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EXPERIMENTAL RESEARCH

Network pharmacology-based analysis: Fufang Xiongdan Diyanye—clinical response and mechanism of action in the treatment of acute bacterial conjunctivitis

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[Abstract] **Objective** To observe the clinical response to Fufang Xiongdan Diyanyein patients with acute bacterial conjunctivitis and to examine its mechanism of action with the use of network pharmacology. **Methods** Eighty patients with acute bacterial conjunctivitis were randomly selected and equally randomized to either levofloxacin eye drops (control group) or Fufang Xiongdan Diyanye(observation group). Responses were compared between the two groups by assessing the patients' symptoms (e.g., foreign body sensation, itchy eyes, frequent blinking) and signs (e.g., conjunctival congestion, edema, discharge) before and after the therapy. The chemical components and relevant pharmacological targets of Fufang Xiongdan Diyanyewere retrieved from the Traditional Chinese Medicine Systems Pharmacology (TCMSP) and the National Center for Biotechnology Information (NCBI) databases. The targets of conjunctivitis were screened with the use of the Therapeutic Target Database (TTD) and the Drugbank database. The STRING (Search Tool for the Retrieval of Interacting Genes/Proteins) database was also accessed to perform protein–protein interaction (PPI) analysis and GO (Gene Ontology) and KEGG (Kyoto Encyclopedia of Genes and Genomes) enrichment analyses. A network made up of compounds, targets, and signaling pathways was created using Cytoscape, from which a key subnetwork was extracted by a cluster analysis with the Molecular Complex Detection plugin. **Results** The response rate was higher in the observation group (97.50%) compared to the control group (85.00%) and the difference was statistically significant ($P < 0.05$). A total of 42 compounds were selected from the bear bile powder and borneol after screening, and 192 compound targets and 85 disease targets were obtained amid the predictions. The compound targets directly act on disease targets, such as STAT3, ICAM1, and SYK, and are involved in the regulation of signaling pathways, such as PI3K-Akt and influenza A. **Conclusion** The effective relief of symptoms of acute bacterial conjunctivitis after treatment with Fufang Xiongdan Diyanyeis possibly related to action on targets (e.g., STAT3 and ICAM1) and regulation of classical inflammatory pathways (e.g., PI3K-Akt).

[Key words] Compound bear bile eye drops; Conjunctivitis; Network pharmacology; Mechanism of action

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1 Introduction

Conjunctivitis is inflammation of the conjunctiva and is often clinically presents as acute bacterial conjunctivitis or epidemic keratoconjunctivitis. Commonly known as pink eye, conjunctivitis is characterized by acute onset and occurs with tearing, photophobia, and conjunctival congestion and redness[1-2]. According to the theories of traditional Chinese medicine (TCM), the disease is caused by excess endogenous heat from the liver and lungs up to the eyes as well as illness with concomitant exogenous pathogenic factors (primarily as wind heat)[3]. Fufang Xiongdan Diyanyeare included in the Pharmacopoeia of the People's Republic of China, 2015. FuFang Xiongdan Diyanyeconsist of bear bile powder, which can calm the liver, improve the sight, and reduce fever; and natural borneol, which can clear the airways, eliminate stagnant heat, treat leukoma, and improve the sight[4].

In this study, data was collected from multiple cases of acute bacterial conjunctivitis at the Zhongshan Ophthalmic Center of Sun Yat-sen University. Our study illustrates the definite clinical response to Fufang Xiongdan Diyanye in patients with acute bacterial conjunctivitis, but the mechanism of action remains unclear. Based on modern medical databases, network pharmacology has been developed to systematically analyze interactions between compound TCM prescriptions and a network of biological components by creating a network map of "drug-gene-target protein-disease". With its holistic and systematic nature[5], network pharmacology is considered an effective tool to examine the mechanisms of compound TCM prescriptions. Thus, this study, from a holistic and systematic perspective, using network pharmacology aims to analyze the mechanisms of action by which Fufang Xiongdan Diyanye improve acute bacterial conjunctivitis and provide the rationale for the clinical use of this Chinese patent medicine.

