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Based on Clinical Research - Network Pharmacology Discussion on the Clinical Observation and Efficacy Evaluation of Qingdu Fuzheng Prescription for the Treatment of COVID-19

Jie Shen[1,2], Bingyue Yang[1,2], Xiwei Zhang[3], Xiucheng Zhang[3], Xia Shen[1,2], Xianfeng Gong[3], Jinbo Zhang[3,*]

[1]Shaanxi University of Chinese Medicine, Xi'an, Shaanxi, China
[2]Engineering Research Centre for Application and Development of Chinese Herbal Medicine in the Qinling Mountains of Shaanxi Province, Xi'an, Shaanxi, China
[3]Department of Integrated Traditional Chinese and Western Medicine, Xi'an Chest Hospital, Xi'an, China
**Corresponding author*

Abstract: *This study analyzes the effect of Qingdu Fuzheng Prescription (QDFZF) on coronavirus disease 2019 (COVID-19) through clinical observation and explores the efficacy functional substance and molecular mechanism of QDFZF treatment for COVID-19 based on UPLC-Q-TOF/MSUPLC-MS/MS. From November 2022 to June 2023, 96 patients diagnosed with new coronavirus infection and treated with QDFZF in Xian Chest Hospital were selected as the research subjects. The study compared whether different influencing factors made a difference in the length of hospital stay for patients. The results showed that QDFZF had a significant therapeutic effect,, which was compared with previous studies.UPLC-Q-TOF/MSUPLC-MS/MS analysis of the components of QDFZF found that QDFZF acts on targets such as IL6,TNF,IL1B,AKT1,TP53,EGFR,IL10,CXCL8,IFNG,BCL2,etc. and regulates the IL-17 signaling pathway, tumor necrosis factor-alpha signaling pathway,Th17 cell differentiation pathway, and toll-like receptor signaling pathway to exert anti-inflammatory and immune function modulation effects. Through RELA and EGFR,it inhibits the main protease 3CLpro and PLpro of influenza A and hepatitis B,as well as ACE2,to intervene in viral infection. Key components were identified: Quercetin, Pseudoephedrine, Ephedrine, Luteolin, and Coixol. QDFZF can exert a therapeutic effect on COVID-19 through multiple pathways by inhibiting inflammatory mediators, blocking viral infection pathways, and regulating immune functions.*

Keywords: *Qingdu Fuzheng Prescription; COVID-19; Clinical Efficacy; Network Pharmacology; Mechanism of Molecular*

1. Foreword

Novel Coronavirus pneumonia (COVID-19) is an acute respiratory infectious disease caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[1]Traditional Chinese medicine has potential value in the treatment of COVID-19 by integrating multiple components, multiple links and multiple targets to regulate the bodys immune system, reduce inflammation and protect organs[2]The Qingdu Fu Zheng Fang (QDFZF) is a commonly used prescription in the clinical treatment of COVID-19 at Xi an Chest Hospital. This study retrospectively analyzes the clinical efficacy of Qingdu Fu Zheng Fang in treating COVID-19 at Xi an Chest Hospital, and uses UPLC-MS/MS to analyze the active components and targets in QDFZF. It also aligns the main active ingredients with relevant targets to provide theoretical support for its clinical application.

2. Clinical data and methods

2.1 Source of medical records

A total of 96 patients diagnosed with novel coronavirus infection who were admitted to Xi an Chest

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Hospital from November 2022 to June 2023 and received detoxification and support treatment were selected as the research subjects.

Inclusion criteria: (1) confirmed as COVID-19 (diagnosis criteria according to the different versions of the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia corresponding to the time); (2) received at least one course of treatment with detoxification and support (3d); (3) relevant evaluation indicators before and after treatment;

Exclusion criteria:(1) the course of detoxification and support is insufficient, the dosage is not appropriate; (2) age <18 years old; (3) patients with severe complications;

2.2 Treatment regimen

Strictly follow the "Diagnosis and Treatment Protocol for Pneumonia Caused by Novel Coronavirus Infection" for treatment, emphasizing effective oxygen therapy and supportive care. The detoxifying and tonifying formula consists of 30g of Astragalus membranaceus, 30g of Codonopsis pilosula, 10g of Atractylodes macrocephala, 15g of Poria cocos, 6g of Ephedra sinica, 6g of Apricot Kernel, 12g of Agastache rugosa, 15g of Lycium barbarum seed, 9g of Tangerine Peel, 9g of Pinellia ternata, 6g of Amomum villosum, 15g of Coix seed, 15g of Verbena officinalis, 15g of Polygonum cuspidatum, 15g of Imperata cylindrica, 15g of Phytolacca acinosa, and 9g of Fried Glycyrrhiza uralensis. Follow medical instructions and adjust according to clinical changes. Take one dose daily.

