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Network Pharmacology Approach to Investigate the Preventive Mechanism of Hunan Expert Group Recommended Chinese Medicine Prevention No. 2 Prescription Against COVID-19

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ABSTRACT

Objective To explore the possible preventive mechanism of Hunan expert group recommended Chinese medicine prescription of No. 2 (Pre-No. 2) against coronavirus disease 2019 (COVID-19) by network pharmacology method.

Methods The target proteins of effective components and active compounds in Pre-No. 2 were screened by searching the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP). A component-target-disease interaction network of Pre-No. 2 was constructed by Cytoscape 3.7.2, gene ontology (GO) analysis, and Kyoto encyclopedia of genes and genomes (KEGG) analysis of target protein pathway by DAVID.

Results A total of 163 compounds and 278 target protein targets in Pre-No. 2 were collected from the TCMSP database. Kaempferol, wogonin, 7-methoxy-2-methyl isoflavone, formononetin, isorhamnetin, and licochalcone A were the most frequent targets in the regulatory network. GO enrichment analysis showed that Pre-No. 2 regulated response to virus, viral processes, humoral immune responses, defense responses to virus and viral entry into host cells. KEGG enrichment analysis showed that the formula regulated the NF-κB signaling pathway, B cell receptor signaling pathway, viral carcinogenesis, T cell signaling pathway and FcγR-mediated phagocytosis signaling pathway.

Conclusions Pre-No. 2 may play a preventive role against COVID-19 through regulation of the Toll-like signaling, T cell signaling, B cell signaling and other signaling pathways. It may regulate the immune system to protect against anti-influenza virus.

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1 Introduction

December 2019, an acute pneumonia (COVID-19) caused by the new coronavirus (SARS-CoV-2) has spread worldwide. Data from the World Health Organization revealed that a total of 216 countries or regions were affected by this disease, with 8 708 008 cases and 461 715 deaths confirmed updated to June 21st, 2020 [1]. SARS-CoV-2 can be considered as a new type of human infectious β-coronavirus. Although phylogenetic analysis indicated that bats may be the original host of the virus, the intermediate host and the exact transmission route have not been determined [2, 3]. Epidemiological studies have confirmed that the new viruse can transmitted from person to person through respiratory droplets or close contact, so it's crucial and necessary to adopt prevention practices in public health [4].

Fever, dry cough and fatigue are the main clinical symptoms. Severe patients may develop dyspnea, hypoxemia, and even acute respiratory distress syndrome and septic shock [5]. At present, integrative Chinese and western medicine treatment is the main powerful method when specific vaccines are absent. Traditional Chinese medicine (TCM) has accumulated many valuable experiences in the prevention and treatment of epidemic diseases. COVID-19 belongs to the category of “epidemic disease” in the TCM. A series of Chinese medicine prescriptions has been used to defend against COVID-19, effectively controlling the development of the pandemic [6]. Prevention is an essential method and a characteristic of Chinese medicine. Therefore, in the early stage of the epidemic, the Hunan Provincial Administration of Traditional Chinese Medicine organized a senior expert group of Chinese medicine with Professor XIONG Ji-Bo as a consultant, and jointly developed the Hunan Province’s New Coronavirus Infected Pneumonia TCM Diagnosis and Treatment Plan (Trial Version 3). The expert group recommended preventive methods for different groups and constitutions in the “Plan”. Pre-No. 2 was consisted of Isatidis Radix (Ban Lan Gen, 板蓝根), Menthae Haplocalycis Herba (Bo He, 薄荷), Glycyrrhizae Radix Et Rhizoma (Gan Cao, 甘草), Lonicerae Japonicae Flos (Jin Yin Hua, 金银花), Schizonepetae Herba (Jing Jie, 荆芥), Forsythiae Fructus (Lian Qiao, 连翘), Phragmitis Rhizoma (Lu Gen, 芦根) and Mori Cortex (Sang Bai Pi, 桑白皮). The prescription was originated from Yin Qiao Powder, which was mainly used in key populations with strong physique and history of close contact with infected people.

Network pharmacology is a new discipline based on the theory of systems biology used to analyze the network of biological systems and select specific signal nodes for multi-target drug molecular design. TCM is a complex system with multiple compounds, multiple targets and synergies among the compounds. Network pharmacology emphasizes the multi-path regulation of signaling pathways and the multi-compound-target-path regulation [7], which can help improve the efficiency and reduce the costs of new drug development in clinical trials. In this study, we utilized the network pharmacology method to screen the core active compounds and metabolic pathways in Pre-No. 2 and to predict its potential preventive mechanisms against COVID-19.

2 Materials and Methods

2.1 Collection of active compounds and targets of Pre-No. 2

The TCM Database@Taiwan [8] and Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP) database [9] were searched for “Isatidis Radix” “Menthae Haplocalycis Herba” “Glycyrrhizae Radix Et Rhizoma” “Lonicerae Japonicae Flos” “Schizonepetae Herba” “Forsythiae Fructus” “Phragmitis Rhizoma” and “Mori Cortex” to collect the compounds of Pre-No. 2 and then to investigate the pharmacokinetic parameters and targets of each active compound in TCMSP. The pharmacokinetic parameters included oral bioavailability (OB), Caco-2 permeability, and drug-like (DL), according to the standards provided by the TCMSP database, and Tanimoto and OBioavail, which are embedded in the database, were used to obtain predicted and calculated DL and OB. OB > 30%, Caco-2 > – 0.4, and DL > 0.18 were used as standards to screen orally absorbable active compounds with pharmacological activity. The protein name of the collected target was entered into UniProtKB (http://www.uniprot.org/). The restricted species is “Homo sapiens”, thus correcting the protein name to the official symbol.

2.2 Collection of COVID-19-related targets and data on protein-protein interactions (PPI)

The Online Mendelian Inheritance in Man (OMIM) database [10] and Genecards [11] were used to collect SARS-CoV-2-related targets in infected humans. The search results of the two databases were summarized and deduplicated. The String database (http://string-db.org/) [12] is usually used to search for interactions between known proteins and predicted proteins, as well as to predict direct and indirect interactions from prokaryotic cells to various other eukaryotes. In

this study, we used the String database to collect data on PPI of Pre-No. 2 and the related targets of COVID-19 in infected cells, with confidence > 0.4.

2.3 Network construction and analysis

Cytoscape 3.7.2 [13] was used as a tool to visualize the PPI network. Four main networks were constructed: (1) an active compound-action target network of Pre-No. 2; (2) an active target of Pre-No. 2-COVID-19-related target protein interaction network; (3) an active compound-biological process/cell component/molecular function-target network; and (4) an active compound-signal pathway-target network. In the network, nodes represent active compounds, targets, or pathways and nodes are connected by edges. Degree represents the number of connections between the nodes and the degree of betweenness represents the shortest path through the nodes.

2.4 Pathway enrichment analysis

Gene Ontology (GO) enrichment analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway annotation analysis can reveal the importance of different biological processes, cell components, molecular functions and signaling pathways in a PPI network. In this study, COVID-19-related targets and the targets of Pre-No. 2 were introduced into the DAVID platform version 6.8 (https://david-d.ncifcrf.gov) [14] for GO enrichment and KEGG enrichment analysis, and the results in the related network were displayed in tables and bubble graphs.

3 Results

3.1 Active compound-action target network of Pre-No. 2

A total of 163 active compounds in Pre-No. 2 and their targets were collected. The details are shown in Table 1. The active compounds and targets were introduced into Cytoscape 3.7.2 to build a network of active compound-targets of Pre-No. 2. The network consists of 163 active component nodes, 278 active target nodes and 2 567 edges. In this network, the size of a node is positively related to its degree. For example, CALM1 has a larger node and can be controlled by active compounds such as Kaempferol, Wogonin, 7-Methoxy-2-methyl isoflavone, Formononetin, Isorhamnetin, Licochalcone A, Medicarpin, 4'-Methoxyglabridin, 1-Methoxyphaseollidin, Vestitol and Licoagrocarpin, etc., while the 1-Monolinolein node is small and can only regulate PTGS1 (Figure 1).

