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**RESEARCH ARTICLE**

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# To explore the material basis and mechanism of Lianhua Qingwen Prescription against COVID-19 based on network pharmacology

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**Abstract** − *Objective*: In the treatment of COVID-19, the application of Lianhua Qingwen Prescription has become growingly widespread, however, the mechanism of action is still unclear. To explore the material basis and mechanism of Lianhua Qingwen Prescription against SARS-CoV-2, to provide a reference for the treatment of COVID-19. *Methods*: Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP), SwissTargetPrediction, and Similarity Ensemble Approach (SEA) database were used to search the chemical constituents and targets of Lianhua Qingwen Prescription. The targets of COVID-19 were screened by GeneCards, Therapeutic Target Database (TTD), and Comparative Toxicogenomics Database (CTD). Cytoscape software was used to construct a "drug-component-target" network diagram and the mechanism of action was predicted by enrichment analysis. *Results*: Two hundred and twenty four active components, 246 drug therapeutic targets, and 16,611 potential targets of Lianhua Qingwen Prescription were mined out. Moreover, 163 common targets were obtained, including PTGS2, IL6, CASP3, mapk1, EGFR, ACE2, etc. Thirty seven items were obtained by Gene Ontology (GO) enrichment analysis, mainly involving T-cell activation, virus receptor, and inflammatory reaction, etc. One hundred and forty items were obtained by Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enriched analysis, including TNF signaling pathway, MAPK signaling pathway, and IL-17 signaling pathway. *Conclusion*: Compounds such as quercetin and kaempferol play an important role in anti-COVID-19 through the TNF signaling pathway and MAPK signaling pathway.

**Keywords:** Lianhua Qingwen, COVID-19, Network Pharmacology, Functioning mechanism

## 1. Introduction

Since December 2019, multiple unexplained types of pneumonias have been discovered in Hubei Province, China, which has been confirmed as an acute respiratory infectious disease caused by the SARS-CoV-2. According to the latest statistics of the World Health Organization (WHO), as of July 20, 2020, the number of confirmed cases is as high as 14.3 million and the number of death is more than 600,000 [1]. The epidemic has been a "global pandemic" and this is also the first one caused by the SARS-CoV-2 [2]. COVID-19 is mainly manifested by fever, dry cough, and fatigue [3]. In addition, a few patients are accompanied by nasal congestion, runny nose, diarrhea, and other upper respiratory tract symptoms [4, 5]. Severe cases often have difficulty breathing after 1 week, accompanying by Acute Respiratory Distress Syndrome (ARDS), septic shock, difficult to correct metabolic acidosis, coagulation dysfunction, and multiple organ failure [6, 7]. Currently, there is no specific medicine for COVID-19 and Traditional Chinese Medicine (TCM) that play an important role in the prevention and treatment of COVID-19. Lianhua Qingwen Prescription [8], as a representative Chinese medicine in respiratory public health events, once played a therapeutic role comparable to oseltamivir in the treatment of H1N1 [9] and has now been recommended for the treatment of COVID-19 in China.

The Prescription was developed by Yiling Wu, an academician of the Chinese Academy of Engineering, for the treatment of SARS, which is mainly used to clearing and detoxifying, open the inhibited luny-energy, and disperse heat [10]. In the prescription, Forsythia is bitter and cold and Honeysuckle is sweet-cold and light. Both of them are good at clearing and detoxification as well as dispersing chill and the medicine pair is regarded as the monarch medicines [11]. Ephedra is characterized by the spread of Xinwen, which can make lung descend, stop cough, and

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relieve asthma; Plaster as a bitter-cold medicine is good at clearing and it is compatible with Ephedra to relieve lung without helping heat, clear lungs without retaining evil [12]; Fried bitter almonds is bitter slightly as well as warm and it can not only stop cough and relieve asthma but also open and release lung. The combination of the three as the minister medicines can not only help the emperor medicine to clear, but also relieve lung [13]. The seven medicines, Radix isatidis, Cyrtomium fortunei, Houttuynia cordata, Patchouli, Menthol, Rheum officinale, and Rhodiola, as the assistant medicines not only help the monarch and ministers to clear, detoxify, and relieve the lungs, but also to regulate the flow of Qi and the middle Jiao. Licorice is used as a guide medicine to reconcile all medicines. Lianhua Qingwen prescription is modified from Yinqiao Powder in "Item Differentiation of Warm Febrile Diseases" and Maxing Shigan Decoction in "Treatise on Febrile Diseases". The basic and clinical research of Lianhua Qingwen Prescription [14] was conducted by Nanshan Zhong has been published successively in international authoritative journals which strongly prove that this prescription has important clinical value for the treatment of COVID-19 [15].

