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Network pharmacology and molecular docking analysis on molecular targets and mechanism prediction of Huanglian Jiedu Decoction in the treatment of COVID-19

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ABSTRACT

Objective To investigate and predict the molecular targets and mechanism of Huanglian Jiedu Decoction (黄连解毒汤, HLJDD) in the treatment of Corona Virus Disease 2019 (COVID-19) through network pharmacology and molecular docking analysis.

Methods The chemical constituents and action targets of HLJDD were retrieved on Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP), SymMap v2, Encyclopedia of Traditional Chinese Medicine (ETCM), a High-throughput Experiment- and Reference-guided Database of Traditional Chinese Medicine (HERB), and Traditional Chinese Medicine Integrated Database (TCMID). UniProt and GeneCards were used to query the target genes that corresponding to the active compounds, and then a compound-target network was constructed using Cytoscape 3.7.2. Gene Ontology (GO) database was used to annotate GO functions. Kyoto Encyclopedia of Genes and Genomes (KEGG) was used to predict the possible mechanisms of active compounds. The Database for Annotation, Visualization and Integrated Discovery (DAVID) was used to analysis the tissue enrichment. The main active compounds in HLJDD are molecularly docked with their corresponding related targets.

Results Seventy-six compounds were screened and 458 corresponding targets in the network were obtained. Gene annotation showed that the targets were involved mainly in 1 953 biological processes. 884 signaling pathways was enriched, involving signaling by interleukins, cytokine signaling in immune system, generic transcription pathway, and RNA polymerase II transcription. The targets mainly distributed in the lung, liver, and placenta, involving a variety of immune cells, such as T cells and B cells. The molecular docking results showed that core compounds such as wogonin, berberine, and baicalein had high affinity with tumor necrosis factor (TNF), insulin (INS), and tumor protein 53 (TP53).

Conclusion The active compounds in HLJDD may have a therapeutic effect on COVID-19 through regulating multiple signal pathways by targeting genes such as vascular endothelial growth factor A (VEGFA), INS, interleukin-6 (IL-6), TNF, caspase-3, TP53, and mitogen-activated protein kinase 3 (MAPK3).

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1 Introduction

Corona Virus Disease 2019 (COVID-19) pneumonia is an acute respiratory infectious disease with a long incubation period, strong contagiousness and pathogenicity, and general susceptibility to the population. The seriousness of novel coronavirus pneumonia is a heavy economic burden on the countries suffering from widespread infection through its long treatment cycle and high consumption of materials^[1,2]. The main clinical symptoms are fever, cough, and asthma. Some patients also experience gastrointestinal symptoms, while some patients enter a severe stage where they develop respiratory failure or even die^[3].

In China, in the treatment for COVID-19, Chinese medicine is a major player, and equal importance is attached to both traditional Chinese medicine (TCM) and western medicine. In order to contend the epidemic, so far, the National Health Commission and the National Administration of Traditional Chinese Medicine have published eight versions of a new coronavirus diagnosis and treatment plan. In the protocol, Huanglian Jiedu Decoction (黄连解毒汤, HLJDD) is used to treat patients with the following clinical symptoms: high fever, cough, little sputum, or yellow sputum, chest tightness, shortness of breath, bloating, and constipation. This prescription is well-known for treating heat-syndrome in China and was first mentioned in the *Medical Secrets of an Official (Wai Tai Mi Yao, 《外台秘要》)* by WANG Tao, a medical scientist in the Tang Dynasty. It is an aqueous extract of four herbal materials with the ratio of 3 : 2 : 2 : 3 in Huanglian (*Coptidis Rhizoma*), Huangqin (*Scutellariae Radix*), Huangbo (*Phellodendri Chinensis Cortex*), and Zhizi (*Gardeniae Fructus*). This formula has been used historically and widely in clinical practice^[4].

In gastrointestinal diseases, inflammation, cardiovascular diseases, and Alzheimer's disease, HLJDD has shown positive clinical effects^[5-7]. A modern pharmacological study has also elucidated the pharmacokinetics and pharmacodynamics of HLJDD, and findings suggest that the main compounds of iridoids, flavonoids and alkaloids in HLJDD can have an anti-inflammatory effect^[8]. In the current study, HLJDD can exert its anti-inflammatory effect by interfering with the MAPKs/NF- κ B pathway^[9]. LI et al.^[10] studied the effect of HLJDD on the urine metabolomics of healthy people and found seven potential biomarkers, including 2-(formylamino)benzoic acid, which has proven the mechanism of treating heat syndrome from pharmacology. However, the mechanism of HLJDD in treating COVID-19 is unclear and needs further investigation.

Network pharmacology is a new discipline that combines the functions of drug compounds, disease targets,

and biological signaling pathways based on computer network analysis^[11,12], which is suitable to analyze TCM, owing to the multiple targets affected by the multi-components. Network pharmacology is able to visualize, systematize, and informatize the principles of the process of treating diseases using TCM. The molecular docking technology predicts the binding mode and affinity between two molecules by analyzing the physical and chemical properties of the molecules, as well as by computer simulation^[13]. Molecular docking plays an important role in detecting the mechanism of active compounds and target proteins of TCM.

The crystal structure of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has been determined by Shanghai Tech University (PDB 6LU7)^[14]. SARS-CoV-2 invades cells by binding the angiotensin-converting enzyme 2 (ACE2) receptor on the surface of human cells with the S protein of its spinous^[15]. It was recently discovered, by German scientist Markus Hoffmann, that SARS-CoV-2 requires the help of the transmembrane protease serine 2 (TMPRSS2) protein to enter cells^[16]. This article intends to analyze the active compounds and target genes in HLJDD through network pharmacology, and dock the main active compounds with their related targets to provide a theoretical basis for its clinical application.

2 Materials and methods

2.1 Components collection and screening in HLJDD and their corresponding targets

This research was based on the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP, <https://old.tcmsp-e.com/tcmsp.php>)^[17], SymMap v2 (<http://www.symmap.org/>), The Encyclopedia of Traditional Chinese Medicine (ETCM, <http://www.tcmip.cn/ETCM/index.php/Home/>), a High-throughput Experiment- and Reference-guided Database of Traditional Chinese Medicine (HERB) (<http://herb.ac.cn/>), and Traditional Chinese Medicine Integrated Database (TCMID, <http://www.megabionet.org/tcmid/>). The keywords "Huanglian (*Coptidis Rhizoma*)" "Huangqin (*Scutellariae Radix*)" "Huangbo (*Phellodendri Chinensis Cortex*)", and "Zhizi (*Gardeniae Fructus*)" were used to obtain all compounds and their targets. The obtained protein and gene information was normalized through the Uniport database. In this study, oral bioavailability (OB) \geq 30% and drug-likeness (DL) \geq 0.18 were used to screen the components of Huanglian (*Coptidis Rhizoma*), Huangqin (*Scutellariae Radix*), Huangbo (*Phellodendri Chinensis Cortex*), and Zhizi (*Gardeniae Fructus*) to obtain the more active components^[18]. Bioavailability refers

to the relative amount of drugs that is absorbed into the systemic blood circulation and metabolized after being administered via an extravascular route. Drug-like properties are usually used to evaluate the possible failure characteristics of a compound. The significance of this standard lies in the bioavailability; the higher the degree of drug-like properties, the more potential research significance the human body presents^[19].

