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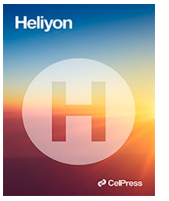

Research article

Decoding the mechanism of Qingjie formula in the prevention of COVID-19 based on network pharmacology and molecular docking

Yu Pan [a], Wanchun Lin [a], Yueyue Huang [b], Jingye Pan [b], Yihua Dong [b,*]

[a] Department of Pharmacy, Zhejiang Chinese Medical University Affiliated Wenzhou Hospital of Integrated Traditional Chinese and Western Medicine, Wenzhou, Zhejiang, 325000, China
[b] Department of Intensive Care Unit, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, 325000, China

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ABSTRACT

Traditional Chinese medicine (TCM) has played a positive role in preventing and controlling the coronavirus disease 2019 (COVID-19) epidemic. Qingjie formula (QJF) developed to prevent COVID-19 is widely used in Wenzhou, Zhejiang province, China. However, the biological active ingredients of QJF and their specific mechanisms for preventing COVID-19 remain unclear. The study focused on exploring the pharmacological mechanism of QJF for the prevention of COVID-19 based on network pharmacology and molecular docking. The active ingredients of QJF were screened by TCMSP database. Databases such as Genecards and Swiss Target Prediction predicted potential targets of QJF against COVID-19. The "drug-active ingredient-potential target" network was constructed by Cytoscape software. We used STRING database to construct the protein-protein interaction (PPI) network. Enrichment of biological functions and signaling pathways were analyzed by using the DAVID database and R language. Then AutoDock Vina and Python software were used for molecular docking of hub targets and active ingredients. 147 active ingredients interacted with 316 potential targets of COVID-19. A PPI network consisting of 30 hub genes was constructed, and the top 10 hub genes were ALB, AKT1, TP53, TNF, IL6, VEGFA, IL1B, CASP3, JUN and STAT3. The results of GO analysis showed that these targets were mainly enriched in cell responses to oxidative stress, chemical stress, and other functions. KEGG analysis revealed that viral protein interactions with cytokines (e.g., human cytomegalovirus infection), endocrine resistance pathways (e.g., AGE-RAGE signaling pathway), PI3K-Akt signaling pathway, and lipid and atherosclerosis signaling pathway were the major signaling pathways. Moreover, the core active ingredients of QJF had good binding affinity with hub genes by molecular docking. QJF plays an important role in the prevention of COVID-19 by regulating host immune inflammatory response and oxidative stress response, inhibiting virus, improving immune function, regulating the hypoxia-cytokine storm, and inhibiting cell migration.

1. Introduction

Coronavirus disease 2019 (COVID-19) was first discovered in Wuhan, China, and is a highly contagious disease caused by severe

* Corresponding author.
E-mail address: dongyihua@126.com (Y. Dong).

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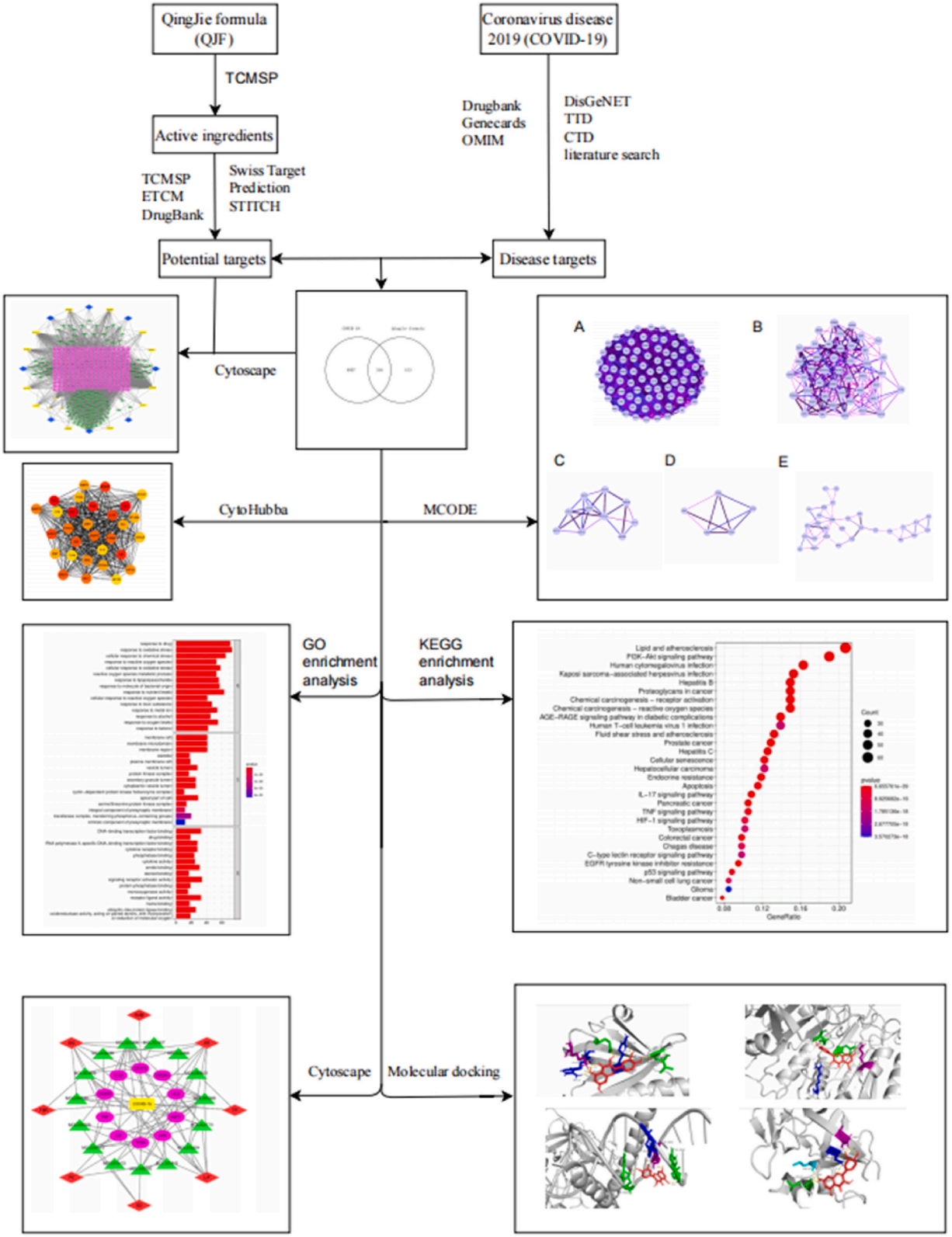

