Target Prediction of Xinyi San for Rhinitis Based on Network Pharmacology

Lingdi Wang*, Ying Wang, Yingxue Lin, Xin Meng

Department of Pharmacy, The Affiliated Hospital of Chengde Medical College, Chengde, China
Email: *363121249@qq.com

Abstract

Objective: To analyze the potential mechanism of Xinyi San in treating rhinitis through network pharmacology. **Methods:** In the database of Traditional Chinese Medicine Systems Pharmacology (TCMSP), chemical composition and potential targets of Xinyi San were got, and the target genes of rhinitis of Xinyi San were extracted from GeneCards databases. Then we constructed protein-protein interactions (PPI) network of target genes, and then analyzed the Key genes in GO analysis and KEGG analysis. **Results:** We got 97 components, 53 potential therapeutic targets, 1009 GO items and 92 pathways in our study. The main pathways included Lipid and atherosclerosis, Chemical carcinogenesis-receptor activation, PI3K-Akt signaling pathway, Human cytomegalovirus infection, Prostate cancer, etc. **Conclusion:** Xinyi San plays a role in treating rhinitis through multiple components, multiple targets and multiple pathways.

Keywords

Rhinitis, Network Pharmacology, Xinyi San

1. Introduction

Rhinitis is the inflammation of nasal mucosa caused by viruses, bacteria, allergens, various physical and chemical factors and some systemic diseases, and which with nasal congestion, runny nose, nasal pruritus, sneezing, decreased smell, headache and dizziness as the main clinical manifestations. Nowadays, rhinitis has become a global health problem. In China, the incidence rate of rhinitis is as high as 37%, and the number of rhinitis cases is increasing at a rate of 20 million - 3 per million per year [1]. Modern medical treatment of rhinitis is mainly to control and alleviate symptoms. However, the side effects of therapeutic drugs are obvious, and it is easy to relapse. Traditional Chinese medicine has

irreplaceable advantages in the treatment of rhinitis. It has significant curative effect and minor side effects.

Xinyi San originated from Yan's Jisheng recipe written by Yan Yonghe in the Song Dynasty [2]. The whole recipe was composed of 10 drugs such as xinyi (Magnoliae Flos), xixin (Asari Radix Et Rhizoma), gaoben (Ligustici Rhizoma Et Radix), shengma (Cimicifugae Rhizoma), chuanxiong (Chuanxiong Rhizoma), mutong (Akebiae Caulis), fangfeng (Saposhnikoviae Radix), qianghuo (Notopterygii Rhizoma Et Radix), gancao (Glycyrrhizae Radix Et Rhizoma) and baizhi (Angelicae Dahuricae Radix). It is effective to evacuate wind cold, dredge nose orifices, and mainly treats lung deficiency, wind cold, damp and heat. In addition, the nose is blocked, the nose is full of tears, or the breath is blocked, or there is no smell. Modern clinical research also shows that Xinyi San has a good therapeutic effect on rhinitis [3] [4]. However, due to the complex clinicopathology of rhinitis and more chemical components contained in Xinyi San, the mechanism of its treatment of rhinitis at the molecular level is not clear. Network pharmacology is a branch of pharmacology that uses network methods to analyze the "multi-component, multi-target and multi-channel" synergistic relationship between drugs, diseases and targets. It can build a complex network between drugs, components, targets and diseases to explore the action mechanism of drugs [5]. Therefore, based on network pharmacology, this study explores the pharmacodynamic material basis and potential mechanism of Xinyi San in the treatment of rhinitis, so as to provide reference for further basic research, clinical application and new drug research and development.

2. Materials and Methods

2.1. Screened for Components and Targets of Xinyi San

Based on TCMSP (http://tcmspw.com), the candidate chemical components and corresponding protein targets were searched with xinyi, xixin, gaoben, shengma, chuanxiong, mutong, fangfeng, qianghuo, gancao and baizhi as keywords. And with UniProt (https://www.uniprot.org/) query the gene name corresponding to the target protein for standardization.

2.2. Screened for Rhinitis Targets

Entered the keyword "rhinitis" in the Genecards database (https://www.genecards.org) to search for disease targets which were related to rhinitis. We integrated targets and eliminated duplicate targets. Then, we obtained the total targets.

2.3. Venn Analysis of Potential Targets in the Treatment of Rhinitis

The potential active ingredient and targets of the Xinyi San and the rhinitis were mapped the intersection through the Venny platform (version 2.1, http://bioinfogp.cnb.csic.es/tools/venny/). And then we obtained the potential targets of Xinyi San in the treatment of rhinitis.

