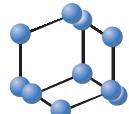


## RESEARCH ARTICLE

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# Research on the Mechanism of Traditional Chinese Medicine Treatment for Diseases caused by Human Coronavirus COVID-19



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**Abstract:** **Background:** Human coronaviruses are a large group of viruses that exist widely in nature and multiply through self-replication. Due to its suddenness and variability, it poses a great threat to global human health and is a major problem currently faced by the medical and health fields.

**Objective:** COVID-19 is the seventh known coronavirus that can infect humans. The main purpose of this paper is to analyze the effective components and action targets of the Longyi Zhengqi formula and Lianhua Qingwen formula, study their mechanism of action in the treatment of new coronavirus pneumonia (new coronavirus pneumonia), compare the similarities and differences of their pharmacological effects, and obtain the pharmacodynamic mechanism of the two traditional Chinese medicine compounds.

**Methods:** Obtain the effective ingredients and targets of Longyi-Zhengqi Formula and Lianhua-Qingwen Formula from ETCM (Encyclopedia of Traditional Chinese Medicine) and other traditional Chinese medicine databases, use GeneCards database to obtain the relevant targets of COVID-19, and use Cytoscape software to build the component COVID-19 target network of Longyi-Zhengqi Formula and the component COVID-19 target network of Lianhua-Qingwen Formula. STRING was used to construct a protein interaction network and screen key targets. GO (Gene Ontology) was used for enrichment analysis and KEGG (Kyoto Encyclopedia of Genes and Genomes) was used for pathways to find out the targets and pathways related to the treatment of COVID-19.

**Results:** In the GO enrichment analysis results, there are 106 biological processes, 31 cell localization and 28 molecular functions of the intersection PPI network targets of Longyi-Zhengqi Formula-COVID-19, 224 biological processes, 51 cell localization and 55 molecular functions of the intersection PPI network targets of Lianhua-Qingwen Formula-COVID-19. In the KEGG pathway analysis results, the number of targets of Longyi-Zhengqi Formula on the COVID-19 pathway is 7, and the number of targets of Lianhua-Qingwen Formula on the COVID-19 pathway is 19; In the regulation analysis results, Longyi-Zhengqi Formula achieves the effect of treating COVID-19 by regulating IL-6, and Lianhua-Qingwen Formula achieves the effect of treating pneumonia by regulating TLR4.

**Conclusion:** This paper explores the mechanism of action of Longyi-Zhengqi Formula and Lianhua-Qingwen Formula in treating COVID-19 based on the method of network pharmacology, and provides a theoretical basis for traditional Chinese medicine to treat sudden diseases caused by human coronavirus in terms of drug targets and disease interactions. It has certain practical significance.

**Keywords:** Target network, PPI network, GO enrichment analysis, KEGG pathway analysis, human coronavirus, traditional chinese medicine.

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## 1. INTRODUCTION

Coronaviruses are a large group of viruses that exist widely in nature and multiply through self-replication [1-5]. In 1965, Tyrrell and Bynoe first cultivated coronaviruses using the ciliated tracheal tissue of embryos. This virus has a coronal-like outer ring visible under electron microscopy, hence the name Coronaviridae [6]. There are currently three known highly pathogenic human coronaviruses: severe acute respiratory syndrome coronavirus(SARS-CoV) [7-9], Middle East respiratory syndrome coronavirus(MERS-CoV) [10-12], and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [13, 14], due to its suddenness and variability, poses a great threat to global human health and is a major problem currently facing the medical and health field.

The treatment of diseases caused by human coronavirus is like the treatment of general diseases. It is mainly divided into two strategies: Western medicine and traditional Chinese medicine. The study found that among the 80 autophagy-related compounds tested, the use of Western medicine treatment with cycloheximide and thapsigargin reduced the infection efficiency of SARS-CoV-2 in a dose-dependent manner [15]. Cycloheximide treatment not only reduced the infection efficiency of six SARS-CoV-2 variant strains but also reduced the infection efficiency of human coronavirus (HCoV)-229E and HCoV-OC43. However, even low-dose ( $1\mu\text{M}$ ) cycloheximide treatment can alter the expression profile of ribosomal RNA, which can lead to side effects such as inhibition of protein synthesis in host cells. Therefore, Western medicine treatment may not necessarily achieve the best results. Domingo-Fernández *et al.* systematically analyzed ethnobotanical patterns across taxonomically related plants, demonstrating that congeneric medicinal plants are more likely to be used for treating similar indications [16]. Traditional Chinese medicine has its unique advantages and potential applications for addressing the challenges posed by future novel viruses and pandemics. Chen *et al.* summarized "Three medicines and three formulas in COVID-19: From bench to bedside." The current article offers an in-depth analysis of TMTF's application in COVID-19 treatment and direction for the use of these herbs at various stages of the illness while also highlighting the advantages of polypharmacology for the treatment of complex diseases such as COVID-19 [17]. In summary, the uniqueness of traditional Chinese medicine lies in its distinct concepts of disease diagnosis and treatment, and its flexibility and practicality when confronted with unknown diseases. These aspects indicate the potential for TCM to play an even more significant role in future epidemic control and prevention, as well as in the development of new drugs [18].

The pneumonia caused by the COVID-19 (coronavirus disease 2019) outbreak in 2019 is highly contagious and has a high mortality rate. It has spread to all parts of the world and caused huge losses to all humanity. This is an unprecedented public health crisis [19]. Since the "Diagnosis and Treatment Plan for Pneumonia Infected by Novel Coronavirus (Trial Third Edition)," traditional Chinese medicine treatment has been included in the treatment plan. Traditional Chinese medi-

cine has participated in the prevention and treatment of new coronavirus pneumonia throughout the entire process, giving full play to the unique advantages of syndrome differentiation and multi-target intervention. It has become an important means of treating patients with COVID-19 [20].

In this article, the active ingredients and targets of Longyi-Zhengqi Formula and Lianhua-Qingwen Formula were obtained from traditional Chinese medicine databases such as ETCM and INPUT, and related targets of COVID-19 were obtained from the GeneCards database. Cytoscape software was used to construct the COVID-19 target network of the Longyi-Zhengqi Formula and Lianhua-Qingwen Formula. Protein interaction networks were constructed using STRING and key targets were screened using the CytoHubba plugin of Cytoscape software. The DAVID database was used for GO enrichment analysis and KEGG pathway enrichment analysis, and finally, the targets of the two were mapped to the COVID-19 pathway. Through the pathway analysis, the number of Longyi-Zhengqi Formula and Lianhua-Qingwen Formula in the treatment of COVID-19 was obtained; through the regulation analysis, the differences between the two in the treatment of COVID-19 were obtained, and the similarities and differences in the pharmacological effects of these two traditional Chinese medicine compounds were explored.

## 2. MATERIALS AND METHOD

### 2.1. Screening of Components and Targets in Longyi-Zhengqi Formula

Longyi-Zhengqi Formula was proposed by Dr. Wu Yingen, the head of the expert group for the prevention and control of new coronary pneumonia in traditional Chinese medicine in Shanghai in 2022. It consists of five traditional Chinese medicines: Licorice, Honeysuckle Flower, Forsythia, Patchouli, and Atractylodes macrocephala. The effect of dissipating dampness, invigorating the spleen, and supplementing qi, strengthening vital energy, and eliminating pathogenic factors [21].

Among them, Licorice has antioxidant [22], anti-inflammatory [23], antitussic and expectorant [24], antiulcerative [25], antiviral [26] and other effects; Honeysuckle Flower has anti-inflammatory [27], antibiosis [28], antiviral [29] and other effects; Forsythia has antibacterial [30], anti-inflammatory [31], anticancer [32], hepatoprotective [33] and other effects; Patchouli has anti-peptic ulcer [34], anti-inflammatory [35], anti-oxidative [36], analgesic [37] and other effects; Atractylodes macrocephala has invigoration of the spleen [38], diuretic [39], antitumor [40], anti-inflammatory [41] and other effects.

In the ETCM database [42] (<http://www.tcmip.cn/ETCM/>), "gancao", "yinhua", "lianqiao", "huoxiang", "baizhu" were used as keywords to retrieve the active ingredients in Longyi-Zhengqi Formula, and the Druglikeness Grading were higher than weak as the Screening conditions to screen out the active ingredients of Longyi-Zhengqi Formula and the target of the ingredients.

