Network Pharmacology Analyses on Polygonum Cuspidatum is a Potential Target to Treat and Prevent COVID-19

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Abstract

Through data mining and bioinformatics analysis platform, the signal pathway of Polygonum cuspidatum extract was constructed and its potential molecular mechanism was predicted. TCMSP, PharmMapper, STITCH and other databases were used to obtain the chemical components and corresponding targets of Polygonum cuspidatum. NCBI-GENE, GeneCards and other databases were used to screen COVID-19 related targets. the "compound target" interaction network and protein interaction (PPI) network were constructed by using Cytoscape software and string database to screen the key components and key targets of therapeutic effect. Go and KEGG pathway enrichment analysis were used to identify the potential mechanism. The results showed that there were 32 active components and 195 targets in the analgesic effect of Polygonum cuspidatum, network pharmacology showed that the main active components of Polygonum cuspidatum, particularly luteolin and quercetin could act on multiple targets. Polygonum cuspidatum had effect to treat SARS-CoV-2 mainly through the following pathways: PI3K–Akt signaling pathway, MAPK signaling pathway. This study provides the basis for the study of the material basis and mechanism of analgesic effect of Polygonum cuspidatum.

Keywords

Polygonum Cuspidatum; Active Ingredients; Analgesia; Signal Pathway.

1. Introduction

Coronavirus disease (COVID-19) was caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a newly discovered coronavirus with a size of 60–140 nm, located in the SARB subgene of the Betacoronavirus family[1]. Moreover, the population's susceptibility to this highly pathogenic coronavirus led to massive global outbreak which turned into an international public health event[2]. No vaccine for SARS-CoV-2 has been published publicly, and there was no medication specific for the treatment of COVID-19 so far[3]. It was proved that Traditional Chinese Medicine (TCM) could obviously shorten fever duration and symptomatic relief of the patients with severe COVID-19[4,5].

According to the theory of TCM, the core pathogenesis of COVID-19 was the wet epidemic caused by the cold and humidity outside the lung and spleen, which was transformed into heat and lead to heat stagnation due to the imbalance of qi mechanism and endogenous stagnated heat[6]. Agastache rugosus and ephedra in Polygonum cuspidatum have the functions of detoxifying dampness, clearing heat, and relieving asthma. Polygonum cuspidatum was applied to the treatment of severe patients, and proved to be effective in resisting SARS-CoV-2, eliminating inflammation, and improving immunity[7]. However, the mechanism of Polygonum cuspidatum for the treatment of COVID-19 was not clear. the components of each herb were complex. The therapeutic effect of each herb or each component was not clear. Network pharmacology was proposed as a promising method to understand herbal formulas[8] and predict potential new drugs or targets for the specific diseases[9]. In this study, we aim to utilize network pharmacology understand the active compounds of Polygonum cuspidatum, predict their potential targets and signal pathways, and explore the association between the active compounds of Polygonum cuspidatum treatment of COVID-19.

2. Materials and methods

2.1 Collection and screening of chemical constituents from Polygonum cuspidatum

This study was conducted through TCMSP. All the active components of Polygonum cuspidatum were searched and the chemical index database was used to match the small molecular compounds. The main active components were further screened according to the oral availability (OB) ≥ 30% and drug like (DL) ≥ 0.18[10]. OB and DL are the key indicators to evaluate the effective utilization of drugs. Generally speaking, the active components with OB ≥ 30% and DL ≥ 0.18 can be regarded as the main active components of drugs.

2.2 Prediction of potential targets

The protein targets of compounds were predicted by using PharmMapper and STITCH, and the retrieval function of UniProtKB in UniProt database was used. By inputting the protein name and limiting the species to human, all target gene names were corrected to official gene symbol, and the active components without target were eliminated. Obtain the information of active components and related targets.

2.3 COVID-19 target prediction

According to NCBI-GENE and GeneCards databases, the key words "COVID-19" were used to search and screen the related targets, remove the duplicate genes, and summarize the potential targets of COVID-19.

2.4 Network construction and analysis

The protein-protein interaction (PPI) network of potential targets and disease targets was constructed by using Cytoscape 3.6.1, and the correlation function in the software was used to fuse and extract the intersection network of the two network graphs, that is, the direct and indirect target regulatory network was obtained.

2.5 Enrichment analysis of biological process and pathway

In order to explain the potential targets of active ingredients in Polygonum cuspidal tum, and the role targets in gene function and signal pathway, this study used R language programming to analyze GO and KEGG pathway signal pathway, set threshold $P<0.05$, and predicted the possible mechanism of Polygonum cuspidatum by gene enrichment analysis.

