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The Molecular Mechanism of Xinyi San for the Treatment of Senile Rhinitis Based on Network Pharmacology

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Abstract

Objective: To study the molecular mechanism of Xinyi San for the treatment of senile rhinitis by applying network pharmacological analysis technology. **Methods:** The effective components and corresponding targets of Xinyi San were collected by TCMSP. The targets of senile rhinitis were collected by the Genecards database. The potential target of Xinyi San in the treatment of senile rhinitis was obtained by Venn analysis. Cytoscape 3.7.2 the software constructs the relationship network model of "disease-single drug-active ingredient-action target". Protein protein interaction (PPI) network was constructed by using a string database. R4.1.1 software was used for GO function enrichment analysis and KEGG pathway enrichment analysis. **Results:** In this study, we obtained 158 active ingredients, 40 potential therapeutic targets, 74 GO projects, and 99 pathways. Major pathways include Lipid and atherosclerosis, Chemical carcinogenesis-receptor activation, PI3K-Akt signaling pathway, AGE-RAGE signaling pathway in diabetic complications, Pathways of neurodegeneration-multiple diseases, etc. **Conclusion:** Xinyi San has the characteristics of multi-component, multi-target, and multi-channel in the treatment of senile rhinitis. This study provides a basis for the in-depth study of Xinyi San.

Keywords

Network Pharmacology, Senile Rhinitis, Xinyi San, Molecular Mechanism

1. Introduction

With the acceleration of the aging process of the population, the number of patients with senile rhinitis has also increased, which has seriously affected the quality of life of the elderly. The elderly are prone to rhinitis and recurrent at-

tacks due to degenerative changes such as nasal mucosal atrophy, decreased glandular secretion function, and vascular sclerosis in the nose. The most common symptoms are nasal dryness, easy bleeding, and dysosmia. Senile rhinitis has its own characteristics, which should be paid attention to clinically.

Xinyi San originated from Yan's Jisheng prescription written by Yan Yonghe in the Song Dynasty [1]. The whole prescription was composed of 10 drugs, such as xinyi, xixin, gaoben, shengma, chuanxiong, mutong, fangfeng, qianghuo, gancao, and baizhi. It had the effect of evading the cold and clearing the nose. Modern clinical research also showed that Xinyi San had a good therapeutic effect on rhinitis [2] [3]. However, due to the complex clinical pathology of rhinitis and the more chemical components contained in Xinyi San, the mechanism of its treatment of rhinitis is not clear. Network pharmacology can build a complex network between drugs, components, targets, and diseases to explore the mechanism of action of drugs [4]. Therefore, this study was based on network pharmacology to explore the pharmacodynamic material basis and mechanism of Xinyi San in the treatment of senile rhinitis, so as to provide a reference for its in-depth research.

2. Materials and Methods

2.1. Screened for Active Components and Target Proteins of Xinyi San

Through tcmsp (https://old.tcmsp-e.com/tcmsp.php), with xinyi, xixin, gaoben, shengma, chuanxiong, mutong, fangfeng, qianghuo, gancao, and baizhi as keywords to search for candidate chemical components and corresponding protein targets. In the search results, oral bioavailability (OB) ≥ 30% and drug-likeness (DL) ≥ 0.18 were limited. With UniProt (https://www.uniprot.org/) query the gene name corresponding to the target protein.

2.2. Acquisition of Targets of Senile Rhinitis

In Genecards database (https://www.genecards.org) entered the keyword "senile rhinitis" to search for disease targets related to senile rhinitis. Merged all targets and eliminated duplicate targets, that was, got the total target of the target disease.

2.3. Venn Analysis of Potential Targets in Treatmenting of Senile Rhinitis

Introduced potential active ingredient targets and disease treatment targets of drugs into Venny platform (version 2.1, https://bioinfogp.cnb.csic.es/tools/venny/), mapped the intersection to obtain the potential target of Xinyi San in treatmenting of senile rhinitis.

2.4. Confirmation of "Disease-Single Drug-Active Ingredient-Target" Network

Imported the above screening results into Cytoscape 3.7.2 software to build the

relationship network model of "disease-single drug-active ingredient-action target".