Fig. 1. The flowchart of this study.

acute respiratory syndrome coronavirus-2 (SARS-CoV-2) [1]. Due to its infectivity, it has been declared a global pandemic by the World Health Organization (WHO) [2], posing an ongoing and serious threat to public health [3]. As of Jul 05, 2023, more than 767 million confirmed cases and more than 6.9 million confirmed deaths have been reported globally, according to WHO (https://covid19.who.int). COVID-19 is a heterogeneous disease that spreads primarily from person to person through respiratory droplets [4], with symptoms ranging from asymptomatic to severe, such as fever, cough, headache, myalgia [5], coagulation dysfunction [6], cardiac inflammation, liver damage [7], and even inflammatory cytokine storm [8]. Therefore, it is not only a respiratory disease, but also a systemic disease that disturbs the immune system and damages multiple organs and systems throughout the body, such as the cardiovascular system and digestive system.

Historically, traditional Chinese medicine (TCM) has been widely used to enhance human immunity and prevent chronic and sudden diseases due to its remarkable efficacy and few side effects. Moreover, some novel technologies can find biological targets of TCM,and interact with cells and tissues in a highly precise manner [9]. Since the outbreak of COVID-19, TCM has achieved remarkable effects and played a positive role in curbing the spread of the virus and preventing and treating diseases [10]. A section on TCM treatment has also been included in the Guideline on Diagnosis and Treatment of COVID-19 (Trial Version 4–7) issued by the National Health Commission of China [11]. Qingjie formula (QJF) was developed on the basis of comprehensive summary of various recommended TCM formulations for the prevention of COVID-19 in the Guideline, combined with the climatic characteristics of southern Zhejiang, and based on the theory of febrile disease in TCM. QJF is consisted of Astragali Radix, Pogostemon cablin, Tangerine Peel, Lonicerae Japonicae Flos, Glycyrrhiza glabra, Rhizoma Atractylodis Macrocephalae, Saposhnikovia divaricate and Fortunes Bossfern Rhizome. During the epidemic, it was widely used in epidemic prevention in Wenzhou and achieved good results. However, the molecular mechanism of QJF in the prevention of COVID-19 is still unclear.

Network pharmacology can explore the effective effects of traditional Chinese medicines or compounds by combining systems biology, bioinformatics and pharmacology, this method is considered to be an effective research strategy for screening the active ingredients of TCM [12–14], searching for potential targets and exploring the mechanisms of action. Molecular docking is an important way to predict the binding pattern and affinity of a small molecule compound by docking with a target receptor.

In order to discover the active ingredients of QJF, decode potential key targets and mechanisms of action, and verify the interactions between important compounds and targets, we integrated network pharmacology and molecular docking method to provide theoretical support and scientific basis for the prevention of COVID-19. The flow chart of this study is shown in Fig. 1.

2. Methods

2.1. Screening of potential active ingredients

The active ingredients of QJF were obtained by using the TCM Systems Pharmacology Database and Analysis Platform (TCMSP, https://tcmsp-e.com/tcmsp.php). TCMSP can provide the active compounds in all Chinese medicines, and the important properties such as half-life (HL), human oral bioavailability (OB), drug similarity (DL), and blood-brain barrier (BBB) of each ingredient. We all know that meeting OB $\geq$ 30 % and DL $\geq$ 0.18 is the threshold for screening potential active ingredients [15]. In addition, the corresponding molecular formula, two-dimensional structure, InChI Key and Canonical SMILES of the active ingredients were all obtained from PubChem.

2.2. Prediction of potential targets of QJF

According to the retrieved active ingredients of QJF, the targets related to these ingredients were derived from the TCMSP. Given these targets may be not complete, we also searched for the potential targets from other Database and Analysis Platform by using the information of the compounds obtained from PubChem. In Swiss Target Prediction (http://www.swisstargetprediction.ch) and STITCH (http://stitch.embl.de), the species was limited to "*Homo sapiens*" and the threshold of confidence score was set as no less than 0.8.

2.3. Acquisition of disease targets

The targets related to COVID-19 disease were obtained by retrieving DrugBank database, Genecards database, OMIM database, DisGeNET database, Therapeutic target database, and Comparative toxicogenomics database. "Novel coronavirus pneumonia", "COVID-19", "coronavirus disease 2019" were used as keywords. The species chosen was "*Homo sapiens*". In addition, considering that angiotensin-converting enzyme 2 (ACE2) is not only the host receptor for SARS-CoV-2, but also can drive the up-regulation of genes related to pulmonary fibrosis [16], we collected the genes co-expressed with ACE2 from previous literature to complement COVID-19 related targets [5,17,18], and eliminate duplicate goals to screen out disease related targets. The UniProt protein database was used to standardize all the targets collected as gene names with the "*Homo sapiens*" species. We used Venn diagram data package to obtain the overlapping targets of the related targets between the active ingredients of QJF and COVID-19, and considered the intersectional targets as potential targets for the prevention of COVID-19.

