The Mechanism of Qingkailing on Acute Tonsillitis Based on Network Pharmacology

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Abstract. Acute tonsillitis is a common inflammation in the population. How to quickly control the development of acute inflammation is a problem worthy of study. Modern studies have found that traditional Chinese medicine has obvious effects in controlling inflammatory reactions, such as anti-virus, anti-bacteria, anti-infection and so on. Based on network pharmacology, this paper explores the mechanism of action of traditional Chinese medicine compound Qingkailing on acute tonsillitis, and further explores the mechanism of anti-inflammatory treatment of traditional Chinese medicine. In this paper, various databases were used to analyze the active ingredients of Qingkailing prescription and the gene targets of acute tonsillitis. The target mechanism and molecular signaling pathway of Qingkailing in the treatment of acute tonsillitis were demonstrated through multiple mappings. It is clarified that Qingkailing regulates the inflammatory process of acute tonsillitis through multi-component, multi-pathway and multi-target. In the course of the study, we found that the active ingredients of Qingkailing may also be related to cancer, diabetes, cancer and other diseases, which is worthy of further exploration.

Keywords: Qingkailing Compound; tonsillitis; network pharmacology; active ingredients; target; protein interaction.

1. Introduction

Acute tonsillitis refers to the acute non-specific inflammation of the palatine tonsil, which belongs to a type of upper respiratory tract infection. Western medicine for the treatment of tonsillitis mainly oral drug therapy, cutting therapy, surgical treatment and other methods of treatment [1]. Traditional Chinese medicine dialectical acute tonsillitis is caused by phlegm heat inside and exogenous wind and fire. The treatment is mainly based on dispelling wind and clearing heat, detumescence and detoxification. Among them, the commonly used clinical compound is Qingkailing granule or Qingkailing capsule. The formula of Qingkailing is derived from Angong Niuhuang Pill in ' differentiation of seasonal febrile diseases '. After the addition and subtraction of the original prescription (Angong Niuhuang Pill), a Qingkailing traditional Chinese medicine compound composed of cholic acid, mother pearl, hyodeoxycholic acid, gardenia, buffalo horn, radix isatidis, baicalin and honeysuckle was formed. The whole flavor is bitter and cold, with the effect of detoxification, clearing heat, tranquilizing and calming. Pig bile has the effects of clearing heat and moistening dryness, relieving cough and asthma, and detoxification. Gardenia has the effects of clearing heat and dampness, cooling blood and detoxification, purging fire and removing troubles. Buffalo horn has the effects of clearing heat and cooling blood, detoxifying and alarming. Banlangen has the effects of clearing heat and detoxifying, cooling blood and relieving sore throat; scutellaria baicalensis Georgi has the effects of clearing heat and drying dampness, purging fire and detoxifying ; honeysuckle has the effect of heat-clearing and detoxifying to evacuate wind-heat [2].

Modern studies have shown that Qingkailing has antibacterial, anti-inflammatory and anti-infective effects, in which a variety of active ingredients act on different targets to exert different pharmacological functions. In order to further explore the mechanism of Qingkailing on acute tonsillitis, this paper uses the method of network pharmacology to analyze the active components and targets of Qingkailing, and studies its molecular mechanism. It is found that the active components of Qingkailing include quercetin, kaempferol, β-sitosterol, stigmasterol, etc. The main targets are

TP53, JUN, AKT1, MAPK1, RELA, TNF, indicating that it has a certain inhibitory effect on anti-inflammation and provides a certain value for clinical research.

2. Materials and methods

2.1. Screening of Drug Targets and Collection of Disease Targets

The TCMSP database (http://tcmspw.com/)) was used to search the active ingredients and targets of the drugs. According to the oral bioavailability (OB) and drug-likeness (DL) of the compounds, the OB≥30 % and DL≥0.18 were used as the thresholds [3]. The active ingredients of 'Zhizi', 'Banlangen', 'Jinyinhua' and 'Huangqin' were summarized and sorted out. With the help of Uniprot database (https://www.uniprot.org), the collected active components of traditional Chinese medicine were matched in the database to find the relevant targets of active components.