2.3 High risk factors for severe illness[3,4]

(1) Age greater than 65 years, especially those who have not been fully vaccinated against novel coronavirus; (2) Cardiovascular and cerebrovascular diseases (including hypertension), chronic lung diseases, diabetes, chronic liver and kidney diseases and tumors; (3) Heavy smokers.

2.4 Evaluation of effectiveness

Referring to the standards of the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 10), the patients condition has significantly improved, vital signs are stable, body temperature is normal for more than 24 hours, nucleic acid is positive, and lung imaging shows significant improvement of acute exudative lesions, and there are no complications requiring further treatment.

2.5 Component analysis of detoxification and support formula based on UPLC-MS/MS

Sample preparation: Prepare the detoxifying and tonifying decoction packets, 200ml per bag, uniformly decocted by the Traditional Chinese Medicine Department of Xian Chest Hospital. After water bath concentration, take 100 μL of the decoction and add it to a 1.5mL centrifuge tube, then add 100 μL of 70% methanol containing an internal standard extract. Vortex, 12000 r/min, and centrifuge at 4℃ for 3 min. Take the supernatant for analysis.

Chromatographic conditions mobile phase: A: water + 0.1% formic acid, B: acetonitrile + 0.1% formic acid; elution gradient: 0.00min,B:5%,9.00min; B:95%,10.00-11.10min, B: 5%,14min; flow rate 0.35mL/min; column temperature 40°C; injection volume 2μL.

The mass spectrometry conditions were as follows: electrospray ion source (ESI), conditions: ion source temperature: 550°C; ion spray voltage: (IS) 5500 V (positive ion mode)/-4500 V (negative ion mode); ion source gas I (GSI), gas II (GSII) and curtain gas (CUR) were set to 50,60 and 25 psi respectively.

2.6 Analysis of the molecular mechanism of detoxification and support based on network pharmacology

The components of detoxification and support were identified by UPLC-MS/MS according to the Chinese Pharmacopoeia[5] ,The principles of ruler-minister and assistant-enemy were applied to screen for targets, and predictions were made using the TCMSP, BATMAN, and Targetnet databases. The intersection with disease targets of "COVID-19" obtained from databases such as GeneCards and CTD was integrated to identify potential targets for QDFZF in treating COVID-19. These identified targets were then imported into the String database for PPI network analysis, and the CytoHubba plugin was

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used to analyze topological properties, selecting target nodes and compound nodes with an Degree> 20 as core protein targets. A "component-target-disease" network map was constructed using Cytoscape to further understand the functions of core genes and the main therapeutic pathways for COVID-19. KEGG enrichment analysis was performed using the DAVID database, and the top twenty pathways from the KEGG results were subjected to secondary classification analysis.

2.7 Molecular docking verification

Using Chem3D software to add hydrogen atoms, minimize energy, and optimize the chemical structure of target proteins and candidate drug molecules. Subsequently, import the processed molecular models into PyMOL for further structural analysis and validation. Then, perform the molecular docking process using AutoDock Vina software. After docking is complete, select the conformation with the highest binding affinity as the final docking result and conduct detailed interaction analysis.

2.8 Statistical methods

Compound identification information was obtained by retrieving the secondary mass spectrometry database built by the laboratory and integrating the public database. Data analysis was carried out by SPSS27.0 software, X±S was used for measurement data, and Kruskal-Wallis H test was used for quantitative data; $p<0.05$ was considered to be significant.