2.2 Establishing the compound-target network

The collected compounds and targets are sorted and imported into the Cytoscape 3.7.2 software (<http://www.cytoscape.org/>)^[20] to construct a network of active compounds-target interactions in HLJDD. Visualize the pharmacological action mechanism of HLJDD.

2.3 Collection of disease targets

Based on GeneCards database (<https://www.genecards.org/>), pharmGKB database (<https://www.pharmgkb.org/>), and DisGeNet database (<http://www.disgenet.org/home/>), “coronavirus” was searched as the keyword, and supplemented targets through literature search to collect the targets of COVID-19.

2.4 Establishment of protein-protein interaction (PPI) network

The collected COVID-19 targets were imported into the search tool for the retrieval of interacting genes/proteins (STRING) database (<https://string-db.org/>) to obtain the PPI network. It was imported into the Cytoscape 3.7.2 software, then merged with the component-target network for intersection. Following this, the target proteins of HLJDD acting on COVID-19 were obtained. The target proteins were imported into the STRING database to obtain the PPI network of target proteins for COVID-19 treatment with HLJDD. Finally, the network was imported into Cytoscape to observe and analyze the topological properties.

2.5 Target pathway analysis

The target proteins obtained after weight reduction of the predicted target point was imported into the Gene Ontology (GO) database (<http://geneontology.org/>) and the threshold was set at $FDR < 0.05$. After annotating the GO function, an analysis of Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway was made through the Reactome Pathway Database (<https://reactome.org/Pathway-Viewer/>). The pathways related to HLJDD for the treatment of novel coronavirus pneumonia were obtained by consulting the literature and the KEGG database. OmicShare Tools (<http://www.omicsshare.com/>

<tools/index.php/>) was used to visualize the enrichment analysis results. Further tissue enrichment analysis on target protein through the Database for Annotation, Visualization and Integrated Discovery (DAVID) (<https://david.ncicrf.gov/>) was carried out.

2.6 Component-target molecular docking

The ZINC Is Not Commercial (ZINC) database was used to collect the “.mol2” format of the structures of the first seven core compounds obtained from the analysis, and then the Protein Data Bank (PDB) database was used to download the “.pdb” format of the corresponding targets^[21]. The target proteins were dehydrated and hydrogenated using the PyMOL software, and the compounds and the target proteins were converted to “.pdbqt” format by AutoDock software^[22]. Binding energy less than 0 indicates that the ligand molecule and the receptor can bind spontaneously. There is no standard for target screening of active molecules, and according to the literature^[23], the binding energy ≤ -5.00 kJ/mol was selected here as the basis for screening the active compound. The docking results were visualized in PyMOL.

The workflow is demonstrated in [Figure 1](#).

3 Results

3.1 Active compounds screening and collection in HLJDD

A total of 429 compounds were obtained from TCMSP, SymMap v2, ETCM, HERB, and TCMID databases and related literature. Among them, there were 143 compounds for Huangqin (*Scutellariae Radix*), 48 compounds for Huanglian (*Coptidis Rhizoma*), 140 compounds for Huangbo (*Phellodendri Chinensis Cortex*), and 98 compounds for Zhizi (*Gardeniae Fructus*). With $OB \geq 30\%$ and $DL \geq 0.18$ as screening criteria, 102 compounds were obtained ([Table 1](#)). After removing the duplicates, there were 76 main compounds in HLJDD.

3.2 Component-target network of HLJDD

The corresponding targets of the main compounds in HLJDD were collected in the databases, and the results were imported into Cytoscape 3.7.2. The active compound-prediction target network was constructed, and 534 nodes (76 active compound nodes and 458 predicted target nodes) and 2 749 interaction relationships were obtained, as shown in [Figure 2](#).

The core target network diagram of the compound of HLJDD ([Figure 3](#)) shows the higher degree of cross-linking between compounds in HLJDD and targets, including 69 core compound nodes and 191 main target nodes. The top-ranked compound nodes are beta-sitosterol, stigmaterol, rivularin, and wogonin. The correlation

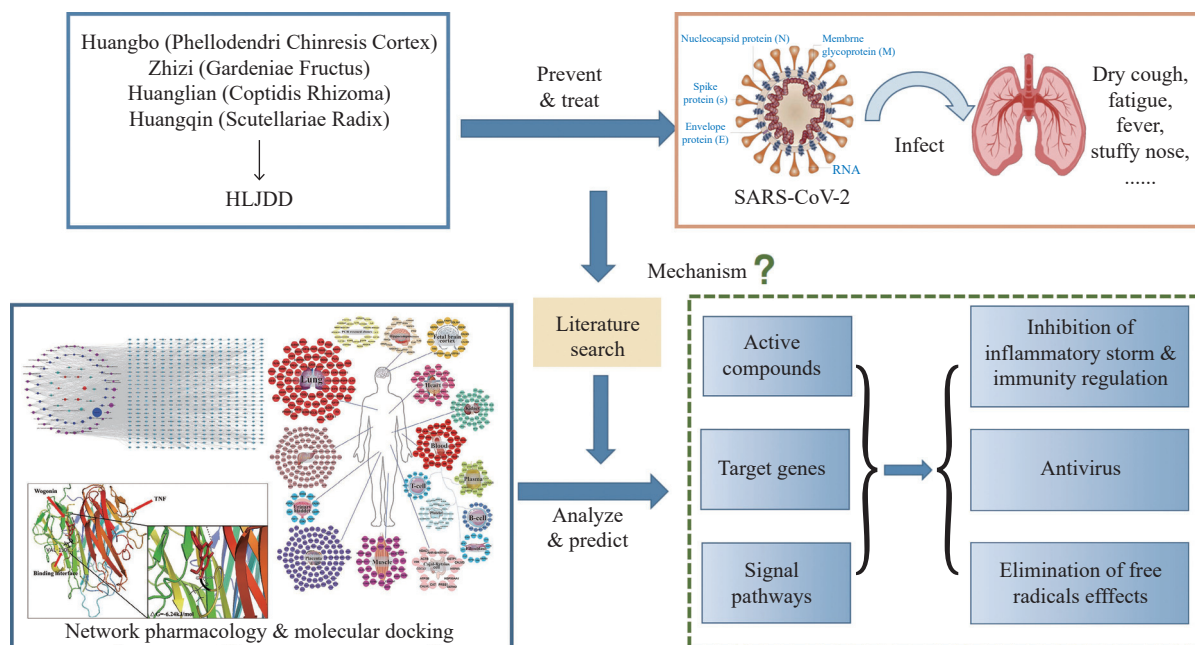


Figure 1 The analysis process of this study

Table 1 Active compounds in HLJDD

Source	MOL ID	Compound	Molecular weight	OB (%)	DL
	MOL000073	Ent-epicatechin	290.29	48.96	0.24
	MOL000173	Wogonin	284.28	30.68	0.23
	MOL000228	(2R)-7-Hydroxy-5-methoxy-2-phenylchroman-4-one	270.30	55.23	0.20
	MOL000358	Beta-sitosterol	414.79	36.91	0.75
	MOL000359	Sitosterol	414.79	36.91	0.75
	MOL000449	Stigmasterol	412.77	43.83	0.76
	MOL000525	Norwogonin	270.25	39.40	0.21
	MOL000552	5,2'-Dihydroxy-6,7,8-trimethoxyflavone	344.34	31.71	0.35
	MOL001458	Coptisine	320.34	30.67	0.86
	MOL001490	Bis[(2s)-2-ethylhexyl] benzene-1,2-dicarboxylate	390.62	43.59	0.35
Huangqin (Scutellariae Radix)	MOL001506	Supraene	410.80	33.55	0.42
	MOL001689	Acacetin	284.28	34.97	0.24
	MOL002714	Baicalein	270.25	33.52	0.21
	MOL002879	Diop	390.62	43.59	0.39
	MOL002897	Epiberberine	336.39	43.09	0.78
	MOL002908	5,8,2'-Trihydroxy-7-methoxyflavone	300.28	37.01	0.27
	MOL002909	5,7,2,5-Tetrahydroxy-8,6-dimethoxyflavone	376.34	33.82	0.45
	MOL002910	Carthamidin	288.27	41.15	0.24
	MOL002911	2,6,2',4'-Tetrahydroxy-6'-methoxychaleone	302.30	69.04	0.22
	MOL002913	Dihydrobaicalin_qt	272.27	40.04	0.21
	MOL002914	Eriodyctiol (flavanone)	288.27	41.35	0.24
	MOL002915	Salvigenin	328.34	49.07	0.33

