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Exploring the bioactive compounds of Feiduqing formula for the prevention and management of COVID-19 through network pharmacology and molecular docking

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Author contributions

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Competing interests

The authors declare no conflicts of interest.

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Peer review information

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Abbreviations

COVID-19, coronavirus disease 2019; ACE2, angiotensin converting enzyme II; TCM, traditional Chinese medicine; DL, drug-likeness; OB, oral bioavailability; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes.

Citation

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Abstract

Background: To explore the effective chemical constituents of Feiduqing formula for prevention and treatment of coronavirus disease 2019 (COVID-19). **Methods:** The compounds and action targets of twelve herbal medicines in Feiduqing formula were collected via Traditional Chinese Medicine Systems Pharmacology Database and Analytic Platform. The genes corresponding to the targets were queried through the UniProt database. The "herbal medicine-ingredient-target" network was established by Cytoscape software. The Gene Ontology function enrichment analysis and Kyoto Encyclopedia of Genes and Genomes pathway enrichment analysis were performed by Database for Annotation, Visualization and Integrated Discovery. Molecular docking was used to analyze the binding force of core active compounds of Feiduqing formula with PTGS2, HSP90AA1, SARS-CoV-2 3CL hydrolase and angiotensin converting enzyme II (ACE2). **Results:** The "herbal medicine-ingredient-target" network included 434 nodes and 1948 edges, including 222 components such as quercetin, kaempferol, luteolin, etc. The key targets are PTGS2, HSP90AA1, PTGS1, ESR1, AR, NOS2, etc. Gene Ontology function enrichment analysis revealed 2530 items, including RNA polymerase II-specific, response to oxidative stress, transcription factor activity, etc. Kyoto Encyclopedia of Genes and Genomes pathway enrichment screened 169 signal pathways, including Human cytomegalovirus infection, Kaposi sarcoma-associated herpesvirus infection, Hepatitis B, Hepatitis C, IL-17, TNF, etc. The results of molecular docking showed that quercetin, luteolin, β-sitosterol, stigmasterol and other core active compounds have a certain degree of affinity with PTGS2, HSP90AA1, SARS-CoV-2 3CL hydrolase and ACE2. **Conclusion:** The active compounds of Feiduqing formula may have a therapeutic effect on COVID-19 pneumonia through the action on PTGS2, HSP90AA1, SARS-CoV-2 3CL hydrolase and ACE2, and regulating many signaling pathways.

Keywords: Feiduqing formula; COVID-19; network pharmacology; molecular docking; SARS-CoV-2 3CL hydrolase

Background

Since the conclusion of December 2019, the novel coronavirus pneumonia has rapidly disseminated throughout the globe. As of 6:00 on March 15, 2023, Beijing time, the cumulative quantity of substantiated cases worldwide has surpassed 624 million, resulting in more than 6.6 million deaths. The World Health Organization has proclaimed the outbreak a global public health emergency, and the unique coronavirus sickness has been dubbed coronavirus disease 2019 (COVID-19) [1]. Due to its quick transmission, increased toxicity, and large population susceptibility, the recently identified coronavirus was given the name "SARS-CoV-2" [2]. Generally, infected individuals exhibit symptoms such as pyrexia, asthenia, and unproductive coughing. Individuals with serious cases may experience exertion, acute respiratory distress syndrome, and septic shock. Currently, the primary focus of efforts aimed at controlling the outbreak lies in the development of prophylactic drugs and vaccines. Traditional Chinese medicine (TCM), due to its holistic approach and dialectical treatment methods, has historically played a significant role in managing previous outbreaks of infectious diseases, including but not limited to SARS, H1N1, H7N9, and Ebola, exhibiting promising clinical outcomes [3–7]. In response to the epidemic, the proposals put forth by the National Health and Medical Commission for the management of epidemic prevention in China encompass the employment of a multitude of Chinese patent medicines and prescriptions [8].