3. Bear Fruit

3.1 Basic information of patients

A total of 93 confirmed cases were included, with males (57/93,61.3%) outnumbering females (36/93,38.7%). The age range was from 19 to 89 years, with an average age of (47.6 ± 14.6) years. Hospital stays ranged from 6 to 24 days, and the predominant type was common. There were 16 mild cases, 75 moderate cases, and 2 severe cases. Among the 93 patients, 38 (40.9%) had high-risk factors for severe illness. These included 24 cases with cardiovascular diseases (including hypertension), 4 cases with chronic lung diseases (such as chronic obstructive pulmonary disease and emphysema), 7 cases with diabetes, 1 case with fatty liver, 7 cases with a history of surgery, and 4 cases with heavy smoking (number of cigarettes smoked per year> 400).

3.2 Clinical manifestations before admission

Among the included cases, 93 patients tested positive for nucleic acid; a total of 92 patients underwent chest and abdominal CT scans, with 66 showing abnormalities and 26 showing no lesions. Among these, 8 had ground-glass opacities, 20 had pulmonary fibrosis, 7 had fibrous lesions, 16 had lung nodules, 4 had pulmonary calcification, and 8 had emphysema. There were 4 patients with bullae.

In the blood routine examination, 5 patients had white blood cell counts below the normal range, and 2 patients had white blood cell counts above the normal range; among 11 patients, neutrophils were below the normal range, while 13 patients had neutrophils above the normal range; 26 patients had a higher proportion of neutrophils than the normal range; 6 patients had a higher proportion of neutrophils than the normal range; regarding infection-related indicators, 83 patients underwent hyper-reactive C-reactive protein testing, with 61 patients having levels above the normal range.

In the liver function index, about 20% of patients had elevated alanine transaminase and aspartate transaminase to varying degrees. Nine patients had albumin below the normal range; 13 patients had creatinine above the normal range, and 13 patients had creatinine below the normal range, as depicted in table 1.

Table 1 Changes in Clinical Indicators of Patients before Treatment

clinical manifestation	Number of cases (percentage%)

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The nucleic acid was positive	93(100%)
Lung imaging	
No lesions	26(27.96%)
Multiple small patchy shadows and interstitial changes	24(25.81%)
	24(25..81%)
Multiple ground glass shadows and fibrous foci in both lungs	18(19.35%)
Lung consolidation, pleural effusion	
Complete blood count (10 9 /L)	
WBC(< 3.5/> 9.5)	7(7.52%)
NEUT(< 1.8/> 6.3)	24(25.80%)
N%(40.0~75.0)	32(34.40%)
Lymphocytes (<1.1/> 3.2)	65(69.89%)
Infection indicators	
Hyper-sensitive CRP (> 3.0)	61(73.50%)
liver function index	
albumin	9(9.68%)
CREA	16(17.20%)
ALT	17(18.28%)
AST	15(16.13%)

3.3 The influence of different influencing factors on the length of hospital stay

To investigate whether the age and gender of patients affect the severity of their illness, a comparison was made of hospital stay durations across different age groups, which showed statistically significant differences (P <0.08). The group aged 18-39 had shorter hospital stays compared to those aged 40-59 (P <0.01), and the group aged 18-39 also had shorter stays compared to those aged 60 and older (P <0.05). Comparing hospital stay durations between different genders showed no statistically significant differences (P = 0.900). (Figure 1)

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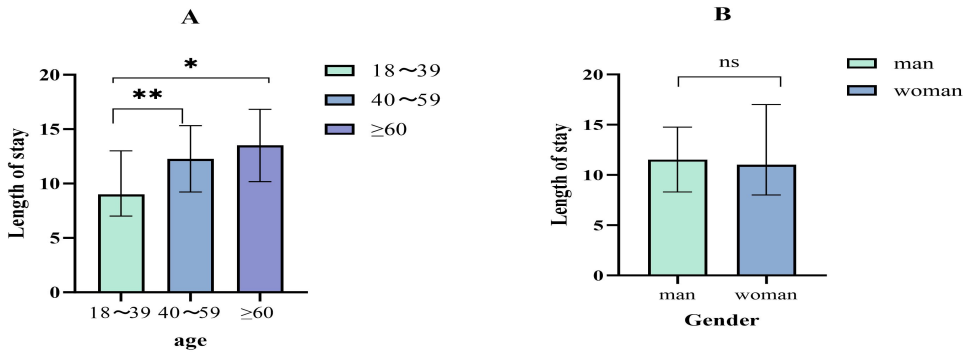

*Figure 1 The Impact of Various Influencing Factors on the Hospital Stay of COVID-19 Patients (*P < 0.0 5 vs control group; **P < 0.01 vs model group)*