3.2 Pre-No. 2 target-COVID-19-related target PPI network

Pre-No. 2 targets (i.e., drug target), COVID-19-related targets (i.e., viral target), and PPI information were

Table 1 Information of 158 active compounds in Pre-No. 2

Source	MOL ID	Compound name	Molecular weight	OB (%)	Caco-2	DL
Forsythiae Fructus (Lian Qiao, 连翘)	MOL000006	Luteolin	286.25	36.16	0.19	0.25
	MOL000173	Wogonin	284.28	30.68	0.79	0.23
	MOL000791	Bicuculline	367.38	69.67	0.72	0.88
	MOL003283	Isolariciresinol	360.44	66.51	– 0.2	0.39
	MOL003290	Dimethylmatairesinol	386.48	52.3	0.78	0.48
	MOL003295	(+)-Pinoresinol Monomethyl Ether	372.45	53.08	0.69	0.57
	MOL003306	4-[(3S,3Ar,6S,6aR)-6-(3,4-dimethoxyphenyl)-1,3,3a,4,6,6a-hexahydrofuro[3,4-c] furan-3-yl]-2-methoxyphenol (Acon1_001697)	372.45	85.12	0.76	0.57
	MOL003308	(+)-Pinoresinol monomethyl ether-4-D-beta-glucoside (MOL003308)	372.45	61.2	0.7	0.57
	MOL003315	3Beta-Acetyl-20,25-Epoxydammarane-24alpha-Ol	502.86	33.07	0.75	0.79
	MOL003322	Forsythinol	372.45	81.25	0.59	0.57
	MOL003330	(-)-Phillygenin	372.45	95.04	0.75	0.57

Table 1 Continued

Source	MOL ID	Compound name	Molecular weight	OB (%)	Caco-2	DL
Forsythiae Fructus (Lian Qiao, 连翘)	MOL003347	Hyperforin	536.87	44.03	0.87	0.6
	MOL003370	Onjixanthone I	302.3	79.16	0.84	0.3
	MOL000211	Mairin	456.78	55.38	0.73	0.78
	MOL000358	Beta-Sitosterol	414.79	36.91	1.32	0.75
	MOL000422	Kaempferol	286.25	41.88	0.26	0.24
Glycyrrhizae Radix Et Rhizoma (Gan Cao, 甘草)	MOL000211	Mairin	456.78	55.38	0.73	0.78
	MOL000098	Quercetin	302.25	46.43	0.05	0.28
	MOL000239	Jaranol	314.31	50.83	0.61	0.29
	MOL000354	Isorhamnetin	316.28	49.6	0.31	0.31
	MOL000359	Sitosterol	414.79	36.91	1.32	0.75
	MOL000392	Formononetin	268.28	69.67	0.78	0.21
	MOL000417	Calycosin	284.28	47.75	0.52	0.24
	MOL000422	Kaempferol	286.25	41.88	0.26	0.24
	MOL000497	Licochalcone A	338.43	40.79	0.82	0.29
	MOL000500	Vestitol	272.32	74.66	0.86	0.21
	MOL001484	Inermine	284.28	75.18	0.89	0.54
	MOL001792	Liquiritigenin	256.27	32.76	0.51	0.18
	MOL002311	Glycyrol	366.39	90.78	0.71	0.67
	MOL002565	Medicarpin	270.3	49.22	1	0.34
	MOL003656	Lupiwighteone	338.38	51.64	0.68	0.37
	MOL003896	7-Methoxy-2-Methyl Isoflavone	266.31	42.56	1.16	0.2
	MOL004328	Naringenin	272.27	59.29	0.28	0.21
	MOL004805	(2S)-2-[4-Hydroxy-3-(3-Methylbut-2-Enyl)Phenyl]-8,8-Dimethyl-2,3-Dihydropyrano[2,3-F]Chromen-4-One	390.51	31.79	1	0.72
	MOL004806	Euchrenone	406.56	30.29	1.09	0.57
	MOL004808	Glyasperin B	370.43	65.22	0.47	0.44
	MOL004810	Glyasperin F	354.38	75.84	0.43	0.54
	MOL004811	Glyasperin C	356.45	45.56	0.71	0.4
	MOL004814	Isotrifoliol	298.26	31.94	0.53	0.42
	MOL004815	(E)-1-(2,4-Dihydroxyphenyl)-3-(2,2-Dimethylchromen-6-Yl)Prop-2-En-1-One	322.38	39.62	0.66	0.35
	MOL004820	Kanzonols W	336.36	50.48	0.63	0.52
	MOL004824	(2S)-6-(2,4-Dihydroxyphenyl)-2-(2-Hydroxypropan-2-Yl)-4-Methoxy-2,3-Dihydrofuro[3,2-G]Chromen-7-One	384.41	60.25	0	0.63
	MOL004827	Semilicoisoflavone B	352.36	48.78	0.45	0.55
	MOL004828	Glepidotin A	338.38	44.72	0.79	0.35
	MOL004829	Glepidotin B	340.4	64.46	0.46	0.34
	MOL004833	Phaseolinisoflavan	324.4	32.01	1.01	0.45

Table 1 Continued

Source	MOL ID	Compound name	Molecular weight	OB (%)	Caco-2	DL
	MOL004835	Glypallichalcone	284.33	61.6	0.76	0.19
	MOL004838	8-(6-Hydroxy-2-Benzofuranyl)-2,2-Dimethyl-5-Chromenol	308.35	58.44	1	0.38
	MOL004841	Licochalcone B	286.3	76.76	0.47	0.19
	MOL004848	Licochalcone G	354.43	49.25	0.64	0.32
	MOL004849	3-(2,4-Dihydroxyphenyl)-8-(1,1-Dimethylprop-2-Enyl)-7-Hydroxy-5-Methoxy-Coumarin	368.41	59.62	0.4	0.43
	MOL004855	Licoricone	382.44	63.58	0.53	0.47
	MOL004856	Gancaonin A	352.41	51.08	0.8	0.4
	MOL004857	Gancaonin B	368.41	48.79	0.58	0.45
	MOL004863	3-(3,4-Dihydroxyphenyl)-5,7-Dihydroxy-8-(3-Methylbut-2-Enyl)Chromone	354.38	66.37	0.52	0.41
	MOL004864	5,7-Dihydroxy-3-(4-Methoxyphenyl)-8-(3-Methylbut-2-Enyl)Chromone	352.41	30.49	0.9	0.41
	MOL004866	2-(3,4-Dihydroxyphenyl)-5,7-Dihydroxy-6-(3-Methylbut-2-Enyl)Chromone	354.38	44.15	0.48	0.41
	MOL004879	Glycyrin	382.44	52.61	0.59	0.47
	MOL004882	Licocoumarone	340.4	33.21	0.84	0.36
	MOL004883	Licoisoflavone	354.38	41.61	0.37	0.42
Glycyrrhizae Radix Et Rhizoma (Gan Cao, 甘草)	MOL004884	Licoisoflavone B	352.36	38.93	0.46	0.55
	MOL004885	Licoisoflavanone	354.38	52.47	0.39	0.54
	MOL004891	Shinpterocarpin	322.38	80.3	1.1	0.73
	MOL004898	(E)-3-[3,4-Dihydroxy-5-(3-Methylbut-2-Enyl)Phenyl]-1-(2,4-Dihydroxyphenyl)Prop-2-En-1-One	340.4	46.27	0.41	0.31
	MOL004904	Licopyranocoumarin	384.41	80.36	0.13	0.65
	MOL004907	Glyzaglabrin	298.26	61.07	0.34	0.35
	MOL004908	Glabridin	324.4	53.25	0.97	0.47
	MOL004910	Glabranin	324.4	52.9	0.97	0.31
	MOL004911	Glabrene	322.38	46.27	0.99	0.44
	MOL004912	Glabrone	336.36	52.51	0.59	0.5
	MOL004913	1,3-Dihydroxy-9-Methoxy-6-Benzofurano[3,2-C]Chromenone	298.26	48.14	0.48	0.43
	MOL004914	1,3-Dihydroxy-8,9-Dimethoxy-6-Benzofurano[3,2-C]Chromenone	328.29	62.9	0.4	0.53
	MOL004915	Eurycarpin A	338.38	43.28	0.43	0.37
	MOL004935	Sigmoidin-B	356.4	34.88	0.42	0.41
	MOL004941	(2R)-7-Hydroxy-2-(4-Hydroxyphenyl)Chroman-4-One	256.27	71.12	0.41	0.18
	MOL004945	(2S)-7-Hydroxy-2-(4-Hydroxyphenyl)-8-(3-Methylbut-2-Enyl)Chroman-4-One	324.4	36.57	0.72	0.32