Using GeneCards (https://www.genecards.org/) database 'Acute tonsillitis' was searched as a keyword to obtain the target of acute tonsillitis [4].

2.2. Construction of Compound-target Network and Protein Interaction Network

The compound-target network was constructed by Cytoscape software. Cytoscape software is a network construction of genes or active ingredients. Each node represents the interaction between genes or active ingredients. The size of the node is related to the degree value, and the higher the degree' value at the core, the higher the degree value [5,6].

The STRING (http://string db.org) database was used to construct a protein-protein interaction network. The species was selected as Homosapiens, the minimum required interaction score was set to 0.900, and the remaining parameters remained the default setting to obtain the PPI network [7].

KEGG analysis was performed using the Metascape database [8]. $P < 0.05$ was set to obtain the first 20 signal pathways enriched by KEGG.

3. Results

3.1. Screening of Potential Active Ingredients and Collection of Corresponding Targets

In the TCMSP database, OB≥30 % and DL≥0.18 were set. There were 15 active components of Lonicerae Japonicae Flos, 36 active components of Scutellariae Radix, 15 active components of Gardeniae Fructus, and 39 active components of Isatidis Radix. Among them, MOL000358 and MOL000449 are the common components of fever of Gardenia jasminoides Ellis, Isatidis Radix and Scutellariae Radix; MOL001494 and MOL003095 are the common components of Gardenia jasminoides Ellis and Lonicerae Japonicae Flos; MOL001689 and MOL000359 are the common components of Isatidis Radix and Scutellariae Radix; MOL002914 is the common component of Lonicerae Japonicae Flos and Scutellariae Radix. The obtained active ingredients were input into the TCMSP database again, and the target proteins of the active ingredients were retrieved and sorted out. Among them, there are 99 target proteins of honeysuckle, 507 target proteins of scutellaria baicalensis, 363 target proteins of gardenia, and 338 target proteins of isatis root. Using the Uniprot database, the target genes corresponding to the target protein were searched and sorted into the Excel table, which corresponded to the target protein one by one.

3.2. Compound-target Network Construction

The active ingredients retrieved from the TCMSP database were numbered in the form of capital letters + numbers '. For example, the active ingredients of gardenia were numbered according to ZZ1, ZZ2, ZZ3... ', and so on. For duplicate active ingredients, another number is given : MOL000358 is labeled A1, MOL000449 is labeled A2, MOL001494 is labeled B1, MOL003095 is labeled B2, MOL001689 is labeled C1, MOL000359 is labeled C2, MOL002914 is labeled D1.

Cytoscape software was used to construct the relationship between active components and targets (Fig.1).