4. UHPLC-Q-TOF-MS/MS analysis of the components of detoxification and support

Early clinical studies have found that the Qingdu Fu Zheng formula is highly effective in treating COVID-19, thus further elucidating its material basis for treatment. A total of 1,566 metabolites were detected under both positive and negative ion conditions. In terms of metabolite types, the secondary metabolites of QDFZF are categorized into nine major classes: flavonoids, alkaloids, phenolic acids, terpenes, lignans, coumarins, quinones, tannins, steroids, and others (Figure 2). Among these, flavonoids account for 31.29%, phenolic acids for 20.56%, and alkaloids for 13.03%. In the treatment of COVID-19, flavonoids, phenolic acids, and alkaloid compounds exhibit potential antiviral, immune regulation, and anti-inflammatory effects[6,7].

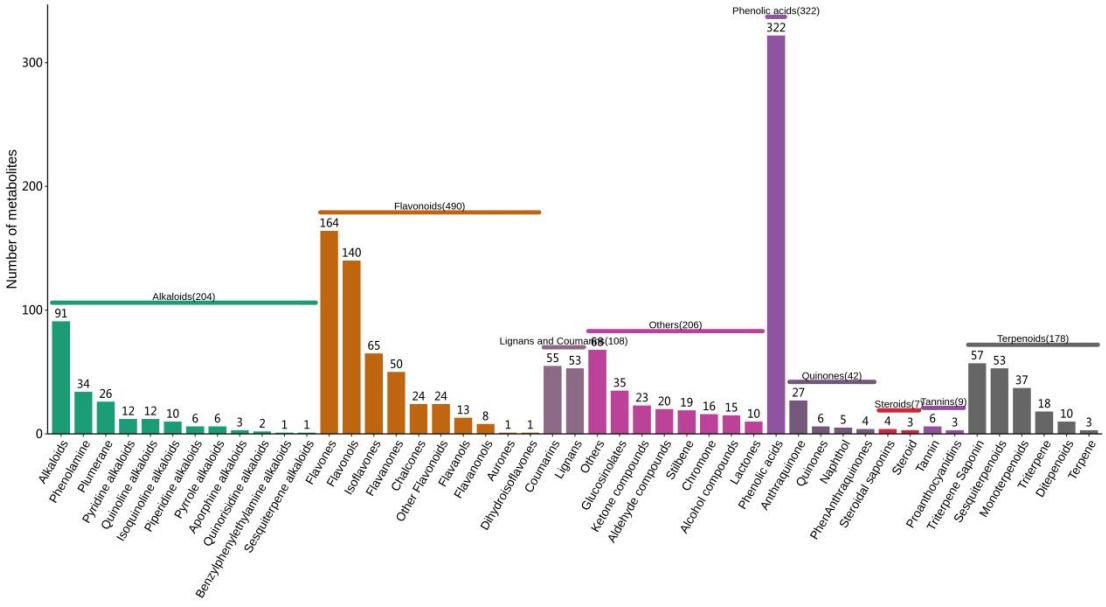

Figure 2 Primary Composition Classification

4.1 Screening of active ingredients and disease-related targets in detoxification and support

Through data mining and virtual screening, a total of 22 active ingredients for detoxification and tonification were identified, including 4 from Ephedra, 2 from Pinellia ternata, 1 from Astragalus, 3 from Tangerine Peel, 4 from Glycyrrhiza, 3 from Agastache, 2 from Lycium barbarum, 1 from Reed Rhizome, 1 from Coix seed, 1 from Amomum villosum, 2 from Codonopsis, 1 from Prunus dulcis, 2 from Verbena officinalis, and 1 from Atractylodes. (Table2), the components correspond to a total of 66.5 target sites, with 1557 disease targets in total. After taking the intersection, there are 11.5 common

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targets, accounting for 5%.5%.

Construct a PPI network using intersecting targets, which consists of 9 8 nodes and 719 edges (Figure 3). Using the Cytohubba plugin to rank core targets based on degree values, the top 23 core targets in the network are IL6, TNF, IL1B, AKT1, TP53, EGFR, IL10, CXCL8, IFNG, BCL2, etc. Among these, IL6, TNF, IL-1β, and IL-10 play crucial roles in immune responses and inflammatory processes. EGFR, TP53, and IFN-γ may be involved in regulating viral invasion of host cells and modulating host immune responses. These genes may be key to QDFZFs treatment of COVID-19.