Table 1 Continued

Source	MOL ID	Compound	Molecular weight	OB (%)	DL
Huangqin (Scutellariae Radix)	MOL002917	5,2',6'-Trihydroxy-7,8-dimethoxyflavone	330.31	45.05	0.33
	MOL002925	5,7,2',6'-Tetrahydroxyflavone	286.25	37.01	0.24
	MOL002926	Dihydrooroxylin A	286.30	38.72	0.23
	MOL002927	Skullcapflavone II	374.37	69.51	0.44
	MOL002928	Oroxylin A	284.28	41.37	0.23
	MOL002932	Panicolin	314.31	76.26	0.29
	MOL002933	5,7,4'-Trihydroxy-8-methoxyflavone	300.28	36.56	0.27
	MOL002934	Neobaicalein	374.37	104.34	0.44
	MOL002937	Dihydrooroxylin	286.30	66.06	0.23
	MOL008206	Moslosooflavone	298.31	44.09	0.25
	MOL010415	11,13-Eicosadienoic acid, methyl ester	322.59	39.28	0.23
	MOL012245	5,7,4'-Trihydroxy-6-methoxyflavanone	302.30	36.63	0.27
	MOL012246	5,7,4'-Trihydroxy-8-methoxyflavanone	302.30	74.24	0.26
MOL012266	Rivularin	344.34	37.94	0.37	
Huanglian (Coptidis Rhizoma)	MOL000098	Quercetin	302.25	46.43	0.28
	MOL000622	Magnograndiolide	266.37	63.71	0.19
	MOL000762	Palmidin A	510.52	35.36	0.65
	MOL000785	Palmatine	352.44	64.60	0.65
	MOL001454	Berberine	336.39	36.86	0.78
	MOL001458	Coptisine	320.34	30.67	0.86
	MOL002668	Worenine	334.37	45.83	0.87
	MOL002894	Berberrubine	322.36	35.74	0.73
	MOL002897	Epiberberine	336.39	43.09	0.78
	MOL002903	(R)-Canadine	339.42	55.37	0.77
	MOL002904	Berlambine	351.38	36.68	0.82
	MOL002907	Corchoroside A qt	404.55	104.95	0.78
	MOL008647	Moupinamide	313.38	86.71	0.26
MOL013352	Obacunone	454.56	43.29	0.77	
Huangbo (Phellodendri Chinensis Cortex)	MOL000098	Quercetin	302.25	46.43	0.28
	MOL000358	Beta-sitosterol	414.79	36.91	0.75
	MOL000449	Stigmasterol	412.77	43.83	0.76
	MOL000622	Magnograndiolide	266.37	63.71	0.19
	MOL000762	Palmidin A	510.52	35.36	0.65
	MOL000785	Palmatine	352.44	64.60	0.65
	MOL000787	Fumarine	353.40	59.26	0.83
	MOL000790	Isocorypalmine	341.44	35.77	0.59
	MOL001131	Phellamurin qt	356.40	56.60	0.39
	MOL001454	Berberine	336.39	36.86	0.78
	MOL001455	(S)-Canadine	339.42	53.83	0.77

Table 1 Continued

Source	MOL ID	Compound	Molecular weight	OB (%)	DL
Huangbo (Phellodendri Chinensis Cortex)	MOL001458	Coptisine	320.34	30.67	0.86
	MOL001771	Poriferast-5-en-3beta-ol	414.79	36.91	0.75
	MOL002636	Kihadalactone A	512.70	34.21	0.82
	MOL002641	Phellavin_qt	374.42	35.86	0.44
	MOL002643	Delta 7-Stigmastenol	414.79	37.42	0.75
	MOL002644	Phellopterin	300.33	40.19	0.28
	MOL002651	Dehydrotanshinone II A	292.35	43.76	0.40
	MOL002652	Delta7-Dehydrosophoramine	242.35	54.45	0.25
	MOL002656	Dihydroniloticin	458.80	36.43	0.81
	MOL002659	Kihadanin A	486.56	31.60	0.70
	MOL002660	Niloticin	456.78	41.41	0.82
	MOL002662	Rutaecarpine	287.34	40.30	0.60
	MOL002663	Skimmianin	259.28	40.14	0.20
	MOL002666	Chelerythrine	332.37	34.18	0.78
	MOL002668	Worenine	334.37	45.83	0.87
	MOL002670	Cavidine	353.45	35.64	0.81
	MOL002671	Candletoxin A	608.79	31.81	0.69
	MOL002672	Hericenone H	580.88	39.00	0.63
	MOL002673	Hispidone	472.78	36.18	0.83
	MOL002894	Berberrubine	322.36	35.74	0.73
	MOL005438	Campesterol	400.76	37.58	0.71
	MOL006392	Dihydroniloticin	458.80	36.43	0.82
	MOL006401	Melianone	470.76	40.53	0.78
	MOL006413	Phellochin	488.83	35.41	0.82
	MOL006422	Thalifendine	322.36	44.41	0.73
	MOL013352	Obacunone	454.56	43.29	0.77
Zhizi (Gardeniae Fructus)	MOL000098	Quercetin	302.25	46.43	0.28
	MOL000358	Beta-sitosterol	414.79	36.91	0.75
	MOL000422	Kaempferol	286.25	41.88	0.24
	MOL000449	Stigmasterol	412.77	43.83	0.76
	MOL001406	Crocetin	328.44	35.30	0.26
	MOL001494	Mandenol	308.56	42.00	0.19
	MOL001506	Supraene	410.80	33.55	0.42
	MOL001663	(4aS,6aR,6aS,6bR,8aR,10R,12aR,14bS)-10-Hydroxy-2,2,6a,6b,9,9,12a-heptamethyl-1,3,4,5,6,6a,7,8,8a,10,11,12,13,14b-Tetradecahydronicene-4a-carboxylic acid	456.78	32.03	0.76
	MOL001941	Ammidin	270.30	34.55	0.22
	MOL001942	Isoimperatorin	270.30	45.46	0.23

Table 1 Continued

Source	MOL ID	Compound	Molecular weight	OB (%)	DL
Zhizi (Gardeniae Fructus)	MOL002883	Ethyl oleate (NF)	310.58	32.40	0.19
	MOL003095	5-Hydroxy-7-methoxy-2-(3,4,5-trimethoxyphenyl)chromone	358.37	51.96	0.41
	MOL004561	Sudan III	352.42	84.07	0.59
	MOL007245	3-Methylkempferol	300.28	60.16	0.26
	MOL009038	GBGB	550.57	45.58	0.83

degrees are 169, 113, 68, and 64, respectively; and the top five target nodes are prostaglandin-endoperoxide synthase 2 (PTGS2), androgen receptor (AR), estrogen receptor 1 (ESR1), prostaglandin-endoperoxide synthase 1 (PTGS1), and nitric oxide synthase 2 (NOS2). Their correlation degrees are 62, 61, 57, 52, and 52, respectively.