Chinese medicine compound is characterized by the multi-component and multi-target which can regulate the organism as a whole. Network pharmacology is an effective method to study the mechanism of action of the compound. Based on network pharmacology, the purpose of this study is to predict the potential active components and mechanism of action of Lianhua Qingwen Prescription against SARS-CoV-2 to provide theoretical support for its wider application.

# 2. Materials and methods

## 2.1. Databases

The applied databases included Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP [16], http://tcmspw.com/tcmsp.php), SwissTargetPrediction (http://www.swisstargetprediction.ch), Similarity Ensemble Approach (SEA, http://sea.bkslab.org), UniProt [17], Universal Protein (http://www.uniprot.org/), STRING [18] (https://string-db.org), The Database for Annotation, Visualization and Integrated Discovery (DAVID [19], https://david.ncifcrf.gov), GeneCards [20] (http://www.genecards.org), Comparative Toxicogenomics Database (CTD [21], http://ctd.mdibl.org), and Therapeutic Target Database (TTD [22], http://bidd.nus.edu.sg/group/ttd/ttd.asp).

## 2.2. Acquisition of potential targets

Potential Lianhua Qingwen Prescription targets were searched through the online databases TCMSP, SEA, and SwissTargetPrediction database, using "Honeysuckle", "Forsythia", "Plaster", "Ephedra", "Bitter almonds", "Radix isatidis", "Cyrtomium fortunei", "Houttuynia cordata", "Patchouli", "Rheum officinale", "Rhodiola", "Menthol", and "Licorice" as the index words. Molecular targets of

**Table 1.** Basic information on Chinese medicine.

| Chinese medicine | Number of ingredients | Number of targets |
|---|---|---|
| Forsythia | 23 | 198 |
| Honeysuckle | 23 | 188 |
| Ephedra | 23 | 198 |
| Bitter almonds | 19 | 63 |
| Radix isatidis | 39 | 72 |
| Cyrtomium fortunei | 7 | 67 |
| Houttuynia cordata | 7 | 149 |
| Patchouli | 11 | 154 |
| Rheum officinale | 16 | 55 |
| Rhodiola | 2 | 146 |
| Menthol | 1 | 7 |
| Licorice | 92 | 199 |

SARS-CoV-2 were determined using "COVID-19" as the index word by searching the database of CTD, TTD, and GeneCards Suite. This search was conducted on 2 July 2020 then the results were pooled by deleting duplicated data.

## 2.3. Acquisition of shared targets

The shared targets for drugs and diseases were intersected via using the VennDiagram package of R software (Version 3.6.1) [23]. And they were considered as potential targets of the treatment of COVID-19 by Lianhua Qingwen Prescription.

## 2.4. Determination of PPIs

The shared targets thus obtained were imported into the STRING database, with the reference species set as Homo sapiens. Dissociative targets were deleted, and the minimum confidence was set to 0.4. The results were imported into Cytoscape software to determine Protein-Protein Interactions (PPIs).

## 2.5. GO and KEGG pathway enrichment analysis

Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were performed to understand the biological functions of the targets determined herein, with reference to the DAVID database. GO generally has three ontologies: molecular function (MF), cellular component (CC), and biological process (BP). Every gene is subjected to several aspects of definition and description. The potential mechanism underlying the effect of Lianhua Qingwen Prescription for COVID-19 treatment was determined through KEGG pathway enrichment analysis.