2 Software and databases

The following software and databases were used in the analysis: TCMSP (http://lsp.new.edu.cn/tcmsp. php), DRAR-CPI (http://cpi.bio-x.cn/drar/), ChemSpider database (http://www.chemspider.com/), PubChem Compound database (https://pubchem.ncbi.nlm.nih.gov/), Therapeutic Target Database (TTD) database (http://bidd.nus.edu.Sg/group/cjttd/), Drugbank database (version 5.1.1, https://www.drugbank.ca/), UniProt database (https://www.uniprot.org/), STRING database (version 10.5, https://string-db.org/), and Cytoscape (version 3.7.1).

3 Methods and results

3.1 Assessment of clinical response

3.1.1 General information Eighty patients with acute bacterial conjunctivitis, who presented to the Zhongshan Ophthalmic Center of Sun Yassin University from February 2018 to December 2018, were randomly selected and equally randomized to either the control group or the observation group. The control group comprised 21 females and 19 males ranging from 18 to 40 years (mean age 29.73 ± 4.45 years). The observation group comprised 22 females and 18 males ranging from 20 to 41 years (mean age 31.73 ± 3.87 years). The difference in the general information between the two groups was not statistically significant (P>0.05), indicating comparability.

3.1.2 Inclusion criteria The control and observation groups were subjected to evaluation for inflammatory reactions of the eyes to exclude other eye disorders. Patients met the diagnosis criteria of acute bacterial conjunctivitis if they had had photophobia, tearing, redness, swelling, eye pain, and purulent discharge[6].

3.1.3 Treatment The control group received levofloxacin eye drops (Hebei Chuangjian Pharmaceutical Co., Ltd.)–two drops in the eyelids, three times a day; the observation group received Fufang Xiongdan Diyanye(Changchun Puhua Pharmaceutical

LLC) –two drops in the eyelids, six times a day. Both drugs were administered for three days.

3.1.4 Assessment measures The clinical responses in both groups were assessed according to the following criteria[7]: cured, if a patient's clinical symptoms and signs resolved after treatment; marked response, if a patient's clinical symptoms and signs improved notably after treatment; moderate response, if a patient's clinical symptoms and signs improved after treatment; no response, if a patient did not show any changes in clinical symptoms and signs after treatment. The overall response rate was calculated using the following formula: cure+marked response+moderate response/total number of cases×100%.

3.1.5 Statistical analysis Statistical analyses were conducted by means of a rank-sum test for the data, with the use of SPSS software, version 21.0. P values less than 0.05 were considered to indicate statistical significance.

3.1.6 Results The response rate was found to be significantly higher in the observation group compared to in the control group, and a statistically significant difference was observed (P<0.05) (Table 1).

3.2 Network pharmacology-based analysis of mechanism of action

3.2.1 Screening of compounds and prediction of their pharmacological targets: The Traditional Chinese Medicine Systems Pharmacology Database (TCMSP) was searched for the compounds of borneol according to the following criteria:OB⩾30%, DL⩾0.18, or consistent with Lipinski's Rule of Five. A total of 31 compounds were obtained, including alpha-pinene, oleanolic acid, and isoborneol. Eleven compounds of bear bile powder were obtained by means of searches of the National Center for Biotechnology Information (NCBI) and ChemSpider databases[8-14], including tauroursodeoxycholic acid, taurodeoxycholic acid, and ursodeoxycholic acid. Three-dimensional structures of these 42 compounds were retrieved from the PubChem Compound database and saved as SDF files. These documents were imported to the DRAR-CPI database for target prediction. The targets were then screened to remove repeat targets according to the docking score (Z-score), where targets with Z-scores lower than −1.5 were removed. (Compound-target binding is possible if the Z-score is lower than −0.5; the lower the value, the more robust the binding). A total of 192 compound targets were defined. The names of these compounds were then corrected using the UniProt database.

