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A Network Pharmacology Study to Uncover the Multiple Molecular Mechanism of the Chinese Patent Medicine Toujiequwen Granules in the Treatment of Corona Virus Disease (COVID-19)

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Abstract

Since the outbreak of the novel Corona Virus Disease 2019 (COVID-19) infected by SARS-CoV-2 at the end of 2019, clinical specific antiviral drugs have been lacking. A Chinese patent medicine called 'Toujiequwen Granules' has been promoted in the treatment of COVID-19. The present study was designed to reveal the molecular mechanism of Toujiequwen Granules against COVID-19. A network pharmacological method was applied to screen the main active ingredients of Tongjiequwen Granules. Network analysis of 149 active ingredients and 330 drug targets showed the most active ingredients interacting with many drug targets are quercetin., drug targets most affected by the active ingredients are PTGS2, PTGS1, and DPP4. Drug target disease enrichment analysis showed drug targets are significantly enriched in cardiovascular diseases, digestive tract diseases and so forth. An 'active ingredient-target-disease' network showed that 57 active ingredients from Toujiequwen Granules, interact with 15 key targets of coronary pneumonia. There are 53 ingredients that can act on DPP4, suggesting that DPP4 may become a potential new key target for the treatment of COVID-19. The GO analysis results showed that key targets were mainly enriched in the cellular response to lipopolysaccharide, cytokine activity and other functions. KEGG analysis showed they were mainly concentrated in viral protein interaction with cytokine and cytokine receptors endocrine resistance pathway, and others. These evidences suggest that Toujiequwen Granules might play an effective role through improving the symptoms of underlying diseases in patients with COVID-19 and multi-target interventions against multiple signaling pathways related to the pathogenesis of SARS-CoV-2.

1. Introduction

Corona Virus Disease 2019 (COVID–19) caused by SARS-CoV–2 (also known as 2019-nCoV) was first reported in Wuhan in December 2019. As of April 10, 2020, it has infected more than 80,000 patients in China, resulting in more than 3000 deaths, especially in the Wuhan area where the epidemic was centered. More than 10,000,000 confirmed cases have been detected in more than 200 countries internationally. World Health Organization (WHO) has defined it as a global pandemic. The virus has the characteristics of being highly contagious, thus threatening human health seriously and causing great harm to society. The International Committee on Taxonomy of Viruses (ICTV) therefore announced the official English name of this new coronavirus as SARS-CoV–2, while the World Health Organization named the disease caused by the new coronavirus as COVID–19, which is translated as '2019 coronavirus infection'. The SARS-CoV–2, the viruses that caused the severe acute respiratory syndrome (SARS) epidemic in 2003 and the Middle East Respiratory Syndrome (MERS) epidemic in 2012, also belong to the coronavirus family, but these viruses are different from each other. SARS-CoV–2 shares 79.5% of the genetic sequence with severe acute respiratory syndrome coronavirus (SARS-CoV) and has 96.2% homology with bat coronavirus[1]. Phylogenetic analysis indicates that SARS-CoV–2 is close to a coronavirus in the Horseshoe Bat. At the same time, evolution analysis based on ORF1a / 1b, S and N genes also showed that SARS-CoV–2 is likely to be a new virus introduced from animals to humans independently[1]. Compared with SARS-CoV and Middle East Respiratory Syndrome Coronavirus (MERS-

CoV), SARS-CoV–2 has greater infectivity (such as higher R0) and lower mortality[2]. Although experts have proposed drug treatment programs for the replication cycle and infectious mechanism of coronaviruses, and they are currently studying some medicines such as favipiravir, chloroquine phosphate, remdesivir, as well as the development of antiviral drugs such as antibodies and vaccines, there is currently no specific medicine against SARS-CoV–2 in treatment of COVID–19[3]. Therefore, there is an urgent need for more effective and less toxic therapies against COVID–19.