2.4. Constructed Disease - Single Drug - Active Ingredient - Target" Network

According to the above screening results, Cytoscape 3.7.2 software constructed the relationship network model of "disease-single drug-active component-target". The node represents single drug, active component and action target, and the edge represents the relationship between single drug-active component-target.

2.5. Constructed PPI Network

String database (https://string-db.org) is a database for searching the interaction between proteins. We imported the intersection targets of Xinyi San obtained by Venn analysis into the string database, with the species' limition as "Homo sapiens", and then we removed the isolated targets. The screening criteria were confidence (0.4).

2.6. Gene Enrichment Analysis

In order to analyze the biological function and biological signal pathway of Xinyi San on rhinitis, GO functional enrichment analysis and KEGG pathway enrichment analysis were performed on R4 1.1 software. With $p < 0.05$, the top 20 biological processes and pathways were selected according to the number of targets involved in each entry and lgP value.

3. Results

3.1. Screened Components of Xinyi San

A total of 97 potential active components of Xinyi San were finally screened by TCMSP platform, the correspondent target proteins of each active ingredient were also obtained (see Table 1).

Table 1. The basic information of potential active components in Xinyi San.

Source	Mol ID	Molecule Name	MW	OB (%)	DL
xixin	MOL000018	(+/−)-Isoborneol	154.28	86.98413	0.05275
xixin	MOL000715	l-Menthone	154.28	57.89753	0.029429
xixin	MOL000254	eugenol	164.22	56.2419	0.036518
xixin	MOL001972	Pulegone	152.26	51.59647	0.029676
xixin	MOL000198	(R)-linalool	154.28	39.8043	0.022686
xixin	MOL000122	1, 8-cineole	154.28	39.72922	0.049041
xixin	MOL000169	alpha-Guaiene	204.39	25.93463	0.072089
xixin	MOL000069	palmitic acid	256.48	19.29656	0.098573
xixin	MOL003127	Germacrene D	204.39	19.22251	0.057074
xixin	MOL000860	stearic acid	284.54	17.82543	0.14086
xinyi	MOL000018	(+/−)-Isoborneol	154.28	86.98413	0.05275

Continued

xinyi	MOL000676	DBP	278.38	64.54164	0.13409
xinyi	MOL013062	BZQ	182.23	58.62326	0.059888
xinyi	MOL000254	eugenol	164.22	56.2419	0.036518
xinyi	MOL002002	cis-Carveol	152.26	45.61104	0.029604
xinyi	MOL000122	1, 8-cineole	154.28	39.72922	0.049041
xinyi	MOL000035	beta-Selinene	204.39	24.38821	0.081081
xinyi	MOL001393	myristic acid	228.42	21.18117	0.066784
xinyi	MOL000069	palmitic acid	256.48	19.29656	0.098573
shengma	MOL000715	l-Menthone	154.28	57.89753	0.029429
shengma	MOL000141	hydroxytyrosol	154.18	57.56917	0.032051
shengma	MOL000254	eugenol	164.22	56.2419	0.036518
shengma	MOL001972	Pulegone	152.26	51.59647	0.029676
shengma	MOL000449	Stigmasterol	412.77	43.82985	0.75665
shengma	MOL000131	EIC	280.5	41.90444	0.14347
shengma	MOL000198	(R)-linalool	154.28	39.8043	0.022686
shengma	MOL000360	FER	194.2	39.55852	0.058069
shengma	MOL000359	sitosterol	414.79	36.91391	0.7512
shengma	MOL001393	myristic acid	228.42	21.18117	0.066784
shengma	MOL000357	Sitogluside	576.95	20.63194	0.6241
shengma	MOL000069	palmitic acid	256.48	19.29656	0.098573
shengma	MOL000879	methyl palmitate	270.51	18.08756	0.11594
qianghuo	MOL000771	p-coumaric acid	164.17	43.29024	0.039118
qianghuo	MOL000360	FER	194.2	39.55852	0.058069
qianghuo	MOL000358	beta-sitosterol	414.79	36.91391	0.75123
qianghuo	MOL000359	sitosterol	414.79	36.91391	0.7512
qianghuo	MOL000114	vanillic acid	168.16	35.47235	0.040917
qianghuo	MOL000035	beta-Selinene	204.39	24.38821	0.081081
qianghuo	MOL001393	myristic acid	228.42	21.18117	0.066784
qianghuo	MOL000357	Sitogluside	576.95	20.63194	0.6241
qianghuo	MOL000069	palmitic acid	256.48	19.29656	0.098573
qianghuo	MOL000879	methyl palmitate	270.51	18.08756	0.11594
qianghuo	MOL000860	stearic acid	284.54	17.82543	0.14086
mutong	MOL000449	Stigmasterol	412.77	43.82985	0.75665
mutong	MOL000360	FER	194.2	39.55852	0.058069
mutong	MOL000358	beta-sitosterol	414.79	36.91391	0.75123