3.2.2 Screening of conjunctivitis-associated targets and analysis of pathogenesis The TTD and Drugbank databases were searched to predict the conjunctivitis-associated targets using the keywords "conjunctivitis", "epidemic kerato-conjunctivitis", and "acute bacterial conjunctivitis". The targets were defined according to the condition of "homo sapiens", and repeat targets were removed. A total of 85 disease targets were subsequently identified. The names of these targets were corrected using the UniProt database. Eighty-five targets were imported into the STRING database. Targets with no interactions in the network were hidden, and an analysis of protein–protein interaction (PPI) was performed. The results of the analysis were saved as TSV files and imported into Cytoscape to create an interaction network (Fig. 1). A high degree of nodes indicates

Table 1 Clinical response to treatment in the two groups [*n* (%)]

Group	*n*	Cure	Marked response	Moderate response	No response	Total response rate
Control group	40	19(47.50)	9(22.50)	6(15.00)	6(15.00)	34(85.00)
Observation group	40	24(60.00)	8(20.00)	7(17.50)	1(2.50)	39(97.50)*

Comparison with the control group: $^{*}P$ <0.05.

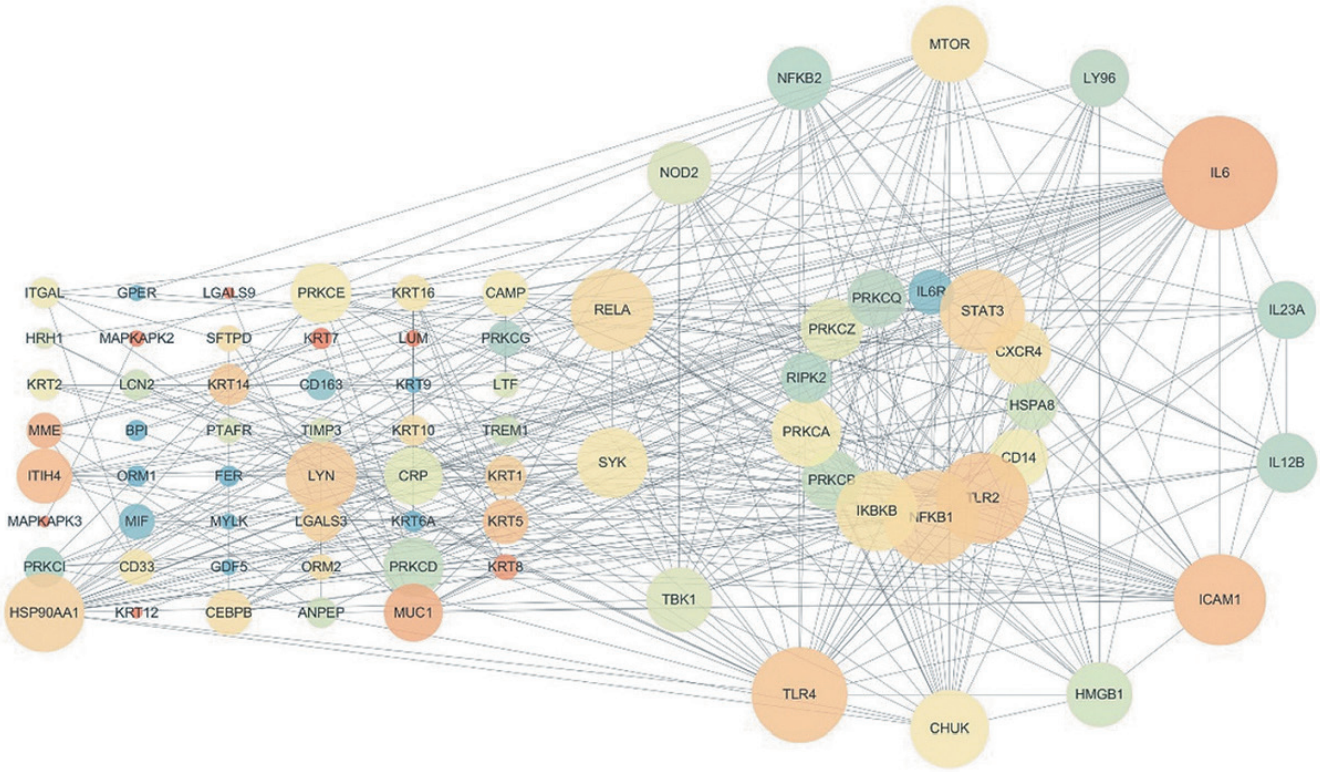

Fig. 1 Protein–protein interaction (PPI) network of disease targets

a key target closely associated with the disease. Researchers can thus identify or develop inhibitors to treat the condition. The top 35 disease targets are listed below in descending order of degree (the degree value of the protein is given in brackets): IL6 (43), TLR4 (32), NFKB1 (32), TLR2 (30), ICAM1 (30), STAT3 (26), RELA (25), IKBKB (24), HSP90AA1 (23), CHUK (22), MTOR (21), SYK (18), LYN (18), PRKCA (17), TBK1 (15), HMGB1 (15), NFKB2 (14), NOD2 (14), CXCR4 (14), PRKCZ (13), PRKCB (12), IL12B (12), PRKCD (12), PRKCE (12), IL23A (11), LY96 (11), PRKCQ (11), CD14 (11), MUC1 (11), CRP (11), ITIH4 (10), RIPK2 (9), HSPA8 (9), IL6R (8), and KRT5 (8).

Analyses by means of Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) show that the pathogenesis of acute bacterial conjunctivitis involves 714 biological processes, including immune regulation, defense reactions to germs, molecular reactions to external stimulation and bacteria, virus receptors, signal transduction, activity of protein kinase, and 38 molecular functions, including protein binding and small molecule binding. The onset of illness involves 47 cellular components, including vesicles, membrane-bound vesicles, extracellular space, the interleukin-6 receptor complex, and immunological synapses. The disease is related to abnormalities of 104 signaling pathways, including influenza A, virus infection, PI3K-Akt, herpes simplex virus infection, modulation of tryptophan channels by inflammatory mediators, and contraction of vascular smooth muscle.