3.3 Intersecting compounds in HLJDD

From the previous result, it is illustrated that the same compound exists in different drugs in HLJDD, which can be obtained from Funrich's Venn diagram (Figure 4). Huanglian (Coptidis Rhizoma) and Huangbo (Phellodendri Chinensis Cortex) both include MOL001454-berberine, MOL002894-berberrubine, MOL000622-magnograndiolide, MOL000785-palmatine, MOL000762-palmitinA, MOL002668-worenine, and MOL001458-coptisine. MOL001458-coptisine, MOL008583-beta-sitosterol, and MOL000449-stigmasterol are common to Huangqin (Scutellariae Radix) and Huangbo (Phellodendri Chinensis

Cortex). Meanwhile, MOL000098-quercetin, MOL008583-beta-sitosterol, and MOL000449-stigmasterol are common to Huangbo (Phellodendri Chinensis Cortex) and Zhizi (Gardeniae Fructus). MOL008583-beta-sitosterol, MOL000449-stigmasterol, and MOL001506-supraene are common to Huangqin (Scutellariae Radix) and Zhizi (Gardeniae Fructus), while MOL008583-beta-sitosterol, MOL000449-stigmasterol, and MOL001506-supraene are common to Zhizi (Gardeniae Fructus) and Huangqin (Scutellariae Radix). Finally MOL006393-epiberberine and MOL001458-coptisine are common to Huangqin (Scutellariae Radix) and Huanglian (Coptidis Rhizoma).

3.4 GO, KEGG, and tissue enrichment analysis

The GO database was used to annotate the GO functional annotation of HLJDD and the pathway analysis of reactome. GO function annotation is used to annotate and classify genes through biological processes (BP), cell components (CC), and molecular function (MF), as

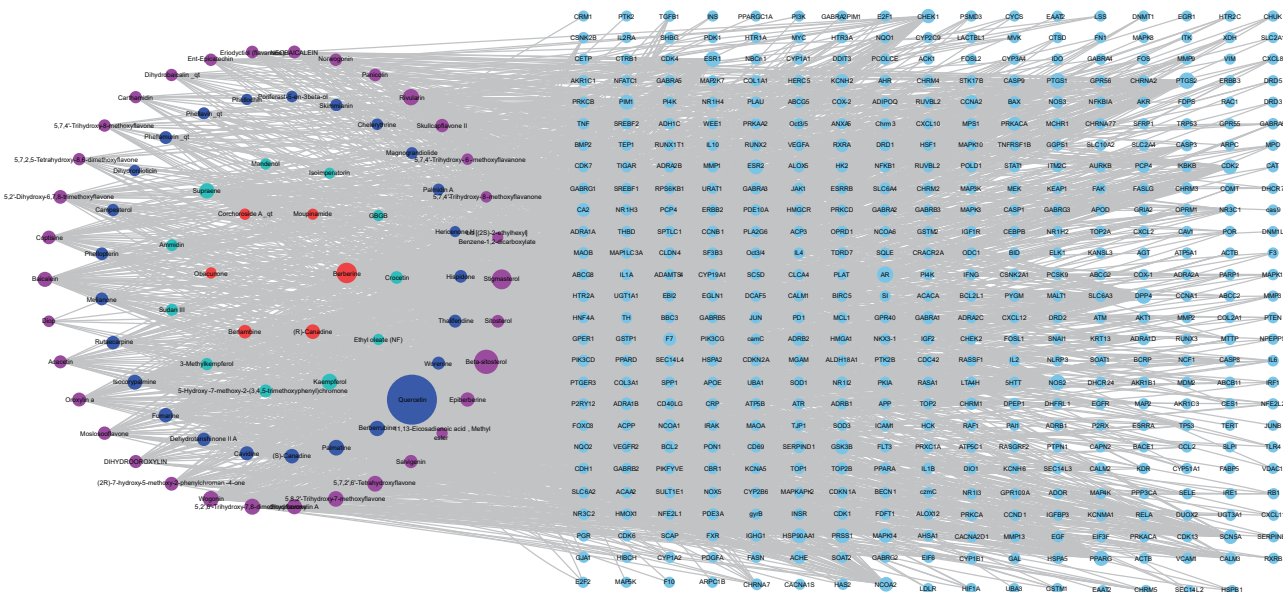


Figure 2 The target network diagram of the compounds in HLJDD. Purple represents the compounds of Huangqin (Scutellariae Radix); red represents the compounds of Huanglian (Coptidis Rhizoma); dark blue represents the compounds of Huangbo (Phellodendri Chinensis Cortex); green represents the compounds of Zhizi (Gardeniae Fructus); light blue represents predicted targets. The size of the nodes represents the degree; and the edges between the nodes represent the interrelations of the active compounds and targets.