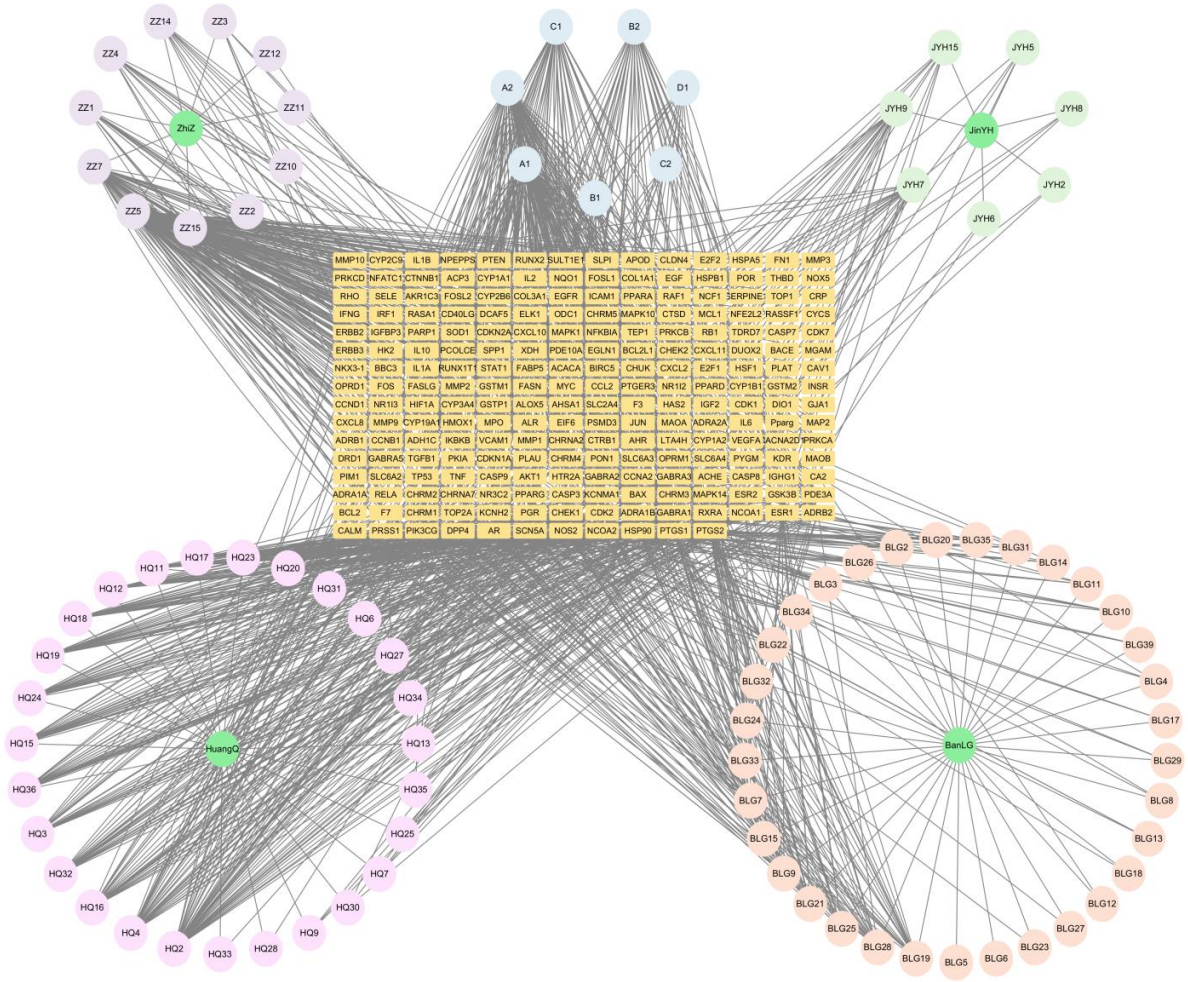

Fig. 1 Drug-compound-target network.

3.3. Screening of Disease-related Targets

Using the GeneCards database, 3301 targets related to acute tonsillitis were obtained by searching for Acute tonsillitis as a keyword. The median of Relevance score was taken by Excel function. After the number of disease genes was halved twice, the Relevance score was≥5.846972466, and 754 disease genes were obtained. Using the Venn diagram, the target genes of the active ingredients of the drug were constructed with the disease genes, and 96 overlapping genes were obtained (Fig.2).