## 2.6. Construction of network diagram

PPIs and the results of KEGG pathway enrichment analysis were inputted in Cytoscape software to generate a PPI network and a "Drug-Ingredients-Target-Disease" network, followed by topology analysis.
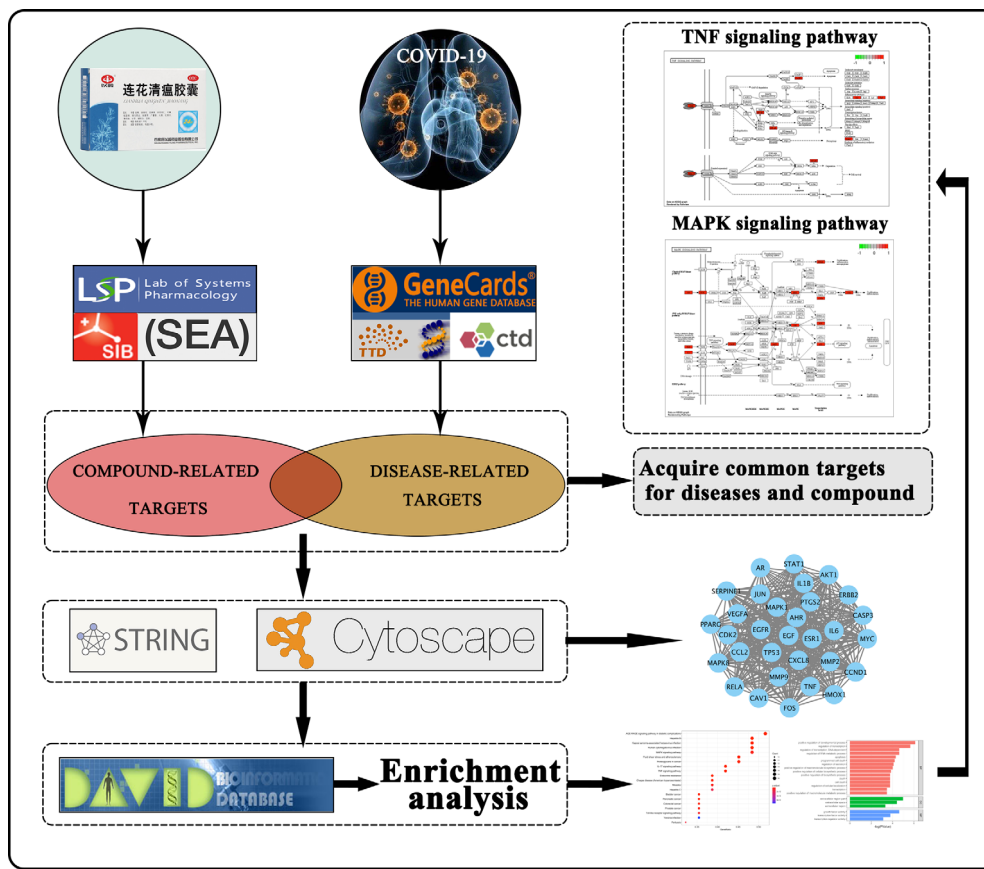
**Figure 1.** Detailed design and workflow of the present study.

# 3. Results

## 3.1. Potential targets of Lianhua Qingwen Prescription

Set oral bioavailability (OB) $\geq$ 30% and drug-likeness (DL) $\geq$ 0.18 [24] in the TCMSP database, and combined the literature data to screen the active ingredients in Lianhua Qingwen Prescription. A total of 224 chemical components were obtained. Integrating the TCMSP, SEA, and SwissTargetPrediction databases, a total of 246 potential drug targets were obtained after deduplication (Tab. 1).

## 3.2. Pathological and pharmacotherapeutic shared targets

After database screening, a total of 246 related targets of Lianhua Qingwen Prescription were obtained, including 208 in monarch medicine, 213 in minister medicines, 189 in assistant medicines, 199 in guide medicine, 16,611 related targets of COVID-19. Map the potential targets of Lianhua Qingwen Prescription to COVID-19 related targets, obtain 163 shared targets, and make a Venn diagram (Fig. 2).

## 3.3. Network diagram drawing

Cytoscape software was used to produce the "drug-component-target-disease" network diagram (Fig. 3) with
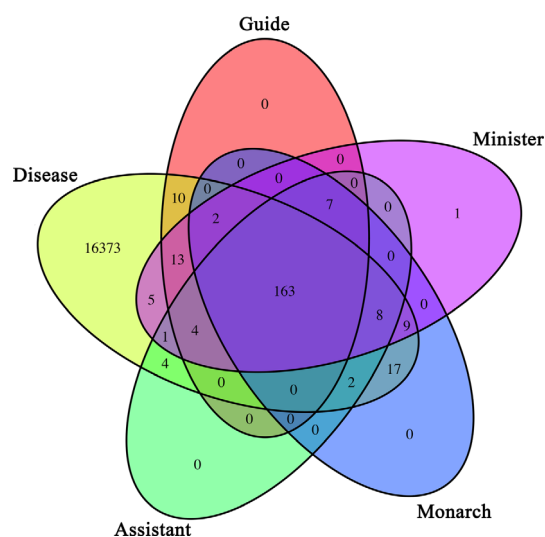


