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Exploration on the Mechanism of Xuanmai Ganjie Decoction in the Treatment of Children's Atopic Cough Based on Network Pharmacology

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Abstract: *In order to explore the pharmacodynamic material basis and mechanism of Xuanmai Ganjie Decocyion in the treatment of Children's atopic cough by means of network pharmacology. Through the Herb database, the main chemical components and targets of Xuanmai Ganjie Decoction were searched, supplemented in the combination with the literature. We searched The targets related to AC diseases were obtained through human gene database (Gencards), online mendelian inheritance in man(OMIM). Then we obtained the common targets of active components of drug and disease targets. The protein-protein interaction network of drug and disease common targets was constructed based on String platform, The PPI network was built through Cytoscape 3.7.2, and the cytohubba analyzed the key targets of Xuanmai Ganjie Decoction in the treatment of AC. GO and KEGG enrichment analysis was carried out using the Metascape website, and bubble charts were drawn using the WeScape online website. Resultly, a total of 82 active ingredients and 86 related targets of Xuanmai Ganjie Decoction and 82 related targets of AC were obtained, Cytohubba finally screened out 10 key edges. The enrichment analysis of KEGG pathway mainly involves calcium signaling pathway, chemokine signaling pathway, Th17 cell differentiation and JAK2/STAT3 signaling pathway. The biological process of GO enrichment analysis mainly involves the activation of protein tyrosine kinase. In conclusion, it may act on the chemokine signaling pathway, Th17 cell activation and tyrosine protein kinase activation through targets such as JAK2, STAT3, VEGFA and other targets to play a therapeutic role in AC.*

Keywords: *Cyberpharmacology; Xuanmai Ganjie Decoction; Atopic cough*

1. Introduction

Atopic Cough(AC) is an inflammatory airway reaction induced in the body after respiratory exposure to allergens, with recurrent episodes of irritating dry cough as the main symptom [1-2]. Affected by environmental pollution, passive smoking and other external factors, the incidence of AC in children in China is increasing day by day [3], and this disease has become an important factor affecting children's health in China. At present, the treatment of this disease is mainly based on antihistamines and glucocorticoids [4-5], and such drugs are prone to recurrence, side effects, and poor parental compliance in the treatment of children's AC. In contrast, Chinese medicine treatment of this disease has little side effects and treats both the symptoms and the root cause, and has achieved definite efficacy in the clinic [6]. Chinese medicine does not have AC disease name related records, Chinese medicine practitioners according to its symptoms trace back to the origin, combined with the "the origin of all diseases, " one of the ten kinds of "a said the wind cough, want to speak because of the cough, the words can not be even is also" will be categorized as "wind cough" [7]. Wind evil good line and several changes, mostly from the mouth and nose or fur and into, invade the lung system, closed lung gas, so that the lung gas XuanShen irregular, airway contracture, hair for cough; wind for Yang evil, easy to hurt Yin fluid, and long cough injury Yin, Yin deficiency, false fire upward, so "wind cough" is mostly for the standard evidence of deficiency. Throughout the ages, various medical doctors have different views on the identification and treatment of "wind cough", but still to "declaring lung qi, nourishing yin and moistening dryness" as the core of treatment. Ulcer medicine Daquan" cloud "dry cough is extremely difficult to treat. This system of fire is very rich, is phlegm and fire evil in the lungs, on the bitter tangerine terrier to open, under the use of tonic yin to lower the fire medicine". Nourishing Yin and clearing the lungs plays an important

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role in the treatment of AC [8]. Xuanmai Ganjie Tang is from the Manual of Preparation of Proprietary Chinese Medicines (edited by the Institute of Traditional Chinese Medicine of the Academy of Traditional Chinese Medicine of the Ministry of Health, 1965) [9], with the bitter and pungent nature of Platycodon grandiflorus, which enters the lung meridian, and is pungent and bitter, and is beneficial to the chest and diaphragm and smooths the pharynx; Xuanmai ginseng enters the spleen, stomach and kidney meridians, and maitake enters the lung and stomach meridians, and the four medicines play the role of clearing away heat and nourishing the yin and eliminating phlegm [10].