Using Cytoscape software to construct a "component-target-disease" network diagram, it includes 13 8 nodes (2 2 components, 11 5 genes) and 1000 edges. The connections between nodes represent the functional relationships among them. Topological analysis shows that quercetin (Quercetin), pseudoephedrine (Pseudoephedrine), ephedrine (Ephedrine), luteolin (Luteolin), and artemisinin (Coixol)have higher Degree values, suggesting they may be key components in the treatment of COVID-19 with QDFZF.

To further clarify the mechanism of action of the active ingredients in the detoxification and support formula, a KEGG enrichment analysis was conducted on 2 3 core target proteins. The enriched pathways revealed that they mainly involve inflammation and immune-related pathways, such as the IL-17 signaling pathway, tumor necrosis factor α signaling pathway, Th17 cell differentiation pathway, toll-like receptor signaling pathway, etc.; and virus infection-related pathways, such as influenza A, hepatitis B, etc.

4.2 Based on molecular docking QDFZF active ingredient validation

To verify the network pharmacological analysis of 22 active ingredients in QDFZF and their core targets identified by PPI, the top 5 components (quercetin, pseudoephedrine, ephedrine, luteolin, and artemisinin) with the highest degree values in the "component-target-disease" network were docked against the core targets TNF (PDB ID: 6Q00) and IL6 (PDB ID: 1ALU). The docking results were obtained using Auto Dock software, and the binding free energies of all compounds to IL6 and TNF were all less than 4.0 kcal·mol⁻1, Indicates that the five active ingredients and core protein have good stability (Table 3). The four compounds with the highest docking scores were selected. Among them, quercetin and luteolin have the highest binding energy with TNF and IL6, which may play an important role in inflammation and immune regulation (Figure 4).

Table 2 Active compounds in QDFZF

Chemical compound	English name	Local Chinese medicine	Criteria for selection
baicalin	Baicalin	prepared RHIZOMA PINELLIAE with juice of rhizima zingiberis rec-ens	Inhibits 3CLpro protease[8]
codonopsine	Codonopsine	Codonopsis pilosula	Immune regulation, anti-inflammatory, antiviral, cell protection
ephedrine	Ephedrine	Chinese ephedra	Dilation of bronchial smooth muscle, immune regulation and anti-inflammatory
d-pseudephedrine	Pseudoephedrine	Chinese ephedra	Reduce edema of nasal mucosa
meletin	Quercetin	Ligusticum,	3CLpro protease inhibitor[9]

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		agastache, astragalus, licorice, ephedra	
hesperidin	Hesperidin	dried tangerine or orange peel	It has good binding force with IL-6 and TNF[10]
polydatin	Polygonum cuspidatum glycoside	Polygonum cuspidatum	It has a good binding with the main protease (Mpro) of SARS-CoV-2[11]
3β-Hydroxycolchicine	3β-Hydroxyatractylon	rhizoma atractylodis	Inhibit viral replication or interact with viral proteins
glycyrrhizic acid	Glycyrrhizic acid	liquorice	Targeting ACE2[12]
melim	Rutin	Tangerine peel, astragalus and licorice	Potential inhibitors of Mpro[13]
luteolin	Luteolin	Tangerine peel, verbena, cardamom	Anti-inflammatory, antiviral and antioxidant
Coix seed extract	Coixol	semen coicis	Enhance immunity and anti-inflammatory
Astragaloside A	Astragaloside A	Astragalus mongholicus	It has good binding force with TNF, TLR4 and IL10[14]
Limonin-7-O-glucoside	Tricin-7-O-Glucoside	rhizoma phragmitis	Anti-inflammatory by HIF-1 pathway and AGE-RAGE pathway[15]
verbenalin	Verbenalin	herba verbenae	Inhibition of IL17A signaling pathway[16]
Dichroa fimbriata glycoside	Hastatoside	herba verbenae	Inhibition of IL17A signaling pathway[17]
kaempferol	Kaempferol	Ephedra, tiger stalk, astragalus, thunbergia seed, licorice	3CLpro inhibitors target bacterial virulence factors[18]
Puerarin	Lobetyol	Codonopsis pilosula	Anti-inflammatory, antiviral and antioxidant[19]
amygdalin	Amygdalin	semen armeniacae amarae	3CLpr and SARS-CoV-2 ACE2 inhibitors[20]