2.4. Construction of the herb-active ingredient-potential target network of QJF in preventing COVID-19

To visualize synergistic interactions between active ingredients and multiple predicted targets, we constructed the herb-active

ingredient-potential target network using Cytoscape 3.8.2. Cytoscape is a leading open source tool for complex network analysis [19]. In this constructed network, herbs, active ingredients, and targets are represented as nodes, and interactions between nodes are represented as edges. In this study, we set the "herb" as a diamond, the "active ingredient" contained by two or more herbs as a rectangle, the "active ingredient" contained by a single herb as a triangle, and the "target" as an oval.

2.5. Conducting protein- protein interaction (PPI) network

We imported the overlapping targets into the STRING(https://string-db.org, version 11.5) online tool to obtain relevant information of PPI network. In this stage work, "*Homo sapiens*" was used as the setting of the organism, the minimum required interaction score was set $\geq$0.4, and other parameters were set by default. Only genes with scores above the median were screened out to construct critical sub-network. Then, PPI results were imported into CytoHubba plug-in in Cytoscape for network topology analysis to filter out important hub genes. Maximum neighborhood component (MNC) method was used to output hub genes [20], and the top 30 genes were selected. Subsequently, the PPI network was visualized by Cytoscape 3.8.2 software. Finally, cluster analysis in PPI network was explored by the plug-in of Molecule Complex Detection (MCODE) of Cytoscape (node score cutoff $\geq$0.2, k core $\geq$2, maximum depth = 100, and degree cutoff $\geq$2) [21].

2.6. GO analysis and KEGG pathway enrichment analysis

Gene Ontology (GO) analysis is used to define and describe the properties and functions of genes and their products in any organism. GO annotation generally includes biological process (BP), cell component (CC), and molecular function (MF). On the basis of the Kyoto Encyclopedia of Genes and Genomes (KEGG) database, pathway enrichment analysis revealed significantly enriched metabolic pathways. GO enrichment analysis and KEGG pathway enrichment analysis were performed using cluster Profiler and DOSE software package in R software. The threshold of statistical significance for enrichment analysis was set at $p \leq 0.05$. The results of enrichment analysis for the top 15 GO functions and the top 30 KEGG pathways were represented by histogram and bubble plot, respectively.

2.7. Molecular docking verification of active ingredients and hub targets

The crystal structure of the hub target obtained from the RCSB PDB database as the receptor and the active ingredient of QJF as the ligand. The two-dimensional structure of the active ingredient was downloaded from the PubChem database. The protein crystal structure was dehydrated and hydrogenated with AutoDock 1.5.6 software. The ligands added hydrogen atoms and displayed rotatable bonds. Finally, all files were saved in pdbqt format. Autodock Vina and PyMol software were used to dock ligands with protein receptors and evaluate their interaction.

3. Results

3.1. Identification of potential active ingredients and related targets in QJF

QJF consists of 8 single TCMs, including Astragali Radix (AR), Pogostemon cablin (PC), Tangerine Peel (TP), Lonicerae Japonicae Flos (LJF), Glycyrrhiza glabra (GG), Rhizoma Atractylodis Macrocephalae (RAM), Saposhnikovia divaricate (SD) and Fortunes Bossfern Rhizome (FBR). We submitted the above 8 TCMs to the TCMSP database and retrieved 1019 active ingredients. A total of 183 compounds were collected using OB $\geq$ 30 % and DL $\geq$ 0.18 as screening criteria, and 166 components were collected after removing the redundancy. Among them, the number of active ingredients of Astragali Radix, Pogostemon Cablin, Tangerine Peel, Lonicerae

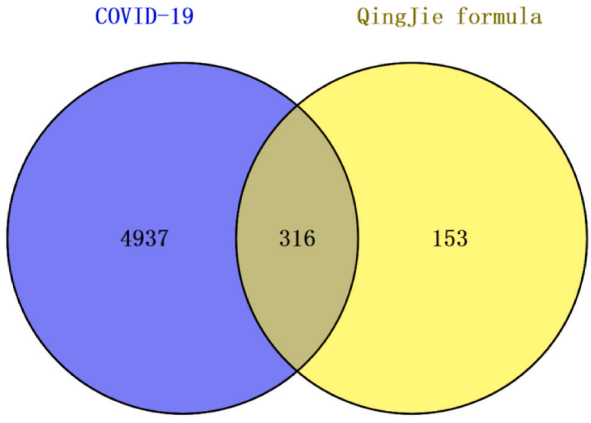

Fig. 2. Common targets of Qingjie formula (QJF) and COVID-19.

Japonicae Flos, Glycyrrhiza Glabra, Rhizoma Atractylodis Macrocephalae, Saposhnikovia Divaricate and Fortunes Bossfern Rhizome were 20, 11, 5, 23, 92, 7, 18, 7, respectively, and there were 12 common compounds (Supplementary File Table S1).

According to the screening results of active ingredients in databases such as TCMSP, Drug Bank, ETCM, Swiss Target Prediction, and STITCH, 469 drug targets matching 149 compounds were collected after removing the duplicates, and 17 compounds had no matching targets. The gene names of potential targets were obtained by using the UniProt protein database with the "*Homo sapiens*" species, as shown in Supplementary File Table S2.

3.2. Prediction results of QJF targets in preventing COVID-19

Using "novel coronavirus pneumonia", "COVID-19" and "coronavirus disease 2019" as keywords, we screened targets in Drug Bank, Gene cards, OMIM, DisGeNET, TTD and CTD databases. Then, the genes co-expressed with ACE2 in literature [17] were integrated to supplement COVID-19 related targets. A total of 5253 targets were obtained. Subsequently, 316 overlapping targets were identified by mapping 469 component targets to 5253 COVID-19 targets, and a Venn diagram was drawn, as shown in Fig. 2. In addition, 147 components had targets that intersected with COVID-19 and 2 ingredients did not. Therefore, 147 active ingredients were correlated with 316 targets (Supplementary File Table S3).