Many clinical expert groups have already tried Traditional Chinese Medicine (TCM) therapy or integrated Chinese and Western medicine treatment at the beginning of the epidemic disease and have received good clinical results. After treatment with Traditional Chinese Medicine, moderate and mild patients with COVID–19 are easily cured, and the number of patients turning from moderate to severe has also decreased significantly. For those with severe and critical illness, Chinese Medicine therapy is not only able to stabilize blood oxygen saturation, but also improve breathing difficulties. Toujiequwen Granules (formerly known as Pneumonia Prescription No. 1 in Guangdong) was approved by the Guangdong Drug Administration for emergency approval and started mass production. It is mainly composed of 16 kinds of traditional Chinese medicine such as forsythia suspensa, cremastra appendiculata, lonicera japonica, scutellaria baicalensis, bupleurum chinense. Guangdong Drug Administration announced in its website that clinical studies of Pneumonia No. 1 have shown that 50 cases of patients who are confirmed COVID–19 with pneumonitis (mild) were treated in Toujiequwen Granules. After one week of clinical observation, the temperature of all patients returned to normal. Cough symptoms from 50% of patients and sore throat symptoms from 52.4% of patients disappeared. The symptoms of fatigue disappeared in 69.6% of patients. The general symptoms were significantly reduced, and no patient's conditions became severe. There also have some clinical studies on patients of COVID–19 treated with Toujiequwen granules and Western medicine. A clinical study on 37 case of COVID–19 treated with integrated traditional Chinese and Western medicine has shown that COVID–19 patients will be alleviated by early and timely use of the combined solution of Toujiequwen granules and Arbidol. The expression of T cell counts can be controlled and the immune function can be restored[4]. Another clinical study on treatment of cases of COVID–19 with Toujiequwen granules has shown that after 10 days of treatment, the TCM syndrome score of the treatment group was significantly reduced($P<0.05$), and the absolute value of lymphocyte was up-regulated, the difference was statistically significant ($P<0.05$) and so on. It means the clinical syndrome and inflammatory particles of COVID–19 can be alleviated by early and timely use of Toujiequwen granules[5]. A few studies have shown that some of the individual Chinese medicines in the composition of Toujiequwen Granules have antiviral effects. For example, forsythia and its main active ingredient, quercetin, have demonstrated good anti-human cytomegalovirus properties in in vitro studies[6,7]. Honeysuckle is a commonly traditional Chinese medicine which used as an antipyretic and antidote. Pharmacological studies have shown that it has the effect of anti-influenza A virus[8,9]. However, the detailed molecular mechanisms of the Toujiequwen Granules as a whole prescription in the treatment of COVID–19 is still unknown.

Network pharmacology is a study strategy that integrates high-throughput data analysis, molecular docking, drug-target network construction, and network feature analysis based on multi-target overall regulation. It breaks the traditional concept of “one drug, one target, one disease” and provides new ideas and methods for the research of the “multi-ingredient, multi-target” approaches of Traditional Chinese Medicine and ethnic medicine[10,11]. Network pharmacology emphasizes multi-channel regulation of biological functions as well as signal pathways, improves the therapeutic effect of drugs, and reduces toxic and side effects, thereby improving the success rate of clinical trials of new drugs and laying a foundation for new drug development.

In this study, a network pharmacology method was used to systematically predict and screen the potential active ingredients of Toujiequwen Granules and the key drug targets, and to analyze and study the mechanisms of the multi-ingredients and multi-target of Toujiequwen Granules against COVID–19. The underlying molecular mechanism of Toujiequwen Granules against COVID–19 provides modern medical theoretical support for understanding the positive effect of this prescription, and may facilitate its widely application and the development of new drugs based on Toujiequwen Granules.

2. Materials And Methods

2.1. Screening of active ingredients and corresponding drug targets in Toujiequwen Granules

This study investigates the Chinese patent medicine Toujiequwen Granules, which is produced by Guangdong E-Fang pharmaceutical Co., Ltd. The TCMSP (Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform, http://tcmspw.com/tcmsp.php) was used to retrieve the compounds, taking oral bioavailability (OB≥30%) and drug-like properties (DL ≥ 0.18) as the conditions for screening the active ingredients of Toujiequwen Granules. Among them, OB is an important indicator to evaluate a drug’s efficacy[12]. DL represents the similarity between a given ingredient and its known equivalent in Western medicine. Both factors are important reference for determining whether the TCM ingredients are active in the body. Toujiequwen Granules is composed of 16 single traditional Chinese medicines, includingforsythia suspensa, cremastra appendiculata, lonicera japonica, scutellaria baicalensis, bupleurum chinense, artemisia annua, angelica decursiva, fritillaria cirrhosa, prunus mume, scrophularia ningpoensis, atractylodes lancea, astragalus mongholicus, pseudostellaria heterophylla, poria cocos, cicadae periostracum and ground beetles. The active ingredient of each single Chinese drug of Toujiequwen Granules were retrieved respectively, and a total of 149 ingredients were obtained after removing redundancies. A total of 330 drug targets (proteins) corresponding to those 149 ingredients were identified by searching in the TCMSP database. The bioDBnet online tool (https: //biodbnet-abcc.ncifcrf.gov/db/db2db.php) was used to change the protein names of drug target to human gene names. Some of the obtained drug targets corresponding to each active ingredients in TCMSP database were obtained from DrugBank (https://www.drugbank.ca/), and some of the drug targets verified by experiments came from the HIT database (http://bigd.big.ac.cn/databasecommons/database/id/690).

The existence of drug targets for the active ingredients without verified targets was predicted by the SysDT model. The database of active ingredients and their corresponding drug targets (ingredients-drug target) was constructed.The cytoscape 3.6.1 software[13] was used to construct an active ingredient-target network to analyze the synergistic relationship between the active ingredients and multiple effective drug targets.

