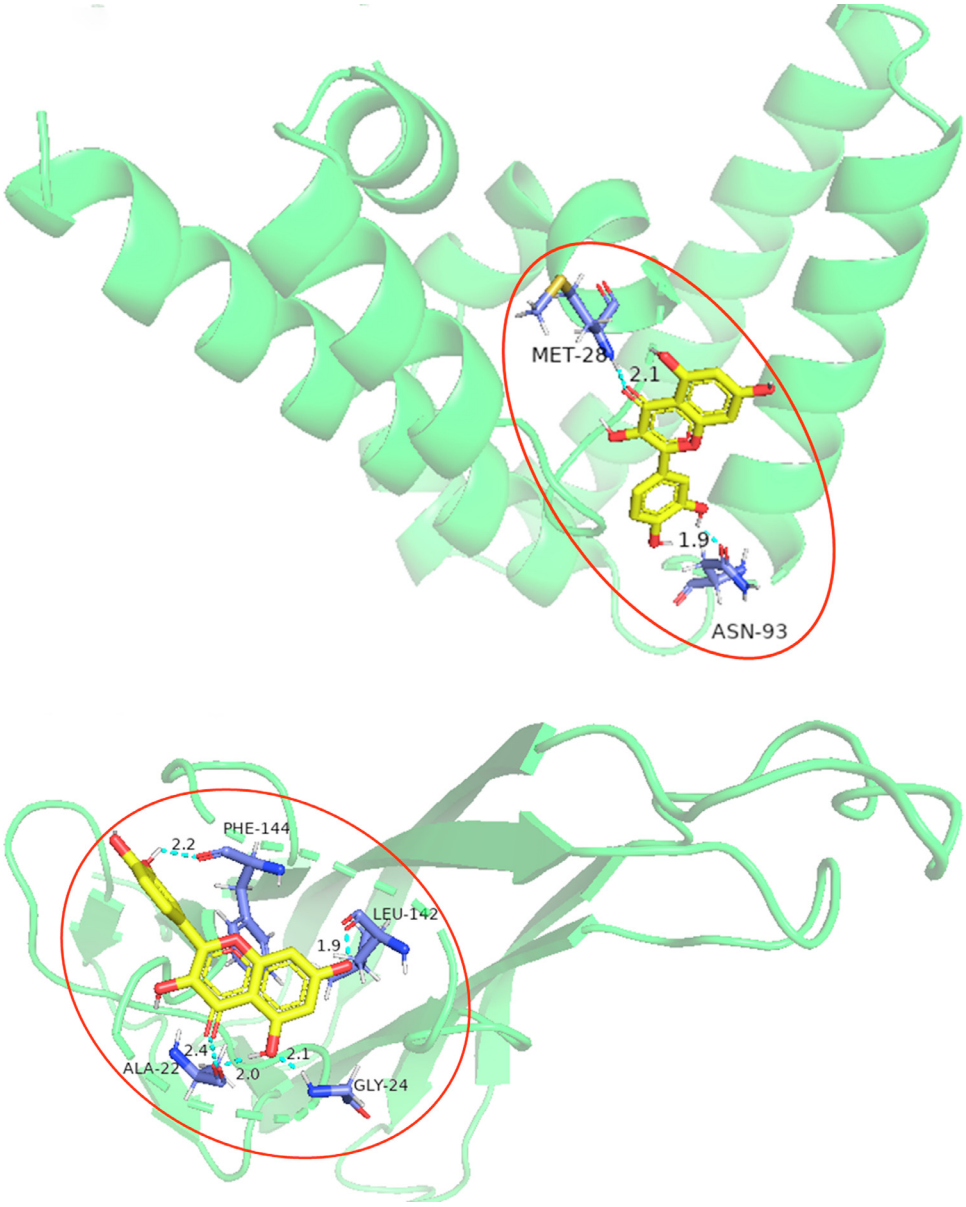
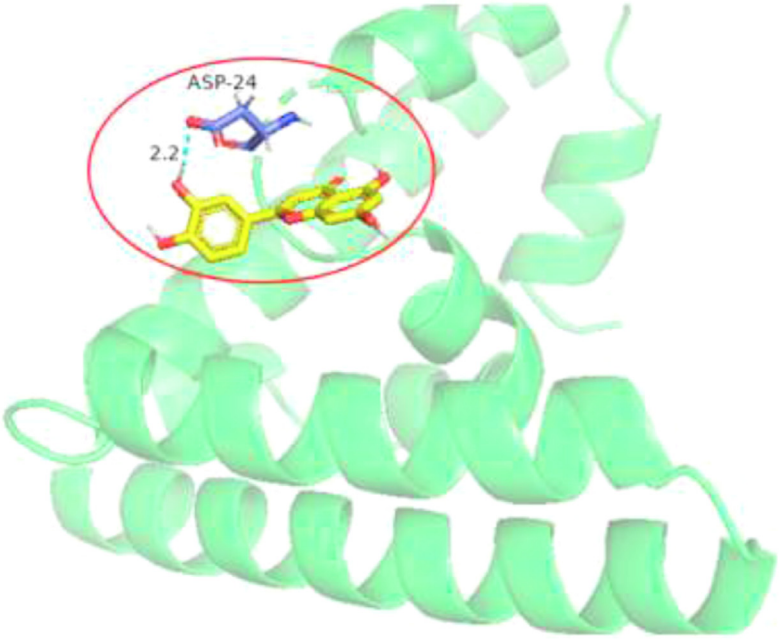