**Figure 2.** Intersecting target of disease and drug.

a total of 360 nodes, including 163 shared targets and 185 active components in Lianhua Qingwen Prescription. Topology analysis showed that the network density was 0.039, network heterogeneity was 1.587, and network center
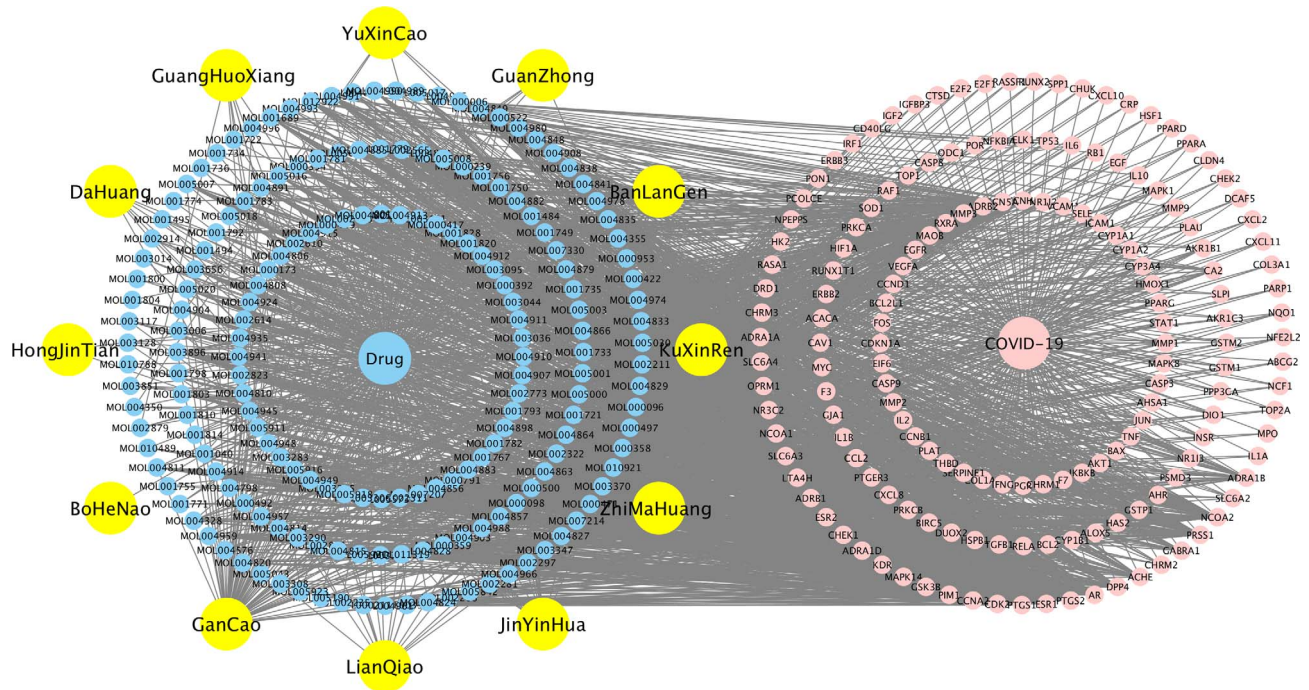
**Figure 3.** "Drug-ingredients-target-disease" network diagram. *Note.* The yellow node represents the drug, the blue node represents the active ingredient, and the pink node represents the target.

aggregation was 0.474. The active component with the highest degree value was quercetin (degree: 273), followed by kaempferol (degree: 107). It can be seen from the above that quercetin and kaempferol are the main compounds that can resist COVID-19.

### 3.4. Core target screening

The degree represents the importance degree of the node, and the betweenness centrality represents the core level of the node in the disease, both of which are important indicators to describe the node. The 163 shared targets obtained were imported into the String online analysis platform to make a PPI graph, and then topology analysis was carried out. The nodes with both the degree value and the betweenness centrality greater than their mean values were taken as core targets (Fig. 4). The results showed that a total of 31 key targets were selected (Tab. 2).

### 3.5. Enrichment analysis

Enrichment analysis was performed on the core targets selected in 2.4. GO enrichment analysis (BP: 15, CC: 3, MF: 3) showed that the role of Lianhua Qingwen Prescription involved T-cell activation, virus receptor, inflammatory response, nucleic acid metabolic process, and protein transcription and translation (Fig. 5). KEGG results showed a total of 140 signaling pathways, and the first 20 were listed according to *p*-values. As shown in Figure 6, the IL-17 signaling pathway (Fig. 7A), the TNF signaling pathway (Fig. 7B), and the MAPK signaling pathway

(Fig. 7C) were most closely related to virus infection. The relationship between these signaling pathways and the selected core targets in 2.4 was shown in Figure 7D.

## 4. Discussion

In the past 20 years, coronavirus has caused three major epidemics of COVID-19, SARS, and MERS, endangering human health [25]. These acute infectious diseases can be classified into the category of epidemic diseases of traditional Chinese medicine. The location of the disease is in the lung. The main pathological factor is dampness, which can enter into the interior to generate heat. Lianhua Qingwen Prescription is approved for the treatment of fever, cough, and fatigue caused by light and common type of COVID-19 [14].