2.2. Enrichment disease analysis of drug target

The gene names of 330 drug targets matching the active ingredients of Toujiequwen Granules were imported into the CTD online analysis platform (http://ctdbase.org) database, the results of disease enrichment analysis corresponding to these drug targets were obtained. This enabled the analysis of the possible role of Toujiequwen Granules in treating the underlying disease of patients with COVID–19.

2.3. Prediction of potential disease targets of COVID–19

The DisGeNET (http://www.disgenet.org/) disease target prediction analysis platform is used to predict disease targets of COVID–19. The screening disease types are selected as respiratory diseases and viral diseases. Because of the similarities between SARS and COVID–19 in the RNA sequences of coronaviruses and relative symptoms, especially in severe cases, the SARS was selected here to predict the disease targets of COVID–19[14]. In total, 84 disease targets of SARS were finally obtained as the disease targets of COVID–19. The database of disease targets and COVID–19 was then constructed.

2.4. Construction of a network of the active ingredients of Toujiequwen Granules, disease target and COVID–19

The database of ingredients and drug targets, including the 149 active ingredients of Toujiequwen Granules and 330 predicted drug target gene, in addition to the database of disease targets-COVID–19 were merged by Cytoscape3.6.1 software to construct an active ingredient-key targets-COVID–19 network. The overlap targets of drug targets of active ingredients and disease targets of COVID–19 were called as key targets for Toujiequwen Granules treating COVID–19.

2.5. GO function enrichment analysis and KEGG pathway enrichmentanalysis

The key targets enrichment on GO and KEGG were analyzed utilizing R language package clusterProfiler[15]. GO enrichment analysis includes GO-BP (gene ontology biological process) analysis, GO-CC (gene ontology cellular ingredient) analysis, GO-MF (gene ontology-molecular function) analysis of biological molecules. The enrichment significant conditions for GO and KEGG are P-value <0.01, FDR <0.2. The enrichment results are sorted according to their statistical significance (P value). The top 20 enrichment results for each enrichment analysis are selected for histogram and bubble chart.

3. Results

3.1. Screening of candidate ingredient and acquisition of targets

First, the 16 traditional Chinese medicines in the composition of Toujiequwen Granules were submitted to the TCSMP website respectively to search for their active ingredients under the condition as OB ≥ 30% and DL ≥ 0.18. We obtained the ingredients 9 in atractylodes lancea, 17 in bupleurum chinense, 13 in fritillaria cirrhosa, 15 in poria cocos, 36 in scutellaria baicalensis, 20 in astragalus mongholicus, 23 in lonicera japonica, 23 in forsythia suspensa, 24 in angelica decursiva, 22 in artemisia annua, 3 in cremastra appendiculata, 8 in pseudostellaria heterophylla, 8 in prunus mume, 9 in scrophularia ningpoensis, cicadae periostracum and ground beetle had no active ingredients according the screening conditions. Total 149 compounds were collected after removing the redundancy of the active ingredients corresponding to each single medicine. Then the above 149 active ingredient compounds were matched in the TCMSP database to find the relevant drug targets of the compounds. Total 330 related drug targets were finally obtained after removing the redundancy.

3.2. Feature analysis of active ingredient-drug target network

The obtained 149 active ingredients and their corresponding 330 drug targets were constructed into a network map by Cytoscape software version 3.6.1. We separated and plotted the top 10% of the most active ingredients and drug targets according to their high degree and betweenness centrality from the whole network data. The result is depicted in Figure 1, including 62 nodes and 1,056 edges. The degree and betweenness is positively related to the importance of the active ingredient and drug target, the red circle represents the active ingredient, the blue triangle represents the drug target, and the size of the node represents the magnitude of its degree. We observed that many ingredients were interacting with multiple drug targets, and many drug targets were hit by multiple active ingredients. Among them, the most important compound was determined to be MOL000098 (quercetin) with 189 edges, representing that there are 189 drug targets hit by this active ingredient. It is reported that quercetin has a wide range of physiological activities, such as anti-oxidation, anti-inflammatory, and anti-tumor properties[6]. Active ingredients that most interact with drug targets also include luteolin, kaempferol, wogonin, formononetin, sagerin, beta-sitosterol, tanshinone IIA, and baicalein. The top 10 drug targets modulated by multiple active ingredients are PTGS2, PTGS1, NCOA2, DPP4, SCN5A, AR, PRSS1, F2, NOS and PRKCA. PTGS2 and PTGS1 are prostaglandin endoperoxide synthases as well as rate-limiting enzymes involved in the synthesis of prostaglandins. Prostaglandins are involved in the pathological processes of various inflammations, cancers, and assorted cardiovascular diseases[16]. DPP4 is dipeptidyl peptidase 4, also known as T cell surface antigen CD26, which is a serine protease on the cell surface. The most widely studied protein substrate of DPP4 is GLP–1. GLP–1 can lower blood sugar by stimulating insulin and

inhibiting glycogen. Therefore, DPP4 inhibitors have become one of the hot drugs for the treatment of diabetes[17]. In addition, a recent study revealed that DPP4 secreted by the liver may enter the bloodstream and then activate inflammatory cells (macrophages)[18]. These data implied that the Toujiequwen Granules might have multi-target synergistic effects on the human body.