Feiduqing formula is a Chinese herbal formula formulated by Dr. Weiwu Wang based on the medical plague theory, which contains 12 Chinese herbs, including *Saposhnikoviae Radix*, fried *Atractylodis Macrocephalae Rhizoma*, *Houttuyniae Herba*, *Paeoniae Rubra Radix*, *Bupleuri Radix*, *Platycodonis Radix*, *Fritillariae Thunbergii Bulbus*, *Mori Folium*, *Cinnamomi Ramulus*, *Paeoniae Alba Radix*, *Isatidis Root*, *Glycyrrhizae Radix* [9]. Feiduqing formula has played a crucial role in containing this outbreak, particularly in preventing and controlling the pandemic in Xianning, Hubei, China. Feiduqing formula has been involved in the treatment of hundreds of patients in Xianning City, and tens of thousands of people have used this prescription for the prevention of the novel coronavirus pneumonia. In this epidemic, a total of 836 novel coronavirus pneumonia patients were diagnosed in Xianning City, 821 were cured, and 15 died, with a cure rate of 98.2%, which has remained stable at present. The successful clinical use of Feiduqing formula has laid a good foundation for its further research and development.

Network pharmacology is a systems biology-based method that analyzes biological networks with a focus on anticipating drug targets and action routes holistically [10, 11]. The research of disease pathophysiology, the understanding of pharmacological action processes, and the screening of active components have all made substantial use of network pharmacology, a relatively young discipline [12–16]. Theoretical simulation through molecular docking technology predicts binding modes and binding energies by analyzing receptor characteristics and receptor-drug molecule interactions. Recent literature shows that this strategy has become widely used in computer-aided drug design [17, 18]. Using network drug analysis and molecular docking technologies, the current study explored the preventative and curative impacts of Feiduqing formula on COVID-19.

Materials and methods

Databases and Software

The TCM Systems Pharmacology Database and Analytic Platform (TCMSP) [19], the Database for Annotation, Visualization, and Integrated Discovery, the UniProt protein database, and the US Research Collaboratory for Structural Bioinformatics Protein Data Bank (PDB) are some of the databases used. Software used for analysis includes PubChem for molecular structure search [20], Graphpad for data visualization, Vina for molecular docking, autodock tools, Cytoscape 3.2.1 for topological analysis, PyMOL for data visualization, and Omishare.

Identification of active compounds and targets in Feiduqing formula

The Feiduqing formula principal ingredients network was obtained using the TCMSP query and a literature search. These were the parameters used to screen the ingredients in Feiduqing formula: more than 0.18 drug-likeness (DL) and better than 30% oral bioavailability (OB) [21, 22]. The TCMSP database's target prediction tool was used to derive the targets associated with these compounds.

Determination of gene name of targets and construction of "herbal medicine-ingredient-target" network

Import the screened targets from the components into the database (UniProt), change the races restriction to "human", update every returned protein targets towards the UniProt ID, then obtain the gene acronym for the targets. Merge the data of "herbal medicine - ingredient" and "ingredient - target" into Cytoscape_3.6.1 construction of "herbal medicine-ingredient-target" network diagram [23].

Target pathway analysis

The goal of adding Feiduqing formula's underlying targets to the database (Database for Annotation, Visualization, and Integrated Discovery) is to examine the biological functions associated with the targeted proteins [24]. The top 20 items were filtered based on the enrichment analysis of Gene Ontology (GO) function and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway after entering a list of objective genes and limiting the species to "home". Graphpad software was utilized to draw a GO analysis histogram. Using the internet mapping tool omicshare, an advanced bubble chart for KEGG analysis was produced.

Component target-molecular docking

The critical proteins in the primary Feiduqing formula pathway were chosen using the KEGG signal pathway enrichment analysis results. The US Research Collaboratory for Structural Bioinformatics Protein Data Bank has been utilized to obtain PDB information for each individual protein, and PyMOL software was used to supply hydrogen in place of water and protein ligands. These were stored as PDB files and converted to pdbqt files with the Autodock Tools software. The 2D structures of the relatively small molecules were retrieved from the PubChem database, and their energy was adjusted using Sybyl application before being converted by Autodock Methods into pdbqt-format data. After molecular docking with Autodock Vina, Feiduqing formula was identified as the screening foundation for the therapy of the COVID-19, and an positive component with a binding energy of ≤ -5 kJ/mol was chosen.