Fig. 7. Molecular docking results. (A) *STAT1*+Quercetin. (B) *TNF*+Quercetin. (C) *STAT1*+Luteolin. (D) *IL2*+Luteolin. (E) *CCL2*+Wogonin. (F) *TNF*+Wogonin. (G) *IL10*+Kaempferol. (H) *IL6*+Kaempferol. NOTES: Yellow represents chemical molecules, blue represents sites for docking proteins, and green represents proteins.

COVID-19 can spread quickly through respiratory tract droplets, close contact, and aerosols. In addition, there are reports that direct evidence of the active *SARS-CoV-2* replication in the patient's rectum during the incubation period, which might explain *SARS-CoV-2* fecal-oral transmission [27]. Clinical studies of patients with COVID-19 have shown that coronavirus can cause a variety of human diseases, including respiratory symptoms, gastrointestinal diseases [28], varying degrees of liver injury or liver dysfunction [29], thrombotic complications, myocardial dysfunction and arrhythmia, acute coronary syndromes, acute kidney injury, ocular symptoms, dermatologic complications [30] and so on.

Most of SFJD components are bitter cold herbs with the effect of clearing heat and detoxification, and mainly belong to the lung meridian, which plays an obvious therapeutic role on the syndrome of wind-heat syndrome of upper scorched lung. Amazingly, the therapeutic effect of each component of SFJD is not only limited to the lung, but also has a certain protective effect on the damage of other tissues and organs. The effective core compounds of SFJD such as quercetin, luteolin, wogonin, Kaempferol, etc. were screened through network pharmacology. They are mainly natural flavonoids, which exist in many natural medicinal materials and have various pharmacological activities. Quercetin can improve immune function via NF-κB signaling pathway triggered by *TNF-α* [31]. It has a protective effect against the liver tissues of rats [32] and colitis of mice [33]. Both in vivo and in vitro experiments have demonstrated that quercetin can alter cell cycle [34]. Highlights Quercetin ameliorates hypoxia-evoked apoptosis [35]. Luteolin has anti-inflammatory [36], anti-oxidation [37,38], protecting the kidneys [39] and other pharmacological effects. It can potently inhibit influenza virus replication in vitro [40]. Kaempferol has the effect of inhibiting cell proliferation and inducing apoptosis [41]. It can protect the liver against propacetamol-induced injury [42] and protect mice from liver failure [43]. Kaempferol showed attenuation in sepsis-induced acute lung injury in mice [44]. In addition, it has the effect of antitumor and cardioprotective [45]. Wogonin attenuated tubular damage, suppressed kidney inflammation and inhibited NF-κB activation in the injured kidney, thereby exhibiting the renoprotective effect [46] and it is a promising nephroprotective agent [47]. Pro-apoptosis effect of wogonin in vivo was verified in situ [48]. Wogonin exhibits a cytotoxic effect on lung cancer cells [49] and exerts potent anticancer effects on colorectal cancer cells [50]. Wogonin has documented a wide