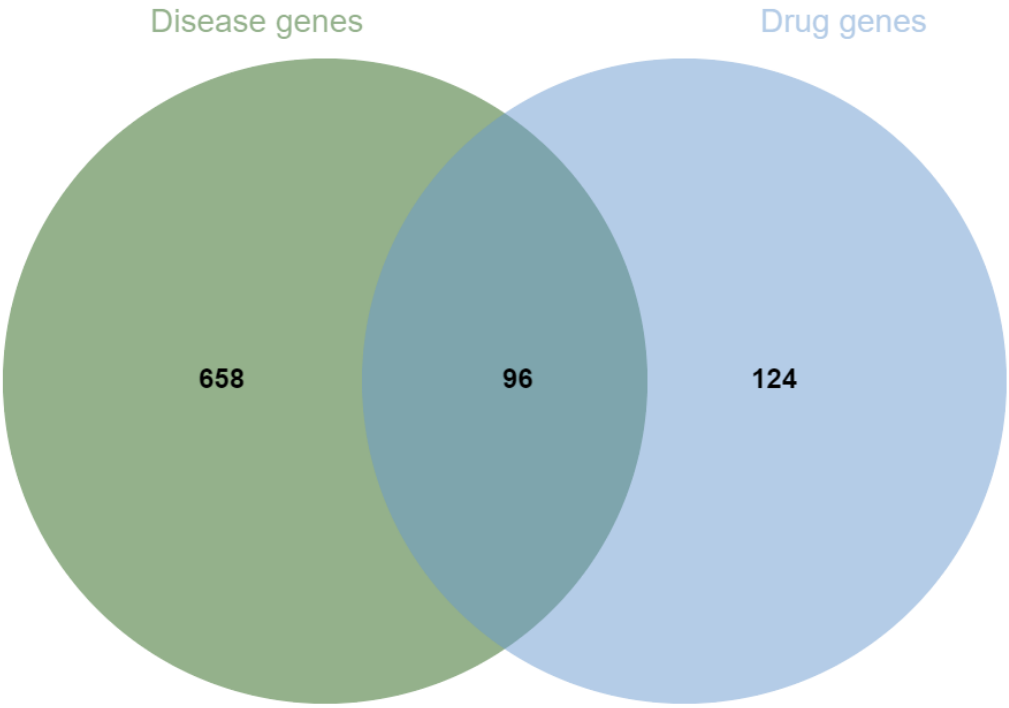

Fig. 2 Venn diagram of coincident genes

A protein-protein interaction network was constructed using the STRING (http://string db.org) database. The PPI network has 110 nodes and 1216 edges. The larger the node, the darker the color, representing the greater the degree value of the target [9]. The network was imported into Cytoscape software for visual analysis (Fig 3), and the core targets were screened out, including TP53, JUN, AKT1, MAPK1, RELA, TNF and so on. It is speculated that Qingkailing may play a role in the inflammatory response at these targets.