Table 1. The effective chemical constituents of Polygonum cuspidatum were searched by TCMSP database

Mol ID	Molecule Name	OB(%)	DL
MOL013281	6,8-Dihydroxy-7-methoxyxanthone	35.83	0.21
MOL013287	Physovenine	106.21	0.19
MOL013288	Picralinal	58.01	0.75
MOL002259	Physciondiglucoside	41.65	0.63
MOL002268	rhein	47.07	0.28
MOL002280	Torachrysone-8-O-beta-D-(6'-oxayl)-glucoside	43.02	0.74
MOL000358	beta-sitosterol	36.91	0.75
MOL000492	(+)-catechin	54.83	0.24
MOL000006	luteolin	36.16	0.25
MOL000098	quercetin	46.43	0.28

3. Results

3.1 Screening of chemical constituents from Polygonum cuspidatum

According to TCMSP database, 32 kinds of active ingredients were obtained from Polygonum cuspidatum, 10 kinds of active ingredients were obtained from chemical index database, and number

was listed, as shown in Table1; according to the principle of OB ≥ 30%, DL ≥ 0.18, According to the degree analysis, the top eight compounds were MOL013281 (6, 8-Dihydroxy-7-methoxyxan thone), MOL013287 (Physov enine), MOL013288 (Picralinal), MOL002259 (Physciondiglucoside), MOL002268 (rhein), MOL002280 (Torachrysone-8-O-beta-D-(6'-oxayl)-glucoside), MOL000358 (beta-sitosterol), MOL000492 ((+)-catechin), MOL000006 (luteolin), MOL000098 (quercetin). More details of these top eight compounds are shown, see Table 1.

3.2 Construction and analysis of drug target disease interaction network

The active components and potential targets of the drug were to establish the Venn diagram of effective extract of Polygonum cuspidatum and COVID-19 targets, as shown. there are 40 targets in the PPI network graph, and each node represents a target. The connecting line between targets is edge, which indicates that there is interaction between connected targets. The number of edges between each target and other targets is the degree of the target. The higher the degree, the more core the target occupies in the network graph,see Fig.1and Fig.2.

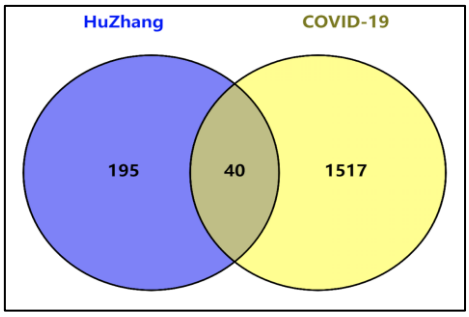

Fig. 1 Venn diagram of drug action targets and COVID-19 related targets of Polygonum cuspidatum extract (LIST1 is the corresponding target of compound, List2 is the COVID-19 related target)

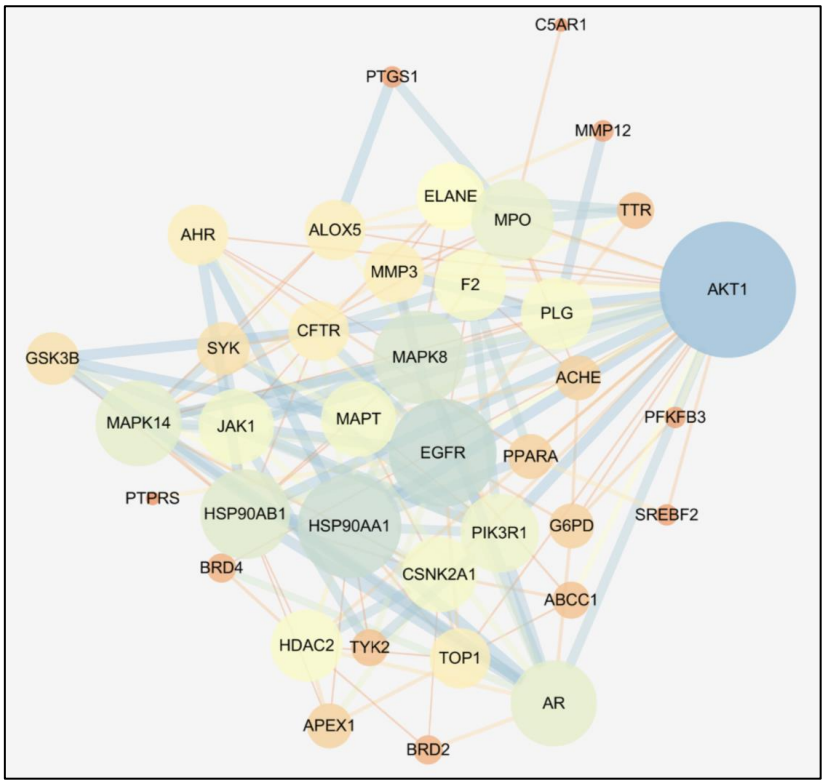

Fig. 2 Network diagram of the effects of extracts from Polygonum cuspidatum on COVID-19 related targets