Results and analysis

Bioactive compound screening and identification of molecular targets

Through retrieval from TCMSP and other databases, a comprehensive set of 1888 active compounds sourced from 12 different herbs found within Feiduqing formula were identified, including 173 through *Saposhnikoviae Radix*, 55 through fried *Atractylodis Macrocephalae Rhizoma*, 50 through *Houttuyniae Herba*, 119 through *Paeoniae Rubra Radix*, 349 through *Bupleuri Radix*, 102 through *Platycodonis Radix*, 17 through *Fritillariae Thunbergii Bulbus*, 269 through *Mori Folium*, 220 through *Cinnamomi Ramulus*, 85 through *Paeoniae Alba Radix*, 169 through *Isatidis Root*, and 280 through *Glycyrrhizae Radix*. A whole 180 bioactive substances were identified from *Saposhnikoviae Radix* using OB $\geq$ 30% and DL $\geq$ 0.15, fried *Atractylodis Macrocephalae Rhizoma*, *Houttuyniae Herba*, *Paeoniae Rubra Radix*, *Bupleuri Radix*, *Platycodonis Radix*, *Fritillariae Thunbergii Bulbus*, *Mori Folium*, *Cinnamomi Ramulus*, *Paeoniae Alba Radix* and *Isatidis Root*, including 18 through *Saposhnik oviae Radix*, 7 through fried *Atractylodis Macrocephalae Rhizoma*, 7 through *Houttuyniae Herba*, 29 through *Paeoniae Rubra Radix*, 17 through *Bupleuri Radix*, 7 through

Platycodonis Radix, 7 through *Fritillariae Thunbergii Bulbus*, 29 through *Mori Folium*, 7 through *Cinnamomi Ramulus*, 13 through *Paeoniae Alba Radix* and 39 through *Isatidis Root*. 42 major compounds from *Glycyrrhizae Radix* were selected depending on OB less than 50% and DL less than 0.15. See Table 1 for some representative constituents.

Table 1 Basic facts on some of the ingredients of Feiduqing formula

Herbs	Molecule ID	Chemical compounds	OB (%)	DL
Saposhnikoviae Radix	MOL011732	anomalin	59.65	0.66
	MOL011737	divaricatacid	87.00	0.32
	MOL011740	divaricatol	31.65	0.38
	MOL001941	Ammidin	34.55	0.22
	MOL011747	ledebouriellol	32.05	0.51
	MOL011749	phelloptorin	43.39	0.28
fried *Atractylodis Macrocephalae Rhizoma*	MOL000028	α-Amyrin	39.51	0.76
	MOL000049	3β-acetoxyatractylone	54.07	0.22
	MOL003851	Isoramanone	39.97	0.51
Houttuyniae Herba	MOL000422	kaempferol	41.88	0.24
	MOL004350	Ruvoside_qt	36.12	0.76
	MOL004351	C09747	37.28	0.25
	MOL004355	Spinasterol	42.98	0.76
	MOL000098	quercetin	46.43	0.28
Paeoniae Rubra Radix	MOL001918	paeoniflorgenone	87.59	0.37
	MOL001921	Lactiflorin	49.12	0.80
	MOL001924	paeoniflorin	53.87	0.79
	MOL001925	paeoniflorin_qt	68.18	0.40
	MOL002714	baicalein	33.52	0.21
	MOL002776	Baicalin	40.12	0.75
	MOL000358	beta-sitosterol	36.91	0.75
	MOL000359	sitosterol	36.91	0.75
	MOL004355	Spinasterol	42.98	0.76
	MOL000449	Stigmasterol	43.83	0.76
Bupleuri Radix	MOL000098	quercetin	46.43	0.28
	MOL004624	Longikaurin A	47.72	0.53
	MOL004628	Octalupine	47.82	0.28
	MOL004609	Areapillin	48.96	0.41
	MOL000354	isorhamnetin	49.60	0.31
Platycodonis Radix	MOL013187	Cubebin	57.13	0.64
	MOL001689	acacetin	34.97	0.24
	MOL004355	Spinasterol	42.98	0.76
	MOL000006	luteolin	36.16	0.25
	MOL006070	robinin	39.84	0.71
Fritillariae Thunbergii Bulbus	MOL000358	beta-sitosterol	36.91	0.75
	MOL001004	pelargonidin	37.99	0.21
	MOL004440	Peimisine	57.40	0.81
	MOL004443	Zhebeiresinol	58.72	0.19
	MOL004444	Ziebeimine	64.25	0.70
	MOL004450	Chaksine	65.63	0.66
Mori Folium	MOL002218	scopolin	56.45	0.39
	MOL003842	Albanol	83.16	0.24
	MOL003851	Isoramanone	39.97	0.51
	MOL003856	Moracin B	55.85	0.23
	MOL003857	Moracin C	82.13	0.29
	MOL003858	Moracin D	60.93	0.38
	MOL003859	Moracin E	56.08	0.38
	MOL003860	Moracin F	53.81	0.23
Cinnamomi Ramulus	MOL001736	(-)-taxifolin	60.51	0.27
	MOL000358	beta-sitosterol	36.91	0.75
	MOL000359	sitosterol	36.91	0.75
	MOL000492	(+)-catechin	54.83	0.24
	MOL004576	taxifolin	57.84	0.27
	MOL011169	Peroxyergosterol	44.39	0.82