2.5. Construction of Protein Protein Interaction (PPI) Network

Imported the intersection target of Xinyi San obtained from Venn analysis into the string database (https://string-db.org), the species was limited to "Homo sapiens", the isolated target was removed, and the confidence (0.4) was used as the screening condition to obtain the protein interaction relationship.

2.6. Gene Enrichment Analysis

R4.1.1 software was used to analyze the GO function enrichment and KEGG pathway enrichment of the key target genes of senile rhinitis corresponding to the main chemical components of Xinyi San. Selected the top 20 biological processes and pathways.

3. Results

3.1. Screened Results of Active Ingredients in Xinyi San

Using TCMSP platform, 158 potential active ingredients of Xinyi San were finally screened, including 10 in xinyi, 6 in xixin, 1 in gaoben, 7 in shengma, 5 in chuanxiong, 8 in mutong, 15 in fangfeng, 9 in qianghuo, 85 in gancao and 12 in baizhi. The active ingredients in the top 20 (from high to low) of OB value were as follows (see **Table 1**).

3.2. Construction of "Disease-Single Drug-Active Ingredient-Target" Network

Imported the information of disease, single drug, active ingredient and action target into the software Cytoscape for visualization, and constructed the network diagram of "disease-single drug-active ingredient-target" (see **Figure 1**), including 189 nodes (1 disease node, 10 drug nodes, 138 active ingredient nodes, 40 action target nodes) and 807 edges. Screening the compound nodes with large degree value. These compounds might be the key compounds of Xinyi San in the treatment of senile rhinitis. The results showed that the compounds with the highest degree value were quercetin, kaempferol, beta-sitosterol, wogonin, isorhamnetin and 7-methoxy-2-methyl isoflavone, could connect with 30, 20, 13, 12, 11 and 10 targets respectively, which was of great significance for the treatment of senile rhinitis.

3.3. Venn Analysis

Through pharmMapper to predict the target, 120 potential active ingredient targets were obtained after weight removal, and the names of the obtained targets were entered into UniProt database. Then searched the Genecards database for "senile rhinitis" and got 447 disease targets. The intersection of mapping is 40 targets that might be related to the effect of Xinyi San in the treatment of senile rhinitis (see **Figure 2**).