3.3. Analysis of drug-active ingredient-common target network

The drug-active ingredient-common target network was constructed using Cytoscape is shown in Fig. 3, involving 471 nodes (including 8 herbs, 147 active ingredients, and 316 targets) and 2551 edges. Diamonds with blue color represent 8 herbs of QJF. The green triangles and yellow rectangles represent their active ingredients, with the green triangles representing compounds contained in a single herb and the yellow rectangles representing compounds contained in two or more herbs. And the 316 pink ellipses in the center

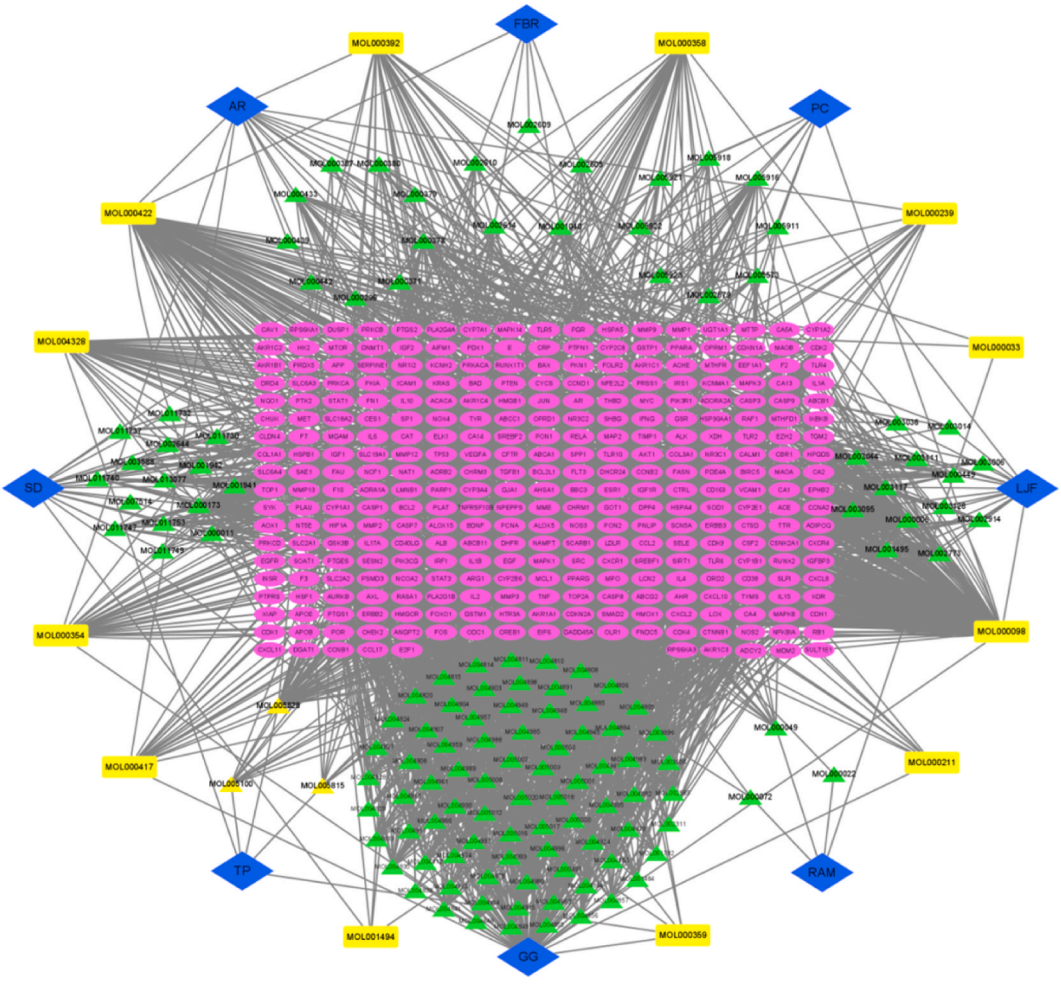

Fig. 3. Network of drug-active ingredient-potential target.

represent potential targets of QJF for COVID-19 prevention. According to the degree values, we identified the top eight key ingredients, which were quercetin (MOL000098), luteolin (MOL000006), kaempferol (MOL000422), wogonin (MOL000173), nobiletin (MOL005828), isorhamnetin (MOL000354), naringenin (MOL004328), and beta-sitosterol (MOL000358) in order.

3.4. Protein-protein interaction network and cluster analysis

PPI network was established by using STRING database to identity functional connections between targets. We then visualized and topologically analyzed the network using Cytoscape software. The network is shown in Fig. 4A, which consisted of 316 nodes and 9130 edges, with an average node degree of 57.8 and a PPI enrichment p value < 1.0e-16. The PPI network was then clustered using the MCODE plug-in in Cytoscape, resulting in 12 clusters (Supplementary File Table S4). Based on the scores, we selected the top five networks (Fig. 5A–E). The top 30 genes were screened as the hub targets of QJF according to MNC method in the network, and visualized by Cytohubba tool. These genes were consistent with the results of the sequencing by degree screening. As shown in Fig. 4B, the color of the nodes ranged from yellow to red, and the corresponding degree value increased gradually. The network was composed of 30 nodes and 431 edges, with an average node degree of 28.7, and a PPI enrichment p value < 1.0e-16. The top 10 targets likely to play a major role in the network were ALB, AKT1, TP53, TNF, IL6, VEGFA, IL1B, CASP3, JUN, and STAT3. Therefore, we considered that these targets were targeted for QJF prevention of COVID-19, and they also played critical roles in gene regulatory networks.