3.2.3 Compound targets and relevant mechanism of action A total of 192 compound targets and 85 disease targets were imported into the STRING database. Those free of interactions were removed. A network, comprising 215 nodes and 1 945 edges, was visualized, with an average degree of 18.1 and a network density of 0.54. Edges with combined scores higher than 0.9 (i.e., PPI) were chosen, and a set of key targets were identified, including 36 compound targets and 15 disease targets. The compound targets incorporated

SRC (34), MAPK3 (33), MAPK1 (32), TP53 (32), EGFR (31), PIK3R1 (30), IL4 (30), JUN (30), VEGFA (30), IL1B (29), TNF (29), JAK2 (26), MAPK14 (29), PIK3CG (28), MAPK8 (28), HGF (27), HRAS (25), APP (25), PLG (24), CCL2 (24), RHOA (23), VCAM1 (22), LCK (21), JAK3 (18), SELE (16), CHRM1 (12), HTR2A (10), ADRA1B (9), GHR (9), CHRM3 (9), BTK (9), ADRA1A (9), ADRA1D (8), CSF2RB (7), B4GALT1 (2), and B4GALT4 (2). The disease targets consisted of STAT3 (29), ICAM1 (26), SYK (20), IL6R (14), LGALS3 (12), PTAFR (12), HRH1 (10), TIMP3 (9), KRT8 (8), LUM (7), ORM2 (6), ORM1 (6), MAPKAPK2 (6), KRT5 (4), and MKL1 (1). The target set comprising these 51 targets was imported into the STRING database. A network with 51 nodes and 461 edges was obtained. The network density was increased to 0.801, illustrating the greater importance of this network compared with the previous network (network density of 0.54). GO and KEGG enrichment analyses were performed for the network. The GO analysis revealed that Fufang Xiongdan Diyanye regulate 789 biological processes (e.g., cell transport, cell migration, leukocyte migration, movement of cellular or subcellular components, reaction to organonitrogen compounds, cellular localization, defense reaction, reaction to organics, and signaling pathway of cell surface receptors) and 55 molecular functions (e.g., protein biding, activity of G protein-coupled receptors, receptor binding, phosphatase binding, activity of non-transmembrane protein tyrosine kinase, signal sensor, enzyme binding, activity of alpha-1 adrenergic receptor and mitogen-activated protein kinase, and phosphatase binding). The primary enrichment KEGG pathways of 51 key targets were listed in descending order of false discovery rate (FDR). The top 10 pathways are shown in Table 2 and suggested that the mechanism of action of Fufang Xiongdan Diyanye in the treatment of conjunctivitis is related to multiple signaling pathways, including proteoglycans in cancer, TNF, Fc epsilon RI, and PI3K-Akt.