Continued

mutong	MOL000114	vanillic acid	168.16	35.47235	0.040917
mutong	MOL000860	stearic acid	284.54	17.82543	0.14086
gaoben	MOL000612	(-)-alpha-cedrene	204.39	55.56099	0.10498
gaoben	MOL000131	EIC	280.5	41.90444	0.14347
gaoben	MOL000360	FER	194.2	39.55852	0.058069
gaoben	MOL000359	sitosterol	414.79	36.91391	0.7512
gancao	MOL000676	DBP	278.38	64.54164	0.13409
gancao	MOL000098	quercetin	302.25	46.43335	0.27525
gancao	MOL000359	sitosterol	414.79	36.91391	0.7512
fangfeng	MOL000018	(+/−)-Isoborneol	154.28	86.98413	0.05275
fangfeng	MOL000676	DBP	278.38	64.54164	0.13409
fangfeng	MOL001889	Methyl linolelaidate	294.53	41.93436	0.16791
fangfeng	MOL000131	EIC	280.5	41.90444	0.14347
fangfeng	MOL000198	(R)-linalool	154.28	39.8043	0.022686
fangfeng	MOL000122	1, 8-cineole	154.28	39.72922	0.049041
fangfeng	MOL000358	beta-sitosterol	414.79	36.91391	0.75123
fangfeng	MOL000359	sitosterol	414.79	36.91391	0.7512
fangfeng	MOL000114	vanillic acid	168.16	35.47235	0.040917
fangfeng	MOL000173	wogonin	284.28	30.68457	0.22942
fangfeng	MOL000035	beta-Selinene	204.39	24.38821	0.081081
fangfeng	MOL001393	myristic acid	228.42	21.18117	0.066784
fangfeng	MOL000357	Sitogluside	576.95	20.63194	0.6241
fangfeng	MOL000069	palmitic acid	256.48	19.29656	0.098573
fangfeng	MOL000879	methyl palmitate	270.51	18.08756	0.11594
fangfeng	MOL000860	stearic acid	284.54	17.82543	0.14086
fangfeng	MOL005402	Methyl margarate	284.54	17.40885	0.13808
chuanxiong	MOL000131	EIC	280.5	41.90444	0.14347
chuanxiong	MOL000198	(R)-linalool	154.28	39.8043	0.022686
chuanxiong	MOL000122	1, 8-cineole	154.28	39.72922	0.049041
chuanxiong	MOL000359	sitosterol	414.79	36.91391	0.7512
chuanxiong	MOL000114	vanillic acid	168.16	35.47235	0.040917
chuanxiong	MOL000035	beta-Selinene	204.39	24.38821	0.081081
chuanxiong	MOL000357	Sitogluside	576.95	20.63194	0.6241
chuanxiong	MOL000069	palmitic acid	256.48	19.29656	0.098573
chuanxiong	MOL003127	Germacrene D	204.39	19.22251	0.057074

Continued

chuanxiong	MOL001729	Crysophanol	254.25	18.63889	0.2094
chuanxiong	MOL000879	methyl palmitate	270.51	18.08756	0.11594
chuanxiong	MOL000860	stearic acid	284.54	17.82543	0.14086
baizhi	MOL000676	DBP	278.38	64.54164	0.13409
baizhi	MOL000254	eugenol	164.22	56.2419	0.036518
baizhi	MOL000449	Stigmasterol	412.77	43.82985	0.75665
baizhi	MOL000131	EIC	280.5	41.90444	0.14347
baizhi	MOL000198	(R)-linalool	154.28	39.8043	0.022686
baizhi	MOL000360	FER	194.2	39.55852	0.058069
baizhi	MOL000358	beta-sitosterol	414.79	36.91391	0.75123
baizhi	MOL000035	beta-Selinene	204.39	24.38821	0.081081
baizhi	MOL001393	myristic acid	228.42	21.18117	0.066784
baizhi	MOL000357	Sitogluside	576.95	20.63194	0.6241
baizhi	MOL000069	palmitic acid	256.48	19.29656	0.098573
baizhi	MOL000879	methyl palmitate	270.51	18.08756	0.11594
baizhi	MOL000860	stearic acid	284.54	17.82543	0.14086