Table 1 Continued

Source	MOL ID	Compound name	Molecular weight	OB (%)	Caco-2	DL
	MOL004948	Isoglycyrol	366.39	44.7	0.91	0.84
	MOL004949	Isolicoflavonol	354.38	45.17	0.54	0.42
	MOL004957	HMO	268.28	38.37	0.79	0.21
	MOL004959	1-Methoxyphaseollidin	354.43	69.98	1.01	0.64
	MOL004961	Quercetin Der.	330.31	46.45	0.39	0.33
	MOL004966	3'-Hydroxy-4'-O-Methylglabridin	354.43	43.71	1	0.57
	MOL004974	3'-Methoxyglabridin	354.43	46.16	0.94	0.57
	MOL004978	2-[(3R)-8,8-Dimethyl-3,4-Dihydro-2H-Pyrano[6,5-F]Chromen-3-Yl]-5-Methoxyphenol	338.43	36.21	1.12	0.52
	MOL004980	Inflacoumarin A	322.38	39.71	0.73	0.33
	MOL004985	Icos-5-Enoic Acid	310.58	30.7	1.22	0.2
	MOL004988	Kanzonol F	420.54	32.47	1.18	0.89
Glycyrrhizae Radix Et Rhizoma (Gan Cao, 甘草)	MOL004989	6-Prenylated Eriodictyol	356.4	39.22	0.4	0.41
	MOL004990	7,2',4'-Trihydroxy-5-Methoxy-3-Arylcoumarin	300.28	83.71	0.24	0.27
	MOL004991	7-Acetoxy-2-Methylisoflavone	294.32	38.92	0.74	0.26
	MOL004993	8-Prenylated Eriodictyol	356.4	53.79	0.43	0.4
	MOL004996	Gadelaidic Acid	310.58	30.7	1.2	0.2
	MOL005000	Gancaonin G	352.41	60.44	0.78	0.39
	MOL005001	Gancaonin H	420.49	50.1	0.6	0.78
	MOL005003	Licoagrocarpin	338.43	58.81	1.23	0.58
	MOL005007	Glyasperins M	368.41	72.67	0.49	0.59
	MOL005008	Glycyrrhiza Flavonol A	370.38	41.28	– 0.09	0.6
	MOL005012	Licoagroisoflavone	336.36	57.28	0.71	0.49
	MOL005016	Odoratin	314.31	49.95	0.42	0.3
	MOL005017	Phaseol	336.36	78.77	0.76	0.58
	MOL005018	Xambioona	388.49	54.85	1.09	0.87
	MOL005020	Dehydroglyasperins C	340.4	53.82	0.68	0.37
	MOL000358	Beta-Sitosterol	414.79	36.91	1.32	0.75
	MOL000359	Sitosterol	414.79	36.91	1.32	0.75
	MOL000449	Stigmasterol	412.77	43.83	1.44	0.76
	MOL000953	Cholesterol	386.73	37.87	1.43	0.68
Isatidis Radix (Ban Lan Gen, 板蓝根)	MOL001689	Acacetin	284.28	34.97	0.67	0.24
	MOL001721	Isaindigodione	326.38	60.12	– 0.09	0.41
	MOL001733	Eupatorin	344.34	30.23	0.7	0.37
	MOL001735	Dinatin	300.28	30.97	0.48	0.27
	MOL001736	(-)-Taxifolin	304.27	60.51	– 0.24	0.27
	MOL001749	Bis[(2R)-2-ethylhexyl] benzene-1,2-dicarboxylate (ZINC03860434)	390.62	43.59	1.04	0.35

Table 1 Continued

Source	MOL ID	Compound name	Molecular weight	OB (%)	Caco-2	DL
	MOL001755	24-Ethylcholest-4-En-3-One	412.77	36.08	1.46	0.76
	MOL001756	Quindoline	218.27	33.17	1.5	0.22
	MOL001767	Hydroxyindirubin	278.28	63.37	0.51	0.3
	MOL001771	Poriferast-5-En-3beta-ol	414.79	36.91	1.45	0.75
	MOL001774	Ineketone	318.5	37.14	0.39	0.3
	MOL001779	Sinoacutine	327.41	49.11	0.7	0.46
	MOL001781	Indigo	262.28	38.2	0.83	0.26
	MOL001782	479-41-4	262.28	48.4	0.85	0.26
	MOL001783	2-(9-((3-Methyl-2-oxopent-3-en-1-yl)oxy)-2-oxo-1,2,8,9-tetrahydrofuro[2,3-h]quinolin-8-yl)propan-2-yl acetate	399.48	64	0.39	0.57
	MOL001792	Liquiritigenin	256.27	32.76	0.51	0.18
Isatidis Radix (Ban Lan Gen, 板蓝根)	MOL001793	(E)-2-[(3-Indole)Cyanomethylene-]-3-Indolinone	300.36	54.59	1.06	0.32
	MOL001798	Neohesperidin	302.3	71.17	0.26	0.27
	MOL001800	Rosasterol	414.79	35.87	1.28	0.75
	MOL001803	Sinensetin	372.4	50.56	1.12	0.45
	MOL001804	Stigmasta-5,22-Diene-3beta,7alpha-Diol	440.83	43.04	1.35	0.82
	MOL001810	Qingdainone	363.39	45.28	1.19	0.89
	MOL001814	(E)-3-(3,5-Dimethoxy-4-Hydroxy-Benzylidene)-2-Indolinone	297.33	57.18	0.69	0.25
	MOL001820	(E)-3-(3,5-Dimethoxy-4-Hydroxyb-Enzylidene)-2-Indolinone	299.35	65.17	0.28	0.25
	MOL001828	3-[(3,5-Dimethoxy-4-oxo-1-cyclohexa-2,5-dienylidene)methyl]-2,4-dihydro-1H-pyrrolo[2,1-b]quinazolin-9-one	350.4	51.84	0.81	0.56
	MOL001833	Glucobrassicin-1-Sulfonate	365.42	42.52	– 0.19	0.24
	MOL000006	Luteolin	286.25	36.16	0.19	0.25
	MOL000098	Quercetin	302.25	46.43	0.05	0.28
	MOL000358	Beta-Sitosterol	414.79	36.91	1.32	0.75
	MOL000422	Kaempferol	286.25	41.88	0.26	0.24
	MOL000449	Stigmasterol	412.77	43.83	1.44	0.76
	MOL001494	Mandenol	308.56	42	1.46	0.19
Lonicerae Japonicae Flos (Jin Yin Hua, 金银花)	MOL001495	Ethyl Linolenate	306.54	46.1	1.54	0.2
	MOL002773	Beta-Carotene	536.96	37.18	2.25	0.58
	MOL002914	Eriodyctiol (Flavanone)	288.27	41.35	0.05	0.24
	MOL003014	Secologanic Dibutylacetal	384.57	53.65	0.34	0.29
	MOL003036	(3S,8R,9R,10R,13R,14S,17R)-17-[(E,2R,5S)-5-Ethyl-6-methylhept-3-en-2-yl]-10,13-dimethyl-2,3,4,7,8,9,11,12,14,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-3-ol	412.77	43.83	1.32	0.76
	MOL003044	Chryseriol	300.28	35.85	0.39	0.27