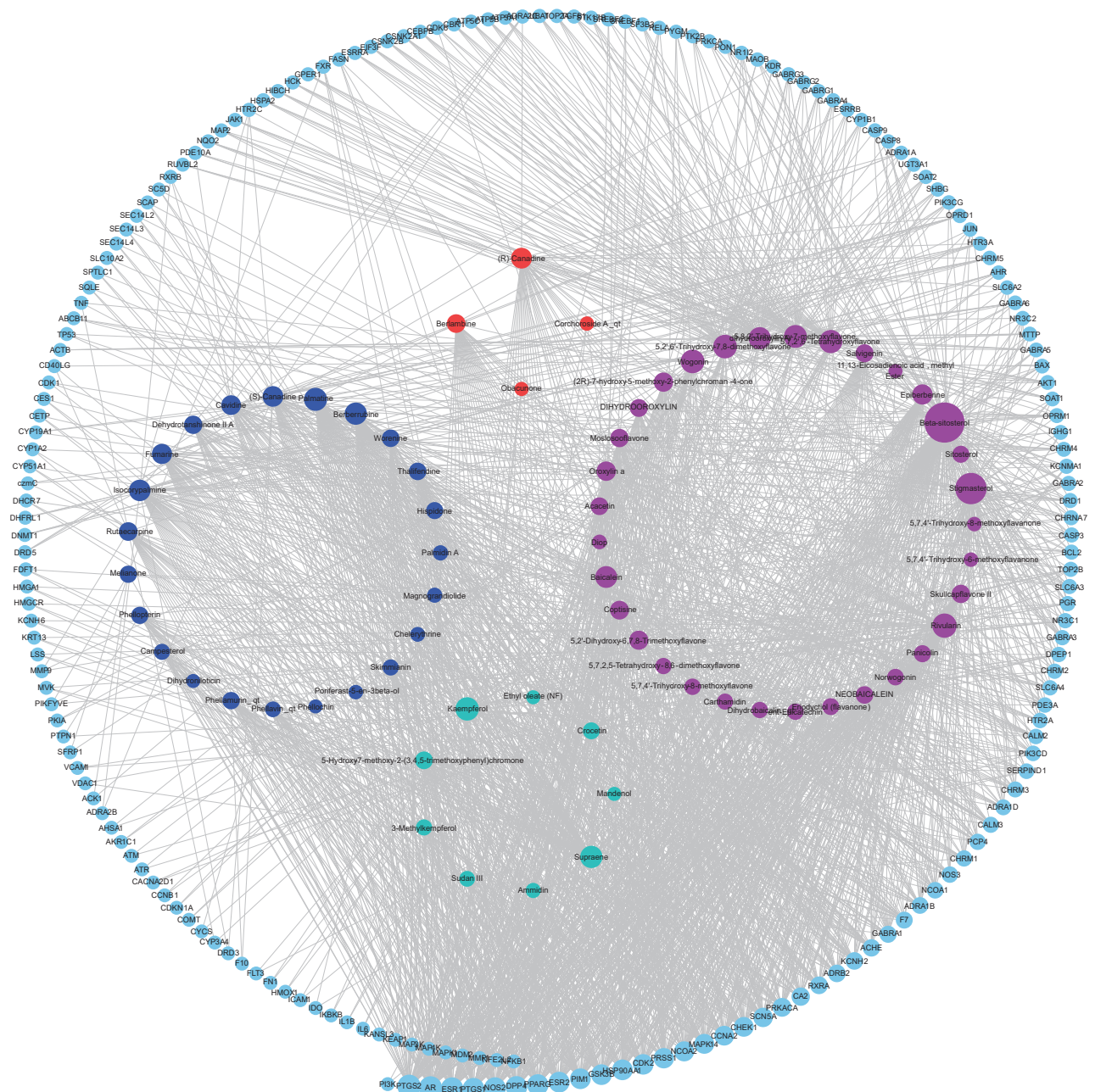


Figure 3 The core target network diagram of the active compounds in HLJDD. Purple represents the compounds of Huangqin (*Scutellariae Radix*); red represents the compounds of Huanglian (*Coptidis Rhizoma*); dark blue represents the compounds of Huangbo (*Phellodendri Chinensis Cortex*); and green represents the compounds of Zhizi (*Gardeniae Fructus*); light blue represents predicted target. The size of the nodes represents the degree; and the edges between the nodes represent the interrelations of the active compounds and targets.

shown in **Figure 5**.

Biological regulation, stress response, and metabolic processes are highly relevant to biological processes. The proportion of membrane, cytosol and endomembrane system in the cell components are relatively high, and protein binding, ion binding, and transferase activity have a great impact on molecular functions.

In KEGG enrichment pathway analysis, 458 signaling pathways are screened using a $P < 0.01$, and with an $FDR < 0.05$. The top 20 items are ranked in descending order by the number of related genes involved in the pathway, and

are visualized using OmicShare Tools (**Figure 6**). Targets with a high degree of cross-linking such as interleukin(IL)-10, IL-6, IL-1 β , and tumor necrosis factor (TNF) are involved in IL-10 signaling.

Further tissue enrichment analysis was carried out on targets. As shown in **Figure 7**, tissue enrichment reveals that target expression sites are mainly distributed in lung tissue, liver, and placenta, and involve a variety of immune cells, such as T cells and B cells. It shows that the key targets of the active compounds in HLJDD are mainly expressed in lung tissue and immune cells.