## 2.2. Screening of Components and Targets in Lianhua-Qingwen Formula

Lianhua-Qingwen Formula once played a therapeutic role equivalent to oseltamivir phosphate in the treatment of influenza and H1N1. In February 2020, it was included in the "Guidelines for the diagnosis and treatment of novel coronavirus pneumonia (trial version sixth)" of the National Health Commission. It is composed of 13 traditional Chinese medicines: Forsythia, Honeysuckle Flower, Ephedra, Apricot kernel, Gypsum, Root of Dyers Woad, Male Fern Rhizome, Houttuynia cordata, Patchouli, Chinese rhubarb, Rhodiola, menthol, Licorice. It has the effect of clearing heat and removing toxicity, propagating the lung, and releasing heat. Through the clinical application of China Resources WISCo General Hospital, Wuhan Ninth Hospital, and China Resources WISCo General Hospital affiliated with Wuhan University of Science and Technology in the treatment of COVID-19, it has been found that Lianhua-Qingwen Formula can significantly improve fever, cough, phlegm, shortness of breath and other clinical symptoms of ordinary patients diagnosed with COVID-19, relieve the disease and shorten the duration of the disease [43, 44].

Among them, Apricot kernel has antihypertensive [45], immunomodulatory [46], anti-inflammatory [47], antimicrobial [48] and other effects; Root of Dyers Woad has anti-inflammatory [49], anti-tumor [50], antioxidant [51] and other effects; Rhodiola has antioxidant [52], antidepressant [53], anticancer [54], hepatoprotective [55], regulate blood sugar [56] and other effects; Chinese rhubarb has purgative [57], promoting blood circulation and hemostasis [58], hypolipidemic [59], kidney protection [60], antipyretic [61], anti-inflammatory [62], anti-fibrosis [63] and other effects.

In the ETCM database, with the keywords "mahuang", "kuxingren", "banlangen", "yuxingcao", "dahuang", "hongjingtiangan" as the keywords, the ingredients of 6 Chinese herbs in Lianhua-Qingwen Formula were retrieved, combined with the data of Forsythia, Honeysuckle Flower, Patchouli, Licorice in Longyi-Zhengqi Formula, a total of 10 Chinese herbs were collected. The effective components and potential targets of these 10 herbal medicines were screened with the Druglikeness Grading being higher than weak. In the INPUT database [64] (<http://cbcb.cdu.edu.cn/INPUT/Home/>), menthol components and their corresponding targets were retrieved with the keyword "menthol".

## 2.3. Target Acquisition and Screening for COVID-19

In the GeneCards database [65] (<https://www.genecards.org>), "COVID-19", "novel coronavirus pneumonia" and "SARS-CoV-2" were used as keywords to search, and the three search results were screened and integrated with a Relevance score greater than or equal to 5. Removing duplicates gives us a potential target for COVID-19 [66].

## 2.4. Target Network

Cytoscape [67] was used to construct the Longyi-Zhengqi Formula - COVID-19 target NetWork and the

Lianhua-Qingwen Formula - COVID-19 target network. Topology analysis was carried out using the Cytoscape Analyze Network tool, and components with high connectivity were screened out.

## 2.5. PPI NetWork

Import Longyi-Zhengqi Formula - COVID-19 Intersection Target and Lianhua-Qingwen Formula - COVID-19 Intersection Target into STRING database [68] (<https://cn.string-db.org/>) respectively, constructing Longyi-Zhengqi Formula - COVID-19 Intersection PPI Network and Lianhua-Qingwen Formula - COVID-19 Intersection PPI Network, import these two networks into Cytoscape, and use the CytoHubba plugin of Cytoscape to screen out key targets.

## 2.6. Enrichment Analysis

Using DAVID [69, 70] (<https://david.ncifcrf.gov/>), GO (gene ontology) enrichment analysis and KEGG (Kyoto Encyclopedia of Genes and Genomes) pathway enrichment analysis were performed on the targets in the Longyi-Zhengqi Formula - COVID-19 intersection PPI network and Lianhua-Qingwen Formula - COVID-19 intersection PPI network respectively. GO (Gene Ontology, A tool for describing the roles of genes and gene products in any organism) enrichment analysis included Biological Process (BP, refers to a biological objective to which the gene or gene product contributes), Cellular Component (CC, refers to the place in the cell where a gene product is active) and Molecular Function (MF, is defined as the biochemical activity). The data filtering used here is mainly based on the method described in reference [71], which screens the top 10 genes ranked by the number of GO enrichment entries.

## 2.7. COVID-19 Pathway Mapping

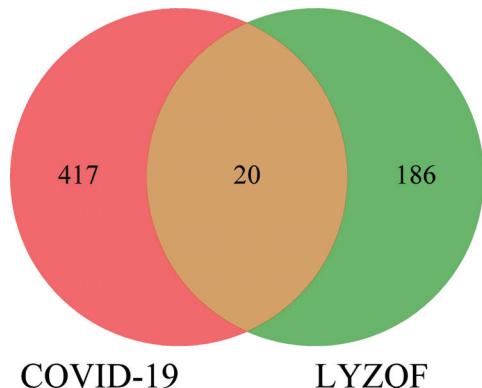
The targets in the PPI network of Longyi-Zhengqi Formula - COVID-19 Intersection and the targets in the PPI Network of Lianhua-Qingwen Formula - COVID-19 Intersection were imported into the KEGG PATHWAY database [72-74] (<https://www.genome.jp/kegg/pathway.html>). Find the COVID-19 pathway in the query results: hsa05171 Coronavirus disease - COVID-19, and view the mapping of these targets in the COVID-19 pathway; the results might change depending on which one they chose.

## 3. RESULTS AND DISCUSSION

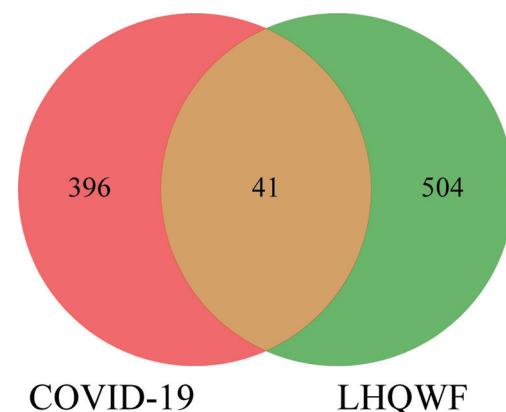
### 3.1. Data Filtering

In the ETCM database, 63 active ingredients of Longyi-Zhengqi Formula were screened and 206 predicted targets were selected based on the condition that the Druglikeness Grading was greater than weak. In addition, 109 active ingredients of Lianhua-Qingwen Formula were screened, and 545 predicted targets were selected based on the cooperation with the INPUT database. In the GeneCards database, "COVID-19", "novel coronavirus pneumonia" and "SARS-

CoV-2" were used as keywords to search, and the three search results were screened and integrated with a Relevance score greater than or equal to 5. After removing duplications, 437 potential targets of COVID-19 were obtained, including 20 intersection targets with the Longyi-Zhengqi Formula and 41 with the Lianhua-Qingwen Formula, as shown in Figs. (1 and 2).