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curcumin	Curcumin	prepared RHIZOMA PINELLIAE with juice of rhizima zingiberis rec-ens	Anti-inflammatory, antiviral, good safety and tolerance
patchoulenone	Pogostone	Pogostemon cablin	Inhibiting Keap1-Nrf2/NF-κB signaling pathway[21]
Ephedrin	Pachypodol	Pogostemon cablin	Inhibits PLpro protease[21]

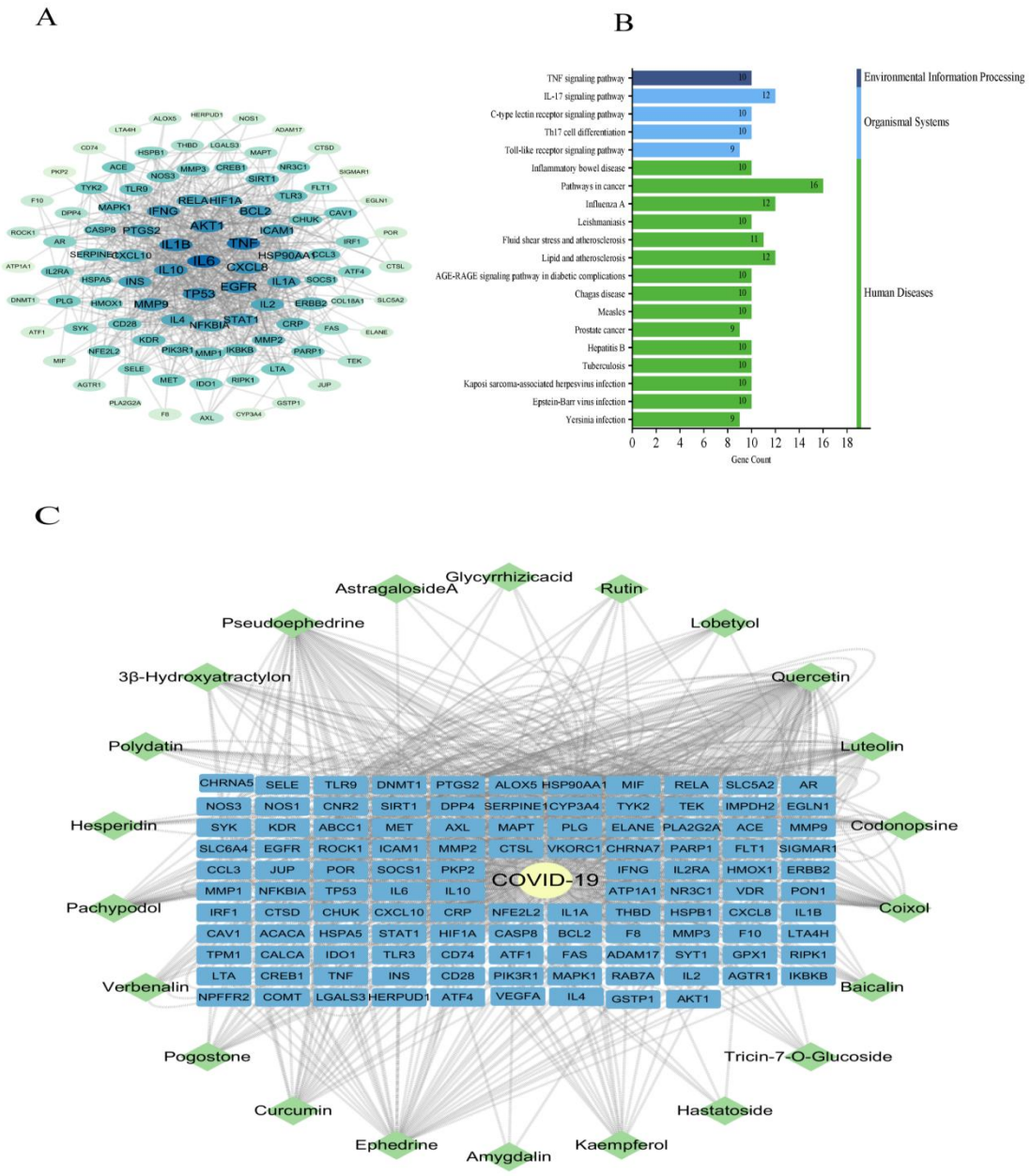

Figure 3 Virtual screening of key targets and functional substances of qindufuzheng in the prevention and treatment of COVID-19.