2. Materials and methods

2.1. Screening of the main components and targets of action of the compound drug of Xuanmai-Ganjie Decoction

By using the high-throughput Chinese medicine experimental and reference guide database HERB (http://www.herb.ac.cn), we searched with the keywords "Xuan Shen, MaiDong, JieGeng, GanCao" to download their pharmaceutical ingredients. The drug components with OB≥30% were screened. We searched for the above ingredients in the pubchem database and downloaded their molecular structures and saved them as 2DSDF files; we uploaded their 2D structures in the Swiss ADME (http://www.swissadme.ch/) database with GL-absorption of "high" and Druglikeness of "high". The 2D structure was uploaded in the Swiss ADME database, and the components with GL-absorption (gastrointestinal absorption) of "high" and Druglikeness prediction (Lipinski, Ghose, Vebar, Egan, Muegge) of at least two "Yes" were recorded, and the 2D structure was uploaded in the Swiss Target Prediction (http://www.swisstargetperdiction.ch/) website for drug targets.

2.2. Target Protein Gene Name Transformation

We selected "Homo Sapiens" in the Uniorot database to download the relevant target information, and standardized the potential targets of the drug components into Gene Symbol with the help of Excel VLOOKUP function.

2.3. Acquisition and screening of AC-related targets

Disease-related targets were searched in Genecard and OMIM databases with the keywords of "Allergic Cough" and "Chronic Cough", and the retrieved data were merged and organized to eliminate duplicate targets; the intersection of the acquired disease targets and drug targets was taken to produce Venn diagrams using Excel.

2.4. Construction of PPI network and screening of core genes for constituent-AC target of Xuanmai GanJie Decoction

Protein-protein interaction (PPI) refers to the systematic analysis of the interactions of a large number of proteins in biological systems from the perspectives of biochemistry, signaling and genetic networks, which is of great significance for understanding the biological signals and functional connections between proteins in special physiological states such as diseases. We uploaded the obtained targets of Xuanmai Ganjie Tang and AC intersection into STRING11.0 database (http://string-db.org), selected the species as "Homo sapiens", set the confidence level of target interconnection as 0.4, and constructed the PPI network. The PPI network was constructed by importing Cytoscape 3.7.2 software, using CytoNCA plug-in in Cytoscape 3.7.2 to export and sort nodes using Betweenness Centrality, and using CytoHubba plug-in in Cytoscape 3.7.2 to identify the Hub genes, which were identified based on the node's position in the network. For Hub genes, the top 10 of them were obtained through Degree sorting based on the ranking of nodes in the network.

2.5. Composition of Xuanmai Ganjie Decoction with AC target GO functional enrichment and KEGG pathway enrichment

Analysis was performed by uploading the intersecting targets of Xuanmai Ganjie Tang and AC on the Metascape online website (www.metascape.org), including biological process (BP), molecular function (MF) and cellular component (CC) analyzed by GO and the results were exported. cellular component, CC) and KEGG pathway, set Min overlap as "3", P value as 0.01, Min enrichment as 1.5,

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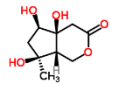
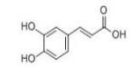
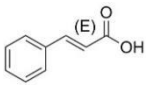
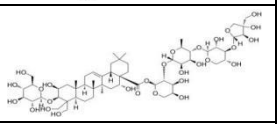
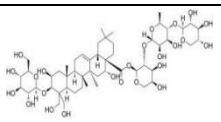
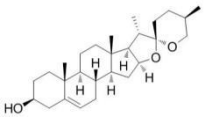
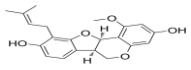
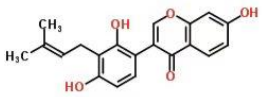
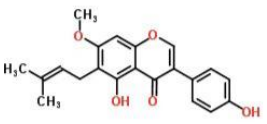
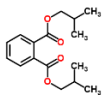
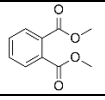
and exported the results to the online website of Microbiotics (www. bioinformatics The results were exported, and the bubble diagrams were created using the microbioinformatics online website (www.bioinformatics.com.cn).

3. Result

3.1. Predicted results of the targets of the main active ingredients of Xuanmai Ganlang Decoction

A total of 733 chemical constituents of Xuanmai Ganjie Decoction drug were obtained through Herb database, and after screening by Swiss ADME database according to GL-absorption as well as Druglikeness the two drugs did not have any common active ingredient, and a total of 82 compliant chemical constituents were obtained, and the 11 active constituents with the highest correlation were screened out according to their Degree values (see Table 1).