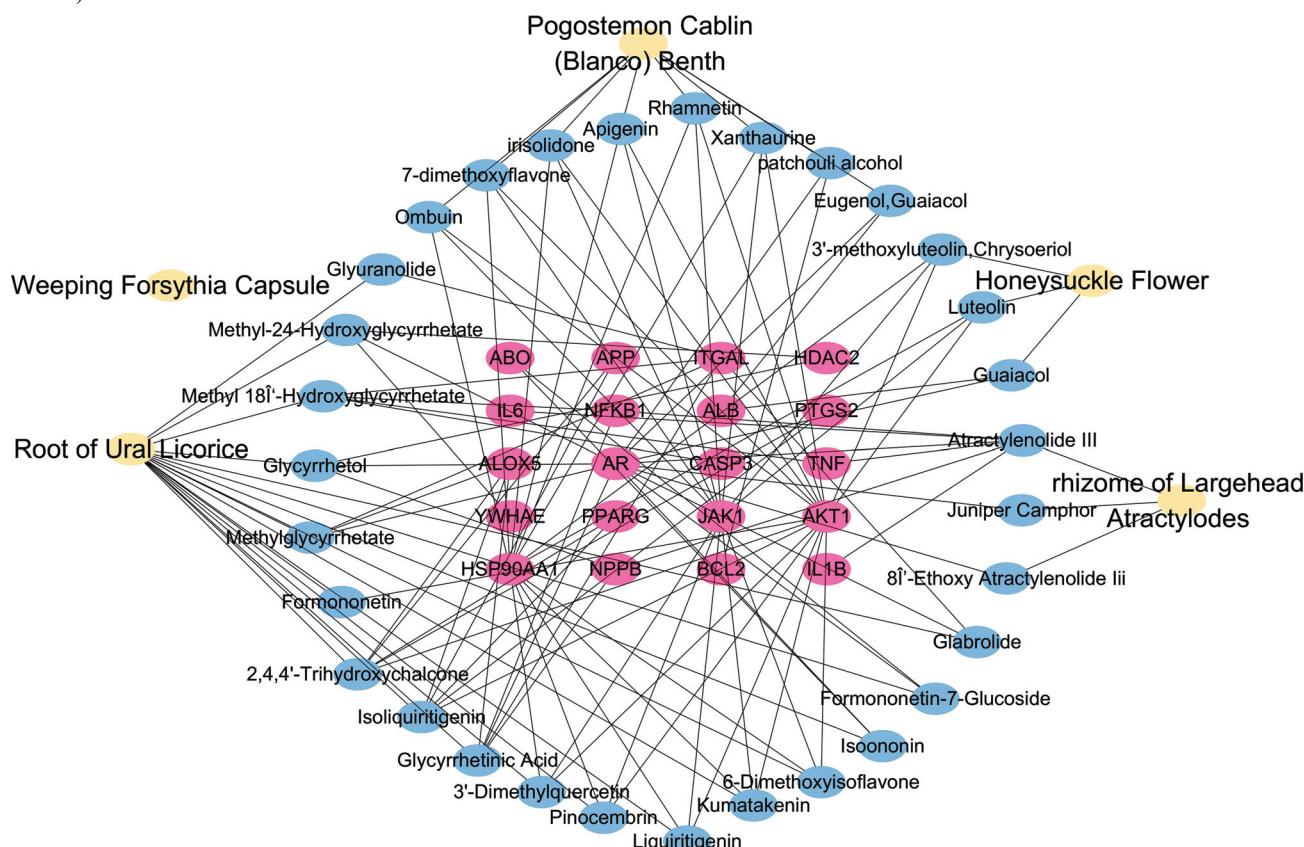
**Fig. (1).** Venn diagram of Longyi-Zhengqi Formula (LYZQF) for COVID-19. The red part represents the target of COVID-19, the green part represents the target of the compound in Longyi-Zhengqi Formula, and the orange part represents the common target of COVID-19 and Longyi-Zhengqi Formula. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).



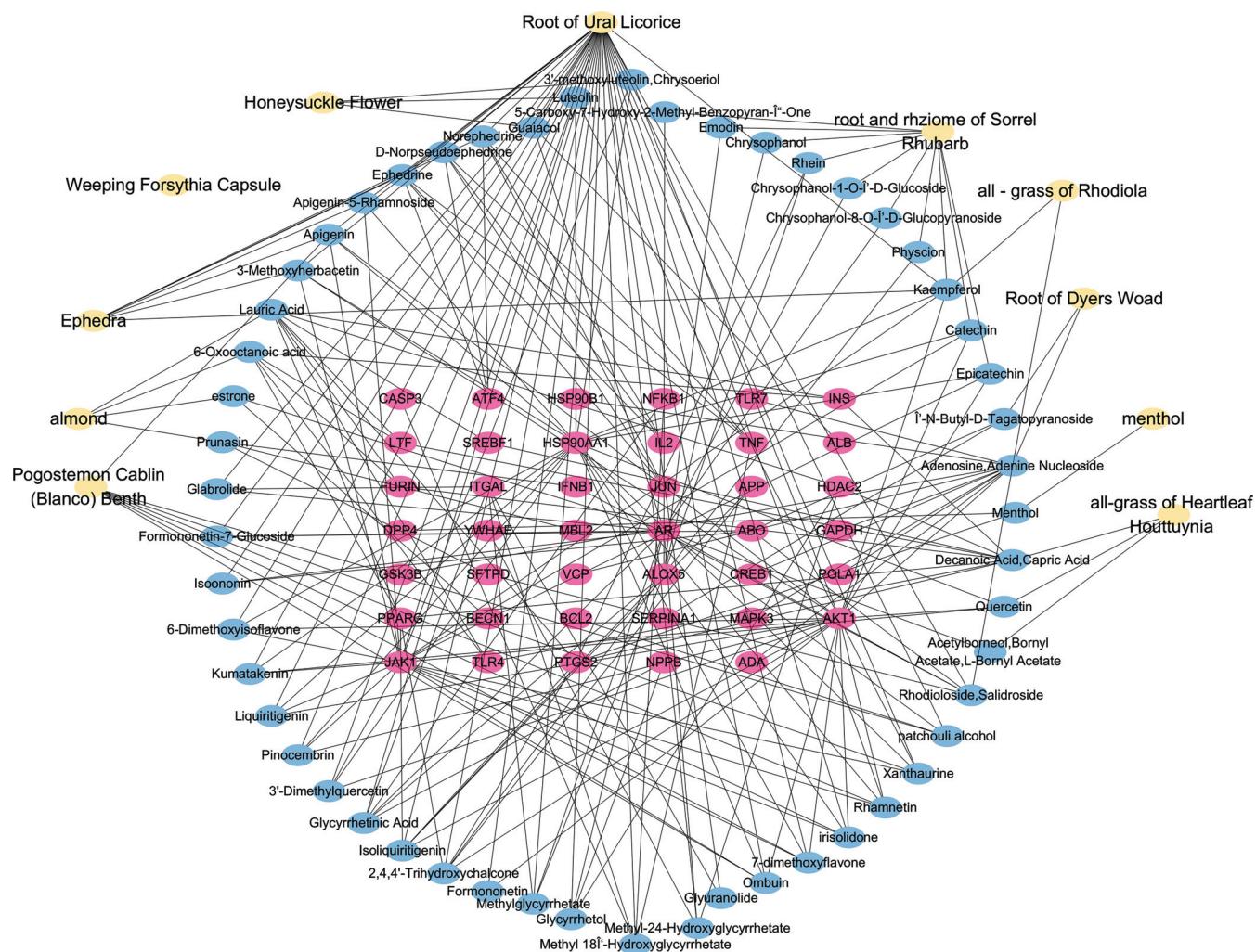
**Fig. (2).** Venn diagram of Lianhua-Qingwen Formula(LHQWF) for COVID-19. The red part represents the target of COVID-19, the green part represents the target of the compound in Lianhua-Qingwen Formula, and the orange part represents the common target of COVID-19 and Lianhua-Qingwen Formula. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

### 3.2. Target Network

Cytoscape is used to construct Longyi-Zhengqi Formula - COVID-19 target network (Fig. 3) and Lianhua-Qingwen Formula - COVID-19 target network (Fig. 4), in which



**Fig. (3).** Components of Longyi-Zhengqi Formula - target network of COVID-19. The yellow nodes represent the components of Longyi-Zhengqi Formula, the blue nodes represent the effective compounds corresponding to Longyi-Zhengqi Formula, and the red nodes represent the common targets of Longyi-Zhengqi Formula and COVID-19. (A higher resolution / colour version of this figure is available in the electronic copy of the article).



**Fig. (4).** Components of Lianhua-Qingwen Formula - target network of COVID-19. The yellow nodes represent the components of Lianhua-Qingwen Formula, the blue nodes represent the effective compounds corresponding to Lianhua-Qingwen Formula, and the red nodes represent the common targets of Lianhua-Qingwen Formula and COVID-19. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

orange nodes represent drugs, blue nodes represent components, and pink nodes represent COVID-19 target.