3.3 Analysis of enriching diseases of drug targets from Toujiequwen Granules:

Some research reports have shown that elderly, male, and underlying conditions or chronic diseases are the key words for patients with COVID–19. Among the basic diseases, diabetes, hypertension, heart disease and kidney disease have become the greatest lethality. For instance, a study by Wang Jianqing's team at Suzhou Hospital Affiliated to Nanjing Medical University recently found that SARS-CoV–2 may infect and damage male testes. Recently, scientists from the National Institutes of Health (NIH) have come to the similar conclusion[19]. Further, the Shanhong research group of Sun Yat-Sen University found that the SARS-CoV–2 receptor ACE–2 was expressed in the patient's stomach, duodenum, and rectal glandular epithelial cells. The SARS-CoV–2 nucleocapsid protein was detected in glandular epithelial cells of these tissues. The digestive tract can be infected with SARS-CoV–2[20]. One study suggested that SARS-CoV–2 also could infect the nervous system[21]. These studies together suggest that the attacks on these tissue cells by SARS-CoV–2 may exacerbate patients' underlying diseases.

In order to understand which basic diseases could be possibly affected by the Toujiequwen Granules in the human body, we performed an enrichment analysis of involved diseases of the 330 drug targets of the Toujiequwen Granules on the CTD online analysis platform. The top ten diseases for enrichment results are shown in the Table 1. We found that the drug targets of Toujiequwen Granules can be highly enriched in cardiovascular diseases, neurological diseases, digestive diseases, respiratory diseases, male urogenital diseases, and other conditions. These enriched diseases affected by Toujiequwen Granules are overlapped with the many clinical study results revealing the underlying diseases of COVID–19 patients. Our results suggested that Toujiequwen Granules can improve symptoms of underlying disease in patients with COVID–19, and may therefore play a role in delaying or reducing disease progression.

3.4 Prediction of disease target database of Coronavirus pneumonia

In order to understand how Toujiequwen Granules directly affect the drug target of COVID–19, we then constructed a drug target database of COVID–19 on the website of DisGeNET (https://www.disgenet.org/). The first study about the postmortem biopsies of a COVID–19 patient revealed that the pathological features of COVID–19 greatly resemble those seen in SARS and Middle Eastern respiratory syndrome (MERS) coronavirus infection[14]. On the other hand, SARS-CoV–2 virus also belongs to the coronavirus category, as does the SARS virus; there is similarity between it and SARS

viruses. They have a high degree of similarity in the whole genome sequence (79%)[22]. They share the same receptor, ACE2. The latest research also shows that the similarity of crystal structure of the resolved protein (such as in Mpro protease and S protein) with SARS-CoV–2 and SARS[2]. Although 4 of the 5 key amino acids bound to the ACE2 protein in the S-protein of the SARS-CoV–2 is different, these different amino acids have perfectly maintained the interaction between the S-protein and ACE2[23]. Based on the reason above, we selected the disease targets of SARS to construct the target library of coronavirus pneumonia disease on the DisGeNET platform. Total 84 disease targets of coronary virus pneumonia disease were obtained as the predicted disease target database of COVID–19.

3.5 Analysis ofcharacteristics in active ingredient-disease target-coronary virus pneumonia (COVID–19) network

The active ingredient-drug target database and the COVID–19 disease target library were merged using Cytoscape software 3.6.1 to generate the active ingredient-disease target-COVID–19 network (Figure 2) and related analysis results (Table 2 and Table 3).

A total of 57 of the 149 active ingredients contained in Toujiequwen Granules may affect the COVID–19 by interacting with 15 disease targets of coronavirus-related pneumonia, including quercetin, luteolin, wogonin, kaempferol, and other compounds. The 15 disease targets that could be acted on are DPP4, MAPK14, TNF, IL–6 and others. Interestingly, DPP4 can interact with up to 54 compounds of the 57 related active ingredients, suggesting that DPP4 may be a new potential key target for Toujiequwen Granules in the treatment of COVID–19. This result indicated that further research can consider investigating the infected ratio in the population of COVID–19 patients with diabetic disease who are taking DPP4 inhibitors, as well as an research the proportion of mild and severe cases. These investigation may suggest whether it is clinically possible to use potent DPP4 inhibitors such as sitagliptin and saxagliptin as one of the treatment strategies for COVID–19.