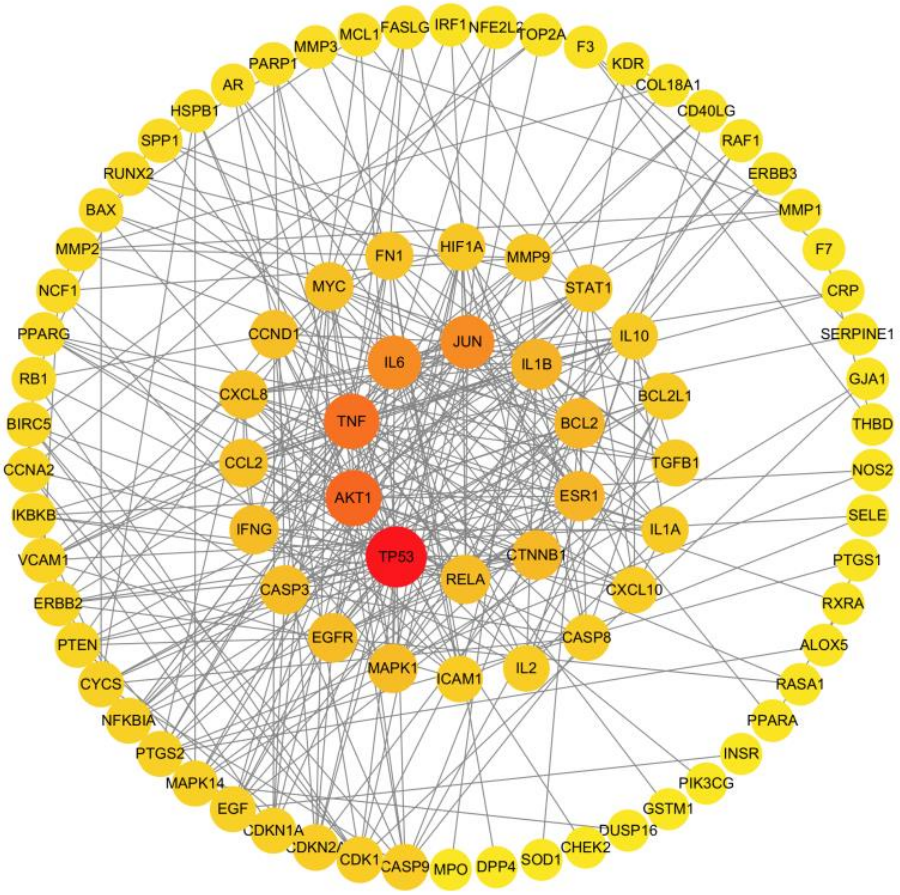

Fig.3 PPI network

3.4. KEGG Enrichment Analysis

Metascape database was used to obtain the top 20 signaling pathways of KEGG enrichment for GO pathway (Fig 4) and KEGG enrichment analysis (Fig 5). The results of KEGG enrichment analysis showed that the signaling pathways involved in common gene targets included but were not limited to cancer, diabetes, and inflammatory response. Among them, NF-kappa B signaling pathway, Mitophagy-animal, Natural killer cell mediated cytotoxicity, Leukocyte transendothelial migration are related to inflammatory response and participate in the body 's immune response.

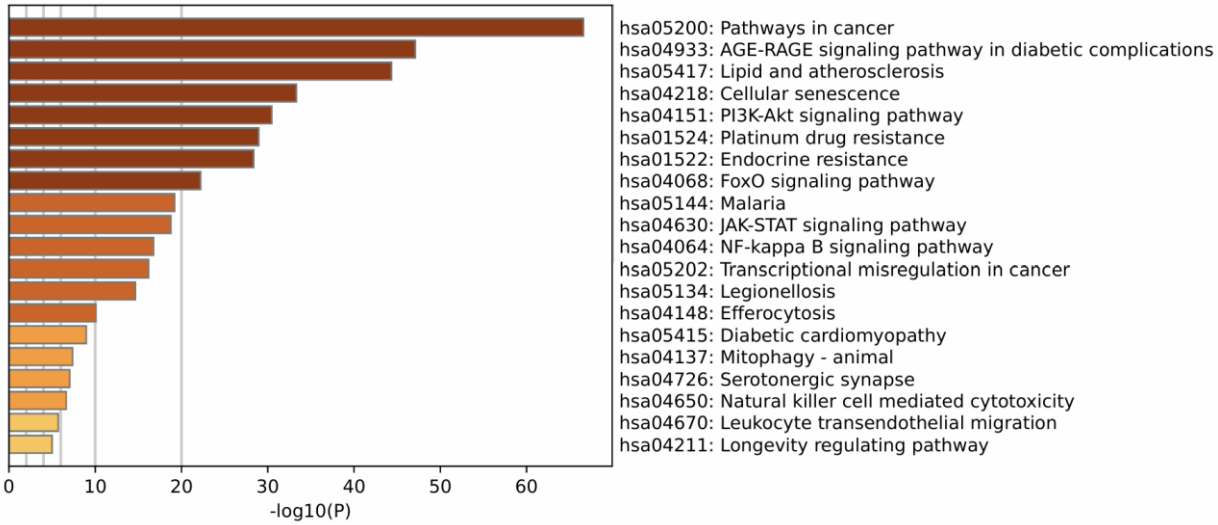

Fig.4 DO pathway.