Table 1 Continued

Source	MOL ID	Compound name	Molecular weight	OB (%)	Caco-2	DL
Menthae Haplocalycis Herba (Bo He, 薄荷)	MOL000006	Luteolin	286.25	36.16	0.19	0.25
	MOL000359	Sitosterol	414.79	36.91	1.32	0.75
	MOL001689	Acacetin	284.28	34.97	0.67	0.24
	MOL000471	Aloe-Emodin	270.25	83.38	– 0.12	0.24
	MOL002881	Diosmetin	300.28	31.14	0.46	0.27
	MOL004328	Naringenin	272.27	59.29	0.28	0.21
	MOL005190	Eriodictyol	288.27	71.79	0.17	0.24
	MOL005573	Genkwanin	284.28	37.13	0.63	0.24
Phragmitis Rhizoma (Lu Gen, 芦根)	MOL000449	Stigmasterol	412.77	43.83	1.44	0.76
Mori Cortex (Sang Bai Pi, 桑白皮)	MOL000358	Beta-Sitosterol	414.79	36.91	1.32	0.75
	MOL000422	Kaempferol	286.25	41.88	0.26	0.24
	MOL000098	Quercetin	302.25	46.43	0.05	0.28
	MOL000211	Mairin	456.78	55.38	0.73	0.78
	MOL001004	Pelargonidin	271.26	37.99	0.31	0.21
	MOL001474	Sanguinarine	332.35	37.81	1.26	0.86
	MOL002514	Sexangularetin	316.28	62.86	0.31	0.3
	MOL003758	Iristectorigenin (9CI)	330.31	71.55	0.55	0.34
	MOL003856	Moracin B	286.3	55.85	0.83	0.23
	MOL003857	Moracin C	310.37	82.13	0.87	0.29
	MOL003858	Moracin D	308.35	60.93	1.03	0.38
	MOL003860	Moracin F	286.3	53.81	0.81	0.23
	MOL004912	Glabrone	336.36	52.51	0.59	0.5
	MOL009653	Cycloeucalenol	426.8	39.73	1.42	0.79
	MOL012681	Dimethyl (Methylenedi-4,1-Phenylene) Biscarbamate(7450-63-7)	314.37	50.84	0.62	0.26
	MOL012686	7-Methoxy-5,4'-Dihydroxyflavanonol	302.3	51.72	0.11	0.26
	MOL012689	Cyclomulberrochromene	418.47	36.79	0.86	0.87
	MOL012692	Kuwanon D	422.51	31.09	0.43	0.8
	MOL012714	Moracin A	286.3	64.39	0.84	0.23
	MOL012719	Moracin O	326.37	62.33	0.52	0.44
	MOL012726	Mulberrofuran G	562.6	92.19	0.35	0.24
	MOL012735	Mulberroside C	326.37	71.39	0.41	0.46
	MOL012749	Sanggenone B	570.63	115.44	– 0.07	0.3
	MOL012753	Sanggenone F	354.38	62.42	0.48	0.54
	MOL012755	Sanggenone H	354.38	37.5	0.42	0.53
	MOL012760	Sanggenone M	436.49	68.29	– 0.05	0.85
	MOL012800	3,5,7-Trihydroxy-2-(3-Hydroxyphenyl) Chromone	286.25	59.71	0.25	0.24

Table 1 Continued

Source	MOL ID	Compound name	Molecular weight	OB (%)	Caco-2	DL
Schizonepetae Herba (Jing Jie, 荆芥)	MOL000098	Quercetin	302.25	46.43	0.05	0.28
	MOL000359	Sitosterol	414.79	36.91	1.32	0.75
	MOL001506	Supraene	410.8	33.55	2.08	0.42
	MOL002881	Diosmetin	300.28	31.14	0.46	0.27
	MOL005043	Campesterol	400.76	37.58	1.32	0.71
	MOL005100	5,7-Dihydroxy-2-(3-hydroxy-4-methoxyphenyl)chroman-4-one (520-26-3)	302.3	47.74	0.28	0.27
	MOL000006	Luteolin	286.25	36.16	0.19	0.25
	MOL000358	Beta-Sitosterol	414.79	36.91	1.32	0.75
	MOL000449	Stigmasterol	412.77	43.83	1.44	0.76

imported into Cytoscape 3.7.2 to construct a Pre-No. 2 target-COVID-19-related target PPI network. The network consisted of 298 nodes (267 drug target nodes, 23 virus target nodes, and 8 drug-virus target nodes) and 6 440 edges. Among them, 31 COVID-19-related targets can be divided into: (1) targets directly regulated by relapse (i.e., drug-virus co-acting targets): CASP3 (131 edges), FOS (119 edges), IL-10 (98 edges), CCL2 (97 edges), BCL2L1 (84 edges), IFNG (72 edges), CXCL10 (66 edges) and DPP4 (31 edges); (2) indirectly regulated targets: CREB1 (108 edges), CCL5 (77 edges), CREBBP (65 edges), IRF3 (46 edges), IFNB1 (43 edges), ATF2 (31 edges), LCN2 (31 edges), IFNA1 (27 sides), BAG3 (20 sides), MX1 (20 sides), CASP6 (19 sides), ACE2 (18 sides), CD209 (18 sides), HLA-A (17 sides), HLA-DRB1 (14 sides), ICAM3 (14 sides), MBL2 (14 sides), HLA-B (11 sides), HELLS (10 sides), SH2D3A (6 sides), FCER2 (5 sides), CLEC12A (3 sides) and CLEC4M (3 sides) (Figure 2).

3.3 GO enrichment analysis

The results of GO enrichment include biological processes (BP), cellular components (CC), and molecular functions (MF). After enrichment analysis, a total of 28 BP, 9 CC and 11 MF were obtained, all of which were related to virus interventions (Figure 3). For example, response to viruses, viral processes, B cell proliferation, defense against viruses, viral entry into host cells, modulation of immune responses, T cell receptor signaling pathways, and neutrophil chemotaxis. The anti-virus-related cell components were extracellular space, plasma membrane, cytosol, extracellular region and membrane raft. The antiviral-related MF included protein homodimerization activity, nitric oxide synthase regulator activity, RNA polymerase II transcription factor activity, activated sequence-specific DNA binding, protein kinase binding, and viral receptor activity (Figure 4). These biological processes and the targets they contain may be the key to the preventive effect of Pre-No. 2. In addition, in this network, Lonicerae Japonicae Flos (Jin Yin Hua, 金银花) can regulate 196 targets; Forsythiae Fructus (Lian Qiao, 连翘) can regulate 137 targets; Menthae Haplocalycis Herba (Bo He, 薄荷) can regulate 105 targets; Schizonepetae Herba (Jing Jie, 荆芥) can regulate 179 targets; Glycyrrhizae Radix Et Rhizoma (Gan Cao, 甘草) can regulate 219 targets; Isatidis Radix (Ban Lan Gen, 板蓝根) can regulate 71 targets; Phragmitis Rhizoma (Lu Gen, 芦根) can regulate 28 targets; and Mori Cortex (Sang Bai Pi, 桑白皮) can regulate 174 targets.

3.4 KEGG pathway enrichment analysis

After KEGG pathway enrichment analysis, 23 signaling pathways related to virus interventions were obtained (Figure 5). For example, NF-κB signaling, B cell receptor signaling, viral carcinogenesis, mTOR signaling and FcγR-mediated phagocytosis pathways (Figure 6). These signaling pathways and the targets may be closely related to the mechanism of Pre-No. 2 against COVID-19. Moreover, in this network, Lonicerae Japonicae Flos (Jin Yin Hua, 金银花), Forsythiae Fructus (Lian Qiao, 连翘), Menthae Haplocalycis Herba (Bo He, 薄荷), Schizonepetae Herba (Jing Jie, 荆芥), Glycyrrhizae Radix Et Rhizoma (Gan Cao, 甘草), Isatidis Radix (Ban Lan Gen, 板蓝根), Phragmitis Rhizoma (Lu Gen, 芦根) and Mori Cortex (Sang Bai Pi, 桑白皮) can regulate 101, 79, 65, 89, 108, 39, 12 and 90 targets, respectively.