Table 1: 11 Most Active Ingredients in Xuanmai Ganlang Decoction

Number	Chemical	CAS	Molecular Formula	Chemistry
XS4	buergerinin B	919769-83-8	$C_9H_{14}O_5$	
XS8	caffeic acid	331-39-5	$C_9H_8O_4$	
XS10	cinnamic acid	140-10-3	$C_9H_8O_2$	
JG3	piatycodin D	58479-68-8	$C_{57}H_{92}O_{28}$	
JG4	Deapi-piatycodin D	78763-58-3	$C_{52}H_{84}O_{24}$	
MD1	diosgenin	512-04-9	$C_{27}H_{42}O_3$	
GC1	1-Methoxyphaseollidin	65428-13-9	$C_{21}H_{22}O_5$	
GC25	Eurycarpin A	166547-20-2	$C_{20}H_{18}O_5$	
GC27	Gancaonin G	126716-34-5	$C_{21}H_{22}O_5$	
GC20	DIBP	84-69-5	$C_{16}H_{22}O_4$	
GC60	Mipax	131-11-3	$C_{10}H_{10}O_4$	

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3.2. Results of gene names of target proteins

The compounds of the drugs exert their biological functions through the corresponding targets. The Swisstargetprediction database was used to predict the corresponding targets of the chemical components of Xuanmai Ganjie decoction, and a total of 1, 691 drug targets were obtained, and 352 drug targets were obtained by combining the targets of each traditional Chinese medicine and deleting the duplicates.

3.3. Acquisition and screening of AC-related targets

A total of 1600 AC-related action targets were obtained from Genecard and OMIM databases, and targets with correlation score Score ≥ 1.1945 were selected as potential targets of AC, and 804 related targets were obtained. Combined with the OMIM database to supplement the relevant targets, a total of 872 AC-related targets were obtained after removing duplicates. Taking the intersection of the 872 disease targets with the obtained 352 drug targets, a total of 86 common targets were obtained, and the Venn diagram was drawn by excel. (Figure 1)

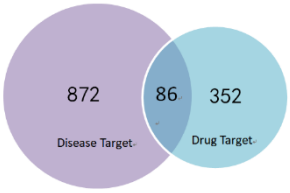

Figure 1: Venn diagram of drug-disease target intersection

3.4. PPI network construction and core gene screening

The 86 intersecting genes were uploaded to String11.0 database for PPI network construction. The confidence level was 0.4 (confidence=0.4), and discrete proteins were removed to obtain 81 protein-interacting networks, which had 81 nodes and 533 edges as in Figure 2. and the nodes were sorted using CytoNCA plug-in to obtain the PPI network graph. Based on the Degree topology analysis of Cytoscape's CytoHubba plug-in the Top10 genes were identified as HSP90AA1, MTOR, PDGFRB, STAT3, KDR, CXXR4, JAK2, MET, CASP3, VEGFA, and there were 10 nodes in the network with 81 edges as shown in Figure 3.

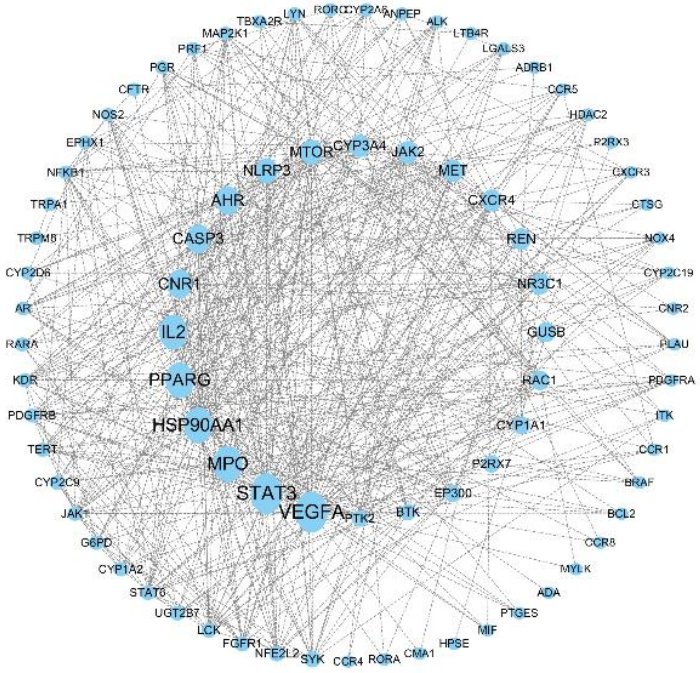

Figure 2: Xuanmai Ganjie Decoction-AC PPI network diagram

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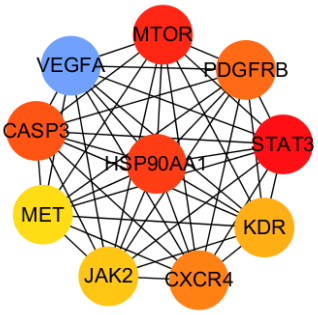