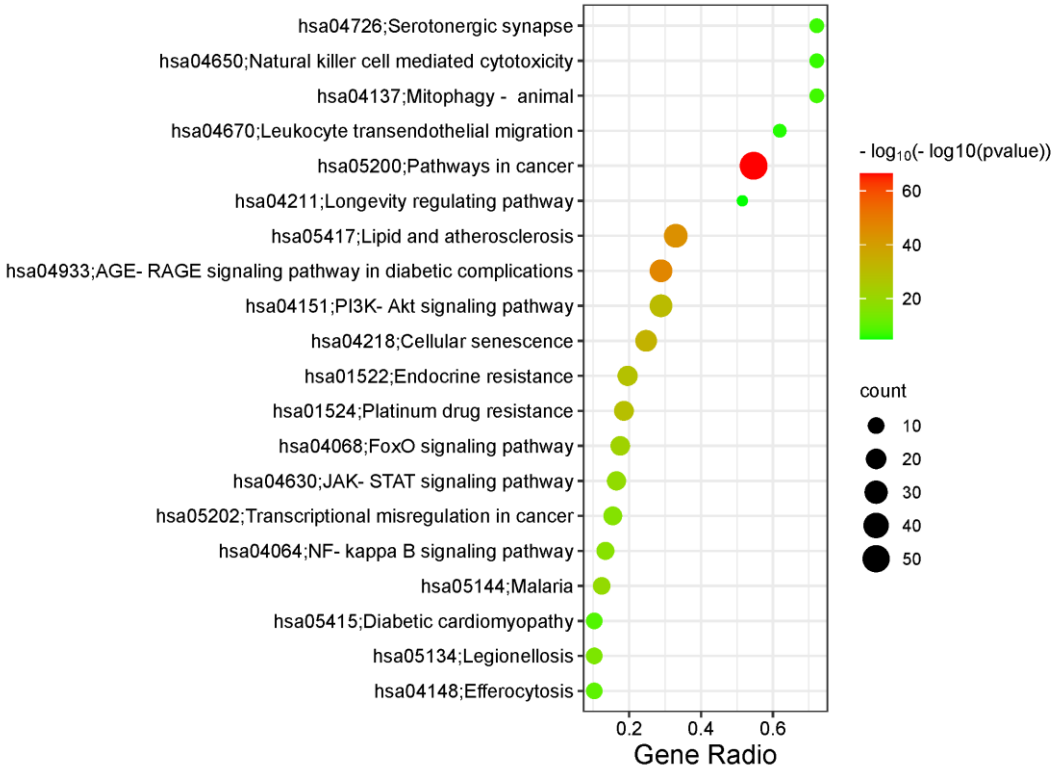

Fig.5 KEGG enrichment analysis

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4. Discussions

4.1. Bioactive Ingredients

In this study, 105 components of Qingkai flexibility were screened by TCMSP database, and 1307 corresponding gene targets were found. Among the active ingredients with a large number of drug targets, quercetin, kaempferol, β-sitosterol and stigmasterol were found. According to the existing research results, quercetin has the function of cleaning up the body 's free radicals, and can inhibit the activity of various inflammatory factors, so as to achieve the effect of reducing the inflammatory response ; kaempferol has the function of inhibiting the release of inflammatory substances in cells, and also has a certain inhibitory effect on the inflammatory response ; β-sitosterol has a good ability to remove free radicals and can play an anti-inflammatory and antipyretic role ; at the same time, studies have shown that stigmasterol has certain antiviral and anti-inflammatory effects [10].

4.2. Inflammation-related Factors

In the gene target PPI network of Qingkailing 's anti-acute tonsillitis, the main targets were TP53, JUN, AKT1, MAPK1, RELA and TNF, indicating that it played a certain inhibitory effect on anti-inflammation. Through KEGG enrichment analysis of gene targets, it was found that the active components were involved in the inflammatory response and immune response of the body through NF-κB signaling pathway, mitophagy, natural killer cell-mediated cytotoxicity, leukocyte transendothelial migration and other pathways.

5. Conclusion

In conclusion, based on the network pharmacology method, this study used various databases to mine and cross-sort the information of the active ingredients of Qingkailing prescription and the gene targets of acute tonsillitis, analyzed and predicted the target mechanism and molecular signaling pathway of Qingkailing in the treatment of acute tonsillitis, and clarified that Qingkailing regulates the occurrence of acute tonsillitis through multi-component, multi-pathway and multi-target [11]. In addition, in the process of KEGG enrichment analysis, we found that the active components of Qingkailing also act on genes related to cancer, diabetes, cancer and other diseases, which is worthy of further exploration.

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