A: Protein-protein interaction(PPI) network of qindufuzheng for treatment of COVID-19; B:Active ingredients-targets-OP network;C: KEGG enrichment secondary classification

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Table 3 Thebinding energy values of the core compounds in HDD and their corresponding targets

chemical compound	IL6	TNF
Quercetin (Quercetin)	-7	-8.3
Pseudoephedrine (Pseudoephedrine)	-4.2	-4.8
Ephedrine (Ephedrine)	-4.3	-5.4
Coix seed extract (Coixol)	- 4.4	- 6.1
Limonin (Luteolin)	-7.1	-8.3

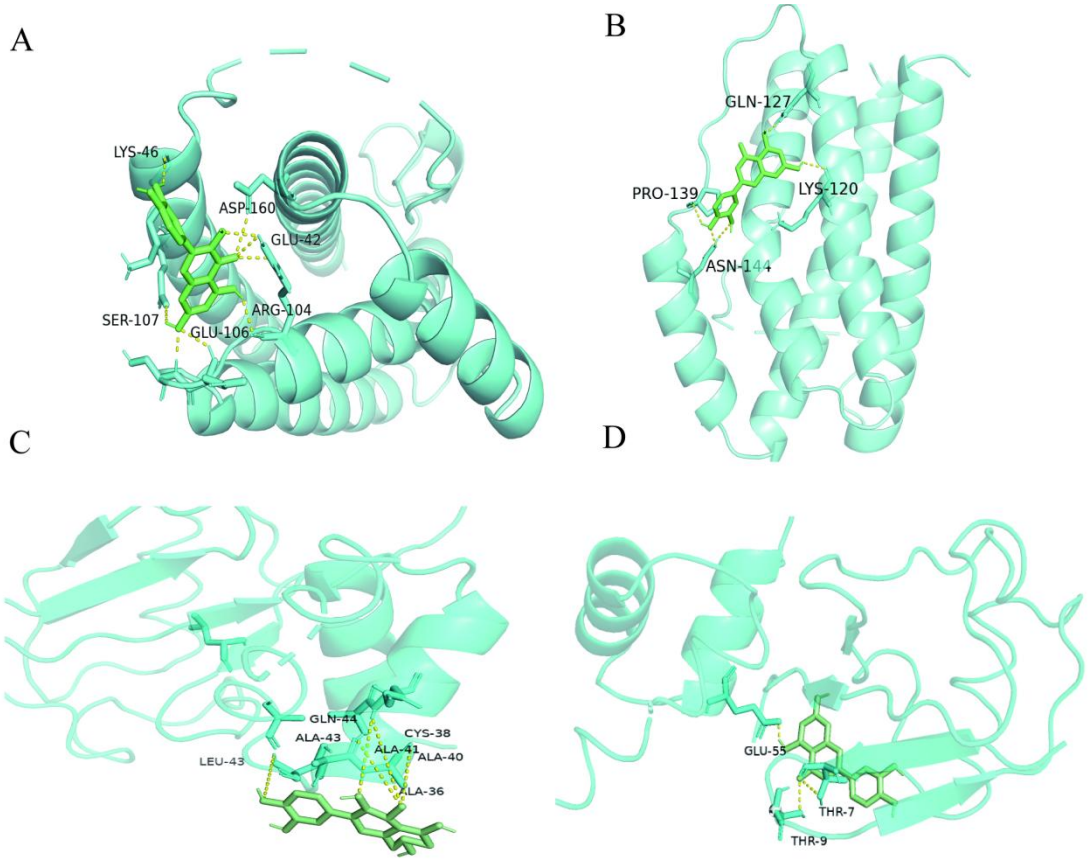

Figure 4 Adiagramofmolecular docking

A: IL6-Quercetin docking; B: IL6-Luteolin docking; C: TNF-Quercetin dockin; D: TNF-Luteolin docking.