Modern pharmacological studies have shown that Lianhua Qingwen Prescription, as a traditional Chinese medicine prescription, has extensive antiviral and immunomodulatory effects on a series of influenza viruses. Nanshan Zhong has found that the prescription can significantly inhibit the replication of SARS-CoV-2, affected the virus form, and exerted anti-inflammatory activity in vitro. Lianhua Qingwen Prescription can significantly inhibit the replication of SARS-CoV-2 in E6 cells at mRNA level in vero, and reduce the production of proinflammatory cytokines (TNF-α, IL-6, CCL-2/MCP-1, and CXCL-10/ IP-10) [15]. In addition, a multi-centered randomized controlled trial, conducted by Nanshan Zhong, Lanjuan Li, Boli Zhang contains 284 cases. After 14 days of treatment, the
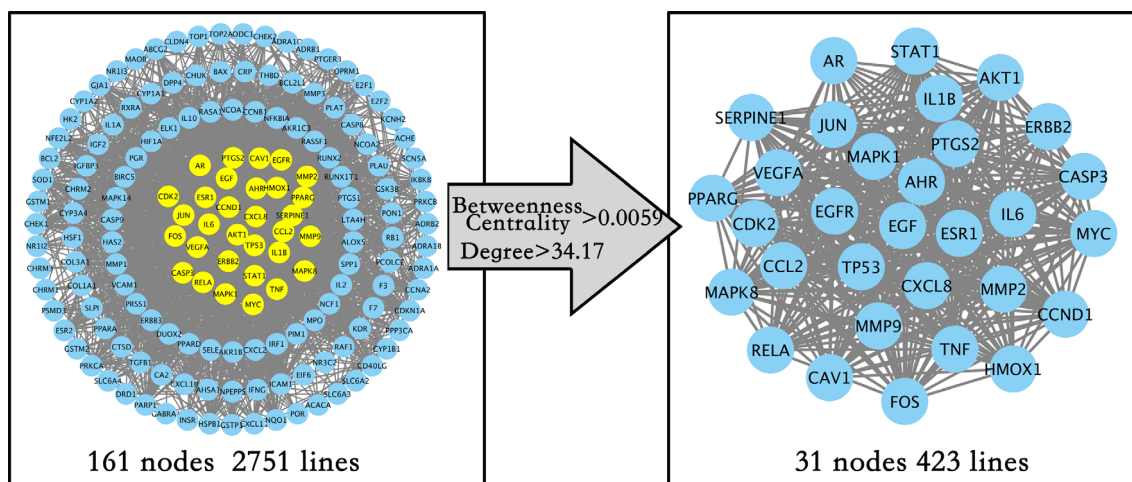
**Figure 4.** Core target screening process.

**Table 2.** The information of core targets.

| Gene symbol | Gene name | Uniprot ID |
|---|---|---|
| AR | Androgen receptor | P10275 |
| AHR | Aryl hydrocarbon receptor | P35869 |
| CASP3 | Caspase 3, apoptosis-related cysteine peptidase | P42574 |
| CAV1 | Caveolin 1, caveolae protein, 22kDa | Q03135 |
| CCL2 | Chemokine (C-C motif) ligand 2 | P13500 |
| CCND1 | Cyclin D1 | P24385 |
| CDK2 | Cyclin-dependent kinase 2 | P24941 |
| EGF | Epidermal growth factor (beta-urogastrone) | p01133 |
| EGFR | Epidermal growth factor receptor (erythroblastic leukemia viral (v-erb-b) Oncogene homolog, avian) | p00533 |
| ESR1 | Estrogen receptor 1 | P03372 |
| HMOX1 | Heme oxygenase (decycling) 1 | P09601 |
| IL1B | Interleukin 1, beta | P01584 |
| IL6 | Interleukin 6 (interferon, beta 2) | P05231 |
| JUN | Jun oncogene | P05412 |
| MMP2 | Matrix metallopeptidase 2 (gelatinase A, 72kDa gelatinase, 72kDa type IV Collagenase) | P08253 |
| MMP9 | Matrix metallopeptidase 9 (gelatinase B, 92kDa gelatinase, 92kDa type IV Collagenase) | P14780 |
| MAPK1 | Mitogen-activated protein kinase 1 | P28482 |
| MAPK8 | Mitogen-activated protein kinase 8 | P45983 |
| PPARG | Peroxisome proliferator-activated receptor gamma | P37231 |
| PTGS2 | Prostaglandin-endoperoxide synthase 2 (prostaglandin G/H synthase and Cyclooxygenase) | P35354 |
| SERPINE1 | Serpin peptidase inhibitor, clade E (nexin, plasminogen activator Inhibitor type 1), member 1 | P05121 |
| STAT1 | Signal transducer and activator of transcription 1, 91kDa | P42224 |
| TNF | Tumor necrosis factor (TNF superfamily, member 2) | P01375 |
| TP53 | Tumor protein p53 | P04637 |
| AKT1 | V-akt murine thymoma viral oncogene homolog 1 | P31749 |
| ERBB2 | V-erb-b2 erythroblastic leukemia viral oncogene homolog 2, neuro/glioblastoma derived oncogene homolog (avian) | P04626 |
| FOS | V-fos FBJ murine osteosarcoma viral oncogene homolog | P01100 |
| MYC | V-myc myelocytomatosis viral oncogene homolog (avian) | P01106 |
| RELA | V-rel reticuloendotheliosis viral oncogene homolog A (avian) | Q04206 |
| VEGFA | Vascular endothelial growth factor A | P15692 |
| CXCL8 | Interleukin-8 | P10145 |