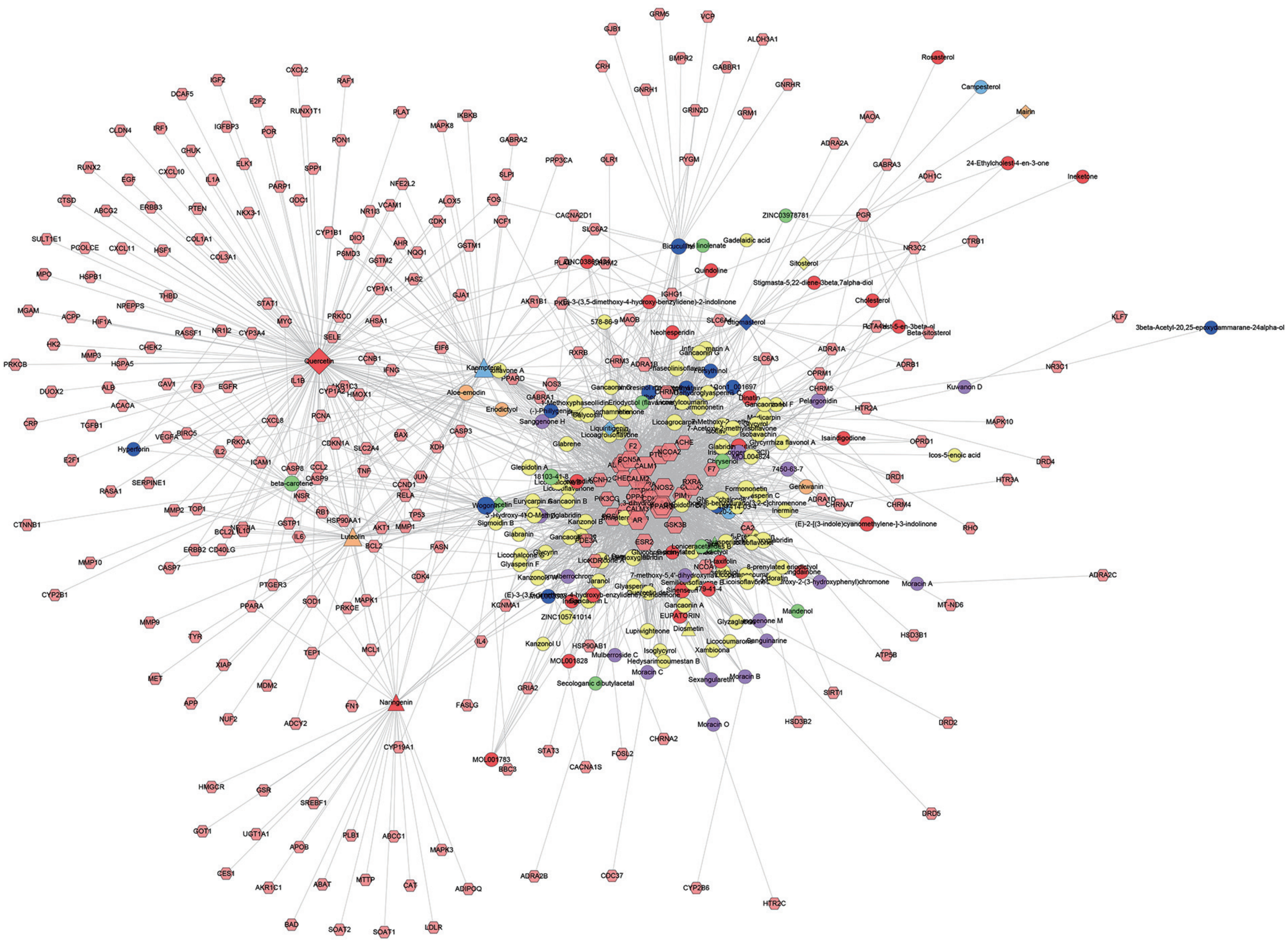

Figure 1 Active compound-target network of Pre-No. 2

Pink hexagons represent the targets. Red, orange, yellow, green, blue, indigo and purple circles represent the active compounds of Isatidis Radix (Ban Lan Gen, 板蓝根), Menthae Haplocalycis Herba (Bo He, 薄荷) , Glycyrrhizae Radix Et Rhizoma (Gan Cao, 甘草), Japonicae Flos (Jin Yin Hua, 金银花), Schizonepetae Herba (Jing Jie, 荆芥), Forsythiae Fructus (Lian Qiao, 连翘) and Mori Cortex (Sang Bai Pi, 桑白皮). Other shapes represent the common compounds of different herbs.

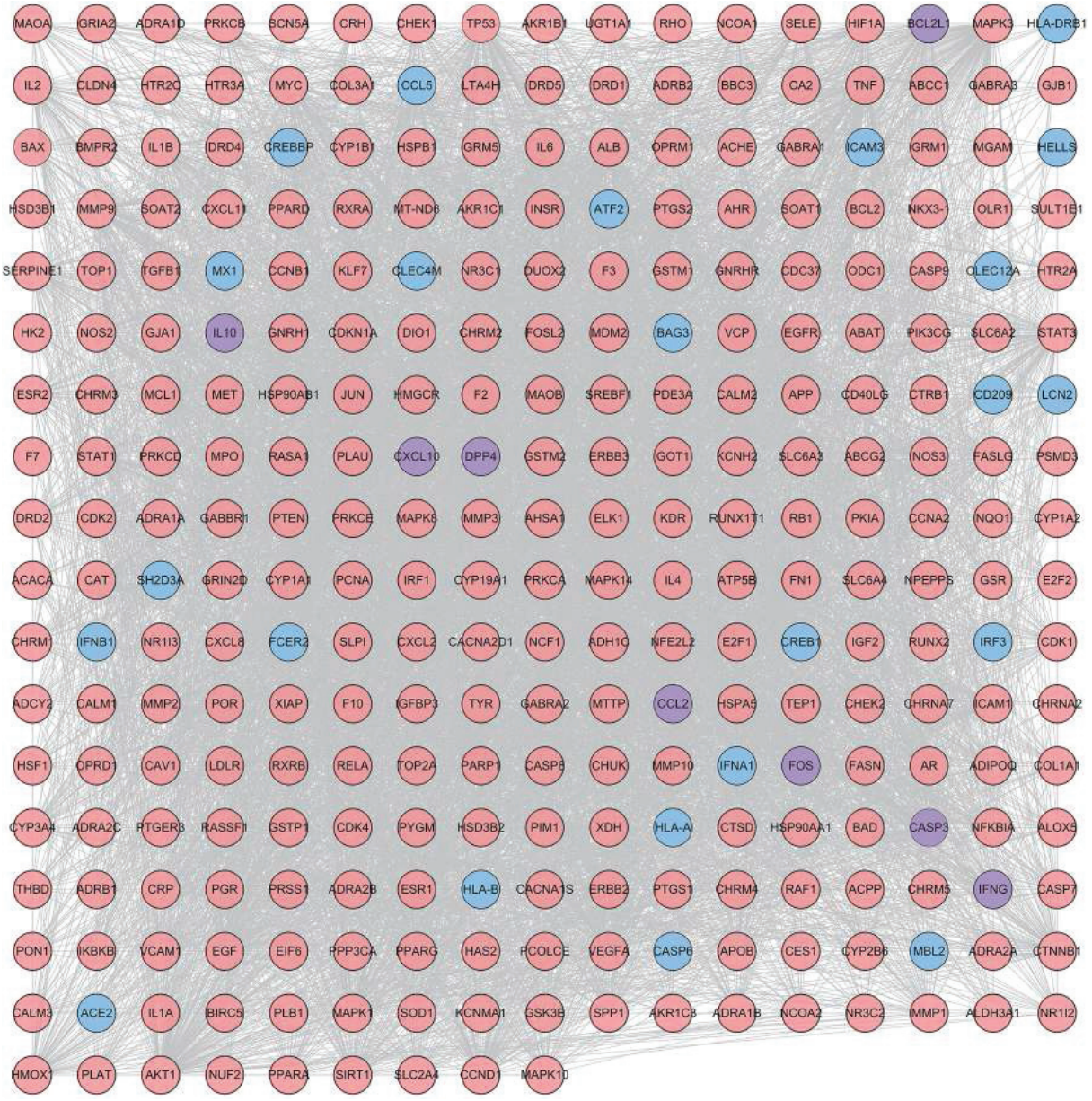

Figure 2 Pre-No. 2 target-COVID-19-related target PPI network

Pink, blue and purple circles represent drug targets, viral targets and drug-virus interaction targets, respectively.