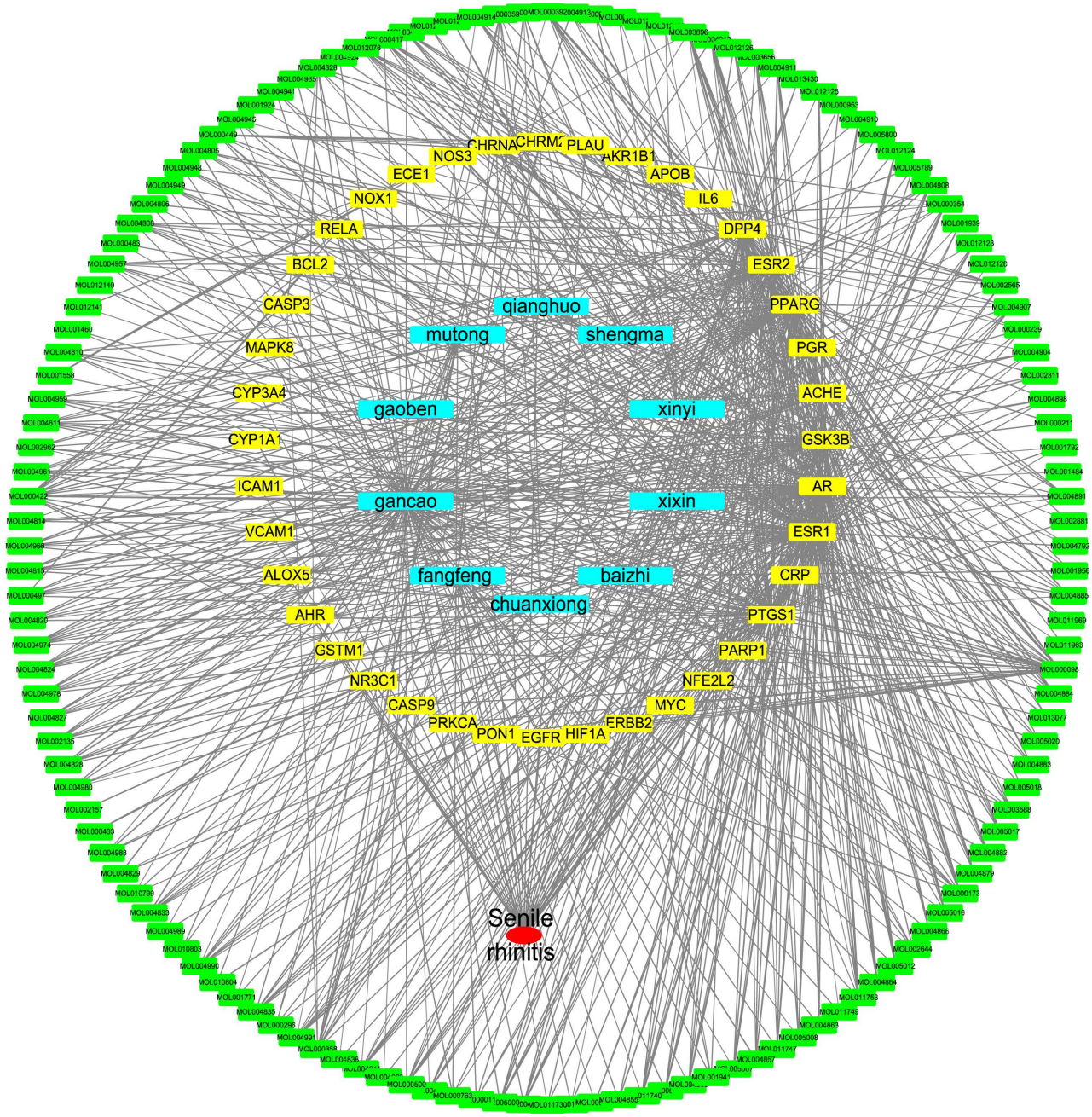

Figure 1. Composition—target network diagram of Xinyi San.

3.4. Constructed PPI Network

The 40 intersection targets obtained from Venn analysis were imported into the String database to build the PPI network (see **Figure 3**). Used R language to process the top 30 targets, and got the core target map (see **Figure 4**). The top 10 targets with visibility value from high to low were IL6, CASP3, PPARG, EGFR, ESR1, HIF1A, MYC, NOS3, ICAM1 and RELA. The corresponding targets of these proteins with higher degrees might be the key targets of Xinyi San in the treatment of senile rhinitis.

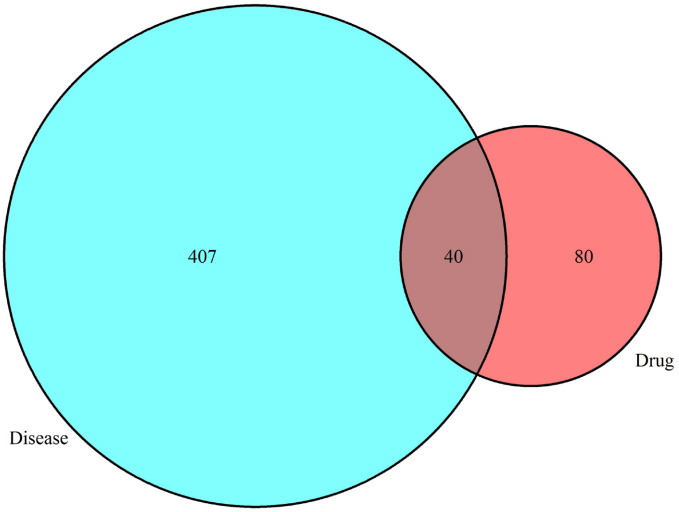

Figure 2. Venn diagram of intersection targets of Xinyi San and senile rhinitis.

Table 1. Some active components of Xinyi San.