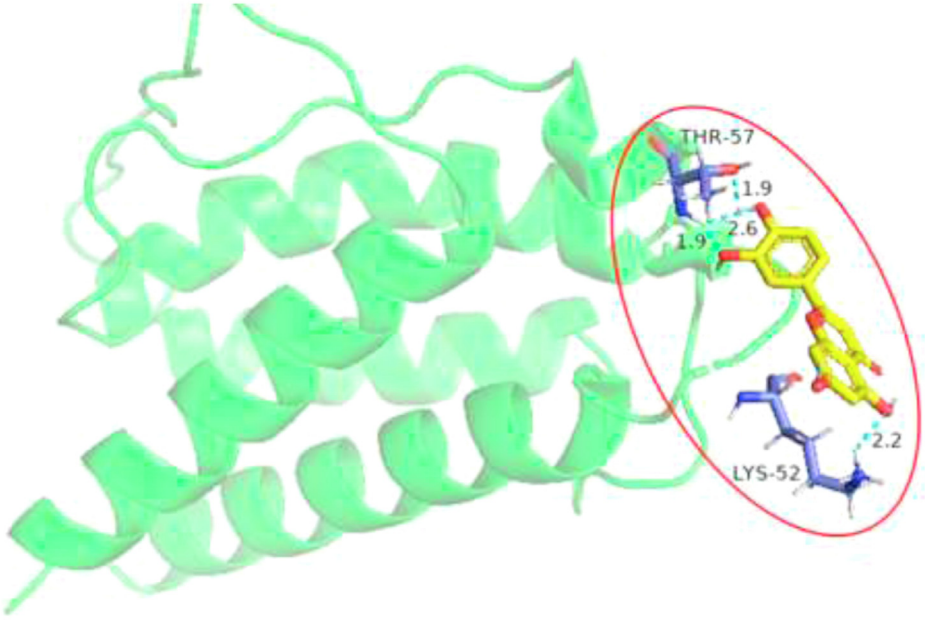


Fig. 7. Continued

spectrum of anti-inflammatory and antitumor activities, including inhibiting regulatory T cells, regulating effector T cell functions, and mediating macrophage immunity [51]. In addition, wogonin possesses a potent anti-influenza activity mediated by regulation of AMPK activation [52]. The multiple protective effects of these active ingredients on other tissues and organs may be one of the reasons for SFJD to reduce the symptoms of COVID-19 patients. TCM is a combination of multiple components to play a therapeutic effect, in addition to these four core compounds, the remaining components also play a pivotal role.

Recently, there are many clinical applications of TCM in the treatment of COVID-19 and many scholars have also studied its mechanism through network pharmacology, as shown in Table 8. Through comparison, it is found that whether it is a single medicine or a prescription, TCM treats COVID-19 mostly by regulating inflammatory factors. Our research found that SFJD not only regulates inflammation, but also mainly participates in regulating the immune system to treat COVID-19.

However, the data in TCMCOVID is based on SARS and is not completely consistent with SARS COV2, and the original data used in this database is the result of analysis of mice. Thus, using this tool to verify