Use the Analyze Network tool of Cytoscape to analyze the topology of the two networks and select the top five component nodes with the largest value of Degree (the connectivity of nodes, the higher the value is, the more important it is) as the key components. The key components of Longyi-Zhengqi Formula can be obtained as follows: Attractylolenolide III, Isoliquiritigenin, Glycyrrhetic Acid, Methyl 18 $\beta$ -Hydroxyglycyrrhetate and Luteolin. The key components of the Lianhua-Qingwen Formula are Adenine Nucleoside, Decanoic Acid, Lauric Acid, Kaempferol, Apigenin and Rhodioloside, as shown in Table 1.

### 3.3. PPI NetWork

Longyi-Zhengqi Formula - COVID-19 intersection target and Lianhua-Qingwen Formula - COVID-19 intersection target were respectively imported into the STRING database, and *Homo sapiens* was selected for species with a confi-

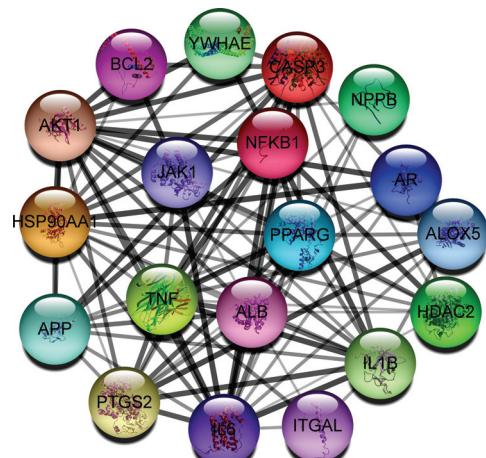
dence level of 0.4 to obtain the Longyi-Zhengqi Formula - COVID-19 intersection PPI network and Lianhua-Qingwen Formula - COVID-19 intersection PPI network. The PPI network of Longyi-Zhengqi Formula - COVID-19 intersection has 19 nodes and 99 edges, as shown in Fig. (5), and the PPI network of Lianhua-Qingwen Formula - COVID-19 intersection has 41 nodes and 319 edges, as shown in Fig. (6). These two networks were imported into Cytoscape, and 10 key targets were selected using Cytoscape's CytoHubba plug-in respectively. The key targets of the Longyi-Zhengqi Formula were as follows: AKT1, IL6, TNF, CASP3, IL1B, PPARG, PTGS2, APP, ALB, HSP90AA1, as shown in Fig. (7). The key targets of the Lianhua-Qingwen Formula are AKT1, GAPDH, JUN, CASP3, TNF, ALB, INS, TLR4, HSP90AA1, and PPARG, as shown in Fig. (8).

### 3.4. Enrichment Analysis

The targets of Longyi-Zhengqi Formula - COVID-19 intersection PPI network and Lianhua-Qingwen Formula -

**Table 1.** The key compounds of two formulas.

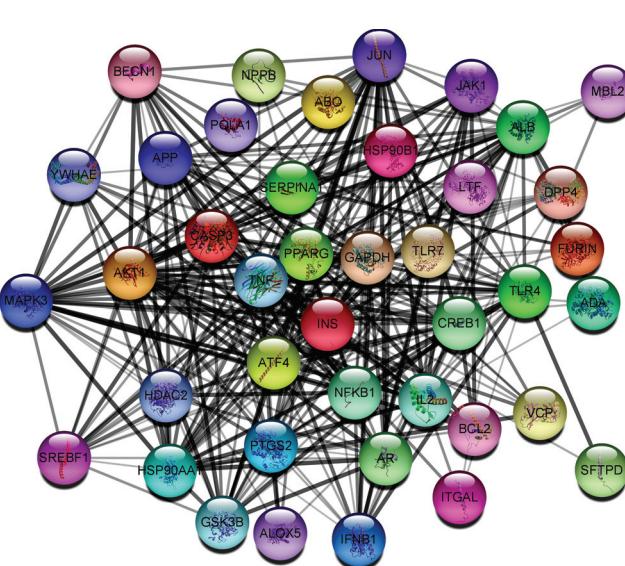
Formula	Components Name	Degree
Longyi-Zhengqi	Atractylenolide III	7
Longyi-Zhengqi	Isoliquiritigenin	6
Longyi-Zhengqi	Glycyrrhetic Acid	6
Longyi-Zhengqi	Methyl 18 $\beta$ -Hydroxyglycyrrhetate	5
Longyi-Zhengqi	Luteolin	4
Lianhua-Qingwen	Adenine Nucleoside	11
Lianhua-Qingwen	Decanoic Acid	9
Lianhua-Qingwen	Lauric Acid	9
Lianhua-Qingwen	Kaempferol	7
Lianhua-Qingwen	Rhodioloside	6



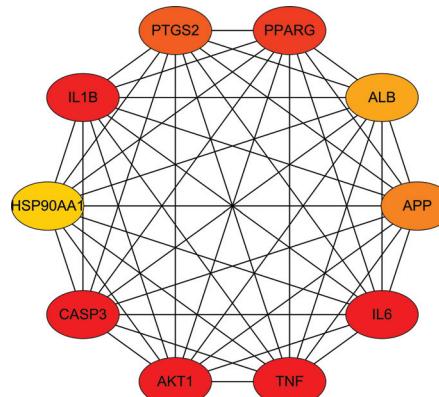
**Fig. (5).** PPI network diagram of Longyi-Zhengqi Formula and COVID-19 intersection. The nodes in the network represent the common target of Longyi-Zhengqi Formula and the novel coronavirus pneumonia. The lines of nodes represent the interaction of two proteins, the wider the connection of nodes in the network, the higher the score of the interaction between the two proteins. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

COVID-19 intersection PPI network were respectively imported into DAVID for GO enrichment analysis and KEGG pathway analysis, and the results were as follows: There were 81 KEGG pathways of Longyi-Zhengqi Formula - COVID-19 intersection PPI network targets. Among the GO analysis results, there were 185 biological processes, 21 cell compositions and 29 molecular functions. There were 127 KEGG pathways related to PPI network targets in Lianhua-Qingwen Formula- COVID-19 intersection. Among the GO analysis results, 270 were biological processes, 45 were cell composition, and 48 were molecular functions.

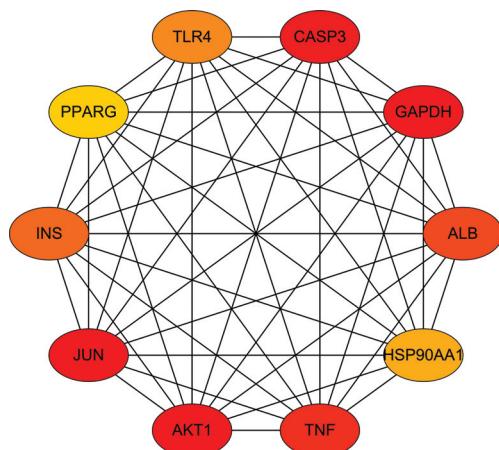
GO enrichment analysis of PPI network targets in the intersection of Longyi-Zhengqi Formula and COVID-19 is shown in Fig. (9). The horizontal axis represents enrichment items, the vertical axis represents quantity, the green bar graph represents Biological Process (BP), the Orange Bar Graph represents Cell Composition (CC), and the blue bar graph represents Molecular Function (MF). Fig. (9) shows that the biological processes mainly involved in PPI network targets of Longyi-Zhengqi Formula - COVID-19 intersection



**Fig. (6).** PPI network diagram of Lianhua-Qingwen Formula and COVID-19 intersection. The nodes in the network represent the common target of Lianhua-Qingwen Formula and the novel coronavirus pneumonia. The lines of nodes represent the interaction of two proteins, the wider the connection of nodes in the network, the higher the score of the interaction between the two proteins. (A higher resolution / colour version of this figure is available in the electronic copy of the article).



**Fig. (7).** PPI network diagram of the key target of Longyi-Zhengqi Formula. Each node represents a protein and the darker the node color, the higher the score, the stronger the significance, and the more critical it is in the entire PPI network. (A higher resolution / colour version of this figure is available in the electronic copy of the article).