recovery rate of the Lianhua Qingwen Prescription treatment group is 91.5%, which is significantly higher than the control group (82.4%) [14]. Conventional treatment assisting the Lianhua Qingwen Prescription can significantly improve clinical symptoms, lung imaging, and shorten the duration.

According to the results of enrichment analysis, Lianhua Qingwen Prescription treats COVID-19 mainly through the
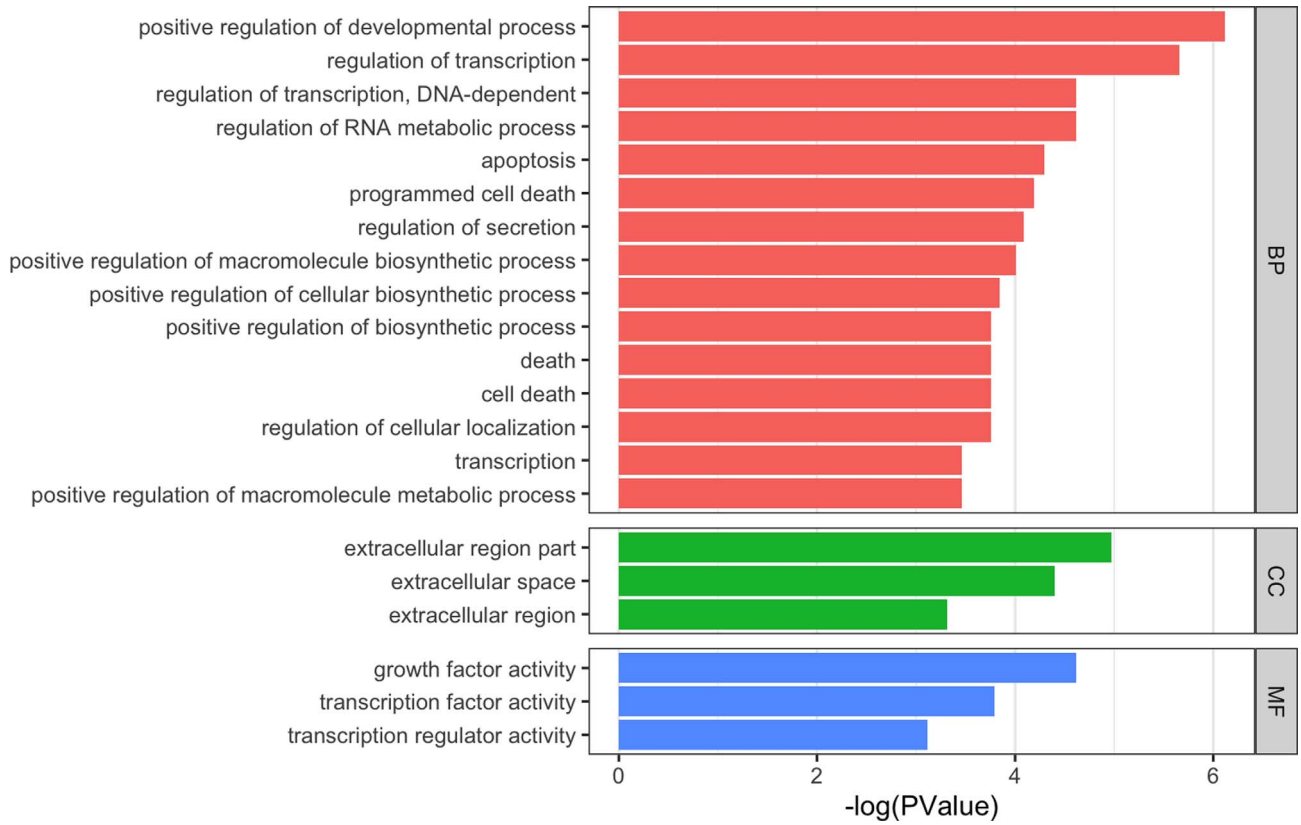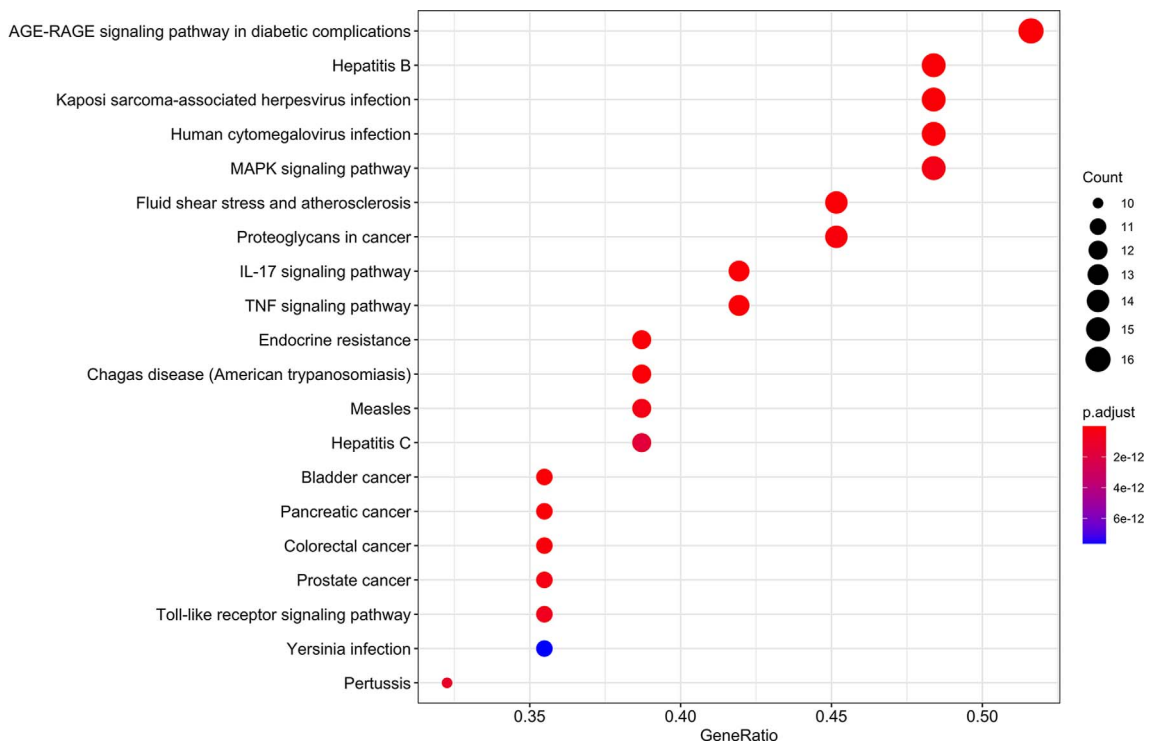
**Figure 5.** The results of GO enrichment analysis.