3.2.4 Creation of network "medicinal material-compound-pharmacological target-signaling pathway"

The compounds of the drug, targets of compounds, and key compounds selected through the above process were exported to Cytoscape. A network was then created (Fig. 2). The results suggested that Fufang Xiongdan Diyanye work by acting on multiple targets and regulating a number of signaling pathways, where the targets of bear bile powder compounds play a primary role.

4 Discussion

4.1 Fufang Xiongdan Diyanye possibly act on targets of STAT3, ICAM1, and HRH1

One of the primary explanations for blindness is seriously disrupted barrier function of corneal endothelial cells as a result of anterior chamber inflammation. Activated STAT3 (signal transducer and activator of transcription-3) signaling regulates various reactions that occur in cells through inflammation and mediates the expression of the barrier function marker[15], ZO-1. The level of phosphorylated STAT3 rises with an increase in cytokines (e.g., LIF, IL-6, and IFN-γ) when inflammation occurs. After administration of bear bile eye drops, expression of ZO-1 was reduced, transendothelial electrical resistance was decreased, and apoptosis was induced. Transcriptional activation of STAT3 directly regulates the promotor region of ZO-1 and the barrier function, which indicates the role of STAT3 in protecting corneal endothelial cells against multiple proinflammatory cytokines and its importance in the homeostasis of corneal endothelial cells[16]. STAT3 increases cell proliferation in the nicotinamide (NA) group and protects retinal pigment epithelial cells from oxidative stress[17]. Our results showed that STAT3 is closely associated with the course of conjunctivitis and is thus considered an essential

Table 2 KEGG enrichment analysis of FuFang Xiongdan Diyanye

Pathway	Number of proteins	Matched protein in the network	FRD
Proteoglycans in cancer	15	TIMP3, LUM, HGF, P53, TNF, VEGFA, PIK3CG, SRC, MAPK1, STAT3, RHOA, MAPK3, MAPK14, EGFR, HRAS	1.04×10^{-15}
TNF signaling pathway	12	TNF, MAPK3, MAPK14, MAPK1, CCL2, PIK3CG, IL1B, VCAM1, JUN, SELE, MAPK8, ICAM1	3.80×10^{-15}
Fc epsilon RI signaling pathway	10	SYK, TNF, MAPK3, MAPK14, MAPK1, IL4, PIK3CG, BTK, MAPK8, HRAS	6.60×10^{-14}
PI3K-Akt signaling pathway	15	SYK, CHRM1, MAPK3, MAPK1, IL4, JAK2, GHR, IL6, VEGFA, JAK3, TP53, HGF, EGFR, HRAS, PIK3CG	1.68×10^{-13}
Influenza A	12	TNF, MAPK3, MAPK1, MAPK14, JAK2, CCL2, PIK3CG, IL1B, JUN, MAPK8, ICAM1, PLG	3.78×10^{-13}
Osteoclast differentiation	11	SYK, TNF, MAPK3, MAPK14, MAPK1, PLG, IL1B, JUN, MAPK8, BTK, LCK	4.38×10^{-13}
Viral carcinogenesis	12	SYK, MAPK3, MAPK1, RHOA, PIK, CG, JUN, JAK3, SRC, STAT3, TP53, MAPKA, HRAS	7.68×10^{-13}
T cell receptor signaling pathway	10	TNF, MAPK3, MAPK14, MAPK1, RHOA, PIK3CG, JUN, IL4, HRAS, LCK	1.55×10^{-12}
Prolactin signaling pathway	9	MAPK3, MAPK14, MAPK1, JAK2, PIK3CG, MAPK8, HRAS, SRC, STAT3	2.85×10^{-12}
Neurotrophin signaling pathway	10	MAPK3, MAPK14, MAPK1, RHOA, PIK3CG, JUN, TP53, MAPKA, MAPK8, HRAS	6.39×10^{-12}