3.6 GO function enrichment analysis

In order to determine the gene enrichment of the 15 key disease targets of COVID–19 affected by Toujiequwen Granules, Gene Ontology (GO) analysis has been performed. GO analysis includes the functional enrichment of target genes based on two parameters: P value ($P < 0.01$) and false discovery rate (FDR), (FDR <0.2). The results obtained from the functions of enrichment or the top 20 (when the qualified enrichment results are more than 20) were analyzed, as shown in Figure 3. The study found that the top 20 biological processes (BP) enriched by these 15 potential disease targets mainly include lipopolysaccharide (LPS), cell response process, bacterial molecular response process, biological stimulus response process, multiple cell-cell adhesion regulation and protein secretion, peptide secretion regulation and other processes. The enriched cellular components (CC) is related to several cell membrane-related components, secreted particles, vesicles, and so on. Enriched protein molecular functions (MF) mainly include cytokine activity, cytokine receptor binding, receptor ligand activity,

chemokine activity, G-protein coupled receptor binding, MAPKK kinase activity, and so on. The above enrichment results on gene functions suggested that Toujiequwen Granules may achieve their therapeutic effect on COVID–19 by mainly acting on inflammation-related cellular response processes and protein targets with cytokine-related functions.

3.7 KEGG pathway enrichment analysis

In order to determine the main signaling pathways involved in the treatment of COVID–19 by Toujiequwen Granules, signal pathways and effects enriched by 15 key disease targets was performed. For the study, the top 20 significantly enriched KEGG signal pathways were identified and selected to analyze (Figure 4). It can be seen from the figure that the enriched cell signaling pathways mainly include viral protein-cytokine and cytokine receptor interaction pathways, cytokine-cytokine receptor interaction pathways, cell aging signaling pathways, chemokine signaling pathways, TGF-β signaling pathway, PI3K-Akt signaling pathway, and endocrine resistance signaling pathway. These evidences suggest that the active ingredients of Toujiequwen Granules can alleviate the lung inflammation and improve the symptoms of COVID–19 mainly through cytokines, inflammation-related signaling pathways, and viral infection-related signaling pathways.

4. Discussion

Since the outbreak of COVID–19 in China at the end of 2019, the virus has proved to be highly contagious, seriously threatening human health. The epidemic has not yet ended, and medical professionals, pharmacologists, and biologists over the world have devoted their efforts to fighting this virus. The latest research on 2019-nCoV (SARS-Cov–2) shows that the development of the disease is related to some blood biochemical indicators, such as cytokines and C-reactive protein (CRP)[24], which can potentially be used as new types of diagnostic markers with COVID–19. Some cytokines are directly related to viral load and lung injury, and the factors that affect these signaling mediators therefore may be potential drugs for the SARS-CoV–2 epidemic[25]. However, the specific antiviral drugs (small molecule monomer compounds), antibodies and vaccines against SARS-Cov–2 have not been officially approved yet due to the specific pathogenicity and transmission mechanism of the virus. On the other hand, scientists are trying to develop some existing drugs in the preclinical stage, and some of them are already in the clinical trials through the virtual screening of so-called “old drugs, new uses”, such as favipiravir, chloroquine phosphate, remdesivir, and others. However, there are no specific drugs against SARS-Cov–2 and COVID–19 so far. At the same time, many medical teams in China have received better clinical effects by utilizing traditional Chinese medicine or integration of traditional Chinese and Western medicines at the beginning of the epidemic.

In this study, a network pharmacology method was applied to analyze the main active ingredients as well as effective targets of Chinese patent medicines Toujiequwen Granules for the treatment of COVID–19. The network analysis was combined with the related disease targets of SARS. GO and KEGG enrichment

analysis with the key target of ingredient-target-disease network has been further resolved. This study systematically explored the molecular mechanism of Toujiequwen Granules for the treatment of COVID–19. It was found that the pharmacological ingredients in Toujiequwen Granules, such as quercetin, luteolin, kaempferol, and baicalein, may be involved in inflammation, cancer, and various cardiovascular diseases based on the analysis of the active ingredient-target disease network. The pathological process of the active ingredients may effectively improve the symptoms of the underlying disease in patients with COVID–19, thereby delaying or reducing the disease process. We also found that DPP4, a key target in the network, can interact with up to 54 of 57 related active ingredients, suggesting that DPP4 may be the potential most important target for the treatment of COVID–19 with Toujiequwen Granules (Fig.1). Furthermore, it was suggested that DPP4 might become a new key target for the prevention and treatment of COVID–19 by utilizing the existing inhibitors. In addition, Toujiequwen Granules may play a role in improving the symptoms of patients with COVID–19 by affecting the cell cycle, regulating immunity, anti-inflammatory, and adjusting cell metabolism and other pathways (Fig.3). There are also studies showing that patients severely affected of COVID–19 are more prone to neurological symptoms, especially acute cerebrovascular disease, disturbance of consciousness, and muscle damage[21]. Some studies found that men are more susceptible to COVID–19 than women, and they symptoms are more severe after infection[14]. This is consistent with our research of enrichment analysis of disease of drug targets in Toujiequwen Granules(Table1). Taken together, these results suggested that Toujiequwen Granules might play an effective role by improving the underlying disease symptoms of patients with COVID–19. It also may improve multi-target interventions against multiple signaling pathways that are responsible for the disease caused by SARS-CoV–2. Our results can provide important theoretical support for Traditional Chinese Medicine therapy against COVID–19, in addition to providing new ideas and references for treatments combining traditional Chinese and Western medicine against COVID–19.