Source	Mol ID	Molecule Name	MW	OB (%)	DL
shengma	MOL000483	(Z)-3-(4-hydroxy-3-methoxy-phenyl)-N-[2-(4-hydroxyphenyl) ethyl]acrylamide	313.38	118.3477	0.26399
mutong	MOL010799	Ariskanin A	341.34	109.5065	0.40252
shengma	MOL012052	Tuberosine A	343.41	102.6668	0.3383
xinyi	MOL012124	denudanolide b	356.45	100.0599	0.35629
gancao	MOL002311	Glycyrol	366.39	90.77578	0.66819
fangfeng	MOL011737	divaricatacid	320.32	86.99614	0.32487
gancao	MOL004990	7,2',4'-trihydroxy-5-methoxy-3-arylcoumarin	300.28	83.71437	0.27136
shengma	MOL012053	cimicifugic acid	372.4	83.0233	0.44544
gancao	MOL004904	licopyranocoumarin	384.41	80.36001	0.6535
gancao	MOL004891	shinpterocarpin	322.38	80.29528	0.72746
gancao	MOL005017	Phaseol	336.36	78.76622	0.57867
xixin	MOL001460	Cryptopin	369.45	78.74265	0.72233
gancao	MOL004841	Licochalcone B	286.3	76.75735	0.1935
gancao	MOL004810	glyasperin F	354.38	75.8368	0.53514
gancao	MOL001484	Inermine	284.28	75.18306	0.53754
gancao	MOL000500	Vestitol	272.32	74.65519	0.20935
gancao	MOL005007	Glyasperins M	368.41	72.67081	0.59274
gancao	MOL004941	(2R)-7-hydroxy-2-(4-hydroxyphenyl)chroman-4-one	256.27	71.12299	0.18303
gancao	MOL004959	1-Methoxyphaseollidin	354.43	69.98098	0.63739
gancao	MOL000392	formononetin	268.28	69.67388	0.21202