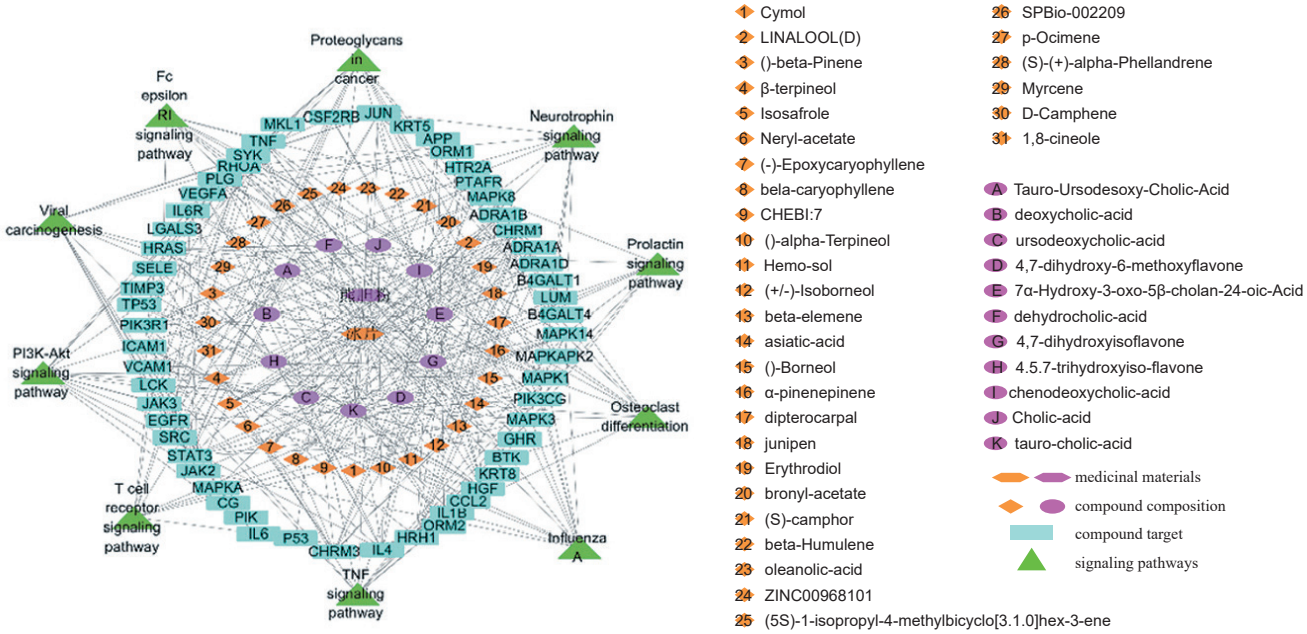

Fig. 2 Network of medicinal material-compound-pharmacological target-signaling pathways

The two items in the center are bear bile powder (purple) and borneol (orange). The two circles represent the compounds of these medicinal materials, the blue rectangles represent the pharmacological targets, and the green triangles represent the signaling pathways

target of the illness. In addition, a network of "core compound targets-core disease targets" also illustrated direct action by Fufang Xiongdan Diyanyeon STAT3 through multiple targets of its compounds, including JAK2, SRC, EGFR, JAK3, LCK, CSF2RB, VEGFA, JUN, and MAPK8. This fact suggests direct action of Fufang Xiongdan Diyanyeon STAT3 via targets of its compounds in the treatment of conjunctivitis.