4 Discussion

Pre-No. 2 is a prescription revised from Yin Qiao Powder and has the effect of clearing heat and detoxification. In the present study, Lonicerae Japonicae Flos (Jin Yin Hua, 金银花), Forsythiae Fructus (Lian Qiao, 连翘), Menthae Haplocalycis Herba (Bo He, 薄荷), Schizonepetae Herba (Jing Jie, 荆芥), Glycyrrhizae Radix Et Rhizoma (Gan Cao, 甘草), Isatidis Radix (Ban Lan Gen, 板蓝根), Mori Cortex (Sang Bai Pi, 桑白皮) and Phragmitis Rhizoma (Lu Gen, 芦根) were shown to affect 101, 79, 65, 89, 108, 39, 12 and 90 targets, respectively. Current research reports revealed that Lonicerae Japonicae Flos (Jin Yin Hua, 金银花) acts on various viruses, such as H1N1 influenza virus, antiviral myocarditis, anti-herpes virus and anti-adenovirus [15]. Pharmacological experiments of Forsythiae Fructus (Lian Qiao, 连翘) proved that it has antiviral, antitumor, antidepressant, anti-inflammatory, antioxidant and immune function-enhancing effects [16]. Pharmacological studies on Menthae Haplocalycis Herba (Bo He, 薄荷) have shown that it can enhance the body's resistance to influenza viruses by adjusting the body's immune status [17]. The pharmacological studies of the active compounds of Schizonepetae Herba (Jing Jie, 荆芥) showed that it has anti-inflammatory, immunity-enhancing, and anti-influenza virus pneumonia effects [18]. Various triterpenoids in licorice have been shown to have a significant and broad-spectrum antiviral activity [19]. The extract of Isatidis Radix (Ban Lan Gen, 板蓝根)

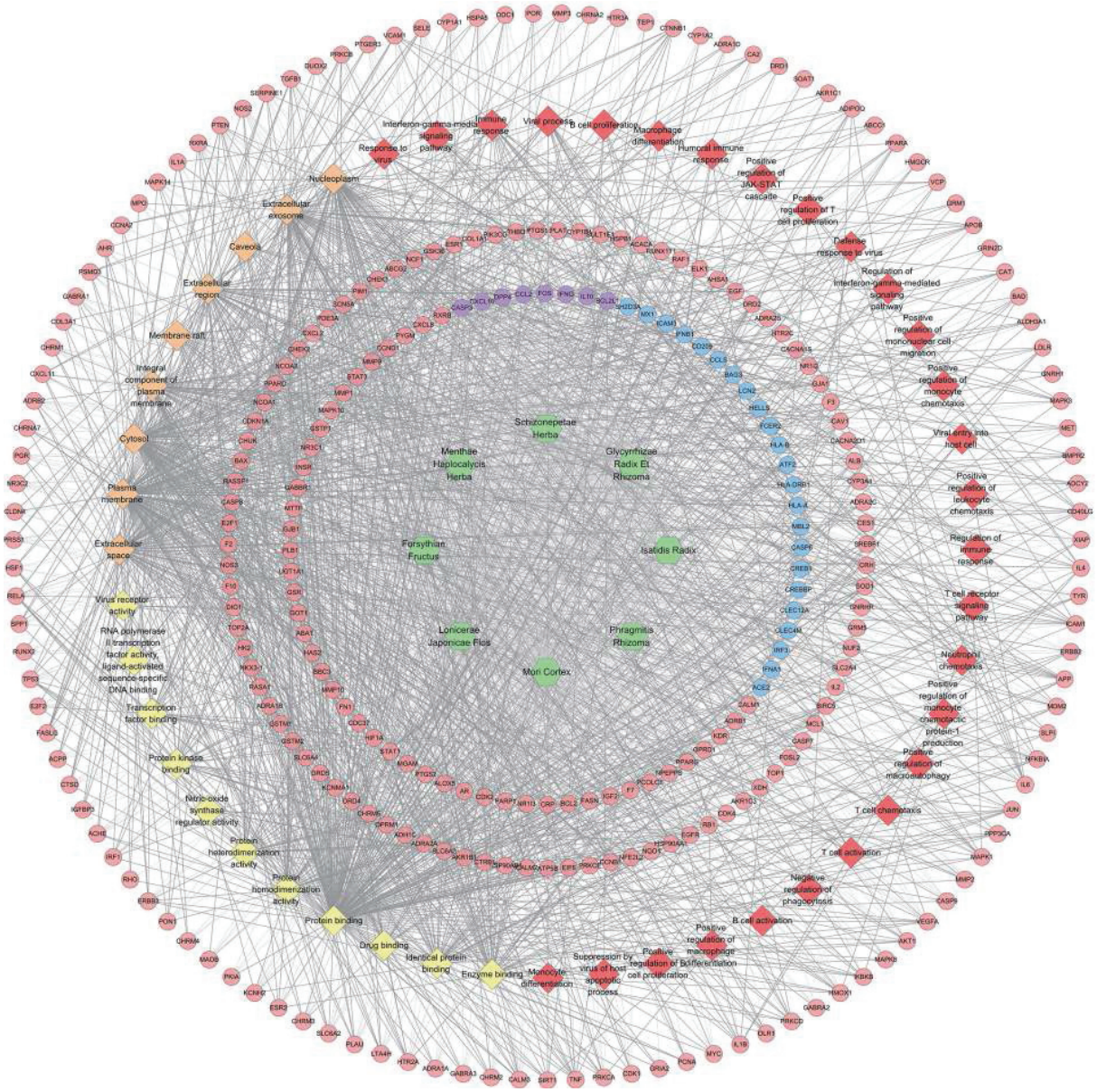

Figure 3 GO enrichment network of Pre-No. 2

Pink, blue and purple circles represent drug targets, virus targets and drug-virus interaction targets, respectively; red prisms represent biological processes, yellow prisms represent molecular functions, and orange prisms represent cellular components; green Hexagon represents single herb.

and its active compounds have antiviral, anti-endotoxin, antibacterial, anti-inflammatory and immune function-enhancing effects [20]. Study showed that Mori Cortex (Sang Bai Pi, 桑白皮) has antihypertensive, diuretic and diarrhea, antibacterial and anti-inflammatory, antitussive, anti-edema, sedative and anticonvulsant effects [21].