DL, drug-likeness; OB, oral bioavailability.

Table 1 Basic facts on some of the ingredients of Feiduqing formula (*Continue*)

Herbs	Molecule ID	Chemical compounds	OB (%)	DL
Paeoniae Alba Radix	MOL001921	Lactiflorin	49.12	0.80
	MOL001924	paeoniflorin	53.87	0.79
	MOL000211	Mairin	55.38	0.78
	MOL000358	beta-sitosterol	36.91	0.75
	MOL000359	sitosterol	36.91	0.75
	MOL000422	kaempferol	41.88	0.24
	MOL001767	hydroxyindirubin	63.37	0.30
Isatidis Root	MOL001781	Indigo	38.20	0.26
	MOL001774	Ineketone	37.14	0.30
	MOL001721	Isaindigodione	60.12	0.41
	MOL002322	isovitexin	31.29	0.72
	MOL001790	Linarin	39.84	0.71
	MOL001484	Inermine	75.18	0.54
Glycyrrhizae Radix	MOL000211	Mairin	55.38	0.78
	MOL002311	Glycyrol	90.78	0.67
	MOL000239	Jaranol	50.83	0.29
	MOL003656	Lupiwighteone	51.64	0.37
	MOL000392	formononetin	69.67	0.21

DL, drug-likeness; OB, oral bioavailability.

Network of herbal medicine ingredients and targets

This network's yellow area symbolizes the herbal treatment, the blue section the component, and the red section the target. The network has 434 nodes and 1948 edges in all (Figure 1). The larger nodes in the network are screened and sorted by the three factors of Betweenness centrality, closeness centrality and degree in the topological properties. The top 10 components include quercetin (MOL000098), kaempferol (MOL000422), luteolin (MOL000006), wogonin (MOL000173), baicalein (MOL002714), β-sitosterol (MOL000358), arachidonic acid (MOL001439), naringenin (MOL004328), Stigmasterol (MOL000449), isorhamnetin (MOL000354), which can interact with 142, 58, 54, 42, 34, 34, 36, 34, 30, and 30 target proteins, respectively. The top 10 targets are PTGS2, HSP90AA1, PTGS1, ESR1, AR, NOS2, CALM1, PRSS1, NCOA2, Cdk2. They are the targets of 116, 79, 68, 68, 63, 58, 53, 52, 51, 48 components in Feiduqing formula.

KEGG pathway analysis and GO function enrichment analysis

Database for Annotation, Visualization, and Integrated Discovery conducted a GO function enrichment research. Among the 2,207 biological processes, 101 cellular components, 222 molecular functions, and 20 items were chosen for depiction (Figure 2). The main components of biological processes are responses to oxidative stress, nutritional levels, metal ions, and oxygen concentrations. However, cellular components demonstrate that the key functional areas were membrane rafts, microdomains and regions, and vesicle lumens. Molecular function primarily involves RNA polymerase II, amide binding, and ubiquitin-like protein ligase binding, as well as DNA-binding transcription activator activity. The antiviral and anti-lung damage processes, elements, and functions are tightly connected.