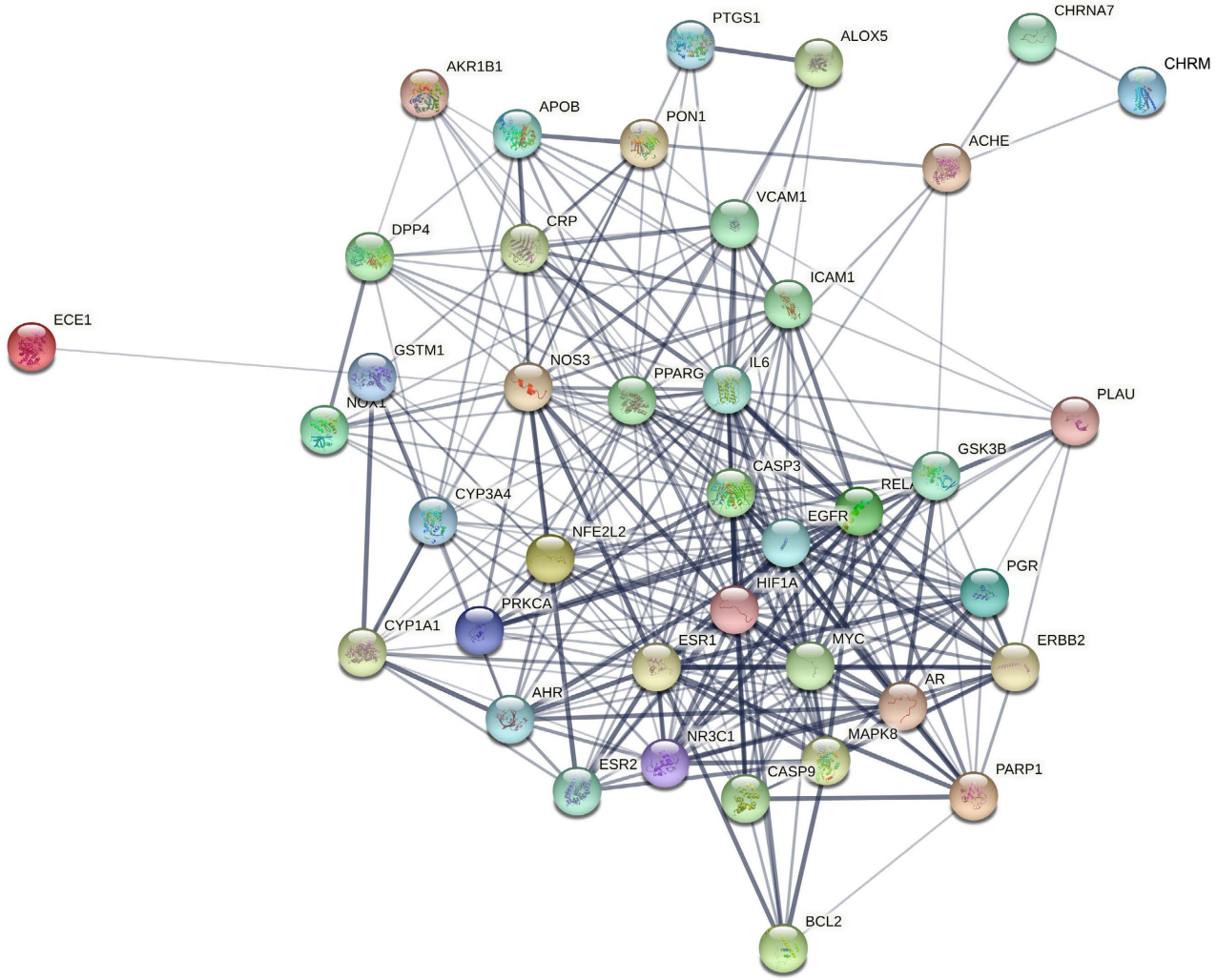

Figure 3. PPI network diagram of intersection targets of Xinyi San.

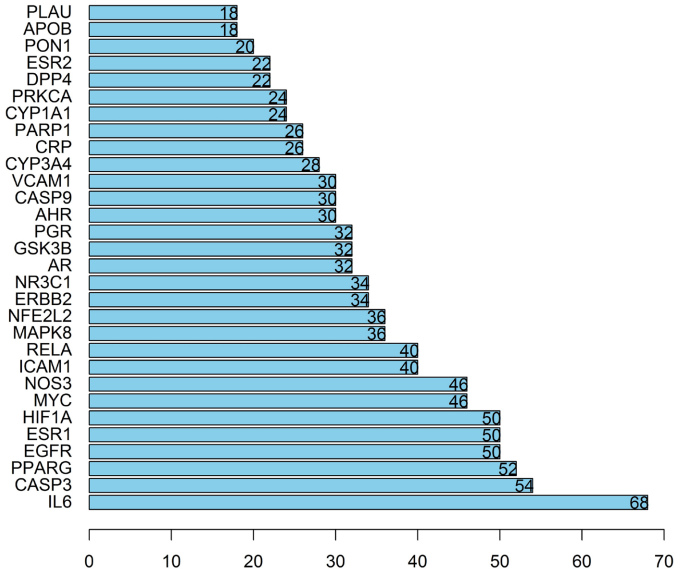

Figure 4. The key targets of Xinyi San.

3.5. GO Enrichment Analysis

A total of 74 functional enrichments were obtained, and the top 20 GO functional enrichments with the greatest significance were made into a bar graph (see Figure 5). The smaller the p-value, the greater the possibility that the biological process was involved in the treatment of senile rhinitis with Xinyi San. In the bar graph, the redder the color, the smaller the p-value, indicating that the enrichment was more obvious.

3.6. KEGG Pathway Analysis

A total of 99 ($P < 0.05$) signal pathways were obtained from the enrichment analysis of KEGG pathway. According to the ranking of –lgP value, the results of the top 20 in significance were made into a bar graph (see Figure 6). In the bar graph, the redder the color, the smaller the p-value and the more obvious the enrichment, indicating that the relationship between this pathway and the treatment of diseases may be greater.