3.2. Venn Analysis of Targets of Xinyi San in the Treatment of Rhinitis

The targets were predicted by Pharmmapper, and 113 potential active ingredient targets were obtained after weight removal. The obtained target names were input into UniProt database and converted into corresponding gene names. 2562 disease targets were obtained by searching "rhinitis" in genecards database. Through Venn analysis, the intersection of mapping is 53 targets that may be related to the effect of Xinyi San on rhinitis (see Figure 1).

3.3. Constructed of Disease - Single Drug - Active Ingredient - Target" Network

The information of disease, single drug, active ingredient and target were imported into the software Cytoscape for visualization, and the network diagram of "disease - single drug - active ingredient - target" is constructed, including 105 nodes (1 disease node, 10 drug nodes, 41 active ingredient nodes and 53 action target nodes) and 335 edges (see Figure 2).

3.4. Constructed PPI Network

53 intersecting targets obtained from Venn analysis were imported into the STRING database to build the PPI network (see Figure 3). The network contained 50 nodes (DCAF5, PCYY1A and ADRA1A were isolated targets and didn't participate in the analysis) and 369 edges. The top 30 targets were processed with
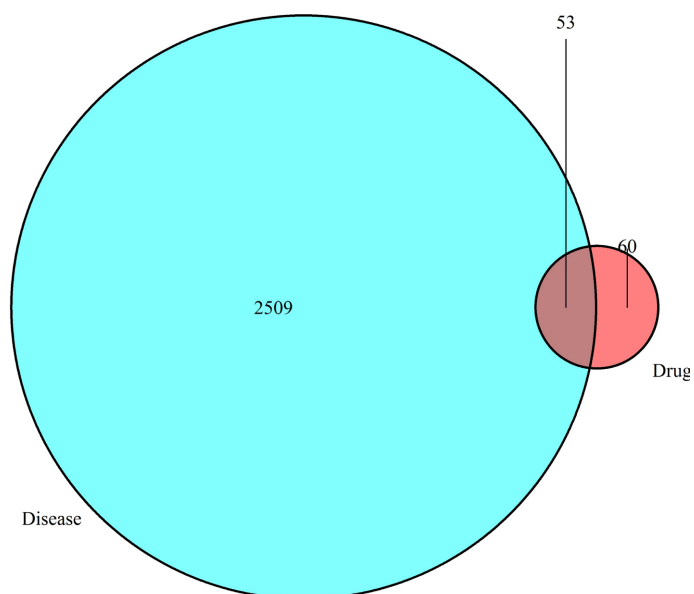
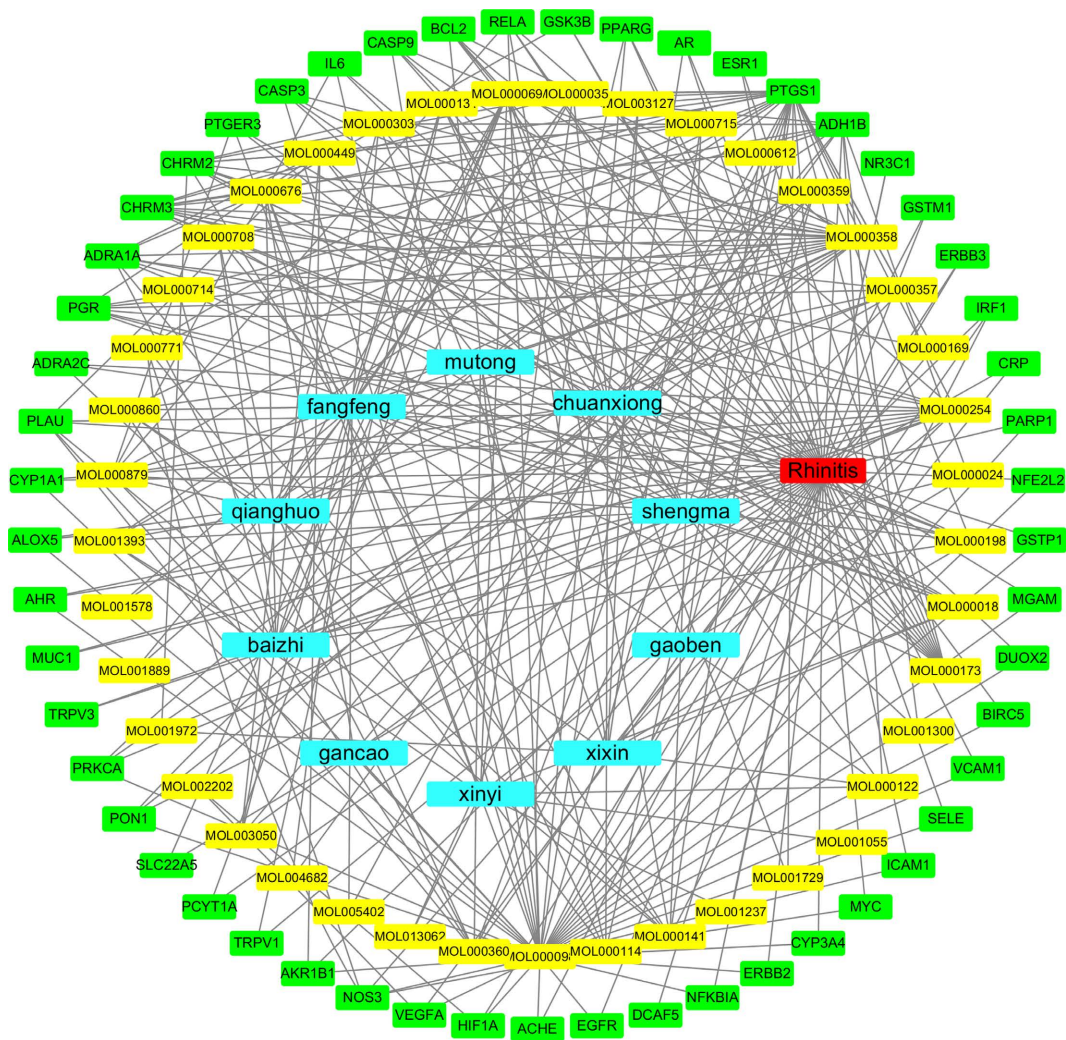**Figure 1.** Venn diagram of intersection targets of Xinyi San and rhinitis.