In this study, Pre-No. 2 was shown to contain 158 chemical compounds, according to the screening of OB, Caco-2 permeability, and DL through network pharmacology strategy and network topology analysis, thereby providing the substance basis of the action of Pre-No. 2. In addition, GO annotation showed that Pre-No. 2 mainly regulated immune BP, such as the proliferation and chemotaxis of immune cells (mononuclear macrophages, T cells and B cells) and immune factors (IFN-γ and IFN-α); inflammatory response processes, such as inflammatory factors and inflammatory signaling pathways mediated by them; chemotactic inflammatory cells (white blood cells and macrophages); and other BP. The enrichment of KEGG signaling pathways showed that the relevant action pathways related to the immune system mainly included Toll-like receptor (TLR) signaling, T cell receptor signaling, B cell receptor signaling, and Jak-STAT signaling pathways. Recent studies have shown that innate immunity is an important body immunity, and the pattern recognition receptor family (PRR) is necessary for the natural immune response to recognize microbial pathogens; the mul-

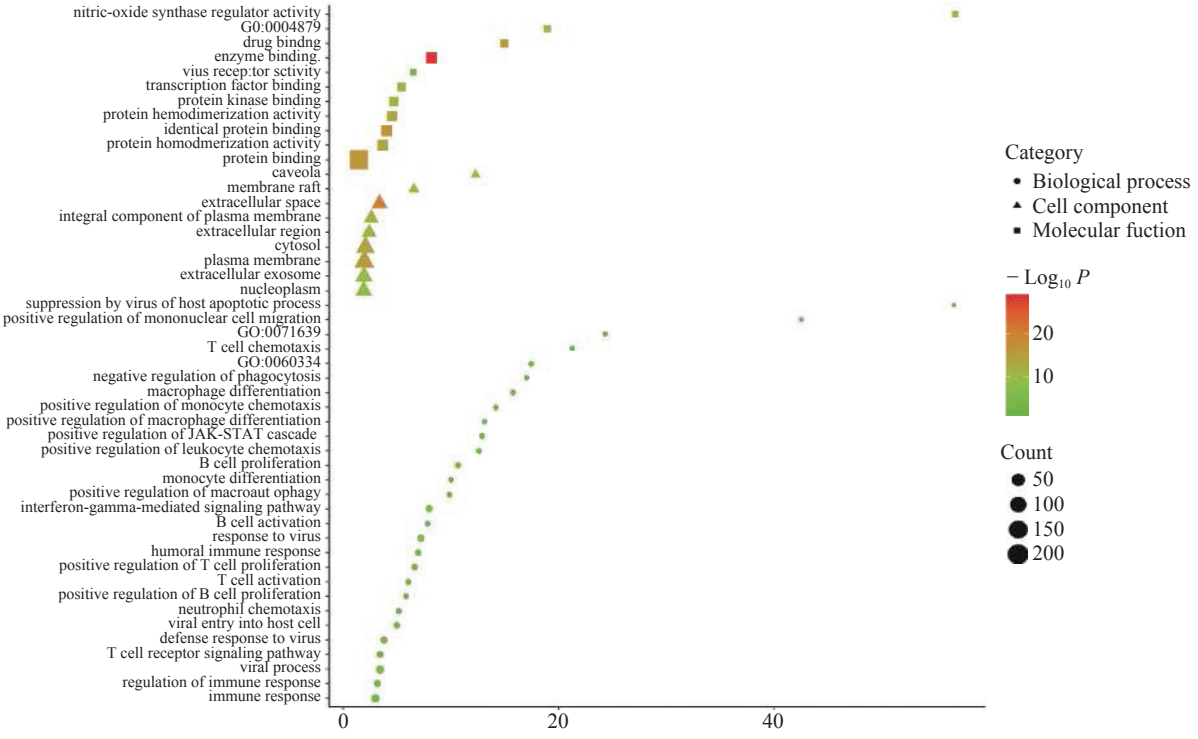

Figure 4 Bubble chart of GO enrichment results for Pre-No. 2

The size of the graph represents the number of targets included; the color represents the size of the *P* value; the shape represents the biological process, cell component, or molecular function; *x* axis represents the fold enrichment value; and *y* axis represents the name of the GO enrichment results.

tiple conservative points of pathogen recognition are called pathogen-related molecular patterns (PAMP) [22]. TLRs, the first members of the PRR family widely present in the immune system, can specifically identify pathogenic microorganisms and transmit extracellular antigen recognition information into cells [23]. The TLR signaling pathway includes myeloid differentiation factor 88 (MyD88)-dependent and MyD88-independent pathways [24]. TLRs can recognize various PAMPs and recruit specific linker molecules to bind TLR functional domains, such as MyD88 and TRIF, and then through a series of signal transduction, the cells will eventually produce inflammatory factors, type I interferon, chemokines and antimicrobial peptides [25]. Intact pathogen microorganisms usually contain a large amount of PAMP, which can activate various PRRs, TLRs and PRRs to coordinate with each other to activate the host's immune responses to resist infection [26]. Therefore, TLRs are essential in the natural immune response against the invasion of pathogenic microorganisms (bacteria, viruses and fungi). In addition, T cell receptors (TCRs) can activate many signal transduction cascades and ultimately determine cell fate by regulating cytokine products, cell survival, proliferation and differentiation [27]. The early event of TCR activation is the phosphorylation of lymphocyte protein tyrosine kinase (Lck) on the immunoreceptor tyrosine-dependent activation motifs on the cytoplasmic side of the TCR/CD3 complex [28].

Owing to the advancement of research on COVID-19, it has been elucidated that the key to the defense against and treatment of new coronavirus infections is the non-specific and specific immunity as well as the subsequent inflammation waterfall factors of host infection [29, 30]. In terms of the innate immune system's defense against COVID-19 infections, the main mechanism involves PRRs, TLRs, RIG-I-like receptors (RLRs), NOD-like receptors (NLRs), C-type lectin-like receptors, interferon and defensin [31]. Furthermore, T cell immune responses and humoral immune responses in the adaptive immune response are equally important, especially CD4+T cells and CD8+T cells, which play an important antiviral role by balancing the risk of fighting pathogens and developing autoimmunity or suppressing inflammatory responses [32]. In addition, the exhaustion of CD4+T cells is related to the reduction of lung lymphocyte recruitment and the production of neutralizing antibodies and cytokines, which in turn leads to strong immune-mediated clearance of interstitial pneumonia and coronavirus from the lung [33]. Laboratory results revealed that the total number of peripheral white blood cells in COVID-19 patients during the early stage was normal or decreased, whereas lymphocyte count decreased; in contrast, in severe cases, D-dimers increase and peripheral blood lymphocytes progressively decrease [5]. Moreover, results of