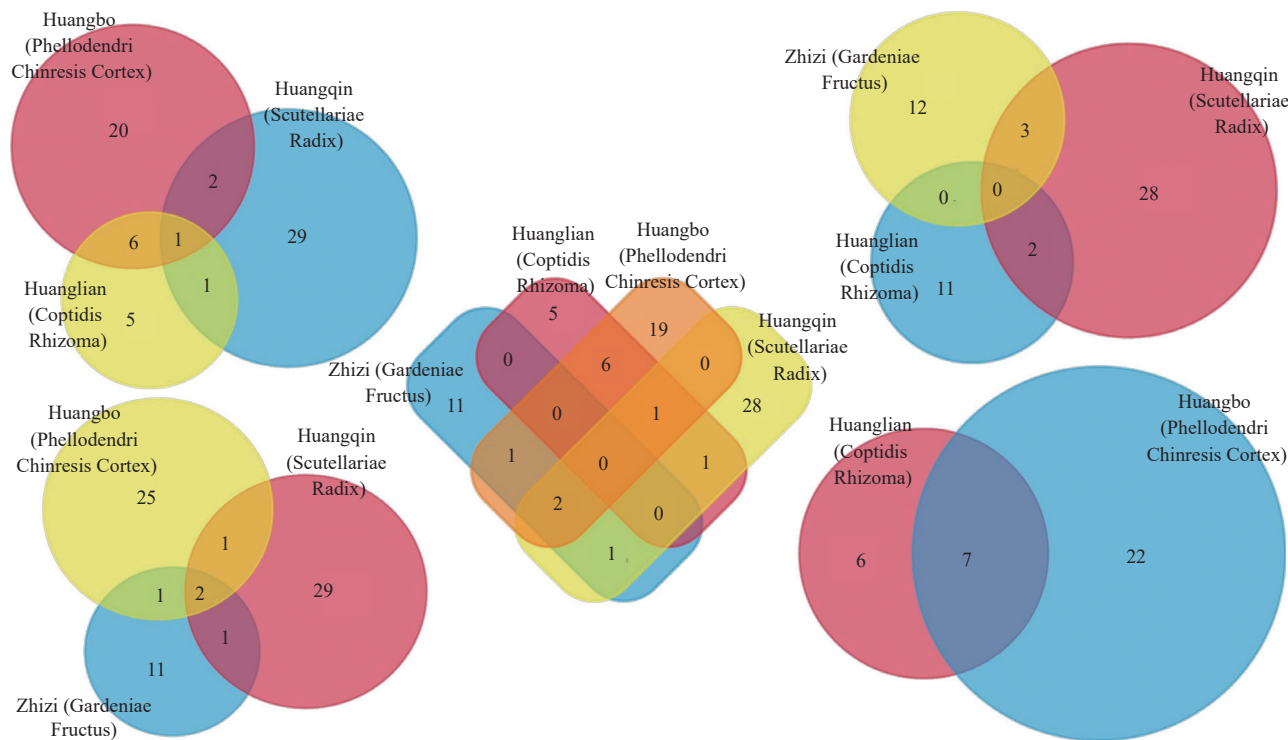


Figure 4 Distribution of active compounds of HLJDD

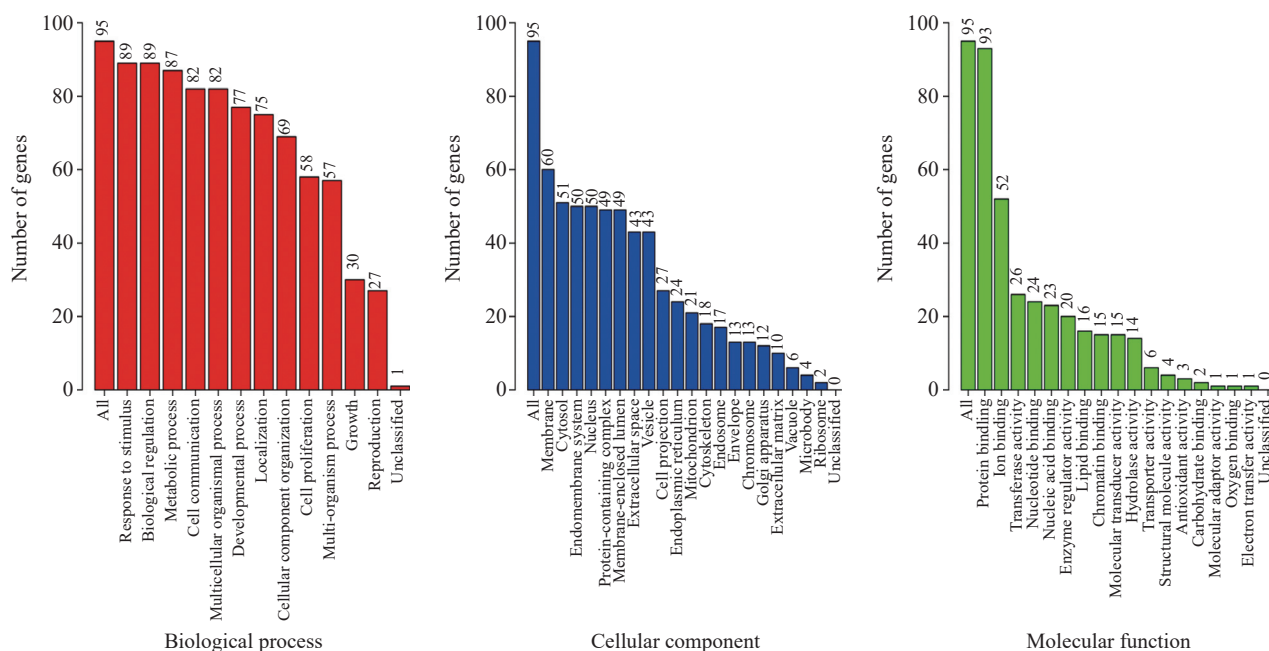


Figure 5 GO enrichment analysis of HLJDD targets

Biological process, cellular component, and molecular function categories are represented by red, blue, and green bars, respectively. The height of the bar graph represents the number of genes in which the annotated genes overlap.

3.5 Component-target molecular docking

In theory, the lower the energy, the more stable conformation of the ligand-receptor binding, the more likely the interaction. It is generally believed that the lower the energy, the more stable the conformation of ligand-receptor binding and the higher the possibility of action. The

molecular docking results (Table 2) show that all of the molecular docking affinity of the core active compounds in HLJDD and their corresponding related targets are less than -5.00 kJ/mol, which indicates that the core active compounds in HLJDD have good binding activity to their related targets. The results of the molecular docking study show that the binding energy of TNF to wogonin is

the lowest at - 6.24 KJ/mol, indicating that this ligand has the most stable conformation with the receptor. The docking results are shown in Figure 8.

Table 2 The binding energy values of the core compounds in HLJDD and their corresponding targets

Gene	Ligand	Binding energy (kJ/mol)
IL-6	Berberine	- 4.82
IL-6	Oroxilyn A	- 4.28
IL-6	Wogonin	- 4.08
IL-6	Quercetin	- 3.64
INS	Berberine	- 5.75
MAPK3	Baicalein	- 3.59
MAPK3	Quercetin	- 2.82
TNF	Wogonin	- 6.24
TNF	Berberine	- 6.18
TNF	Baicalein	- 5.10
TNF	Quercetin	- 3.73
TP53	Baicalein	- 5.39
TP53	Berberine	- 5.26
TP53	Wogonin	- 4.84
TP53	Acacetin	- 4.36
TP53	Quercetin	- 4.04
VEGFA	Berberine	- 5.07
VEGFA	Baicalein	- 3.26
VEGFA	Quercetin	- 2.80