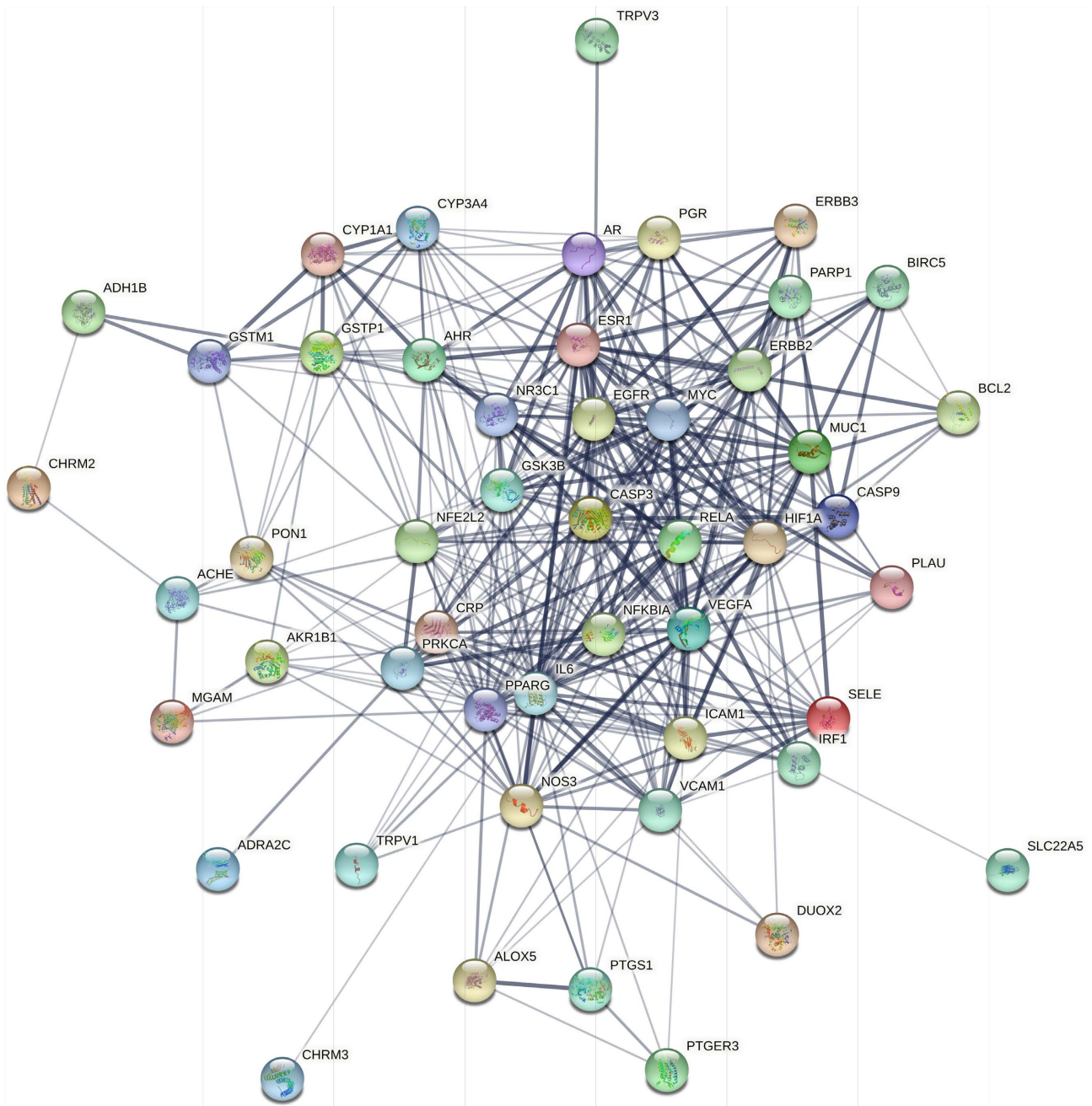**Figure 2.** Composition target network of Xinyi San.