**Figure 6.** The results of KEGG enrichment analysis.
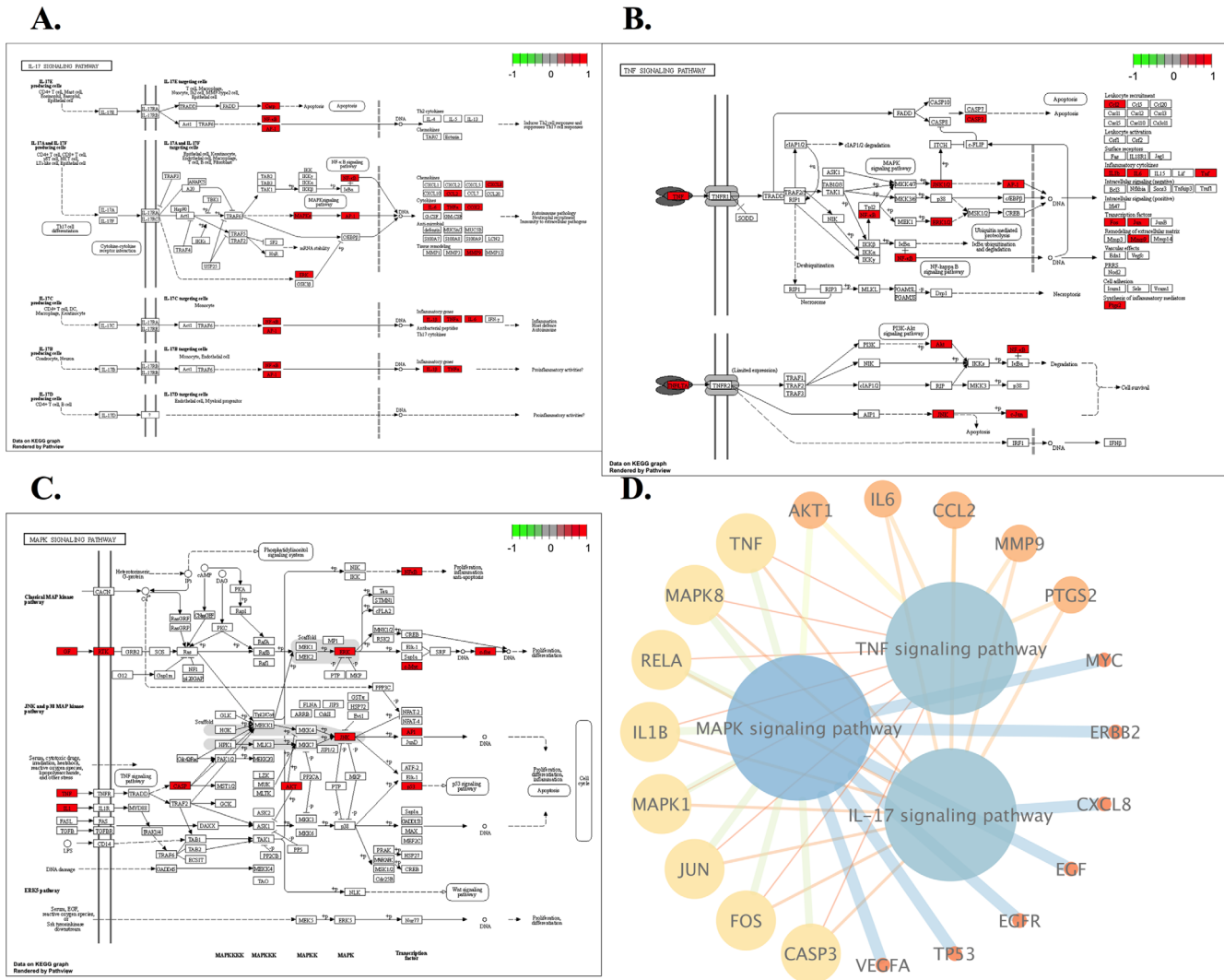
**A.**



**B.**



**C.**



**D.**



**Figure 7.** Key signaling pathway. *Abbreviations.* A: IL-17 signaling pathway; B: TNF signaling pathway; C: MAPK signaling pathway; D: Relationship between key signaling pathways and targets

IL-17 signaling pathway, TNF signaling pathway, and MAPK signaling pathway. The most important targets include IL-6, TNF-α, CASP3, and NF-κB (p65 subunit). Wei Wang et al. found that a purified recombinant S protein was used to stimulate mouse macrophages (RAW264.7) to produce pro-inflammatory cytokines (IL-6 and TNF-α) and further experiments confirmed that the production of IL-6 and TNF-α depend on nuclear factor kappa B (NF-κB) [26]. It can be seen from Figure 7A that the activation of NF-κB will impact IL-6 and TNF-α in downstream which can regulate virus replication and inflammation in cells. When SARS-CoV-2 infects respiratory tract, it can cause an acute respiratory syndrome and then release pro-inflammatory factors, including IL-1β and IL-6. Most front-line clinical experts believe that the patients with COVID-19 develop ARDS rapidly which may be associated with a "cytokine storm". During cytokine storms, the virus that has infected the body rapidly activates T cells and generates GM-CSF and IL-6 which will lead to excessive inflammation response, block the gas exchange between alveoli and capillaries, and cause ARDS and multiple organ failure [27]. The main substrate of CASP3 is PARP, which is related to DNA repair and gene integrity monitoring. At the initiation of apoptosis, PARP was cleaved into two fragments by CASP3 between the two sites of asp216 and gly217, which change the spatial structure of PARP that binds to DNA [28-30].

## 5. Conclusions

In this study, network pharmacology technology was used to preliminarily explore the potential material basis of Lianhua Qingwen Prescription for the treatment of COVID-19. Through the above study, it was found that the prescription could treat COVID-19 by targeting IL-6, TNF-α, CASP3, and NF-κ B in IL-17 signaling pathway, TNF signaling pathway, and MAPK signaling pathway.

However, the effective components and targets of Lianhua Qingwen Prescription were only retrieved from the existing database, without considering the factors such as drug origin, processing, and dosage. The results of this study need to be further verified by basic experiments.

## Authors' contributions

Conceptualization, Z.X.M. and H.H.L.; methodology, P.W.P. and H.D.; software, X.Y.; formal analysis, H.D. and F.F.C.; investigation, Z.Z.C. and G.C.; resources, P.W.P. and X.Y.; data curation, P.W.P.; writing-original draft preparation, P.W.P and X.Y.; writing-review and editing, Z.X.M.; supervision, X.Y.; project administration, P.W.P.; funding acquisition, Z.X.M. All authors have read and agreed to the published version of the manuscript.

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## Conflict of interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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