Figure 3: Core network interoperability diagram

3.5. Functional enrichment of GO with KEGG function at the target of Xuanmai-Ganjie Tang and AC intersection

3.5.1. GO Biofunctional Enrichment

The information of the acquired intersecting targets was analyzed by GO enrichment using metascape, and the top 20 enriched entries were visualized according to the corrected-logP and represented by bubble plots. The molecular functions (e.g. , Figure 4) involve protein tyrosine kinase activity, binding of ferrous heme, specific binding of protein structural domains, and protein dimerization activity. Biological processes (e.g. , Figure 5) involve regulation of the immune system, response to external stimuli, inflammatory response, cellular response to organic nitrogen compounds, cellular activation, response to hormones, and chemotaxis. Cellular components (e.g. , Figure 6) include extracellular membranes, lysosomal vesicles, receptor complexes, membrane rafts, dendrites, cytoplasmic lysates, adhesion spots, etc.

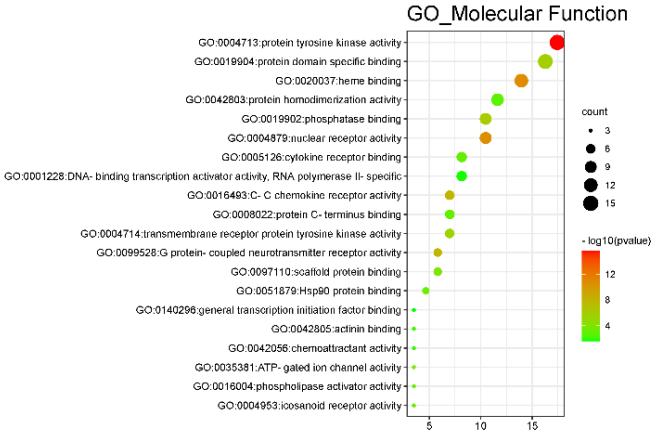

Figure 4: GO enrichment analysis of molecular functions

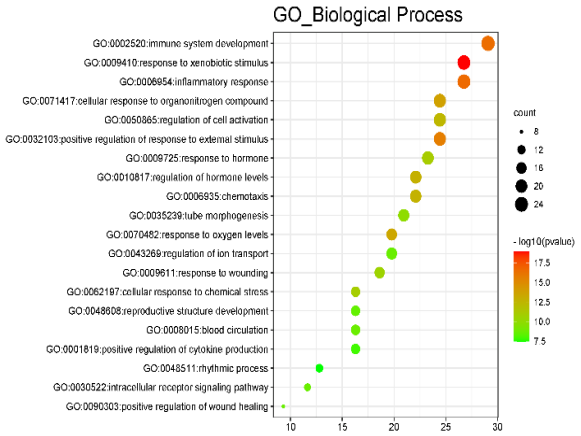

Figure 5: GO enrichment analysis of biological processes

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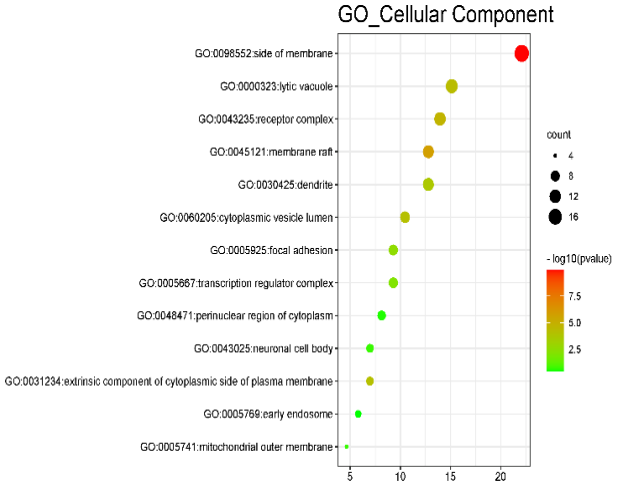

Figure 6: GO enrichment analysis of cellular fractions

3.5.2. KEGG enrichment analysis

The obtained intersecting target information was subjected to KEGG enrichment by metascape and screened at p≤0.01, and the top 20 were visualized according to the corrected p-value (e.g. , Figure 7), among which the ones related to the disease were: chemokine signaling pathway, calcium channel signaling pathway, HIF-1 signaling pathway, and TH17 cellular differentiation related. It suggests that the active ingredients of Xuanmai Ganjie Tang may treat AC according to the above signaling pathways.