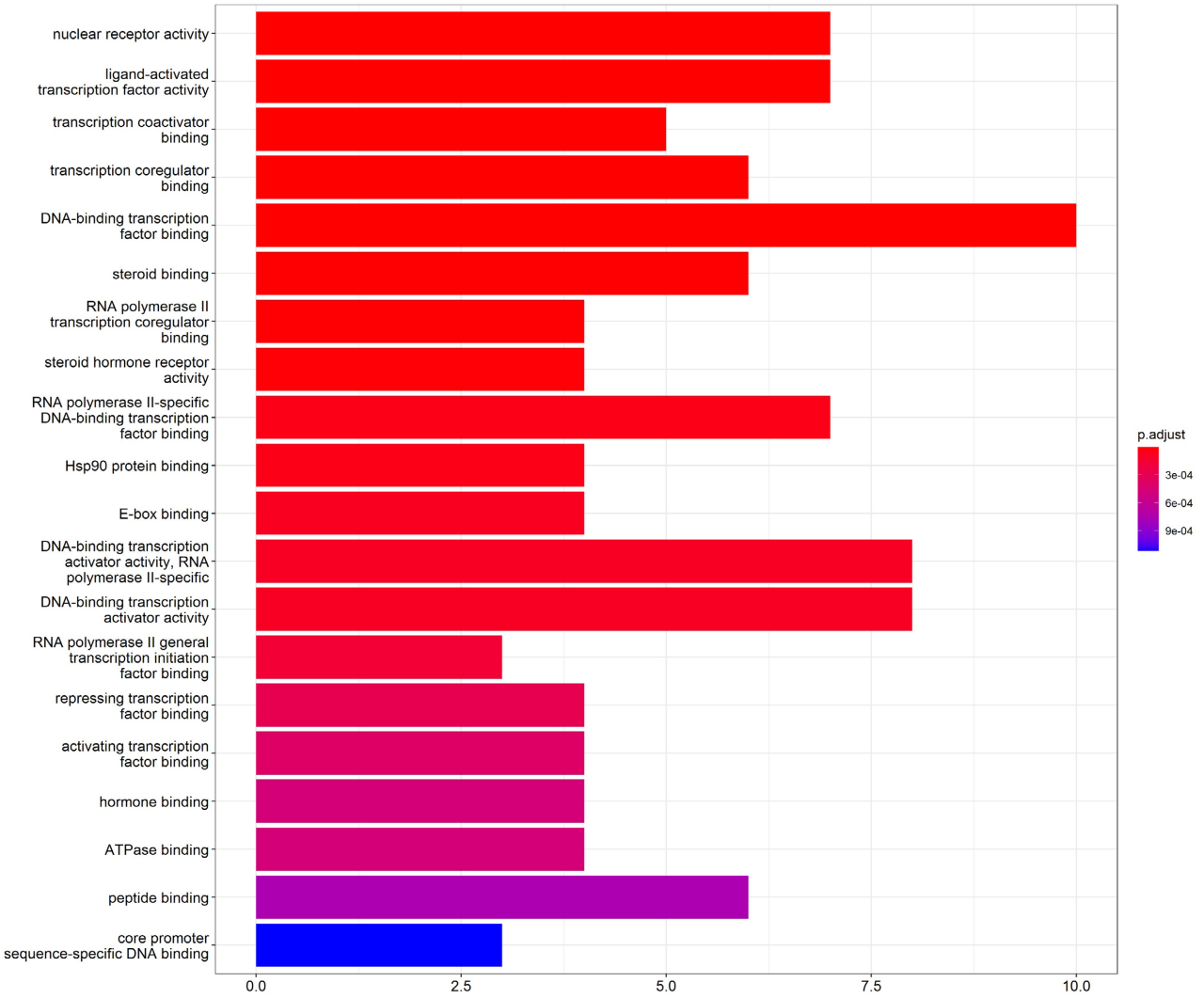

Figure 5. GO enrichment map.