In the present study, we only used the methods of bioinformatics database mining and bioinformatics software analysis to predict the possible molecular mechanism of Toujiequwen Granule against COVID–19. Further research is needed at the cellular and animal levels to study the detailed molecular mechanisms. This study attempts to predict and explore the molecular mechanism of Toujiequwen Granules against COVID–19 from the perspective of modern medicine, which may help to understand how the Toujiequwen Granules and the other traditional Chinese prescriptions work on curing the COVID–19. We hope our data may facilitate the wider use of traditional Chinese medicines in the treatment of COVID–19 over the world, especially as there is still no anti-viral specific drugs or vaccines available.

Declarations

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Tables

Due to technical limitations, Tables 1-3 are provided in the Supplementary Files section.

Figures

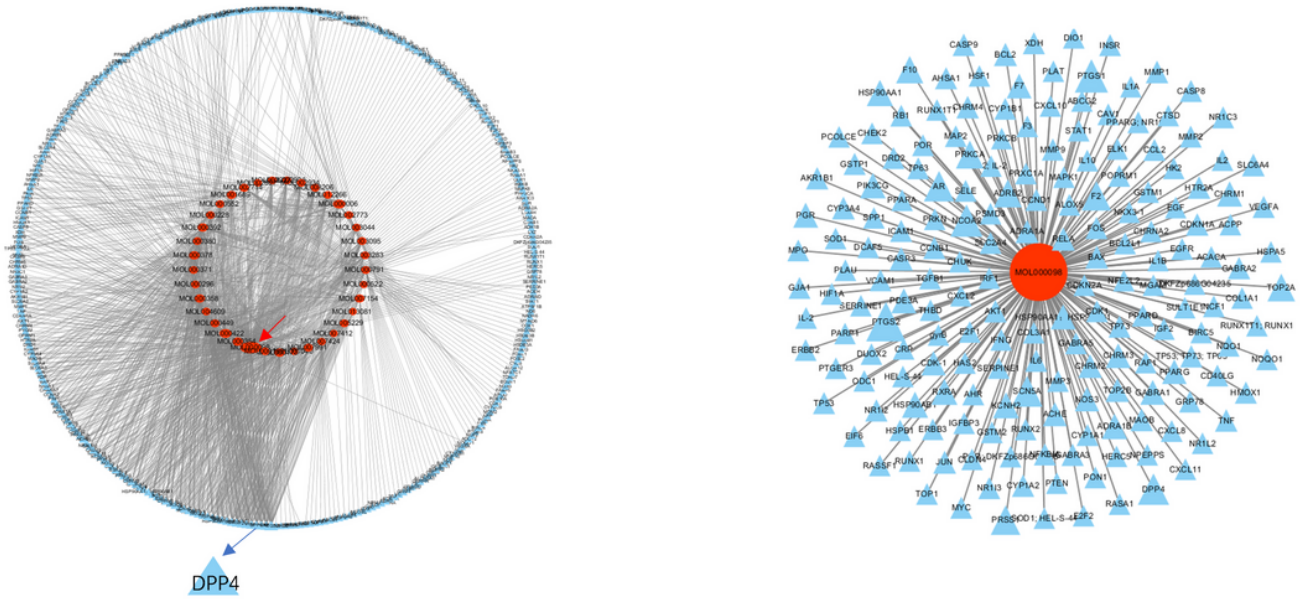

Figure 1

Network model of active components -drug target (Red plots represent compounds contained in Toujiequwen Granules. Blue plots represent compound targets).