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

R language to obtain the core target map (see **Figure 4**). The top 10 targets with visibility value were IL6, EGFR, VEGFA, HIF1A, CASP3, ESR1, PPARG, MYC, RELA, NFKBIA.

3.5. GO Enrichment Analysis and KEGG Pathway Analysis

Through the analysis of 53 potential targets by R software, 1009 GO entries were obtained, including 84 molecular function (MF), 8 cellular component (CC) and 917 biological process (BP) (see **Figure 5**). We got 92 KEGG pathways (P < 0.05) (see **Figure 6**), such as Lipid and atherosclerosis, Chemical carcinogenesis
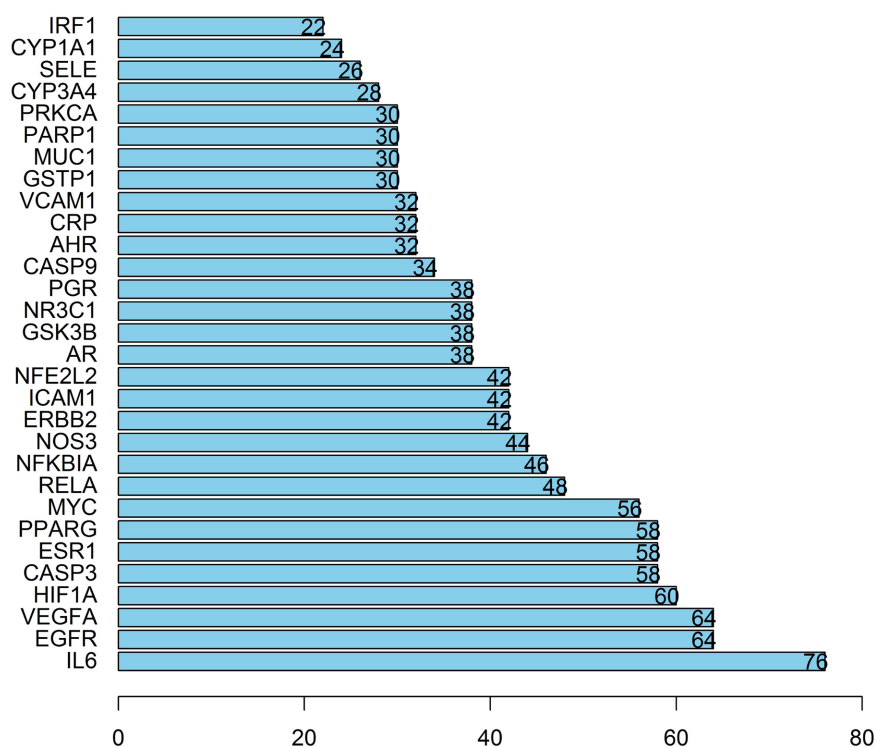
Figure 4. Key targets of Xinyi San.

receptor activation, PI3K-Akt signaling pathway, Human cytomegalovirus infection, Prostate cancer, AGE-RAGE signaling pathway in diabetic complications, Fluid shear stress and atherosclerosis, Kaposi sarcoma-associated herpesvirus infection and Calcium signaling pathway.