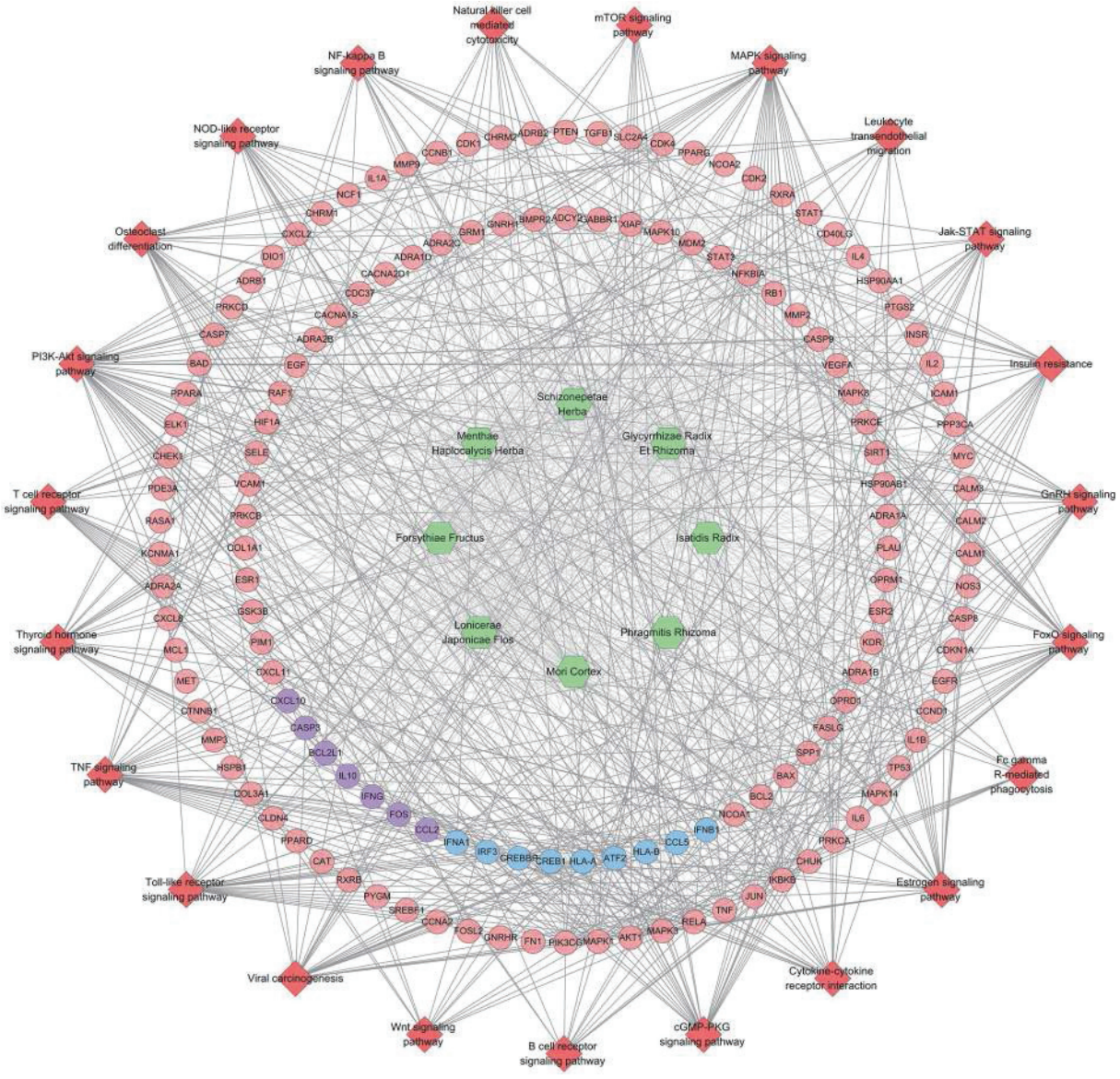

Figure 5 KEGG signaling pathway enrichment network of Pre-No. 2

Pink, blue and purple circles represent drug targets, virus targets and drug-virus interaction targets, respectively. Red prisms represent signaling pathways. Green hexagons represent single herb.

pathological examination of deceased COVID-19 patients showed serious damage to the lungs caused by inflammatory factor storm and collapsed immune system [34]. Cytokine storm refers to rapid and massive production of cytokines, (such as TNF-α, IL-1, IL-6, IL-12, IFN-α, IFN-β, IFN-γ, MCP-1 and IL-8), caused by infection of microorganisms in the body fluids, and it is an important cause of acute respiratory distress syndrome and multiple organ failure [35]. Current research reports showed that the main elevated inflammatory factors in patients with COVID-19 are IL-2, IL-1B, IL-1RA, IL-7, IL-8, IL-9, IL-10, TNF-α and VEGF [5, 36]. In this study, we found that Pre-No. 2 regulated innate and adaptive immune responses, such as NOD-like receptor signaling, TLR signaling, T cell receptor signaling, and B cell receptor signaling pathways which targeted IL-10, IL-6, TNF and VEGFA.

In summary, Pre-No. 2 may play a preventive role against COVID-19 through regulation of the Toll-like signaling, T cell signaling, B cell signaling and other signaling pathways. It may regulate the immune system to protect against anti-influenza virus according to the network pharmacology.

Acknowledgements

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Competing Interests

The authors declare no conflict of interest.

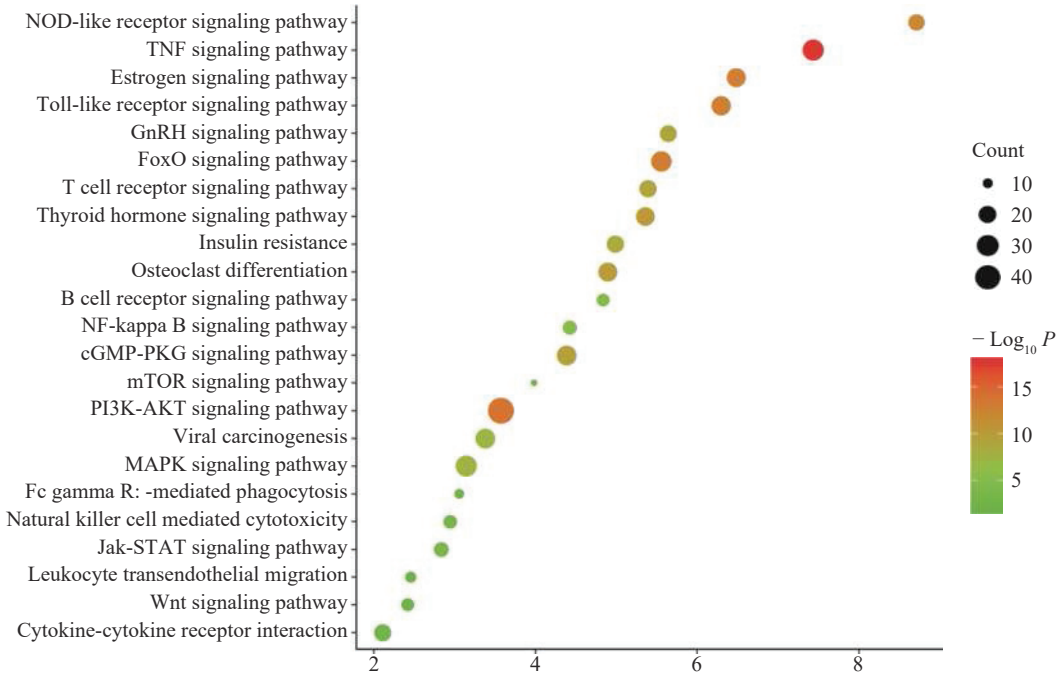

Figure 6 KEGG signaling pathway enrichment analysis

The dot size represents the number of targets included, the color represents the *P* value, *x* axis represents the fold enrichment value, and *y* axis represents the signaling pathway.

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基于网络药理学探讨湖南省专家组推荐的新型冠状病毒肺炎中药预防用方二的预防机制

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【摘要】目的 采用网络药理学方法探讨湖南省专家组推荐的新型冠状病毒肺炎中药预防用方二(以下简称"预防用方二")可能的预防机制。**方法** 通过检索 TCMSP 数据库筛选"预防用方二"中有效成分及其靶蛋白,利用 Cytoscape 3.7.2 构建"预防用方二"的"有效成分–靶点–疾病相互作用网络",DAVID 进行 GO 分析和 KEGG 的富集分析。**结果** 通过 TCMSP 数据库药代动力学活性化合物条件筛选到复方中的 163 个化合物,278 个目标蛋白靶点,调控网络中靶点最多的成分为山柰酚、汉黄芩素、7-甲氧基-2-甲基异黄酮、刺芒柄花素、异鼠李素、甘草查尔酮 A 等成分。GO 富集分析结果显示"预防用方二"可以调控对炎症反应、病毒过程、体液免疫反应、对病毒的防御反应、病毒进入宿主细胞等生物过程,KEGG 信号通路富集显示其可以调节 NF-κB 信号通路、B 细胞受体信号传导途径、病毒致癌作用、T 细胞信号通路、FcγR 介导的吞噬作用等信号通路。**结论** 湖南省专家组推荐的新型冠状病毒肺炎中药预防用方二与免疫和炎症代谢关系最为密切,可能主要通过调控 Toll 样信号通路、T 细胞信号通路、B 细胞信号通路等多条信号通路途径发挥其防治作用;在抗流感病毒方面,其有效成分可能主要是通过调控机体免疫机制对密切接触人群起到预防效果。

【关键词】湖南省专家组推荐新型冠状病毒肺炎中药预防用方二;新型冠状病毒肺炎;网络药理学;免疫系统