3.3 Enrichment analysis of biological process and pathway

R language programming is used to annotate and analyze the go function of the target, and the results are shown; KEGG pathway enrichment analysis is carried out through of Cytoscape software, and the results are shown. The biological process network diagram of target enrichment shows that the related targets of drug participate in multiple biological processes, and different biological process involve different types of diseases. These targets play an important biological function in the body by regulating multiple biological process, see Fig.3 and Fig.4.

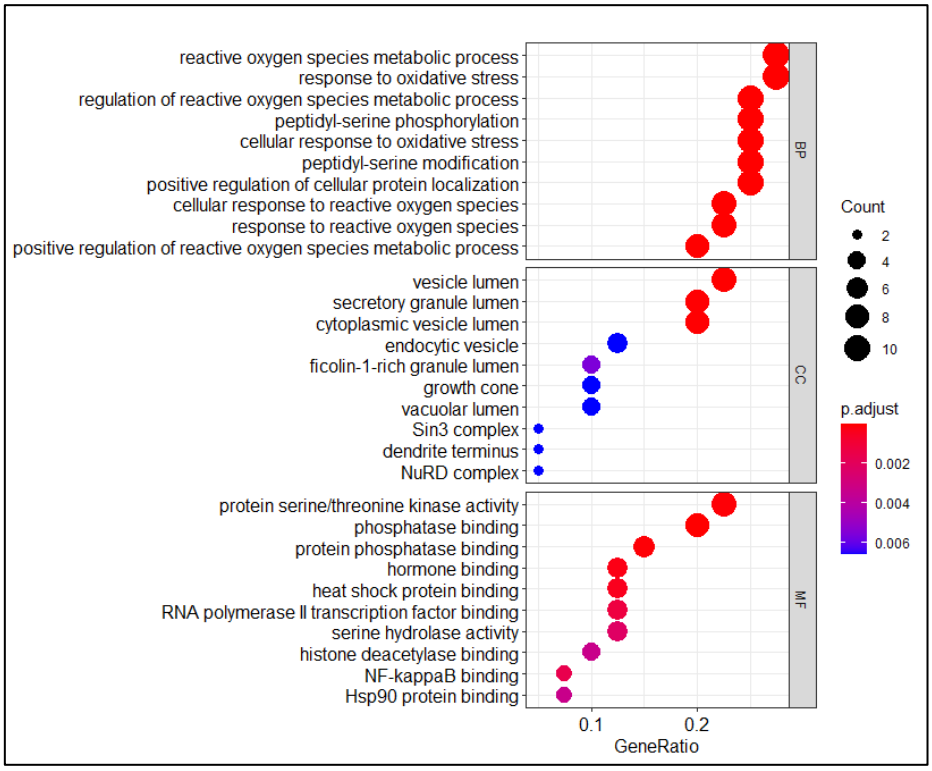

Fig. 3 Construction of the drug-target pharmacology network and GO enrichment analysis.