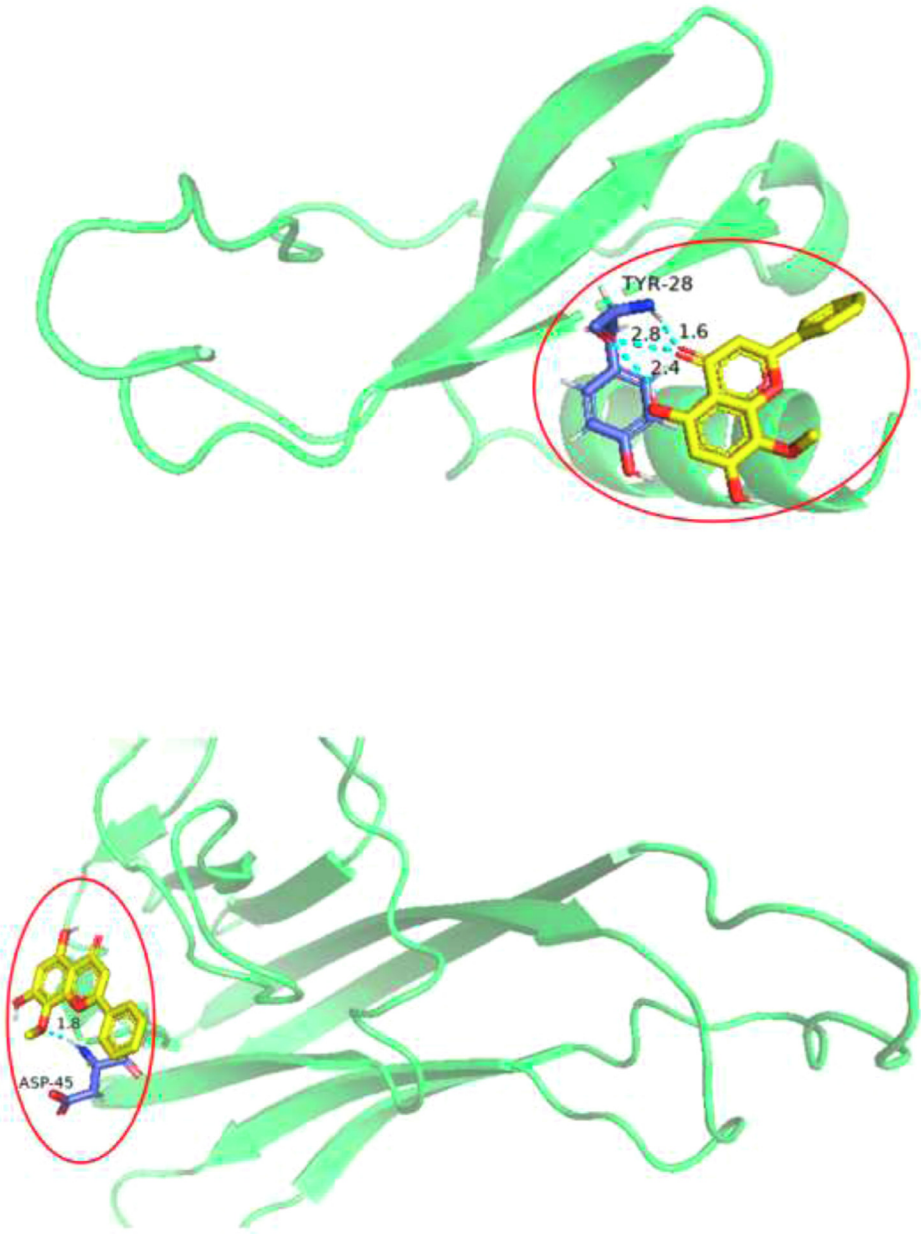


Fig. 7. Continued

analysis results has certain limitations. In addition, TCM prescription is a complex system, not simply the accumulation of ingredients, and network pharmacology has limitations. In order to be safe and effective for clinical use, further in vivo and in vitro activity evaluation and pharmacological verification are needed.

5. Conclusion

The preventive and therapeutic effect of SFJD on COVID-19 may contribute in participating in the moderate immune system, anti-inflammatory, anti-virus and other methods through the action of quercetin, luteolin, kaempferol, baicalein and other active ingredients on core targets such as *IL-6, IL-10, TNF*, etc. Combined with clinical research and network pharmacological analysis, in the early onset of COVID-19, non-infant patients with acute upper respiratory tract infection with heat toxin attacking the lung syndrome, fever, fatigue and other symptoms, timely oral SFJD capsule for a certain course of treatment can reduce or eliminate the patient's clinical symptoms.