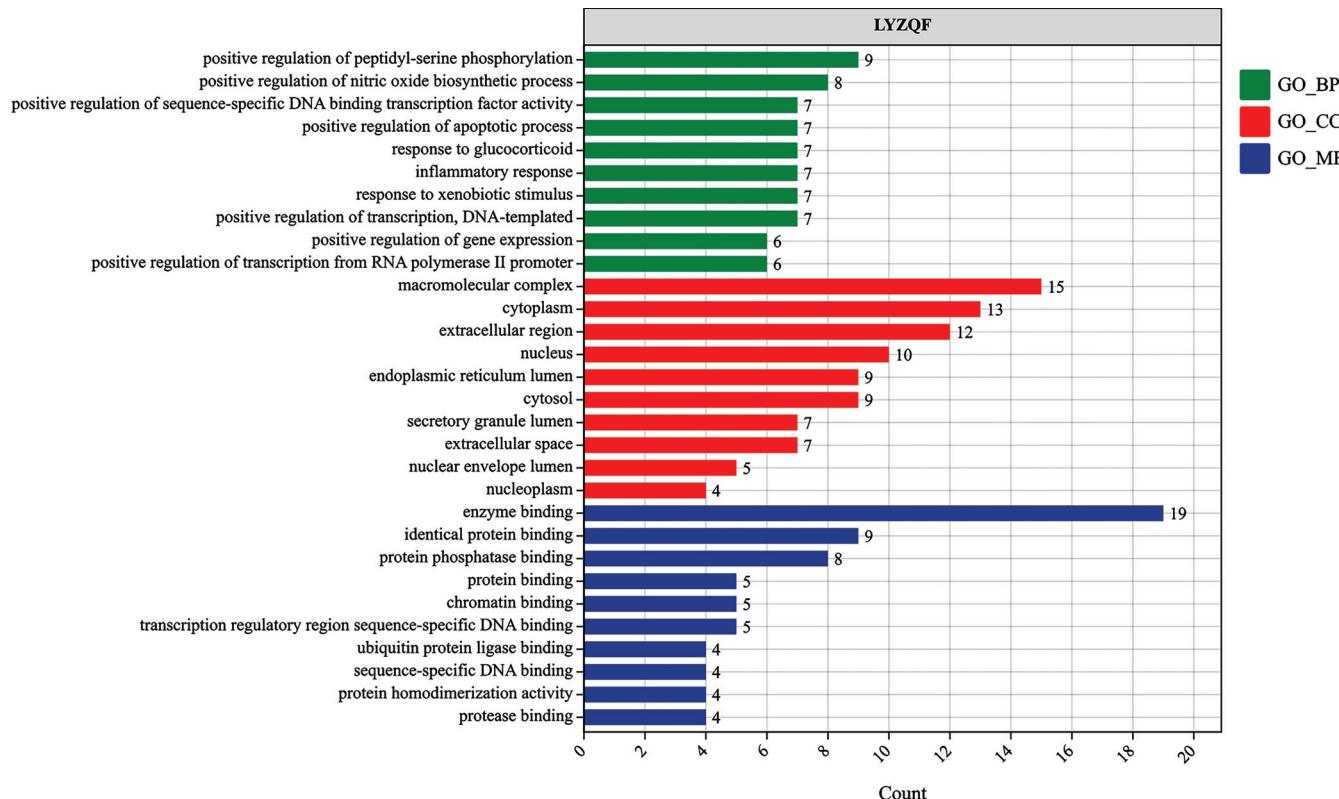
**Fig. (8).** PPI network diagram of the key target of Lianhua-Qingwen Formula. Each node represents a protein and the darker the node color, the higher the score, the stronger the significance, and the more critical it is in the entire PPI network. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

are positive regulation of peptidyl-serine phosphorylation, positive regulation of nitric oxide biosynthetic process, positive regulation of sequence-specific DNA binding transcription factor activity, positive regulation of apoptotic process, response to glucocorticoid, inflammatory response, response

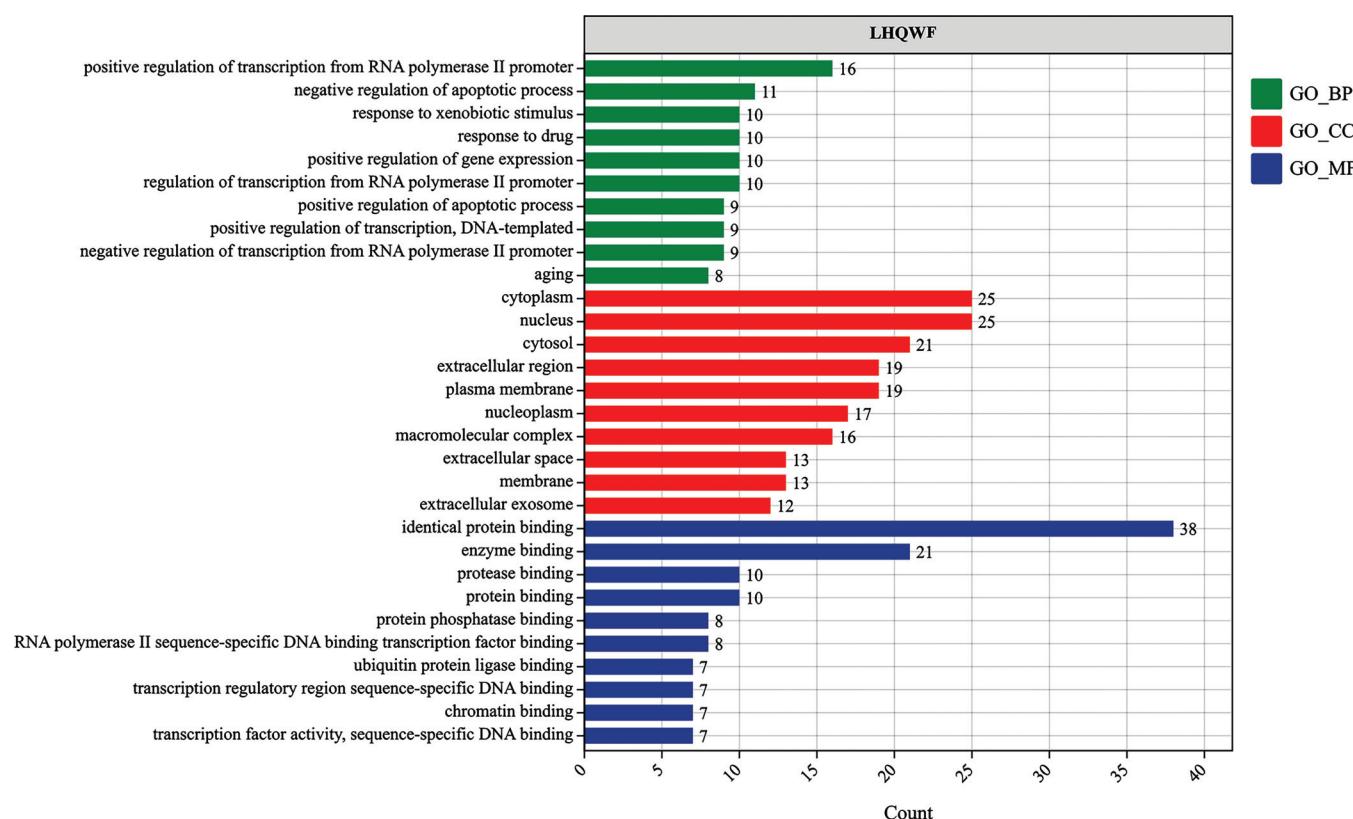
to xenobiotic stimulus, positive regulation of transcription, DNA-templated, cell composition is macromolecular complex, cytoplasm, extracellular region, nucleus, endoplasmic reticulum lumen, cytosol, secretory granule lumen, and molecular function is enzyme binding, identical protein binding, protein phosphatase binding, protein binding, chromatin binding, transcription regulatory region sequence-specific DNA binding, ubiquitin protein ligase binding.

GO enrichment analysis of PPI network targets in the intersection of Lianhua-Qingwen Formula - COVID-19 is shown in Fig. (10). Fig. (10) shows that biological processes with the largest number of PPI network targets in the intersection of Lianhua-Qingwen Formula- COVID-19 are positive regulation of transcription from RNA polymerase II promoter, negative regulation of apoptotic process, response to xenobiotic stimulus, response to drug, positive regulation of gene expression, regulation of transcription from RNA polymerase II promoter, positive regulation of apoptotic process, cell composition is the cytoplasm, nucleus, cytosol, extracellular region, plasma membrane, nucleoplasm, macromolecular complex, and molecular function is identical protein binding, enzyme binding, protease binding, protein binding, protein phosphatase binding, RNA polymerase II sequence-specific DNA binding transcription factor binding, ubiquitin protein ligase binding.