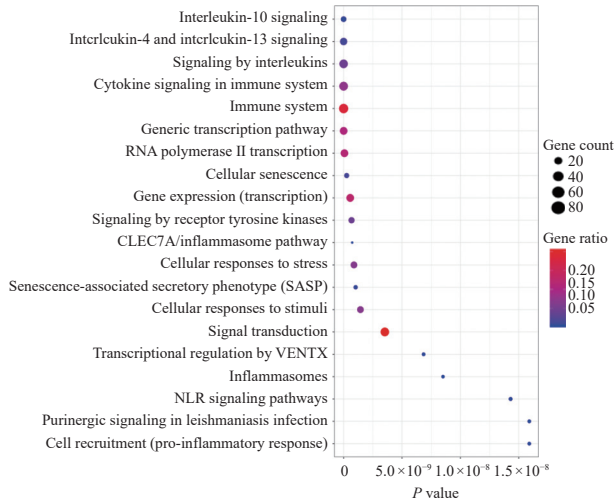


Figure 6 Visualization of KEGG enrichment pathway

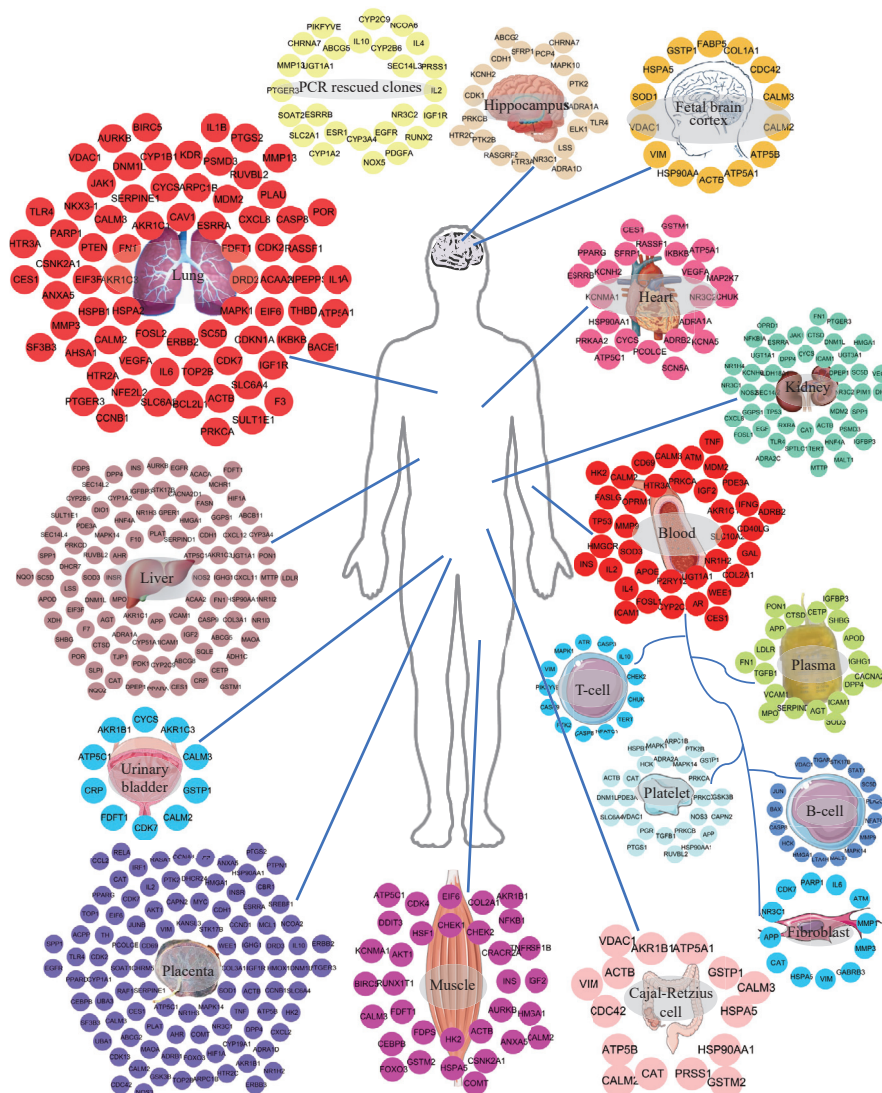


Figure 7 Tissue enrichment analysis of HLJDD targets

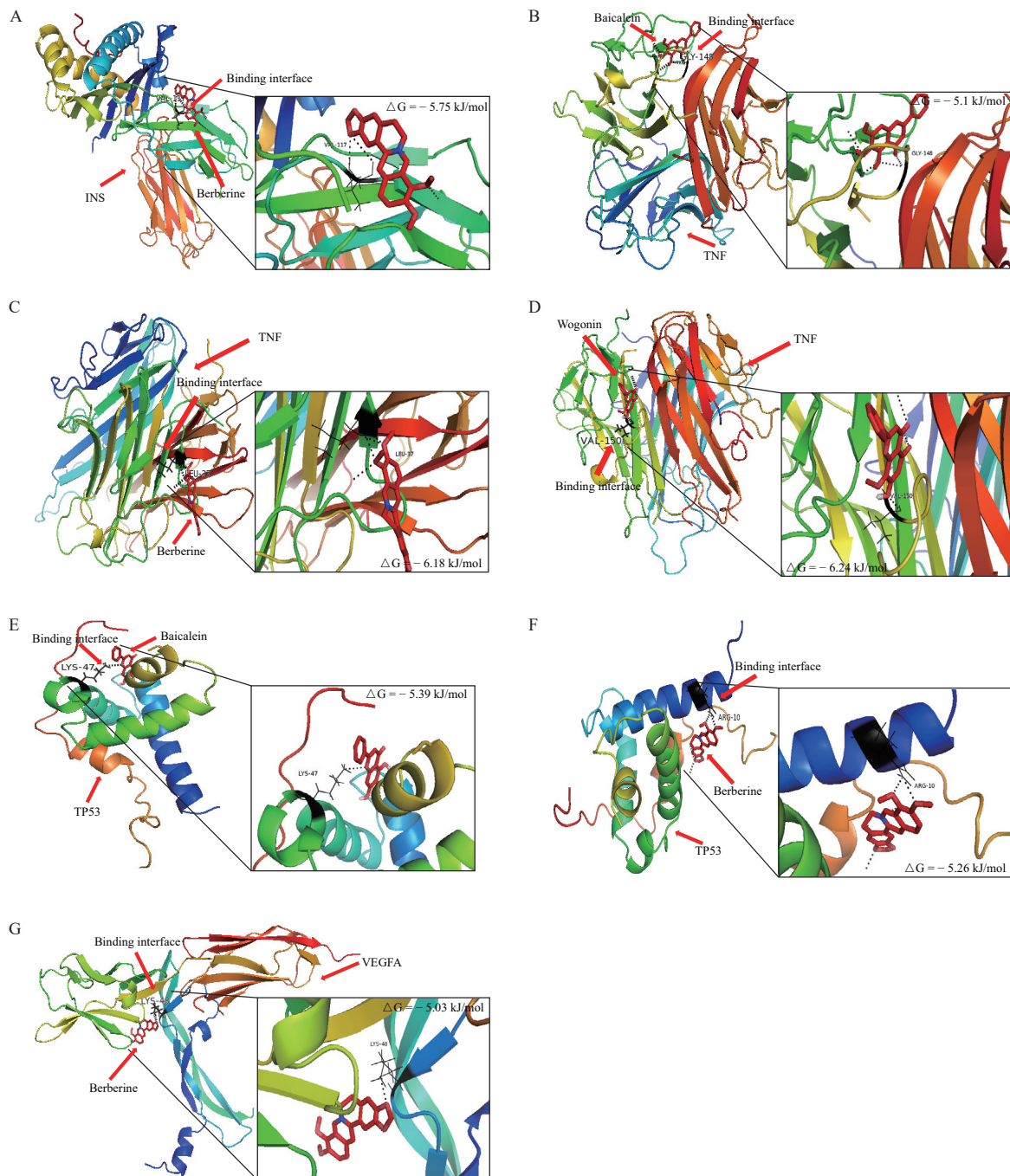


Figure 8 A diagram of molecular docking

A, INS-berberine docking. B, TNF-baicalein docking. C, TNF-berberine docking. D, TNF-wogonin docking. E, TP53-baicalein docking. F, TP53-berberine docking. G, VEGFA-berberine docking. Black box shows the docking site.

4 Discussion

4.1 Foundations of HLJDD as a treatment for COVID-19 in TCM

Since the outbreak of the COVID-19 pneumonia, the National Health Commission and other relevant units in various regions have successively issued a number of diagnosis and treatment plans. Among them, the recommended prescription for severe stages of COVID-19 pneumonia, HLJDD is in line with the blazing of both Qi and

Ying Phases in “Novel Coronavirus Pneumonia Diagnosis and Treatment Plan (Trial Operation Seventh Edition)” [18]. ZOU et al. [24] analyzed the contents of Chinese medicine in the “Diagnosis and Treatment of Novel Coronavirus Pneumonia” issued by 24 provinces, cities, and autonomous regions. Among the 17 types of Chinese medicine formulas, 13 types of Chinese patent medicines, and 25 types of unnamed prescriptions for severe and critical illnesses, HLJDD appeared 9 times. WANG et al. [25] analyzed 33 COVID-19 TCM diagnosis and treatment plans (including one national plan and 32 regional plans)

released before February 19, 2020. According to the statistical analysis of 65 types of Chinese patent medicines, HLJDD appeared six times, and all of these were used for treatment in the severe stage of the disease.

HLJDD is an effective remedy for acute heat syndrome, as it is excess-cold and bitter in nature and can clear the pattern of excess heat-toxicity in triple-jiao thoroughly. The main points of clinical application are a fever with vexation and thirst, dry mouth and dry throat, a red tongue with a yellow coating, as well as a rapid and strong pulse [17]. The pathogenicity of COVID-19 is similar to the one of the “epidemic Qi” of TCM [18]. It penetrates the triple-jiao from the exterior to the interior, and can also reverse transmission into the pericardium. It is also characteristic of strong contagiousness and high fatality rate, and it manifests itself in different periods of disease development. The symptoms are slightly different: the main manifestations of the intermediate stage are fever, cough, excessive sputum, general fatigue, headache, wheezing, diarrhea, red urine, constipation; or dry mouth, bitterness, red and dry tongue, with a yellow or greasy coating, and slippery; or soft, rapid pulse [19]. The main pathogenesis is heat-toxin blockage in the lungs, and dysfunction of Qi in the fu-organs. Therefore, HLJDD can be prescribed, as it has the effects of clearing heat in the lungs and fu-organs, and dispersing lung Qi.