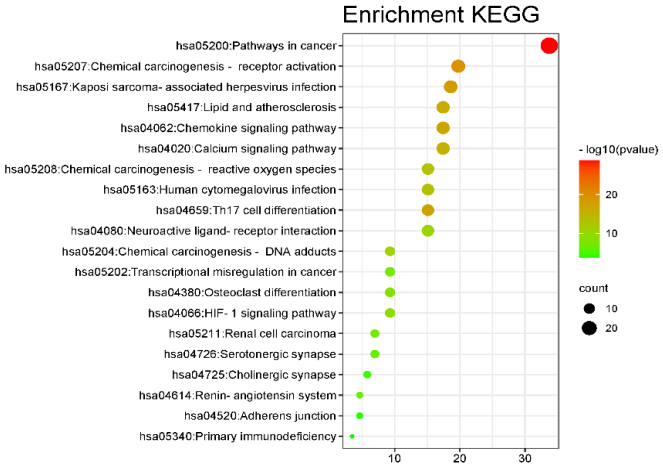

Figure 7: KEGG enrichment analysis

4. Deliberations

AC is the exposure of the organism to or inhalation of allergens, which induces the production of specific IgE antibodies by B lymphocytes, which bind to high-affinity receptors (FcεRI) on the surface of mast cells and eosinophils, and the organism is in a state of hypersensitivity to such antigens [10]. If the organism is re-exposed to or inhales the allergen, which cross-links and activates the FcεRI on the surface of the mast cell membrane, the phosphorylation of the C-terminal end of its γ-chain activates different types of protein tyrosinases (Syk, Lyn, Fyn) [11], and the activation of these protein tyrosinases activates the connectors (junction proteins) of the T, and B cells, which act as presenting signaling activation pathway proteins to Activation of pathways such as chemokine signaling pathways and calcium ions [12-13], which ultimately leads to mast cell degranulation to produce inflammatory mediators such as leukotrienes, histamine, and prostaglandin D2, leading to airway edema and increased airway mucus secretion, which leads to respiratory symptoms such as coughing and coughing up sputum, and thus AC is prone to recurrence and prolonged healing [14].

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4.1. Pharmaceutical active ingredient analysis

Xuanmai Ganjie Decoction, Platycodonopsis and Licorice are the principal medicines, and "Pearl Capsule Medicinal Fugue" recorded that Platycodonopsis "relieves diaphragmatic qi and treats carbuncles of the lungs; one of them is the oar of all medicines; the other one is the lead meridian of the lungs". Platycodonopsis Tang, composed of licorice and Platycodonopsis, was first published in the Treatise on Typhoid Fever - Discussion of Shaoyin Disease and Treatment of Pulse Evidence, which was used for the treatment of sore throat caused by deficiency heat. Qian Yi recorded in the "Pediatric Drugs Directly Decided" that licorice and tangerine soup could treat lung fever in children, pinching the eyebrows, nose and face. In the Qing Dynasty, Gu Shicheng added Ophiopogon, which enters the lung, stomach and heart meridians, and Xuan Shen, which enters the lung, stomach and kidney meridians, to the original formula of Platycodon, to treat dry cough in children. Gancaonin Gin licorice, yellow licorice isEurycarpin A, 1-methoxyphaseollidin are flavonoids; maitake in the diosgenin diosgenin and piatycodin D in the Platycodon grandiflorus and maitake D are saponin compounds. belong to the saponin group of compounds. Saponins and flavonoids are the core components of the anti-inflammatory and expectorant properties of Xuanmai Ganjie Decoction [15-17]. Modern pharmacological studies of the total saponins of Platycodon grandiflorum exert anti-inflammatory and cough-relieving effects by regulating the metabolism of linoleic acid and thus inhibiting the secretion of inflammatory mediators such as NO, TNF and IL-8 by fibroblasts in the airway [18]. Flavonoids in Glycyrrhiza glabra can reduce the levels of IgE and IgG in the body to play an anti-allergic role, and can also inhibit the inflammatory response by activating the protein kinase signaling pathway and thus the expression of TNF-α, IL-1β, and IL-6 [19]. It has been shown that the secretion of IgE, Th1 (IL-4, IL-5, and IL-13)/Th2 (TNF-α and IFN-γ) cytokines, and MCP-1 chemokines in OVA-induced pneumonitis mice was inhibited by the total saponins of Platycodon grandiflorum (cks), confirming that the total saponins of Platycodon grandiflorum (cks) inhibit respiratory inflammation by attenuating allergic responses [14]. Maitake saponins can play a protective role in respiratory epithelial cells by decreasing intracellular IL-6 and IL-17 and increasing IL-10 mRNA expression [20]. Guan Yan et al [21] experimentally verified that total flavonoids of Glycyrrhiza glabra attenuated lung inflammation by inhibiting the intrapulmonary expression of TNF-αmRNA, IL-1βmRNA and TNF-α in lung tissue. Xuanmai-Ganjie Tang sensitized cough by inhibiting the activation of cough receptors by reducing the release of transmitters such as SP, NKA, CGRP [22,23].