Intercellular adhesion molecule 1 (ICAM1) is a glycoprotein that is expressed on the surface of cells and mediates interactions between cells or between cells and the extracellular matrix. It can be found on the surface of activated lymphocytes, macrophages, endothelial cells, epithelial cells, and fibroblasts. It binds components on the surface of multiple types of cells and forms networks, by which cell functions are regulated. Therefore, it is pivotal in the repair of inflammation, immune response, and trauma. ICAM1 facilitates the occurrence and development of inflammation by binding lymphocyte function-associated antigen-1 on the surface of leukocytes and mediating leukocyte adhesion to, and migration through, the vascular epithelium to the inflammatory tissue and impaired areas. Immune-mediated injuries to retinal tissue are triggered as a result[18-19]. According to our results, it was presumed that compound targets such as SELE, TNF, and VCAM1 directly act on ICAM1 to ameliorate the inflammatory response induced by conjunctivitis.

Histamine H1 receptor (HRH1) is the earliest recorded inflammatory mediator. Mainly present on mast cells and basophils, it is responsible for mediating smooth muscle contraction and the inflammatory response and regulating vascular constriction and permeability (increased capillary permeability due to constriction of peripheral veins). It also plays roles in anaphylaxis, gastric acid secretion, and vascular regulation. Activated mast cells release histamine, thereby contributing to the production of proinflammatory cytokines (e.g., IL-6, IL-8) by orbital fibroblasts; the development of inflammation is therefore indirectly affected[20]. HRH1 enables vasodilation, reduces capillary permeability, and thus its production results in hyperemia and edema. It also increases tear production by the lacrimal gland. Additionally, it is a well-known cause of pruritus since it can stimulate nerve endings, creating itching[21]. These functions imply the consistence of HRH1 with the symptoms of conjunctivitis. HRH1 is intimately related to the onset and development of conjunctivitis. According to our results, Fufang Xiongdan Diyanye relieve the symptoms of conjunctivitis, including congestion, tearing, and itching, possibly by acting on HRH1 via eight compound targets (e.g., CHRM1, APP, PIK3R1, and ADRA1D).

4.2 Fufang Xiongdan Diyanyepossibly engage in multiple signaling pathways, including PI3K-Akt and influenza A

The PI3K/Akt signaling pathway is activated by viral protein synthesis within the cells and viral attachment after viral infection. Pro-apoptotic signals are subsequently interrupted. Cell viability and proliferation are maintained, and downstream transcription factors are activated to promote virus replication. This process indicates that PI3K aids the viral life cycle, including entry and replication[22-24]. The compound targets (e.g., SYK, JAK2) mediate signaling pathways of influenza A and PI3K/Akt and are involved in life activities, such as cell proliferation and survival, neoangiogenesis, cytokine regulation, viral protein expression, and chemotaxis of macrophages. They also modulate the expression of pathogenic factors, such as IL-6 and ICAM1. In this study, a PPI network that visualized compound and disease targets was created, and GO and KEGG enrichment analyses were performed. The GO enrichment analysis showed the key targets noted in biological activities and molecular function, such

as regulation of multiple cells, as well as migration, proliferation, and apoptosis of leukocytes. The KEGG enrichment analysis showed enrichment of key targets in conjunctivitis-associated pathways, such as inflammation, herpes virus infection, influenza, and cancer.

This study predicts the targets of Fufang Xiongdan Diyanyeand acute bacterial conjunctivitis by means of network pharmacology, establishes a network of "compound-target-signaling pathway" and conducted a PPI analysis. The mechanism of action of Fufang Xiongdan Diyanyein the treatment of acute bacterial conjunctivitis is revealed by the results. Based on these results, it is feasible to investigate this mechanism of action at the molecular level by further screening effective drug components and core disease targets in a virtual environment.

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