The KEGG pathway analysis of the target of the Longyi-Zhengqi Formula - COVID-19 intersection PPI network is



**Fig. (9).** GO analysis diagram of Longyi-Zhengqi Formula. The vertical coordinate represents the GO enrichment items of the common target of Longyi-Zhengqi Formula and COVID-19, the horizontal coordinate represents the amount of action on the GO enrichment items, the green item represents Biological Process, the orange item represents Cellular Component, and the blue item represents Molecular Function. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).



**Fig. (10).** GO analysis diagram of Lianhua-Qingwen Formula. The vertical coordinate represents the GO enrichment items of the common target of Lianhua-Qingwen Formula and COVID-19, the horizontal coordinate represents the amount of action on the GO enrichment items, the green item represents Biological Process, the orange item represents Cellular Component, and the blue item represents Molecular Function. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

shown in Fig. (11). Fig. (11) shows that the main pathways involved in PPI network targets at the intersection of Longyi-Zhengqi Formula- COVID-19 include Epstein-Barr virus infection, Lipid and atherosclerosis, IL-17 signaling pathway, Pathways in cancer, AGE-RAGE signaling pathway in diabetic complications, Tuberculosis, NOD-like receptor signaling pathway, TNF signaling pathway.

The KEGG pathway analysis of the PPI network target of Lianhua-Qingwen Formula - COVID-19 is shown in Fig. (12). Fig. (12) shows that the intersection of Lianhua-Qingwen Formula- COVID-19 PPI network targets mainly involve the following pathways: Lipid and atherosclerosis, Prostate cancer, Hepatitis B, PI3K-Akt signaling pathway, Measles, TNF signaling pathway, IL-17 signaling pathway.

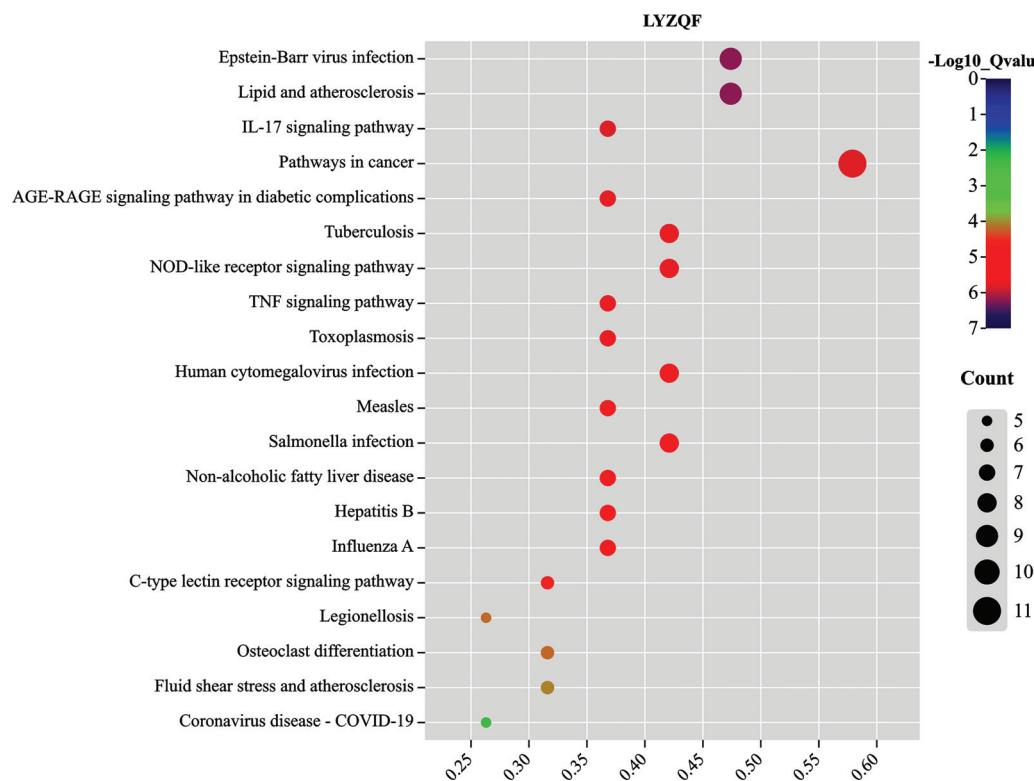
### 3.5. COVID-19 Pathway Mapping

KEGG PATHWAY was used to map the PPI network targets of Longyi-Zhengqi Formula - COVID-19 intersection and Lianhua-Qingwen Formula - COVID-19 intersection into the COVID-19 pathway, as shown in Figs. (13 and 14), the number of PPI network targets mapped into the COVID-19 pathway was 5. The number of PPI network targets mapped on the COVID-19 pathway of Lianhua-Qingwen Formula and COVID-19 is 10, indicating that the overall treatment effect of Lianhua-Qingwen Formula on COVID-19

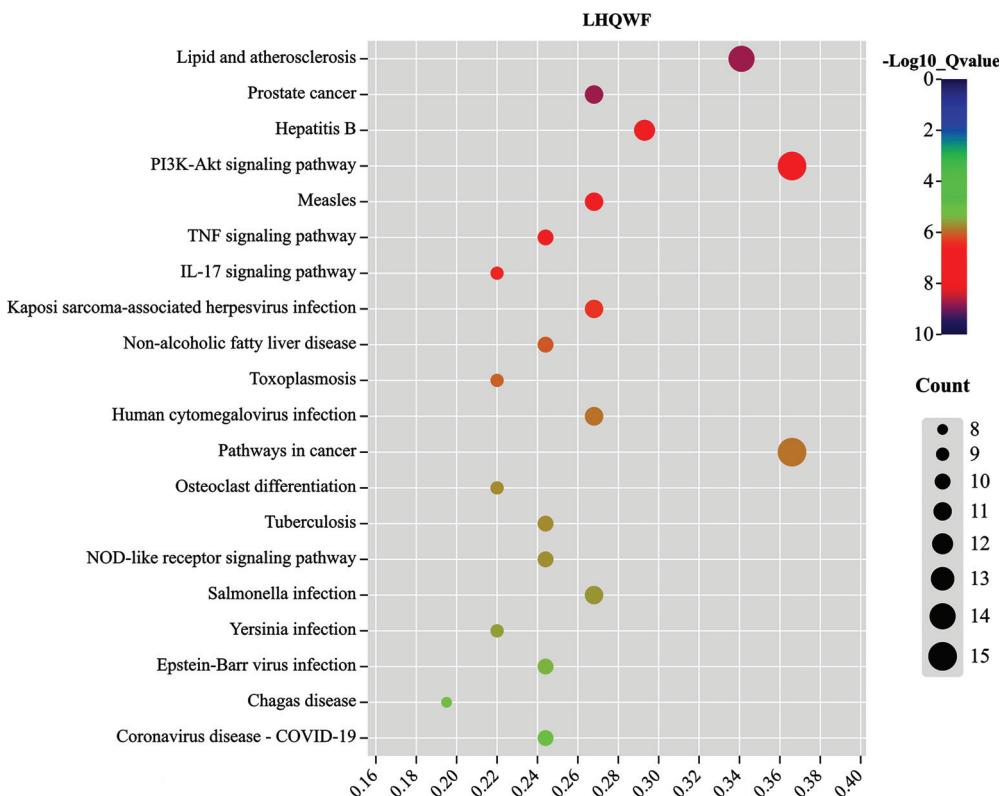
is better than that of Longyi-Zhengqi Formula. The main difference between the two is that the intersection target of the Longyi-Zhengqi Formula contains IL-6, and the intersection target of the Lianhua-Qingwen Formula contains TLR4 (Supplementary Material).