4. Discussion

Rhinitis is a high risk factor for sinusitis, nasal polyps, otitis media and bronchial asthma. This disease has a serious impact on the patient's mental state, work and life. Modern medical treatment of this disease mainly includes drug treatment, immunotherapy and surgical treatment. It mainly focuses on controlling and alleviating symptoms, but the condition is very easy to repeat.

Our study showed that quercetin, beta-sitosterol, eugenol, palmitic acid, wogonin and Stigmasterol can match more targets, which were likely to be the key effective components of Xinyi San in treating rhinitis. Quercetin, as a flavonoid, is a research hotspot in recent years. It can significantly improve IL-2 and IFN-γ. Inhibit the levels of IL-4 and IL-5, regulate the balance of Th1/Th2 cytokines, and have a protective effect on allergic rhinitis [6], and many experiments [7] [8] [9] have confirmed that quercetin has a significant effect on rhinitis. Beta sitosterol and Stigmasterol can reduce inflammatory cytokines IL-6 and TNF-α [10] [11]. Eugenol can reduce allergic reactions through suppression of cPLA2 and 5-L0 activation and through inhibition of COX-2 activity [12]. Toll-like receptors and their mediated innate immunity play an important role in the response of nasal sinus mucosal defense [13]. Palmitic acid has been shown to induce TLR4

Figure 5. GO enrichment diagram of candidate targets of Xinyi San in the treatment of rhinitis.
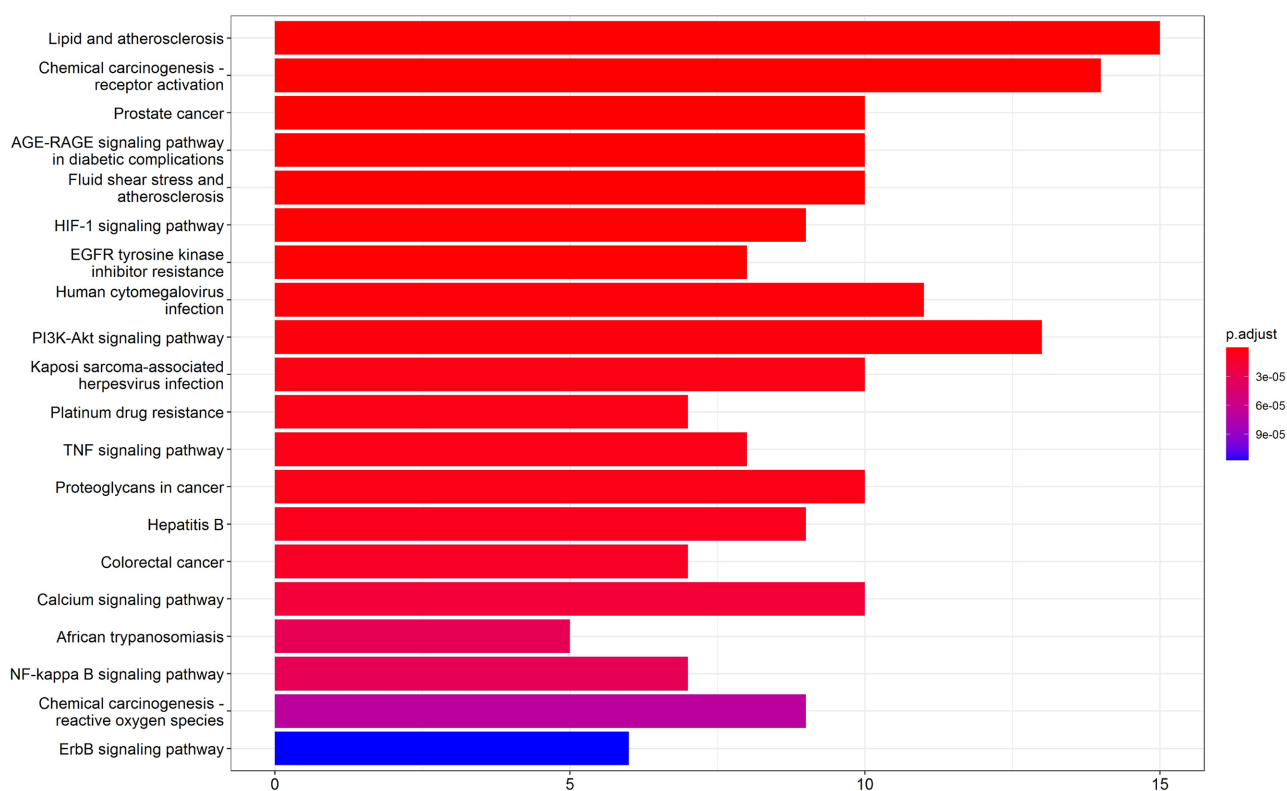
Figure 6. KEGG pathway enrichment analysis of potential target of Xinyi San-rhinitis