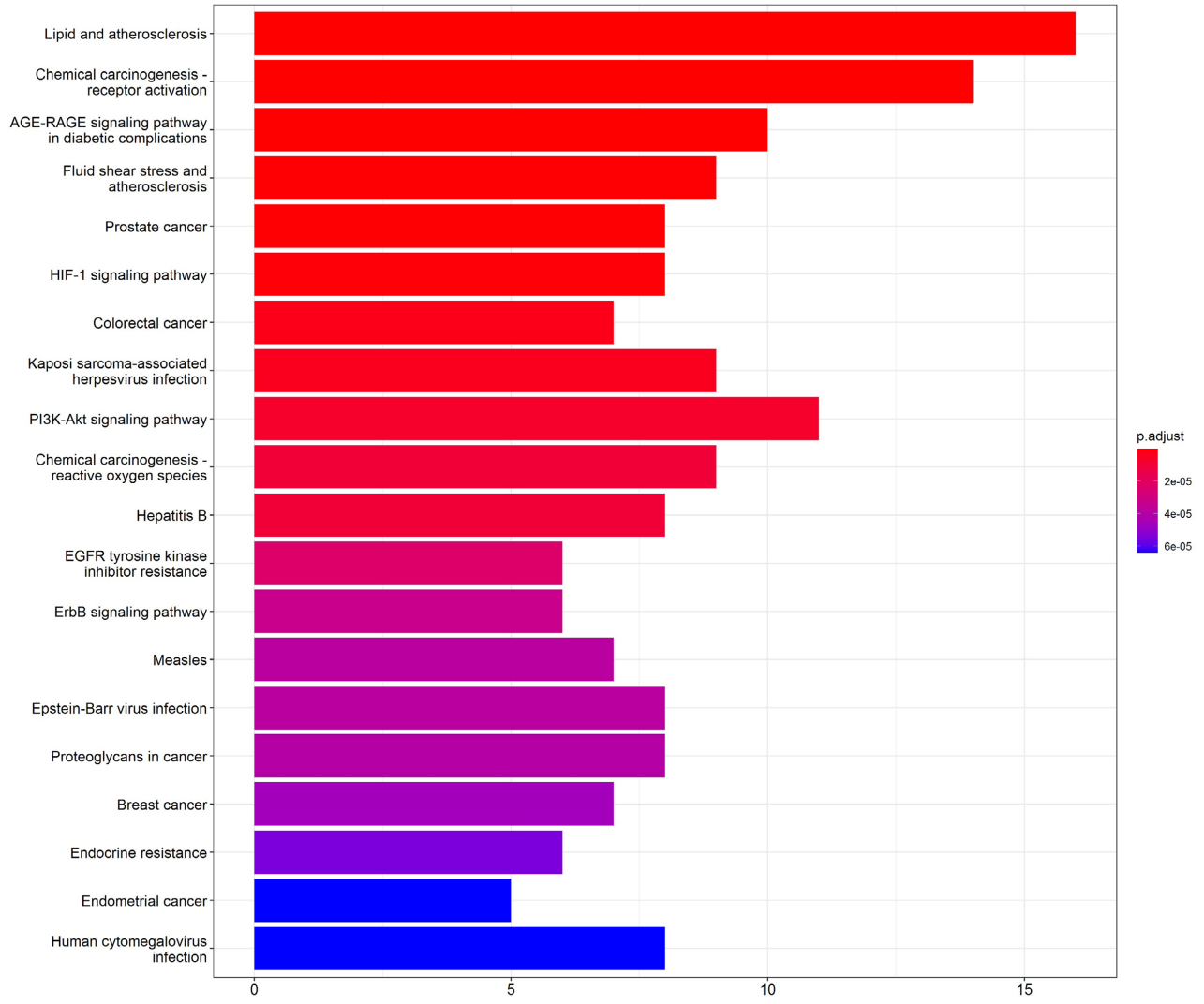

Figure 6. KEGG pathway enrichment analysis diagram.

4. Discussion

The construction results of "disease-single drug-active ingredient-target" network showed that quercetin, kaempferol, beta-sitosterol, wogonin, isorhamnetin and 7-methoxy-2-methyl isoflavone could match more targets, and might be the key effective components of Xinyi San in the treatment of senile rhinitis. Quercetin could significantly improve IL-2 and IFN-γ, inhibiting the levels of IL-4 and IL-5, regulating the balance of Th1/th2 cytokines, and having a protective effect on rhinitis [5] and many experiments [6] [7] had confirmed that quercetin had a significant effect on rhinitis. Kaempferol improvesd the symptoms of rhinitis by regulating the balance of Th1 and Th2 lymphocyte subsets [8]. Beta-sitosterol could reduce inflammatory cytokines IL-6 and TNF-α, etc. [9]. Wogonin [10] could inhibit the level of Th2 inflammatory cytokines and reduced the number of eosinophils in nasal mucosa. It also reduced the levels of ovalbumin specific IgE, IL-4, IL-5 and IL-13, thus having a better therapeutic effect on rhinitis. Li *et al.* [11] confirmed through experiments that the inhibitory effect of

isorhamnetin on inflammation may be related to the inhibition of NF-κB signal path. At present, there is no research on the effect of 7-methoxy-2-methyl isoflavone on rhinitis, which may be a new discovery and needs further experimental research for verification.