5. Discuss

The overall theory and treatment methods of Traditional Chinese medicine have unique advantages in epidemic prevention. According to the Huangdi Neijing, "If the righteous qi is preserved inside, evil cannot be dry. Where evil gathers, its qi must be weak"[22]The detoxification and support formula was developed by Dr. Gong Xianfeng, a famous TCM doctor in Xi an Chest Hospital, based on his years of clinical experience with three formulas (lung detoxification soup, dampness transformation and toxin elimination formula, lung detoxification formula)[23]It was made by adding and subtracting. Among the included cases, male patients were more than female, which may be related to different lifestyles of men and women, especially smoking. Cai G et al[24]Research has found that smoking can increase the

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expression of angiotensin-converting enzyme 2 (ACE 2) in lung tissue. The main clinical symptoms of COVID-19 patients are fever and cough, with 60% of patients showing imaging changes. After infection, lymphocytes and hyper-reactive CRP show significant alterations, while indicators such as white blood cells, neutrophils, albumin, ALT, AST, and CREA do not change significantly. By comparing hospital stays, there is a significant difference in the number of days hospitalized across different age groups; elderly COVID-19 patients have a treatment duration of 12.4 ± 4.0 days, according to QianyiPeng et al [25]Studies showed that the length of hospital stay for patients over 60 years old was 23.1±11.0 days, so we concluded that QDFZFZ treatment for COVID-19 was significantly effective.

In order to further explore the pharmacological basis and potential biological mechanism of Qingdu Fu Zheng Fang in treating COVID-19, we detected the active ingredients of Qingdu Fu Zheng Fang by UPLC-MS/MS and found that the main components of Qingdu Fu Zheng Fang in treating COVID-19 were flavonoids and alkaloids. Sopjani et al[26]The study found that flavonoids have a dual antiviral mechanism: directly interfering with viral invasion and inhibiting replication, and have the potential to alleviate the progression of COVID-19 lipid metabolism in obese individuals. Xu Jiameng et al[27]Studies have shown that the quinoline alkaloid drugs chloroquine and hydroxychloroquine have been preliminarily proved to have anti-SARS-CoV-2 activity. Phenolic acid compounds play an important role in anti-inflammatory, scavenging reactive oxygen species, reducing inflammation and directly inhibiting viral replication[28]Therefore, we screened out 23 active ingredients through the combination of sovereign, minister, assistant and agent, as well as reference data. Based on UPLC-MS/MS and network pharmacology methods, it was found that the detoxification and support formula mainly treated COVID-19 through three synergistic ways.

First, it can alleviate the inflammatory storm caused by coronavirus infection. Active ingredients such as quercetin (Quercetin), pseudoephedrine (Pseudoephedrine), ephedrine (Ephedrine), luteolin (Luteolin), and coptisine (Coixol) target IL-17 signaling pathway, tumor necrosis factor α signaling pathway, Th17 cell differentiation pathway, and toll-like receptor signaling pathway through their effects on IL6, TNF, AKT1, IL6B, TP53, CXCL6, and NFKBIA, thereby reducing the abnormal increase of inflammatory cytokines and subsequently triggering a series of extensive inflammatory cascades that damage multiple organs in the body[29] .

Secondly, directly intervene in the entire process of viral infection to block the proliferation and spread within the coronavirus. Components such as baicalin, amygdalin, naringin, stephania glycosides, and kaempferol act on SARS-CoV-2s main proteases 3CLpro, PLpro, and ACE2 through RELA and EGFR pathways, inhibiting influenza A and hepatitis B.

In addition, the immune system can be regulated to prevent and treat coronavirus. Quercetin and luteolin both play a regulatory role in IL-6 through nod-like receptors and signaling pathways, which then affect the process of immune response[30]The results of molecular docking showed that quercetin and luteolin had the most stable conformation with TNF, and quercetin and luteolin could inhibit the NF-κB signaling pathway to reduce apoptosis and inflammation caused by TNF-α[31,32]Quercetin and luteolin can regulate IL-6 expression through signaling pathways such as NF-κB, MAPK, and IL-6/JAK/STAT3 to mitigate inflammatory responses. In summary, the detoxification and tonifying formula can exert therapeutic effects on COVID-19 (COVID-19) by inhibiting inflammatory mediators, blocking viral infection pathways, and modulating immune functions, with multiple pathways working synergistically.

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