4.2. Target analysis

Through network pharmacology for drug composition screening, target prediction and PPI analysis, it was found that 10 proteins, including signal transducer and activator of transcription 3 (STAT3) and Janus kinase 2 (JAK2) proteins, occupied a central position in the network. STAT3, as a member of the STAT family, plays an important role in the growth, survival and differentiation of cells [24]. In the process of airway inflammation, STAT3 is highly expressed in bronchial epithelial cells at all levels, and its phosphorylation by JAK2 can up-regulate the expression of IL-6, which can activate the STAT3 pathway to cause inflammatory infiltration of bronchial epithelial cells and airway inflammation. Studies have shown that inhibition of STAT3 phosphorylation in lung tissue results in a corresponding reduction in airway inflammation, suggesting that STAT3 plays an important role in allergen-induced Th2 airway inflammation. Chen Yue [25] confirmed that JAK2 and STAT3 protein expression levels increased in the lung tissues of guinea pigs with ovalbumin-induced airway inflammation, whereas both JAK2 and STAT3 protein expression levels were reduced in guinea pigs' lung tissues under the effect of traditional Chinese medicine [26].

4.3. Bioenrichment analysis

Biological processes including protein tyrosinase activity, regulation of the immune system, response to external stimuli, and inflammatory response can be known by GO function enrichment analysis. By KEGG enrichment analysis, it can be inferred that the treatment of AC in children with Xuanmai Ganjie Tang is mainly related to the activation of Th17 cells and the HIF cell pathway.

An important pathophysiological factor in the development of AC during airway inflammation, it has been found that three kinases, Syk, Lyn and Fyn, play a crucial role in FcεRI receptor-mediated mast cell activation [19]. A very large number of egg tyrosine kinase inhibitors such as SFKs have appeared on the market in recent years, but their effects on allergic diseases are limited and side effects are high. Prof. Wang Mengqing [14] used Xuanmai Ganjie Tang as a basic formula to treat pediatric respiratory allergic diseases and achieved great efficacy. However, the mechanism of TCM in the treatment of this disease

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is still unknown. According to the pharmacological GO enrichment analysis of this network, Xuanmai Ganjie Tang may treat AC by regulating the activity of protein tyrosine kinase and thus inhibiting airway inflammatory response.

Th17 cells are a newly discovered subpopulation of CD4+ T cells in recent years. when the body is attacked by pathogens or allergens, CD4+ T cells are induced by IL-23 to differentiate into Th17 cells, and STAT3 acts as a signaling molecule for IL-23 during this process. th17 cells release cytokines such as IL-17, which stimulate the body to induce the production of chemokines such as CCR4 and chemokines such as CCR6. They can induce the directional chemotaxis of nearby response cells (monocytes, neutrophils, eosinophils), so that the surrounding eosinophils chemotaxis to gather on the surface of the airway mucosa, secreting and releasing a large number of inflammatory mediators [19,24,27], which leads to the damage of the bronchial epithelium. Zhu Li [25] et al. found that CCL3 was abnormally highly expressed in the serum of children with bronchial asthma, and was negatively correlated with the lung function of the children and positively correlated with the severity of airway inflammation.

5. Conclusion

Chinese herbal formulas have unique advantages and characteristics in disease treatment, but the large number of chemical components and targets makes it difficult to penetrate into the mechanism of important formulas for treating diseases. Network pharmacology is characterized by holistic, systemic, multi-pathway and multi-targets, which coincides with the holistic concept and the concept of identification and treatment in TCM. In summary, the main components of Xuanmai Ganjie Tang are saponins and flavonoids, which interact with JAK3, STAT3, VEGFA and other targets to regulate the chemokine signaling pathway, Th17 cell activation, and protein tyrosine kinase activity individually or in combination to play a therapeutic role in AC.

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