The protein interaction network showed that IL6, CASP3, PPARG, EGFR, ESR1, HIF1A, MYC, NOS3, ICAM1 and RELA might be the key targets of Xinyi San in the treatment of senile rhinitis. IL6, as an inflammatory cytokine with multiple immune regulation functions, had been proved to be closely related to the occurrence and development of rhinitis [12] [13]. The experimental results of Li Yan *et al.* [14] suggested that the occurrence of rhinosinusitis might promote apoptosis by activating CASP3, an apoptotic executive protein, through the upstream protein of the internal and external pathways of apoptosis. PPARG [15] could regulate the inflammatory response of macrophages, mast cells, T cells and eosinophils. PPARG activator could reduce the rhinitis symptom score of allergic rhinitis mice and inhibit the inflammatory response. The activation of EGFR signaling pathway was inhibited, which could improve immune adhesion and affect the inflammatory response of nasal mucosa in allergic rhinitis [16]. It was reported in the literature that [17] ESR1 was of great significance in the occurrence and development of rhinitis. HIF1A had a certain impact on the structural changes of nasal mucosa, and had the effects of regulating immunity, promoting inflammation, inducing neovascularization and so on [18]. MYC gene was involved in cell cycle regulation, cell growth regulation, cell proliferation, differentiation and transformation [19]. Some studies had found that [20] the genetic polymorphism of NOS3 gene will affect the course of allergic respiratory disease. Microvascular endothelial cells in nasal mucosa infiltrate, adhere and aggregate eosinophils in nasal mucosa by regulating the expression of ICAM1, aggravating the pathological damage of nasal mucosa [21]. RELA could limit inflammatory reaction [22].

The results of GO enrichment analysis showed that the gene functions of Xinyi San in the treatment of senile rhinitis were mainly reflected in DNA binding transcription factor binding, (DNA binding transcription activation activity, RNA polymerase II specificity), DNA binding transcription activation activity, nuclear receptor activity and ligand-activated transcription factor activity. KEGG pathway enrichment analysis further confirmed that the main signal pathways of Xinyi San in the treatment of senile rhinitis mainly include lipid and atherosclerosis, chemical carcinogen receptor activation, PI3K-Akt signal pathway, AGE-RAGE signal pathway in diabetes complications, neurodegenerative pathways of various diseases, fluid shear stress and atherosclerosis, Kaposi's sarcoma related herpesvirus infection, chemical carcinogenic reactive oxygen species, prostate cancer HIF-1 signaling pathway, hepatitis B, EB virus infection, proteoglycans in cancer, human cytomegalovirus infection, Alzheimer's disease, colorectal cancer, measles, breast cancer, MAPK signaling pathway, microRNA and cancer are mainly involved in virus infection, inflammation, cell apoptosis, etc., suggesting that Xinyi San may act on a variety of cytokines to play an anti-inflammatory role, inhibit

cytokine storm and treat senile rhinitis.

In conclusion, this study showed that the active ingredients of Xinyi San in the treatment of senile rhinitis might be quercetin, kaempferol, beta-sitosterol, wogonin, isorhamnetin and 7-methoxy-2-methyl isoflavone, etc. These active ingredients might act on lipid and atherosclerosis, chemical carcinogen receptor activation, PI3K-Akt signaling pathway, AGE-RAGE signaling pathway in diabetes complications, and neurodegenerative pathway in a variety of diseases through targets such as IL6, CASP3, PPARG, EGFR, ESR1, and HIF1A.

5. Conclusion

This study systematically analyzed the mechanism of Xinyi San in the treatment of senile rhinitis at the molecular level by using network pharmacology, but its mechanism needs further experimental verification and clinical research.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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