A KEGG pathway enrichment analysis was utilized to screen 169 ($P < 0.05$) signal pathways for presentation, and 20 pathways ($P < 0.05$) (Figure 3), largely covering several disease pathways such as Kaposi sarcoma-associated herpesvirus infection, hepatitis B and C, as well as various inflammatory and cancer pathways such as IL-17, TNF, prostate cancer, and so on.

Molecular docking investigation of targets with Feiduqing formula core compounds

A decreased share an emphasis between the ligand and receptor results in a complex that is relatively unstable and less likely to have biological consequences. Conversely, when the ligand and receptor exhibit a higher degree of binding affinity, the resulting complex is more thermodynamically stable, thereby increasing the probability of a biological response occurring. According to the centrality value (Betweenness centrality), the closeness centrality value (closeness centrality) and the degree value (degree) in the "herbal medicine-ingredient-target" network, the ingredients of Feiduqing formula are ranked to get top 10 active compounds. The 10 compounds were analyzed for molecular docking with PTGS2 (PDB ID: 5f1a) and HSP90AA1 (PDB ID: 5h22), and those compounds were also analyzed for molecular docking with SARS-CoV-2 3CL hydrolase (PDB ID: 6lu7) and angiotensin converting enzyme II (ACE2) (PDB ID: 1R42), which are the targets for treatment of COVID-19 (Table 2).

Utilizing the binding affinity (less than –5 kcal/mol) as the screening criterion, the results show that the interaction between the Feiduqing formula core chemicals and receptor proteins has obvious properties such as low power, continuous phase, and strong affinity activity (Table 2). The most stable compound to PTGS2 was kaempferol with the binding energy of –9.6 kcal/mol. The most stable compound to HSP90AA1 was baicalein with the binding energy of –10 kcal/mol. Luteolin has the most stable binding energy with SARS-CoV-2 3CL (–6.3 kcal/mol). Stigmasterol has the most stable binding energy with ACE2 (–8.5 kcal/mol) (Figure 4).

Discussion

According to TCM, COVID-19 belongs to the category of epidemic disorders known as "the evil of the plague" and "turbid toxin of wind-warmth nature". This novel coronavirus pneumonia is epidemic and contagious, belonging to the epidemic of TCM, and is caused by external virus infection, which is an external evil [25, 26]. To date, there is yet to be a distinct therapeutic agent for COVID-19 in Western medicine, and several current clinical Western medications exhibit restricted amelioration of COVID-19 symptoms. Owing to its multi-target impact, TCM demonstrates glaring advantages in the prevention and treatment of many conditions [27]. Technology development has made it possible to use current technical approaches to conduct scientific investigation of TCM's therapeutic mechanisms. As a paradigm and approach for the synthesis of TCM clinical research in the setting of novel coronary pneumonia, TCM medicines for COVID-19 have been investigated using network pharmacology and

molecular docking (NPMD) [28].

According to network pharmacology, the top ten active components in Feiduqing formula include: quercetin, kaempferol, luteolin, wogonin, skullcap baicalein, beta-sitosterol, arachidonic acid, naringenin, stigmasterol, isorhamnetin. The top 10 targets are PTGS2, HSP90AA1, PTGS1, ESR1, AR, NOS2, CALM1, PRSS1, NCOA2 and Cdk2. PTGS2 and HSP90AA1 play an important role in the treatment of inflammation and the replication of RNA viruses [29, 30]. Molecular docking analysis was performed on 10 chemical constituents with PTGS2, HSP90AA1, SARS-CoV-2 3CL hydrolase and ACE2, respectively. It has been demonstrated that the interaction between the Feiduqing formula core chemicals and receptor proteins has obvious properties such as low power, continuous phase, and strong affinity activity (Table 2). The most stable compound to PTGS2 was kaempferol; The most stable compound to HSP90AA1 was baicalein; Luteolin has the most stable binding energy with SARS-CoV-2 3CL; And stigmasterol has the most stable binding energy with ACE2 (Figure 4). Feiduqing formula can modulate a variety of targets and pathways that are connected to viral infections and inflammation, according to assessments of GO function and KEGG pathway enrichment in particular. These findings give the compound's apparent clinical efficacy a theoretical foundation.