3.5. GO function enrichment analysis and KEGG pathway enrichment analysis

To investigate the biological functions of QJF in the prevention of COVID-19, we performed GO annotation and KEGG enrichment analysis for the above 316 targets. GO annotation analysis results included BP, CC and MF. Fig. 6 shows the top 15 terms, where the X-axis represents the number of enrichment and the Y-axis represents the type of enrichment. The biological processes mainly included drug response, oxidative stress response, chemical stress cellular response, nutrient levels response, oxidative stress cellular response, molecule of bacterial origin response and lipopolysaccharide response. The top three enrichment results of cell components were membrane raft, membrane microdomain and membrane region. The top three enrichment results of molecular functions included signaling receptor activator activity, DNA-binging transcription factor binding and receptor ligand activity.

Through KEGG pathway enrichment analysis, major pathways associated with QJF were identified, and the top 30 entries are shown in Fig. 7. The X-axis represents the number of enrichment, and the Y-axis represents the enrichment pathway name. The enriched cell signaling pathways mainly included PI3K-Akt signaling pathway, cytomegalovirus infection signaling pathway, lipid and atherosclerosis signaling pathway, Kaposi sarcoma-associated herpes virus infection signaling pathway, receptor activation signaling pathway and reactive oxygen species signaling pathway.

3.6. Hub gene-active ingredient-herb-disease network

We constructed the hub gene-active ingredient-herb-disease network based on the active ingredients associated with the 10 hub

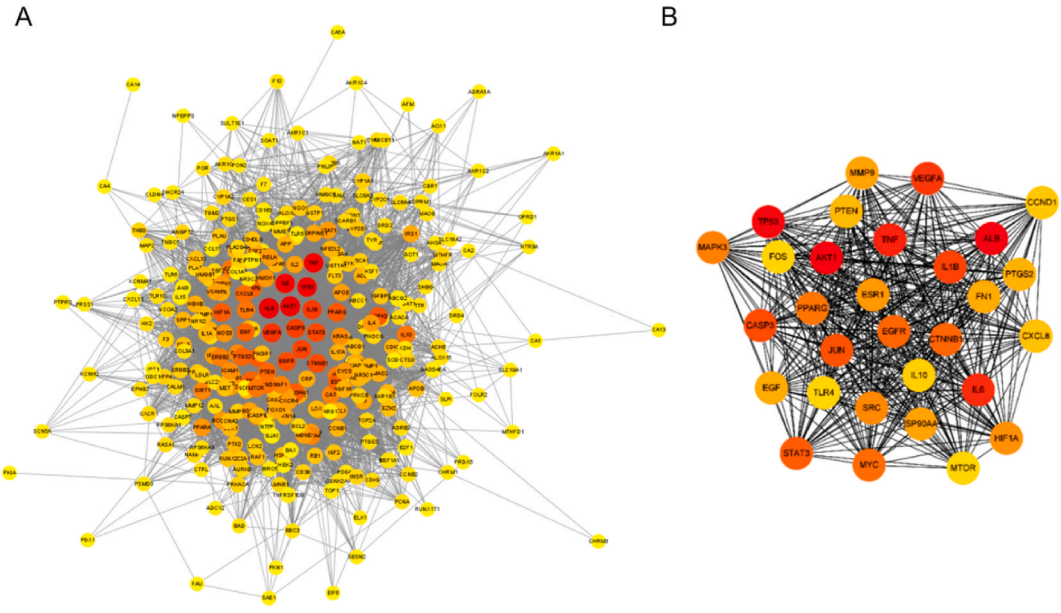

Fig. 4. A. PPI network of QJF and COVID-19 related targets. **B.** PPI network of top 30 hub genes. The node color changes from yellow to red, and the corresponding degree increases gradually.

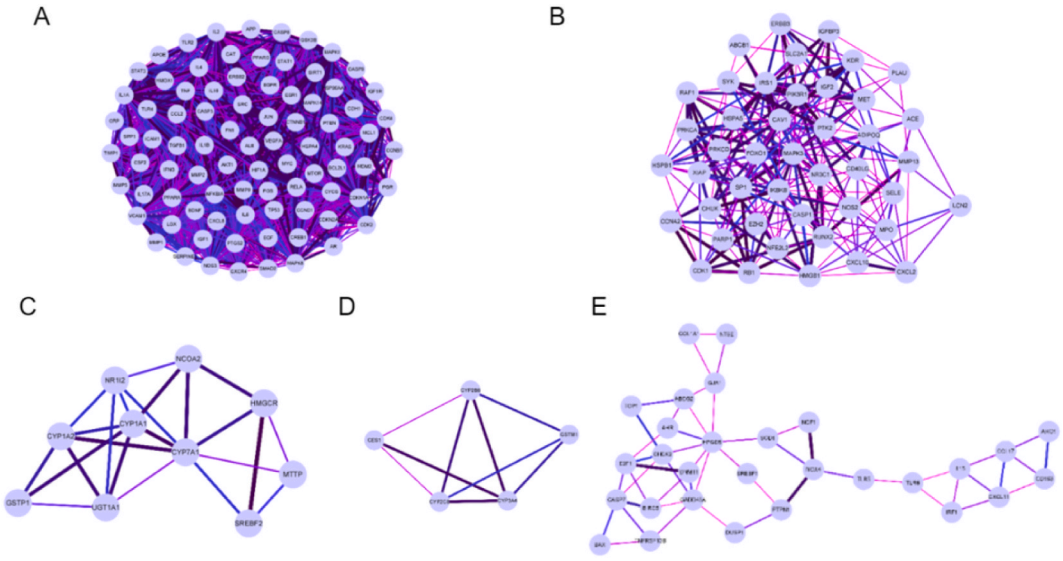

Fig. 5. A–E. Top five clustering graphs from the PPI network of COVID-19.