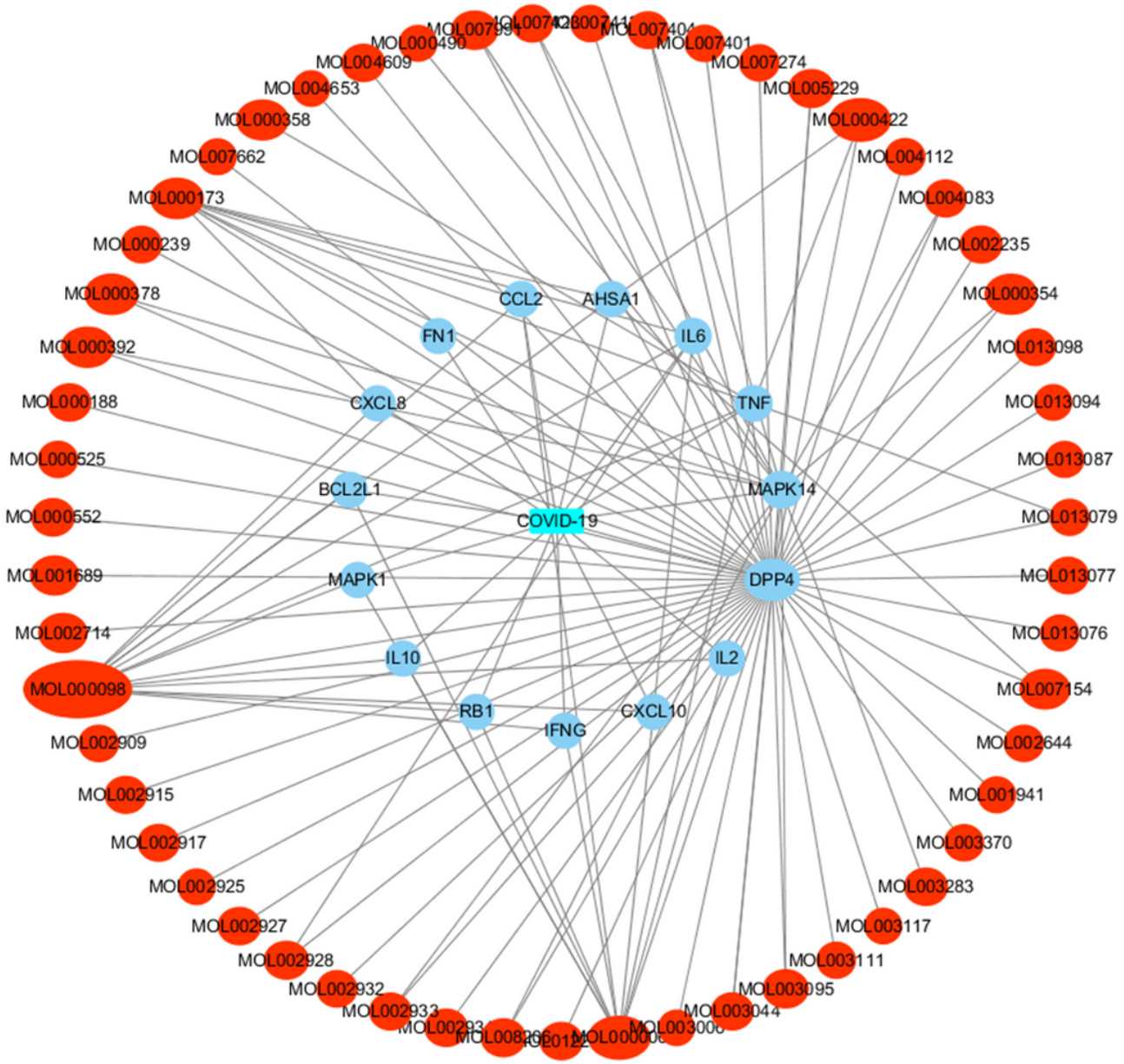

Figure 2

Components-disease target-disease network. The size of the graphic area indicates the importance of the nodes in the network. (Red plots represent compounds contained in Toujiequwen Granules related to COVID-19. Blue plots represent compound targets which are related to Toujiequwen Granules and COVID-19).