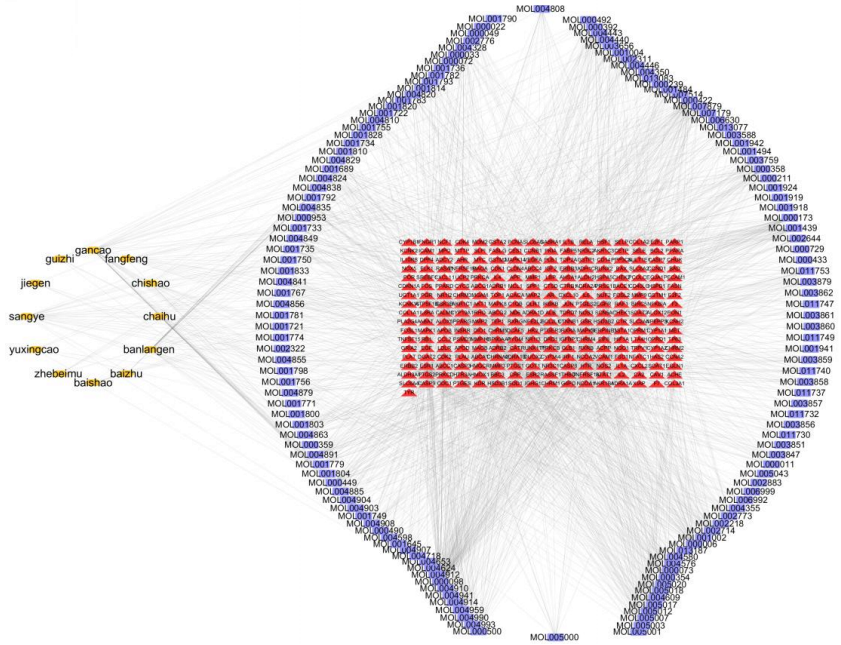

Figure 1 Herbal medicine-ingredient-target network of Feiduqing formula. gancao, *Glycyrrhizae Radix*; fangfeng, *Saposhnikoviae Radix*; chishao, *Paeoniae Rubra Radix*; chaihu, *Bupleuri Radix*; banlangen, *Isatidis Root*; baizhu, *Largehead Atractylodes Rhizome*; baishao, *Paeoniae Alba Radix*; zhebeimu, *Fritillariae Thunbergii Bulbus*; yuxingcao, *Houttuyniae Herba*; sangye, *Mori Folium*; jiegen, *Platycodonis Radix*; guizhi, *Cinnamomi Ramulus*.