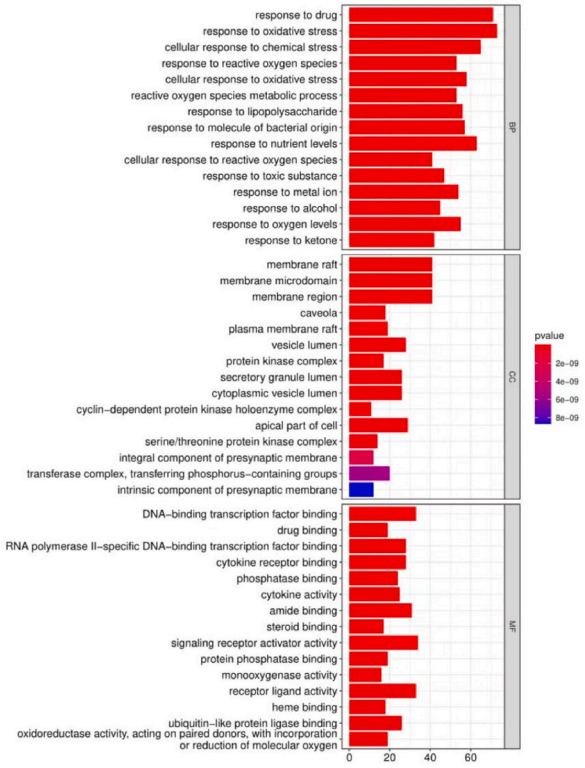

Fig. 6. GO function enrichment analysis graph.

genes. The network had 34 nodes and 81 edges, containing 1 disease, 10 hub genes, 15 active ingredients, and 8 herbs (Fig. 8). We then identified the top five components, which were luteolin (MOL000006), quercetin (MOL000098), wogonin (MOL000173), kaempferol (MOL000422) and beta-carotene (MOL002773).

3.7. Validation by molecular docking

We used ten hub genes and five pivotal active ingredients as receptors and ligands, and conducted molecular docking to validate

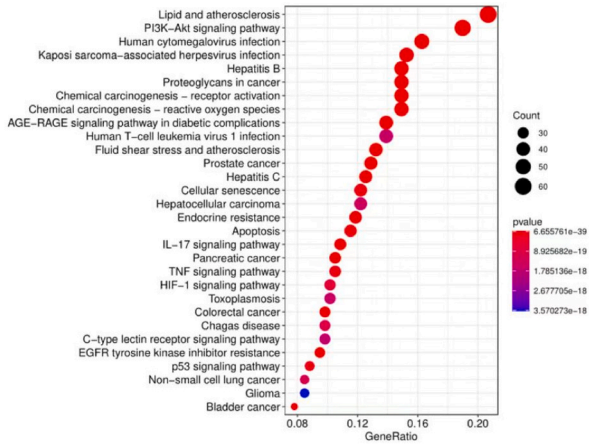

Fig. 7. KEGG pathway enrichment analysis.

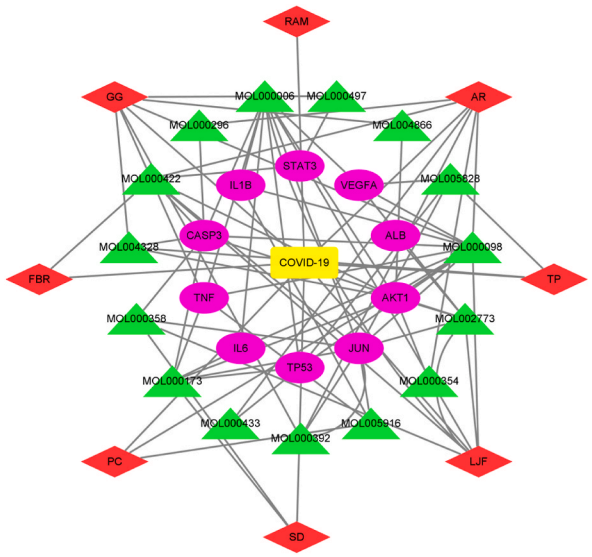

Fig. 8. Hub gene network.

whether these active ingredients bind to hub targets. Crystal structures of ten hub targets and two-dimensional structures of five active ingredients were downloaded from the RCSB PDB database and PubChem database, respectively. Binding energy represents the affinity between the receptor and the ligand and the stability of the binding of them. The lower the binding energy, the better the affinity and the more stable the binding. The binding energy between the ingredient and the target was calculated to explore the binding interaction between them. And the binding energy of −5.0 kcal/mol was set as the threshold to determine whether the binding affinity

Table 1
Screening docking results between receptor and ligand (kcal/mol).

Hub targets	luteolin	quercetin	wogonin	kaempferol	beta-carotene
ALB	/	/	/	/	−9.7
AKT1	−6.4	−6.3	−6.1	−6.1	−6.8
TP53	−6.4	−6.3	−5.9	/	/
TNF	/	−7.1	−7.9	−6.9	/
IL6	−7.2	−7.0	−6.4	/	/
VEGFA	−7.6	−8.0	/	/	−8.2
IL1B	−7.4	−7.3	/	/	/
CASP3	−7.8	−7.9	−7.4	−7.7	−8.1
JUN	−8.5	−8.3	−8.6	−8.1	−9.3
STAT3	/	/	/	−8.2	/

between the receptor and the ligand was good [22]. The docking results of the active ingredient-target interaction are listed in Table 1. It can be seen that their binding energies were all lower than −5.0 kcal/mol. The results indicated that there is a good combination between the active ingredient and the target. The binding poses of the hub targets and active ingredients were shown in Fig. 9A–J.