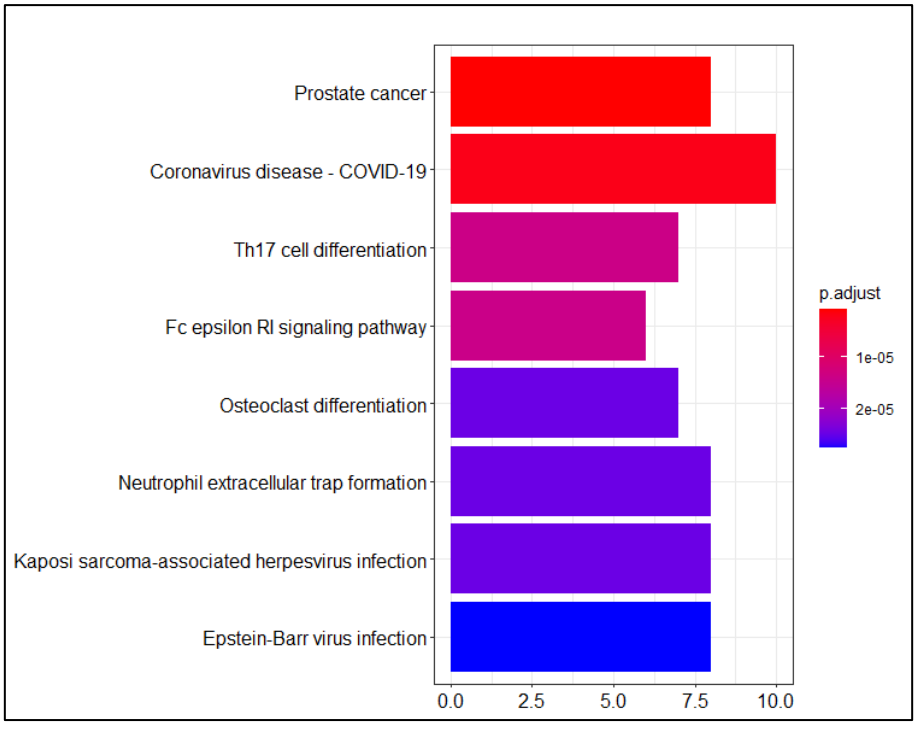

Fig. 4 KEGG enrichment analysis and pathway map.

4. Discussion

Over the past ten months, COVID-19 has rapidly spread around the world. SARS-CoV-2 pandemic is still raging in most countries due to the lack of target drugs. Notably, China, as a country with a population of more than 1.3 billion, has successfully con- trolled the epidemic outbreak. TCM has made an indispensable contribution to prevent and cure SARS-CoV-2 infection.

In the present study, we constructed an drug target COVID-19–related gene set that consisted of target genes by analysing the active components from ingredients of Polygonum cuspidatum. GO and KEGG analysis revealed that drug can regulate the process of immune pathways and virus defence. PPI network and critical network analyses found hub targets out of genes. We focus on the most significant gene, Akt1, and performed molecular docking to verify the interaction between active compounds of drug and Akt1. The results of the research demonstrate the effectiveness of Polygonum cuspidatum in the treatment of COVID-19 from a bioinformatics perspective, and provide a landscape on the mechanism of Polygonum cuspidatum. The results may also promote target drug design and basic research on SARS-CoV-2 infection.

We screened several ingredients of Polygonum cuspidatum in TCMSP database. In this study, we screened out eight main active components of Polygonum cuspidatum: luteolin and quercetin were both flavonoids. Flavonoids reduced the barrier dysfunction induced by influenza A virus by inhibiting the NOX4/NF-jB/ MLCK pathway, which might be a potential drug for the prevention and treatment of influenza A virus and pulmonary endothelial barrier dysfunction [11]. Since both SARS and COVID-19 were caused via binding S-protein to ACE2 [12,13], quercetin acted as a competitive antagonist to inhibit infection of SARS-CoV-2. Other research also reported that quercetin had the functions of reducing capillary brittleness, angiogenesis, detoxification, apoptosis, cell cycle, and antioxidant replication [14]. The results of PPI network showed that, MMP3, MAPK8, MAPK14 and JAK1 were considered to be hub genes. According to these results, we think Polygonum cuspidatum had effect to treat SARS-CoV-2 through the following pathways. (1) MAPK signaling pathway: Previous studies showed that MAPK signaling pathway participated in the progression of ARDS [15]. Many inflammatory factors such as IL1b, TNF-a, and IL-6 were produced via MAPK signaling pathway [16]. Some anti-inflammatory medications work by targeting MAPK signaling pathway [17,18]. Quercetin was found to regulate the activation of MAPK signaling pathway in retinoblastoma, cardiomyocytes, and chorionic carcinoma cells[19]. Other studies have found that baicalin may inhibit the expression and invasion of cancer cells by inhibiting the p38 MAPK signaling pathway [20]. (2) PI3K–Akt signaling pathway: The PI3K/AKT signaling pathway regulated the activation of inflammatory response cells and the release of inflammatory transmitters to play a role in chronic inflammatory response in the lungs and airways. Quercetin inhibited the PI3K–Akt signaling pathway by inhibiting the expression of AKT1 to silence the anti-apoptotic effect of lung fibroblast, thus realize the treatment of pulmonary fibrosis.

There are several limitations in our study. First, our results need to be further verified by experiments. Second, more comprehensive TCM target genes database was needed, which made the results of network pharmacology analysis more reliable. Third, even if the results of network pharmacology were combined, we still could not completely understand the accurate therapeutic mechanism of Polygonum cuspidatum. A comprehensive understanding of Polygonum cuspidatum and COVID-19 depended on the common development of multi-disciplines.

5. Conclusions

In summary, network pharmacology showed that the main active components of Polygonum cuspidatum, particularly luteolin and quercetin could act on multiple targets. Polygonum cuspidatum had effect to treat SARS-CoV-2 mainly through the following pathways: PI3K–Akt signaling pathway, MAPK signaling pathway. luteolin and quercetin were the two compounds which indicated that they might play an important role in the treatment of SARS-CoV-2.

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