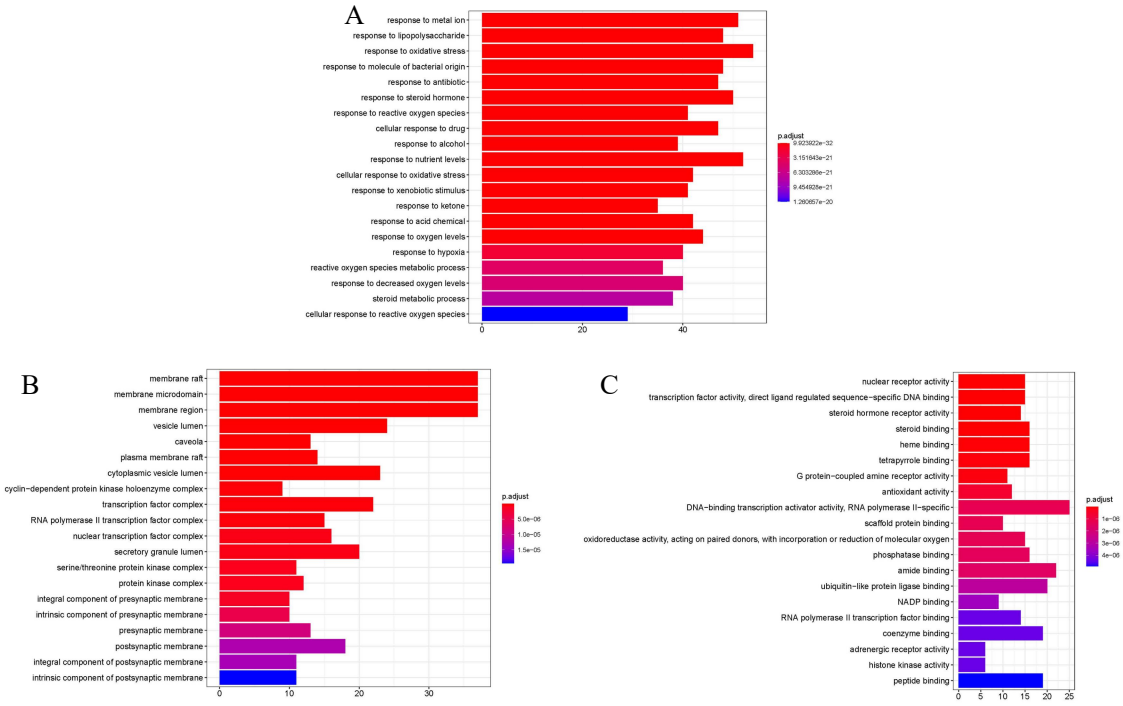

Figure 2 GO enrichment analysis of targets of Feiduqing formula. (A) Analysis of the GO (BP) function histogram. (B) Analysis of the GO (CC) function histogram. (C) Analysis of the GO (MF) function histogram. GO, Gene Ontology; BP, biological progress; CC, cellular component; MF, molecular function.

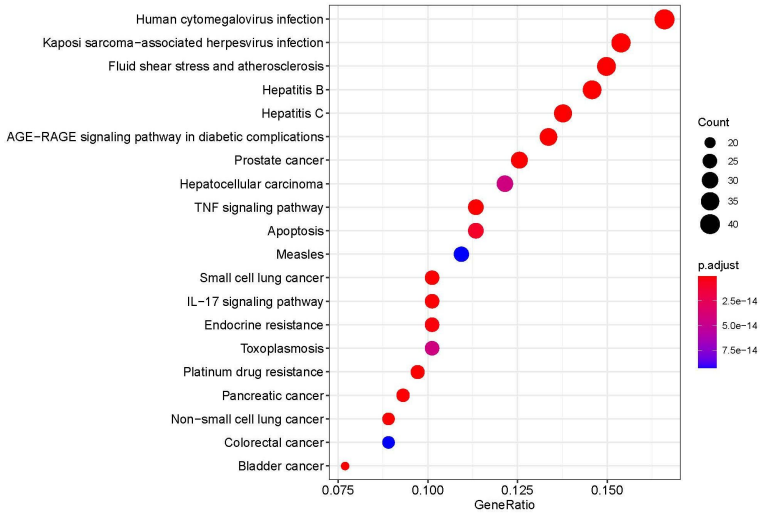

Figure 3 KEGG enrichment analysis of 20 pathways of effect targets of Feiduqing formula. KEGG, Kyoto Encyclopedia of Genes and Genomes.

Table 2 Binding energy values of key compounds in Feiduqing formula with key targets

Compounds	Molecule ID	CAS	Binding energy (kcal/mol)			
			PTGS2	HSP90AA1	SARS-CoV-2 3CL hydrolase	ACE2
quercetin	MOL000098	117-39-5	–9.2	–9.0	–6.2	–8.1
kaempferol	MOL000422	520-18-3	–9.6	–8.8	–5.7	–7.7
luteolin	MOL000006	491-70-3	–9.5	–9.3	–6.3	–8.0
wogonin	MOL000173	632-85-9	–8.8	–9.0	–6.0	–7.3
baicalein	MOL002714	491-67-8	–9.5	–10.0	–6.1	–7.6
β-sitosterol	MOL000358	83-46-5	–8.1	–8.2	–6.0	–8.1
arachidonic acid	MOL001439	506-32-1	–7.1	–6.9	–4.5	–6.2
naringenin	MOL004328	480-41-1	–7.8	–7.9	–5.8	–6.9
stigmasterol	MOL000449	83-48-7	–8.1	–9.0	–6.1	–8.5
isorhamnetin	MOL000354	480-19-3	–9.5	9.0	–5.6	–7.5

ACE2, angiotensin converting enzyme II.