4. Discussion

Since the outbreak of COVID-19 in late 2019, the combination of traditional Chinese and Western medicine has been effective in the prevention and treatment of COVID-19, which is significantly better than Western medicine in improving clinical symptoms and shortening the average length of hospital stay [23]. The development of confirmed curative effective drugs is becoming increasingly important for improving the physical condition of patients and preventing the ongoing outbreak of COVID-19. Since its application in Wenzhou, QJF has achieved good results in the prevention of mild and general cases of COVID-19. By means of network pharmacology and molecular docking, this study explored the potential mechanisms of QJF in the prevention of COVID-19, and provided support for subsequent clinical behavior.

In this study, 149 active ingredients and 469 corresponding targets were screened through database and visualized by network pharmacology. In the analysis of QJF-active ingredient-potential target-disease network, quercetin, beta-sitosterol, formononetin, kaempferol, and naringenin were common compounds in two or more TCMs, which may be involved in potential anti-inflammatory and antiviral effects, as well as fighting various cardiovascular diseases. Quercetin has been reported to inhibit viral replication and growth by affecting viral regulation of its mediated immune response [24], and to inhibit the activation of the NLRP3 inflammasome [25]. In addition, quercetin can also reduce the production of reactive oxygen species, further alleviating the pro-inflammatory response [26]. Beta-sitosterol has beneficial effects on immune regulation, swelling reduction [27], and chronic diseases such as diabetes [28], liver disease [29] and cancer [30]. Kaempferol has anti-inflammatory and antioxidant effects [31], and can inhibit the progression of pulmonary fibrosis by regulating the activation of proteinase-activated receptor-1 [32]. Besides, formononetin can regulate lipid metabolism and inflammatory responses [33]. In vitro, in vivo and clinical studies have confirmed that naringenin has

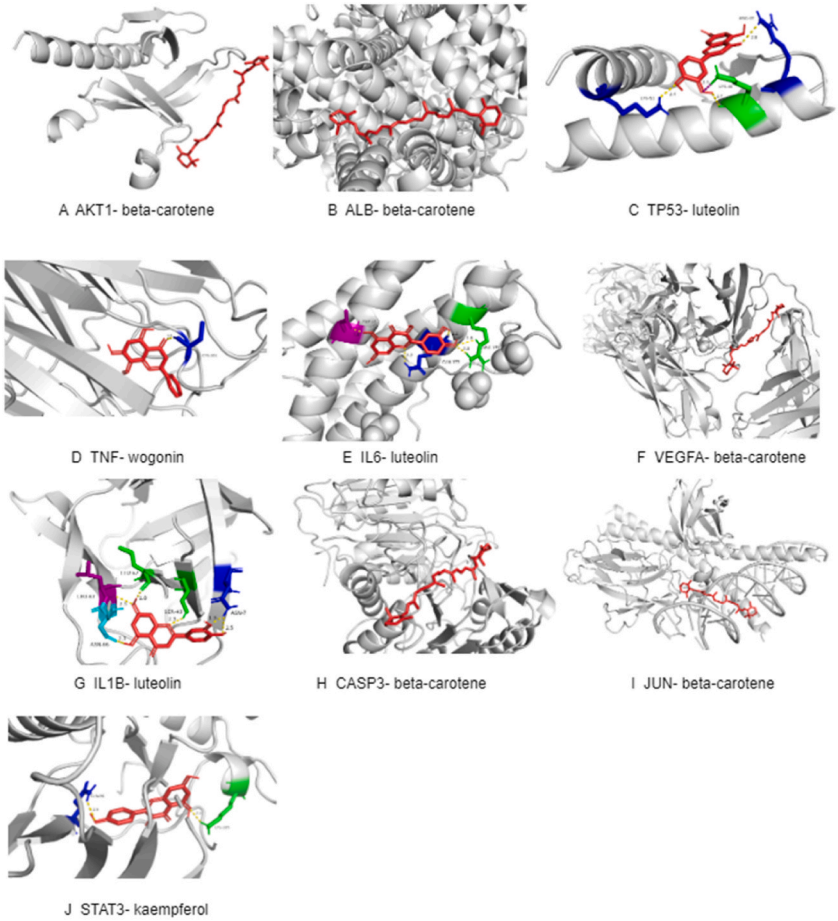

Fig. 9. Molecular docking of active ingredients and hub targets. (A) AKT1, (B) ALB, (C) TP53, (D) TNF, (E) IL6, (F) VEGFA, (G) IL1B, (H) CASP3, (I) JUN, (J) STAT3. Gray represents the targets, red represents the compounds, and other different colors represent the groups acting on the target. The yellow dotted line represents conventional hydrogen bonding, and the purple dotted line represents pi-cation.

pharmacological effects such as anti-inflammatory, antioxidant, antiviral, and prevention of tissue fibrosis [34]. In the analysis of QJF-active ingredient-potential target network diagram, quercetin, luteolin, kaempferol, baicalein and nobiletin were the core active ingredients with the largest number of targets, some advanced techniques are available for the extraction and preparation of these active ingredients [35]. Among them, quercetin had the highest frequency of interaction with the targets. Quercetin and kaempferol can inhibit the production of pro-inflammatory cytokine interleukin-6 (IL6) and help to reduce the inflammatory response associated with COX-2 expression, thereby alleviating inflammatory damage. Luteolin may inhibit inflammation by reducing the expression of EGFR, MAPK1, MMP9 and other core genes [36]. In summary, QJF has been shown to have antiviral, anti-inflammatory, and antioxidant activities to prevent COVID-19.