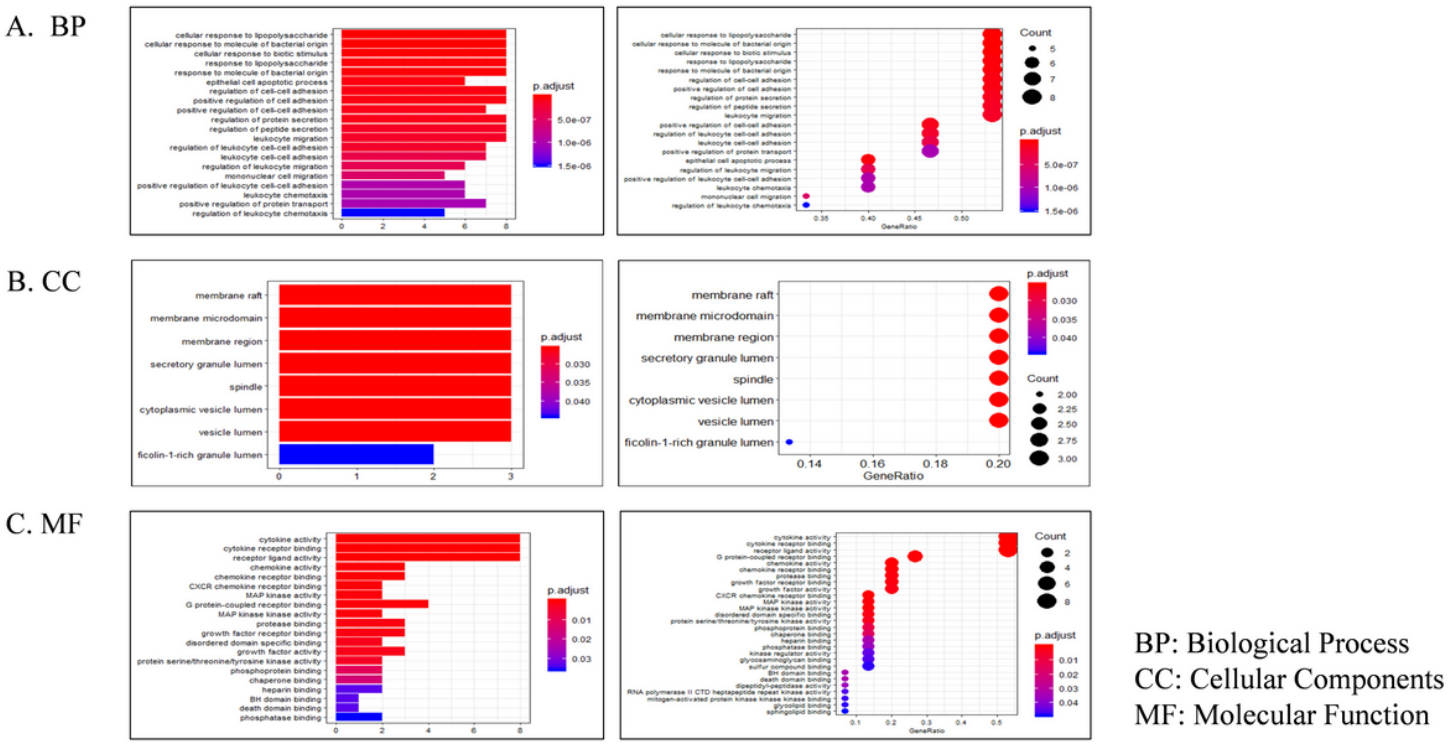

Figure 3

Analysis of GO enrichment results of Toujiequwen granules related to the possible disease targets of COVID-19 (The y-axis shows significantly enriched GO categories of the target genes, and the x-axis shows the counts of targets or GeneRatio (FDR < 0.02).)

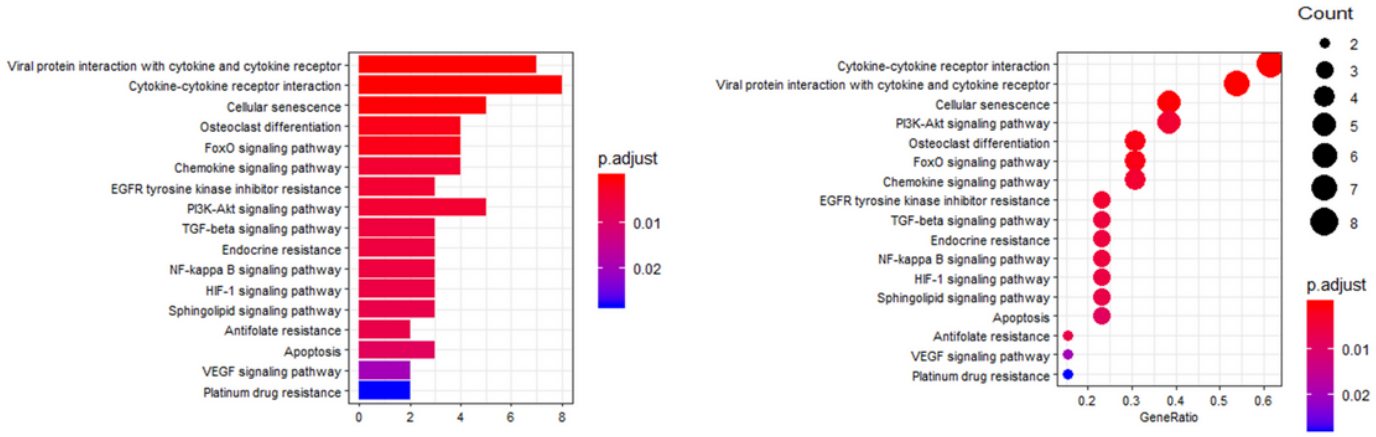

Figure 4

Analysis of KEGG enrichment results of Toujiequwen granules related to the possible disease targets of COVID-19 (The y-axis shows significantly enriched KEGG pathways of the target genes, and the x-axis shows the GeneRatio (FDR < 0.02). GeneRatio stands for the ratio of the number of target genes belonging to a pathway to the number of all the annotated genes located in the pathway. The higher GeneRatio represents the higher level of enrichment. The size of the dot indicates the number of target genes in the pathway, and the color of the dot reflects the different p.adjust)

Supplementary Files

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- table.docx
- GraphicalAbstracts.png