Author contributions

Q-WH is the corresponding authors on the study. H-JX and Z-WD are first authors and responsible for collecting materials and writing the paper. G-HL, Q-XG and JW helped in organizing the information and edited the article pictures. All authors read and approved the final manuscript.

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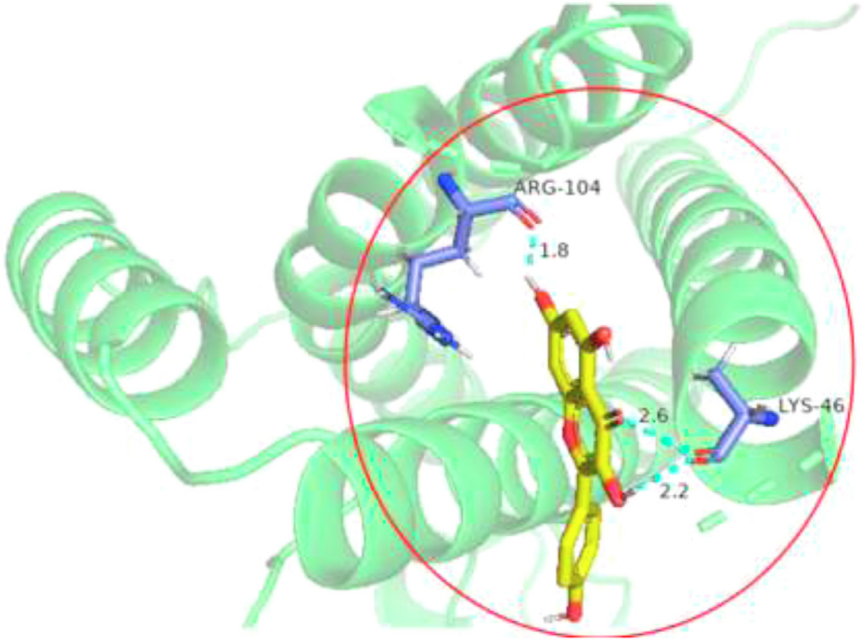
Declaration of Competing Interests

The authors declare that they have no competing interests.



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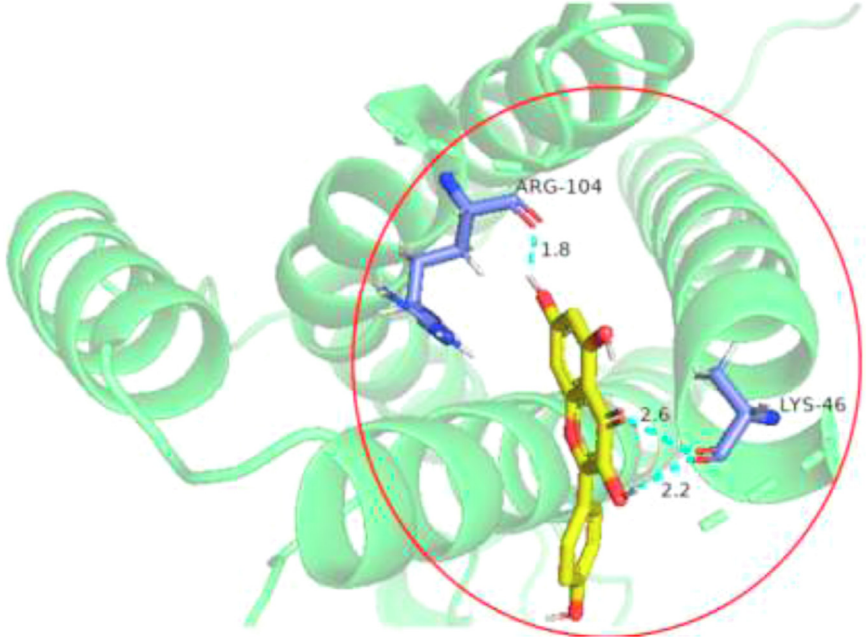

Data availability

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.eujim.2020.101241.

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