## CONCLUSION

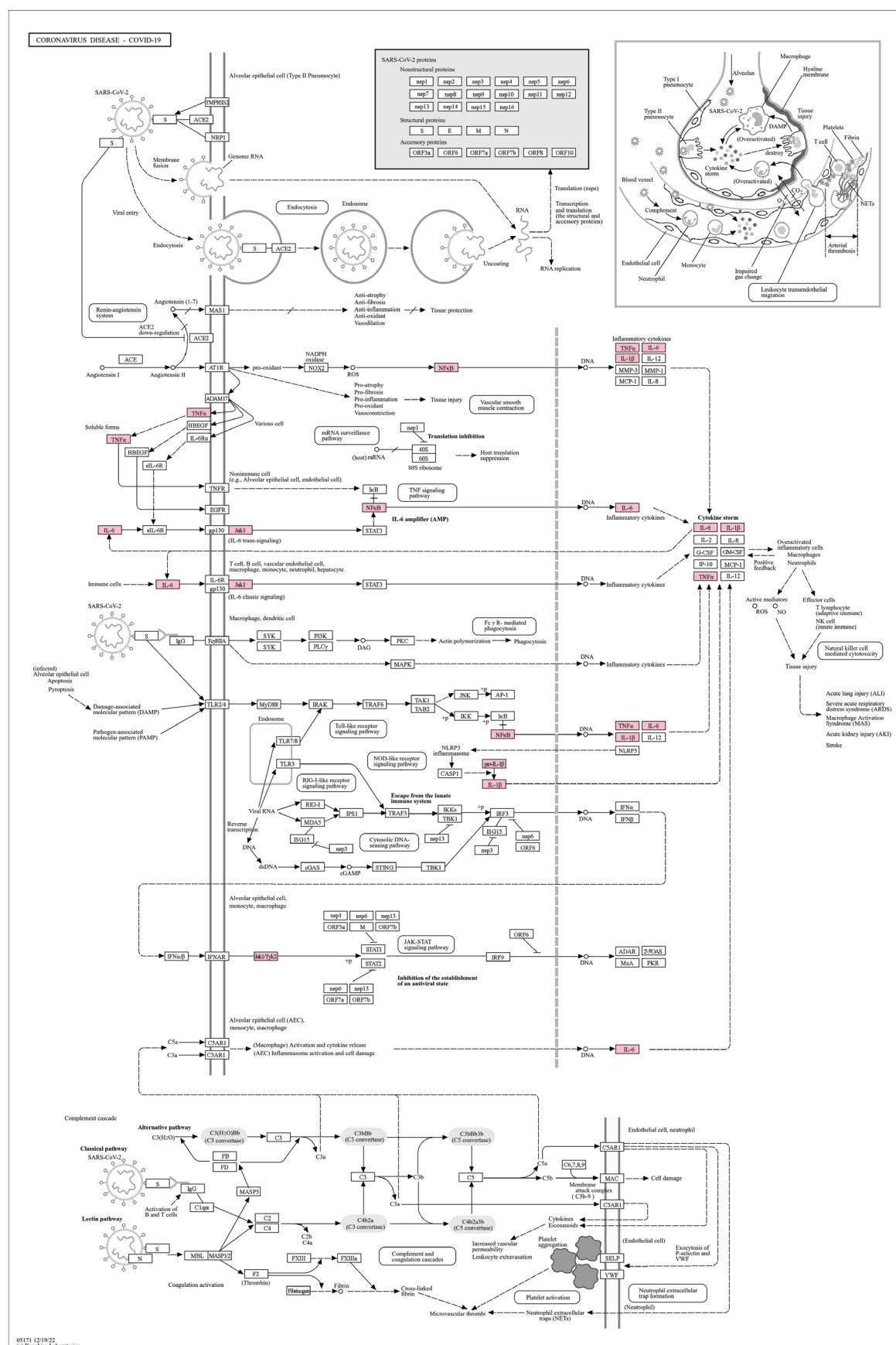
The novel coronavirus epidemic has caused great losses to the world, but there is no specific medicine for COVID-19. Traditional Chinese medicine has become an important method to treat the novel coronavirus and plays an important role in the prevention and treatment of the epidemic. The novel coronavirus pneumonia belongs to the category of plague in traditional Chinese medicine, and its main disease is dampness, which can be called "dampness-toxicity plague". The treatment methods are mainly to dispel filth with aroma, strengthen vital energy and eliminate pathogenic factors, dispel dampness and heat, and dredge the functional activity of Qi [75]. Longyin-Zhengqi Formula dissipates dampness, invigorating the spleen and supplementing qi, strengthening vital energy and eliminating pathogenic factors, and Lianhua-Qingwen Formula clears heat and removes toxicity, propagating the lung and releasing heat. Both can treat the symptoms of exogenous wind evil and the syndrome of pathogenic heat obstructing the lung of COVID-19.



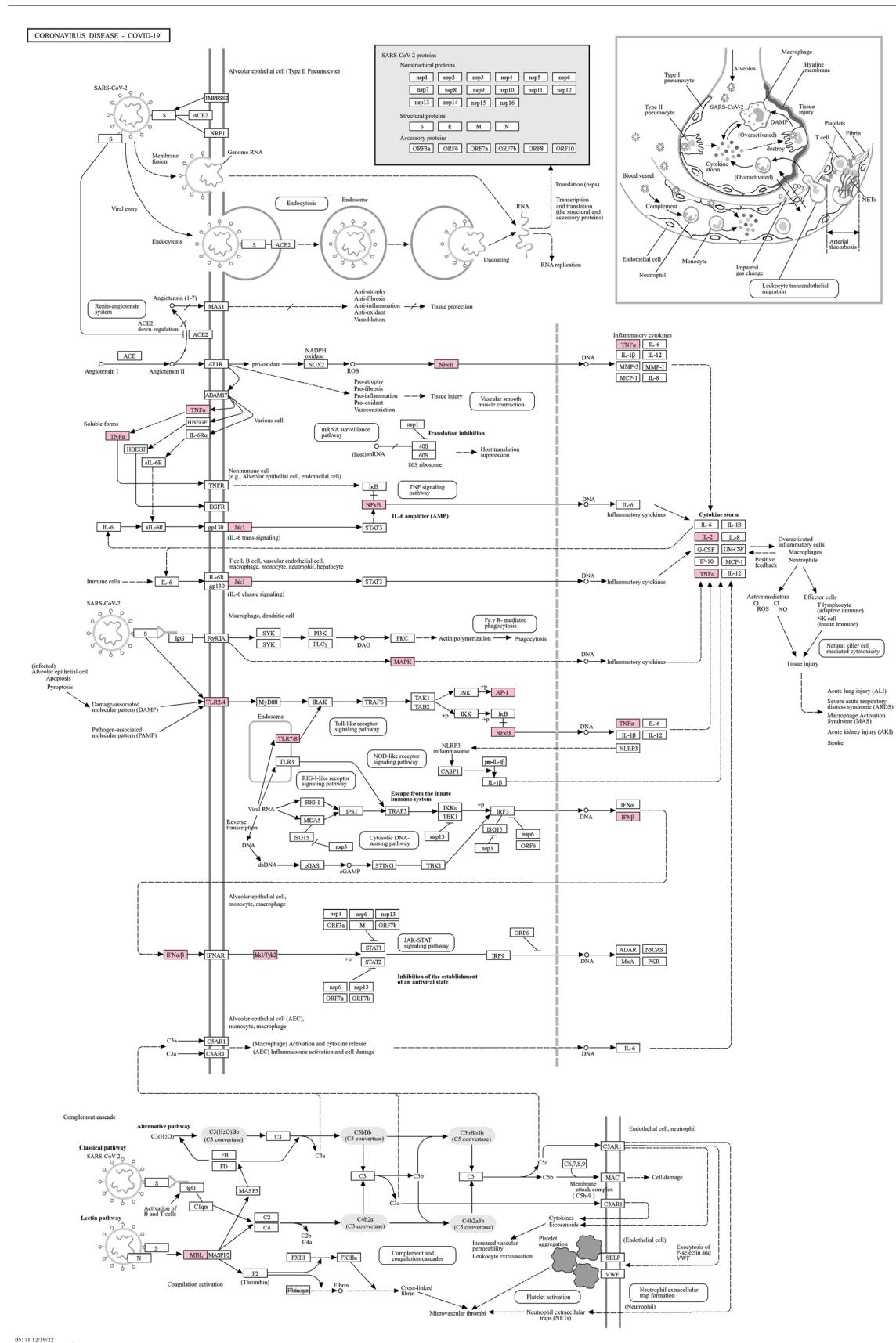
**Fig. (11).** KEGG diagram of Longyi-Zhengqi Formula. The vertical coordinate represents the first 15 KEGG pathway entries in which the Longyi-Zhengqi Formula and the common target of COVID-19 participate, and the horizontal coordinate represents the enrichment score, the size of nodes represents the number of targets on the pathway, and the color of nodes from green to red represents the enrichment degree from small to large. (A higher resolution / colour version of this figure is available in the electronic copy of the article).