A total of 316 target genes of QJF for prevention of COVID-19 were obtained by intersecting drug target genes and disease-related genes. PPI network analysis revealed that ALB, AKT1, TP53, TNF, IL6, VEGFA, IL1B, CASP3, JUN and STAT3 were the hub genes in QJF prevention of COVID-19. These genes were mainly related to host immunity, inflammatory response and cellular stress processes, and play a key role in QJF prevention of COVID-19. IL-6 is a member of the interleukin family and is found in high levels in the plasma of COVID-19 patients. Down-regulation of IL-6 inflammatory factor can effectively reduce the mortality of patients [37]. Schultheiβ C et al. [38] found that the post-acute sequelae of COVID-19 (PASC) was associated with increased plasma levels of IL-1B, IL-6 and TNF. CASP3 is an enzyme that plays a critical role in cell apoptosis. When activated, CASP3 can induce apoptosis. IL-6 and VEGFA levels have been reported to be significantly associated with COVID-19, and the mortality of COVID-19 patients increases with increasing levels of these markers [39]. Pro-inflammatory cytokines such as IL-6, TNF and IL-1β are often produced locally or systemically in patients with poor prognosis of COVID-19, creating an uncontrolled cytokine storm [40].

Functional enrichment analysis of QJF target genes showed that BP terms were mainly related to biological response processes to oxidative stress, drugs, chemical stress, nutrient levels, molecule of bacterial origin, and lipopolysaccharide signaling pathway. CC terms were mainly associated with membrane raft, membrane microdomain, membrane region, plasma membrane raft, vesicle lumen, caveola, and protein kinase complex. MF terms were mainly related to cytokine, signaling receptor activator, cytokine receptor, and binding functions (DNA-binding transcription factor, amide, RNA polymerase II-specific DNA-binding transcription factor, phosphatase, drug, and steroid). Moreover, KEGG enrichment analysis showed that the main related pathways were lipid and atherosclerosis, PI3K-Akt signaling pathway, cytomegalovirus infection, AGE-RAGE signaling pathway, and IL-17 signaling pathway. The prevention of COVID-19 by QJF may act through these signaling pathways. The PI3K-Akt signaling pathway plays a key role in many biological and cellular processes, and is involved in the regulation of cell genesis, growth, proliferation, migration, and the development and progression of cardiac fibrosis [41] and cancer [42]. It has been proved that this pathway plays an important role in the cell entry and immune response of SARS-CoV-2 virus [43], and inhibiting this pathway can reduce the expression of inflammatory cytokines [40]. The activation of AGE-RAGE signaling pathway is important in inducing the production of tissue factors, inflammatory cytokines, VCAM-1 and NF-κB. In the process of viral infection, IL-17 directly synergizes with antiviral signaling to enhance the pro-inflammatory response. IL-17 pathway is not only involved in the body's inflammatory response, but also related to the immune response [44]. In addition, molecular docking was performed to validate whether the ingredients of QJF could bind to these hub targets. The binding energy of these hub targets with most compounds is lower than −5.0 kcal/mol. This indicates that they have good binding affinity and are able to inhibit the host-virus protein interactions in which they are involved. In this study, only bioinformatics databases and software were used to predict the potential molecular mechanisms of QJF in prevention of COVID-19.

Through network pharmacology and molecular docking, the core active ingredients of QJF and the key targets of these ingredients against COVID-19 were systematically analyzed, and the possible action mechanisms of these targets were explored. COVID-19 is highly contagious and can spread rapidly, resulting in high rates of infection and death worldwide that have taken enormous efforts and costs to bring under control. Due to the special nature of the disease itself, we are, however, unable to perform biological system experiments related to this virus for the time being.

5. Conclusion

Given its multi-target and multi-pathway characteristics of QJF in the prevention of COVID-19, it is worthy of clinical application and promotion. These results provide theoretical support and scientific basis for the prevention of COVID-19 by integrated traditional Chinese and western medicine, and also provide a reference for predicting the mechanisms of action of traditional Chinese medicine in the prevention of COVID-19.

CRediT authorship contribution statement

Yu Pan: Funding acquisition, Formal analysis, Data curation. **Wanchun Lin:** Writing – original draft, Resources. **Yueyue Huang:** Writing – original draft, Software. **Jingye Pan:** Supervision, Funding acquisition. **Yihua Dong:** Writing – review & editing, Formal analysis, Data curation.

Ethical approval

Not required.

Ethics statement

Not applicable.

Data availability statement

Data will be made available on request.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Abbreviation

COVID-19	Coronavirus Disease 2019
TCM	Traditional Chinese Medicine
QJF	Qingjie formula
SARS-CoV-2	severe acute respiratory syndrome coronavirus-2
WHO	World Health Organization
AR	Astragali Radix
PC	Pogostemon Cablin
TP	Tangerine Peel
LJF	Lonicerae Japonicae Flos
GG	Glycyrrhiza Glabra
RAM	Rhizoma Atractylodis Macrocephalae
SD	Saposhnikovia Divaricate
FBR	Fortunes Bossfern Rhizome
TCMSP	Traditional Chinese Medicine Systems Pharmacology database and analysis platform
ADME	absorption, distribution, metabolism, and excretion
HL	half-life
OB	human oral bioavailability
DL	drug likeness
BBB	blood-brain barrier
ETCM	Encyclopedia of Traditional Chinese Medicine
ACE2	angiotensin-converting enzyme 2
PPI	Protein-Protein Interaction
STRING	Search Tool for the Retrieval of Interacting Genes/Proteins
DC	Degree Centrality
CC	Closeness Centrality
BC	Betweenness Centrality
MNC	maximum neighborhood component
MCODE	Molecule Complex Detection
GO	Gene Ontology
BP	biological process
CC	cell component
MF	molecular function
KEGG	Kyoto Encyclopedia of Genes and Genomes.

Appendix A. Supplementary data

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