4.2 Therapeutic effects of HLJDD in modern pharmacology

In modern clinical research, HLJDD is widely used in various departments, and has significant therapeutic effects on many viral and bacterial infectious diseases [26-28]. GAO et al. [29] found that the effective rate of HLJDD in treating high fever in children was as high as 94.55%, which was not significantly different from the western medicine treatment group (92.93%). The Huangqin (*Scutellariae Radix*) in HLJDD has a positive, protective effect on cells, and a significant effect of inhibiting the virus [30]. Huanglian (*Coptidis Rhizoma*) can also inhibit a variety of influenza viruses [31]. Huanglian (*Coptidis Rhizoma*) can effectively inhibit the expression level of the influenza virus mRNA in lung cancer A549 cells, reduce inflammation, and significantly increase Th1/Th2 and Th17/Treg values [32]. Another clinical study has shown that HLJDD can significantly exert antiviral, anti-inflammatory and antipyretic, antioxidant, immune regulation, antibacterial, and tissue protection pharmacological effects, and reduce the risk of COVID-19 turning into a severe condition [18]. HLJDD can also reduce blood pressure, hemostasis, and prevents thrombosis [33].

4.3 The positive curative effects of HLJDD on COVID-19

HLJDD has a positive curative effect on novel coronavirus pneumonia. It can reduce the incidence of

complications of COVID-19 pneumonia in many ways, improve the treatment efficiency of patients, improve the prognosis of patients, improve medical resource cost-effectiveness, as well as reduce the burden on the country, society, and individuals, which are all of great significance to hasten the ending of the epidemic [34]. Therefore, studying the active compounds, therapeutic targets, and molecular docking mechanisms of HLJDD can provide a theoretical basis for the treatment of a large number of patients with moderate or severe COVID-19.

In this study, after analyzing the active compounds through the network pharmacology method, 458 potential targets, 1 953 biological processes, 130 molecular functions, and 458 KEGG pathways were obtained. After preliminary clinical observation, the common clinical symptoms of the new COVID-19 strain are dyspnea, and severe cases will have a significant increase in proinflammatory cytokines such as IL-6, TNF- α , Interferon- γ (IFN- γ), which has the characteristics of cytokine storm [35]. The cytokine storm, also known as the “inflammatory storm”, is actually an important node in the transition from mild patients to severe patients, and it is also a cause of death of severe patients [36-39]. Once an inflammatory storm is formed, the immune system kills the virus, but it will also kill a large number of normal cells in the lung, severely destroying the lung's ventilation function, leading to respiratory failure until hypoxia and death. IL-6 is a pro-inflammatory factor, and its main function is to accelerate the alveolar inflammation in the early stage of pulmonary fibrosis through chemotactic inflammatory cell aggregation and promote inflammatory cell infiltration, and then mediate the occurrence of idiopathic pulmonary fibrosis [38, 40]. The latest researches found that IL-6 is an important inflammatory marker that induces the inflammatory storm of COVID-19 pneumonia [40, 41]. Based on the preliminary understanding of the mechanism and the KEGG analysis results, it is speculated that the core active compounds in HLJDD may regulate cytokine signaling and IL signaling in the immune system by acting on targets such as IL-6. Vascular endothelial growth factor (VEGF) is an important factor that promotes angiogenesis. It mainly exerts its physiological function by binding with receptors VEGF Receptor 1 (VEGFR1), VEGF Receptor 2 (VEGFR2), etc. [42]. Under pathological conditions, their combination can inhibit the apoptosis of vascular endothelial cells, promote their proliferation, migration and differentiation, increase vascular permeability, and stimulate neovascularization in the body [43]. Therefore, it is speculated that HLJDD may inhibit VEGF signal transduction by acting on VEGFA reduce pulmonary fibrosis, and play a role in treating COVID-19. Tumor protein 53 (TP53) is a known target of several viral oncoproteins, including SARS-CoV-2. Studies have observed that human coronaviruses antagonize the viral inhibitor p53 by

stabilizing CHY-zinc finger domain-containing 1 (RCHY1) as an interaction partner of the viral SARS-CoV-2 unique structural domain and promoting RCHY1-mediated degradation of p53 [44-46]. Potentially, viruses can use its downregulation to aid their own replication, and pharmacological rescue of p53 function can be explored to monitor viruses [47].

The results of molecular docking showed that the conformation of TNF and wogonin was the most stable and the possibility of their action was the greatest. This indicates that wogonin in Huangqin (*Scutellariae Radix*) plays a more important role in the treatment of COVID-19. Baicalein and berberine also showed good binding activity to TNF. Study has shown that wogonin and baicalein have inhibiting inflammatory mediators, regulating immunity, and eliminating free radical effects [48]. Some studies have shown that berberine has certain anti-inflammatory effects [48, 49], and can be combined with pneumolysin cholesterol binding site to prevent the toxin from binding to membrane, playing a competitive antagonistic role, thus to have an anti-infective effect [50]. Therefore, it is speculated that HLJDD may play a better role in the treatment of COVID-19 through its inhibiting inflammatory mediators, regulating immunity, and eliminating free radical effects.

5 Conclusion

Overall, this study used network pharmacology and molecular docking analysis to explore the chemical constituents, action targets, and the core active compounds in HLJDD. The active compounds such as berberine, baicalein, and wogonin in HLJDD may have a therapeutic effect on COVID-19 through regulating multiple signaling pathways by targeting genes such as VEGF, IL-6, TNF, TP53, etc. However, since this study is mainly discussed at the theoretical level, further experimental research on pharmacodynamic evaluation, metabolomics, and clinical efficacy is needed to provide a solid basis for the treatment and drug development of COVID-19.

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Competing interests

The authors declare no conflict of interest.

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基于网络药理学和分子对接技术预测黄连解毒汤治疗新型冠状病毒肺炎的潜在靶点及作用机制

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【摘要】目的 本研究通过网络药理学和分子对接技术预测黄连解毒汤 (HLJDD) 治疗新型冠状病毒肺炎 (COVID-19) 的潜在靶点和作用机制。**方法** 在中药系统药理学数据库和分析平台 (TCMSP)、SymMap v2、中药百科全书 (ETCM)、高通量中医药实验和参考指导数据库 (HERB)、中医药综合数据库 (TCMID) 中检索 HLJDD 的化学成分和作用靶点。通过 UniProt、GeneCards 等数据库获取靶点对应的基因, 运用 Cytoscape 3.7.2 构建化合物-靶点 (基因) 网络。通过基因本体 (GO) 数据库进行 GO 功能注释, 运用 GO 和基因组百科全书 (KEGG) 预测活性化合物可能的作用机制。运用注释、可视化和集成发现数据库 (DAVID) 进行组织富集分析。将 HLJDD 的主要活性成分与其相应的相关靶点进行分子对接分析。**结果** 化合物-靶点网络包含 76 个化合物和 458 个相应靶点。基因注释显示预测的靶标主要参与了 1 953 个生物过程; 884 条信号通路, 包括白介素信号通路、免疫系统细胞因子信号通路、通用转录通路和 RNA 聚合酶 II 转录。药物潜在靶点主要分布在肺、肝和胎盘, 涉及多种免疫细胞, 如 T 细胞、B 细胞。分子对接结果表明: 汉黄芩素、小檗碱、黄芩素等核心化合物与肿瘤坏死因子 (TNF)、胰岛素 (INS) 和肿瘤蛋白 P53 (TP53) 具有高亲和力。**结论** HLJDD 中的活性化合物可能通过血管内皮生长因子 A (VEGFA)、INS、白细胞介素 6 (IL-6)、TNF、半胱氨酸蛋白酶 3、TP53 和丝裂原活化蛋白激酶 3 (MAPK3) 等靶向基因调节多条信号通路对 COVID-19 发挥治疗作用。

【关键词】 黄连解毒汤; 活性化合物; 新型冠状病毒肺炎; 新型冠状病毒; 网络药理学; 分子对接