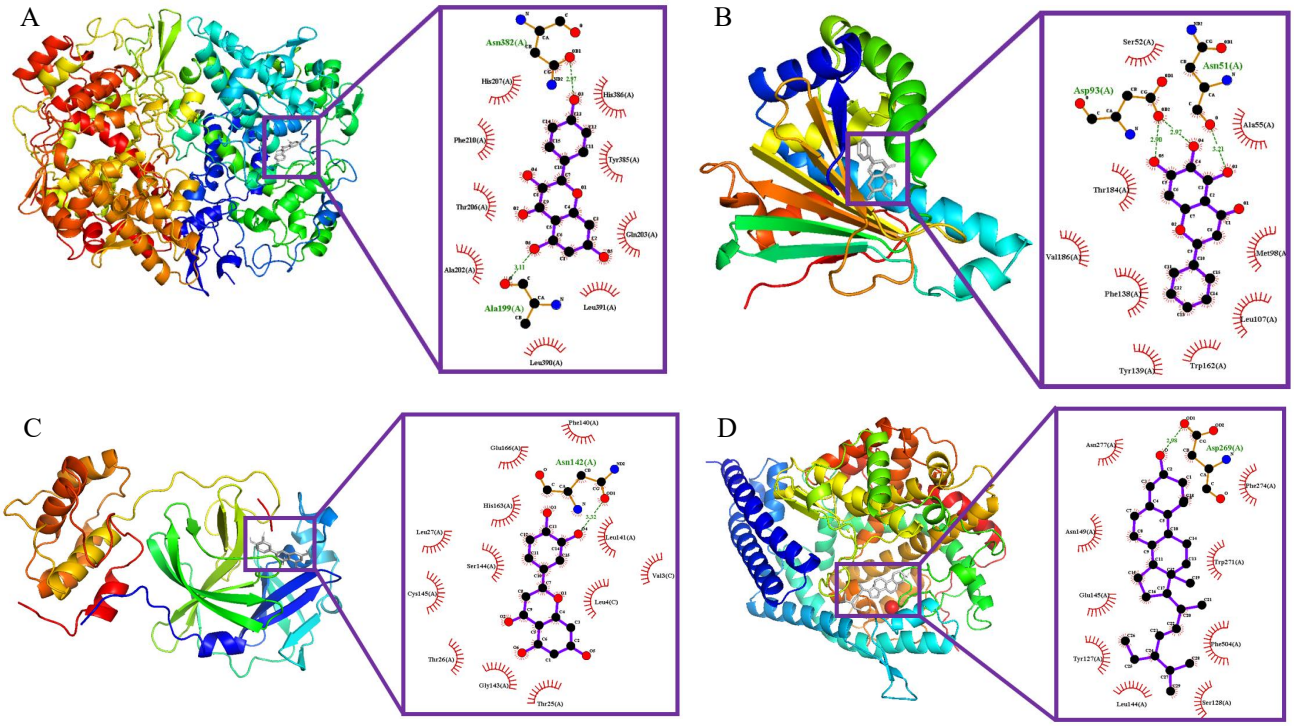

Figure 4 Molecular docking of key compounds in Feiduqing formula with key targets. (A) kaempferol-PTGS2; (B) baicalein-HSP90AA1; (C) luteolin-SARS-CoV-2 3CL hydrolase; (D) stigmasterol-ACE2. ACE2, angiotensin converting enzyme II.

Using NPMD techniques, the band structure of the main constituents of Feiduqing formula on PTGS2, HSP90AA1, SARS-CoV-2 3CL hydrolase and ACE2 were determined, and its putative molecular mechanism was explored. The results indicate that Feiduqing formula exerts its effects by targeting PTGS2, HSP90AA1, SARS-CoV-2 3CL hydrolase and ACE2 through a multiplicity of components, targets, and pathways. This study provides both data and theoretical foundation for the identification and evaluation of COVID-19 therapeutic medications using active constituents derived from TCM. Based on the findings of the NPMD investigations, additional study into the specific mechanism of Feiduqing formula may be done in the future.

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