**Fig. (12).** KEGG diagram of Lianhua-Qingwen Formula. The vertical coordinate represents the first 15 KEGG pathway entries in which Lianhua-Qingwen Formula and the common target of COVID-19 participate; the horizontal coordinate represents the enrichment score; the size of nodes represents the number of targets on the pathway; and the color of nodes from green to red represents the enrichment degree from small to large. (A higher resolution / colour version of this figure is available in the electronic copy of the article).



**Fig. (13).** Mapping of the target of Longyi-Zhengqi Formula in the COVID-19 KEGG pathway. The pink nodes represent the mapping of the common target of Longyi-Zhengqi Formula and COVID-19 on the COVID-19 pathway. (A higher resolution / colour version of this figure is available in the electronic copy of the article).



**Fig. (14).** Mapping of the target of Lianhua-Qingwen Formula in the COVID-19 KEGG pathway. The pink nodes represent the mapping of Lianhua-Qingwen Formula and the common target of COVID-19 on the COVID-19 pathway. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

In this study, 63 active ingredients and 206 targets of Longyi-Zhengqi Formula were collected and screened using traditional Chinese medicine databases, such as ETCM and INPUT, 109 active ingredients and 545 targets of Lianhua-Qingwen Formula, and then 437 targets of COVID-19 were screened using GeneCards database. Twenty potential targets of the Longyi-Zhengqi Formula and 41 potential targets of the Lianhua-Qingwen Formula for the treatment of COVID-19 were obtained.

By constructing the target network of Longyi-Zhengqi Formula - COVID-19 and the target network of Lianhua-Qingwen Formula- COVID-19, the key components of Longyi-Zhengqi Formula were Atractylenolide III, Isoliquiritigenin, Glycyrrhetic Acid, Methyl 18 $\alpha$ -Hydroxyglycyrhinate and Luteolin, and the key components of Lianhua-Qingwen Formula were Adenine Nucleoside, Decanoic Acid, Lauric Acid, Kaempferol and Rhodioloside. Among them, Atractylenolide III has anti-inflammatory, anti-tumor, diuretic and other effects [76]. Isoliquiritigenin inhibits the inflammatory response [77]. Glycyrrhetic Acid has a marvelous effect of inhibiting tumor bacteria and antiviral infection [78]. Luteolin can inhibit the activity of transcription factor NF- $\kappa$ B, which has anti-tumor, anti-oxidation, antibacterial and anti-inflammatory effects [79] and the NF- $\kappa$ B pathway belongs to the COVID-19 pathway; Kaempferol can play an anti-inflammatory role by reducing the mRNA expression of TNF- $\alpha$ , IL- $\beta$  and IL-8 [80]. Lauric Acid has anti-bacterial, anti-cancer and blood pressure lowering [81]. Adenosine has anti-inflammatory, antiarrhythmic properties and antiplatelet effect [82]. Rhodioloside has the effects of anti-apoptosis, anti-cancer, anti-inflammation, anti-aging, anti-fatigue and anti-hypoxia [83]. Therefore, it is speculated that these key ingredients can treat COVID-19 by playing anti-inflammatory, antibacterial, anti-viral infection, and respiratory improvement functions.

According to the intersection target of Longyi-Zhengqi Formula and COVID-19, construct the Longyi-Zhengqi Formula - COVID-19 intersection PPI network, and obtain the key targets: AKT1, IL6, TNF, CASP3, IL1B, PPARG, PTGS2, APP, ALB, HSP90AA1, according to the intersection target of Lianhua-Qingwen Formula and the COVID-19, Lianhua-Qingwen Formula - COVID-19 intersection PPI network was constructed, and the key targets were obtained: AKT1, GAPDH, JUN, CASP3, TNF, ALB, INS, TLR4, HSP90AA1, PPARG. AKT1 is one of the threonine-protein kinases, and which regulates numerous processes, including metabolism, proliferation, cell survival and angiogenesis. IL6 is essential for activating and regulating immune cells and inflammatory responses; TNF can stimulate cell proliferation and, induce cell differentiation, and regulate immune cells; ALB is the main protein of plasma, has a good binding capacity for water, Ca(2+), Na(+), K(+), fatty acids, hormones, bilirubin and drugs. It can regulate the colloidal osmotic pressure of blood. TLR4 is an important member of the toll-like receptor family, and the expression levels of TLR4 and its pathway-related proteins are closely related to inflammatory lesions in numerous organs and tissues [84].

GO enrichment analysis and KEGG pathway analysis were conducted for PPI network targets in the intersection of Longyi-Zhengqi Formula and COVID-19. KEGG pathway analysis results included IL-17 signaling pathway, TNF signaling pathway, tuberculosis pathway, cancer pathway and other disease pathways related to COVID-19. GO enrichment analysis results included biological processes such as inflammatory response, positive regulation of the apoptotic process, positive regulation of peptidyl-serine phosphorylation, and positive regulation of nitric oxide biosynthetic process. GO and KEGG pathway analysis was performed on the PPI network targets of the Lianhua-Qingwen Formula-COVID-19 intersection, among which the KEGG pathway analysis results included PI3K-Akt signaling pathway, IL-17 signaling pathway, TNF signaling pathway, cancer pathway, and tuberculosis pathway. GO enrichment analysis results included biological processes such as response to the drug, positive regulation of transcription from RNA polymerase II promoter, inflammatory response, and response to the xenobiotic stimulus. It is speculated that both can play a role in treating COVID-19 by reducing inflammation and regulating the function of the immune system.

Finally, the PPI network targets of the Longyi-Zhengqi Formula - COVID-19 intersection and the Lianhua-Qingwen Formula - COVID-19 intersection were mapped into the COVID-19 pathway, respectively. The PPI network targets of the Longyi-Zhengqi Formula - COVID-19 intersection contained IL-6, and the PPI network targets of the Lianhua-Qingwen Formula - COVID-19 intersection contained TLR4. IL-6 is an important link in the human cytokine storm caused by the novel coronavirus infection, which is an important factor in the development of severe disease in COVID-19 patients [85]. After entering the human body, the novel coronavirus will activate the molecular mechanism of the TLR4 pathway, causing inflammation [86]. Therefore, it can be speculated that the difference between the two is that the Longyi-Zhengqi Formula can produce a therapeutic effect on COVID-19 by regulating IL-6, while the Lianhua-Qingwen Formula can produce a therapeutic effect on COVID-19 by regulating TLR4.

In conclusion, this paper discusses the mechanism of action of the Longyi-Zhengqi Formula and Lianhua-Qingwen Formula in the treatment of COVID-19 based on the method of network pharmacology and provides ideas for the study of traditional Chinese medicine treatment of COVID-19. This study failed to find out the constituents and targets of the gypsum and the Scallop, which affected the predicted results to some extent.

## AUTHORS' CONTRIBUTION

It is hereby acknowledged that all authors have accepted responsibility for the manuscript's content and consented to its submission. They have meticulously reviewed all results and unanimously approved the final version of the manuscript.

## LIST OF ABBREVIATIONS

- ETCM = Encyclopedia of Traditional Chinese Medicine  
 GO = Gene Ontology  
 KEGG = Kyoto Encyclopedia of Genes and Genomes

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

## HUMAN AND ANIMAL RIGHTS

Not applicable.

## CONSENT FOR PUBLICATION

Not applicable.

## AVAILABILITY OF DATA AND MATERIALS

The data supporting the findings of the article is available at <https://github.com/xfwang1969/RMTCMT-COVID-19>.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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## SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's website along with the published article.

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