protein expression in vascular endothelial cells and significantly increase the TLR4 protein level of endothelial cell membrane, accompanied by significant activation of TLR4 inflammatory signaling pathway [14], which may have good therapeutic effect on allergic rhinitis; Wogonin was shown to be active chemicals in the anti Infammatory induced angiogenesis [15].

The PPI network shows that IL6, EGFR, VEGFA, HIF1A, CASP3, ESR1, PPARG, MYC, RELA and NFKBIA may be the key targets of Xinyi San in treating rhinitis. IL6 has been proved to be closely related to the occurrence and development of rhinitis [16] [17]. The activation of EGFR/EGF signaling pathway is inhibited, which can improve immune adhesion and affect the inflammatory response of AR nasal mucosa [18]. VEGF family mainly includes VEGFA, B, C, D, E and F, among which VEGFA is the most studied. Certain structural changes will occur in nasal mucosa of patients with rhinitis, and VEGF can promote angiogenesis, increase vascular permeability and vascular remodeling of nasal mucosa, promote damaged tissue repair and protect tissue cells [19]. HIF1A can regulate immunity, promote inflammation and induce neovascularization, and has a certain impact on the structural changes of nasal mucosa [20]. The experimental results of Li Yan *et al.* [21] suggest that the occurrence of rhinosinusitis may promote cell apoptosis by activating the apoptosis executive protein CASP3 through the upstream protein of the internal and external pathways of apoptosis. It is reported in the literature [22] that the prevalence of rhinitis in women is significantly higher than that in men, speculating that sex hormone ESR1 is of

great significance in the occurrence and development of rhinitis. PPARG can regulate the inflammatory response of macrophages, mast cells, T cells and eosinophils, PPARG activator can reduce the rhinitis symptom score and inhibit the inflammatory response in allergic rhinitis mice [23]. MYC gene is a cell oncogene, which is involved in cell cycle regulation, cell growth regulation, cell proliferation, differentiation and transformation [24]. XIAO LF *et al.* [25] found that RELA, a gene known to be involved in regulating inflammation, can limit inflammatory response and treat rhinitis; NFKBIA plays a central role in inflammatory regulation and immune response [26], and has positive significance for the recovery of rhinitis.

GO enrichment analysis showed that the gene function of Xinyi San in the treatment of rhinitis was mainly reflected in DNA-binding transcription factor binding, (DNA-binding transcription activator activity, RNA polymerase II-specific), DNA-binding transcription activator activity, ubiquitin protein ligase binding, ubiquitin-like protein ligase binding, protein heterodimerization activity and so on. KEGG pathway enrichment analysis further confirmed the main signal pathways of Xinyi San in the treatment of rhinitis, mainly including Lipid and atherosclerosis, Chemical carcinogenesis - receptor activation and PI3K-Akt signaling pathway, which are mainly related to virus infection, inflammation and apoptosis, suggesting that Xinyi San may play on varieties of cytokines to play an anti-inflammatory and anti-inflammatory role Inhibit cytokine storm and treat rhinitis.

This study used network pharmacology to analyze the potential mechanism of Xinyi San in the treatment of rhinitis. The results confirmed the multi-component, multi-target and multi-channel characteristics of Xinyi San in the treatment of rhinitis, which provided a new idea for further experimental research and clinical application of Xinyi San.

5. Conclusion

In summary, we analyzed the main components of Xinyi San in treating rhinitis, and thus had a further understanding of its pharmacodynamic basis. By using the method of network pharmacology, the mechanism of Xinyi San in treating rhinitis was analyzed systematically at the molecular level. But the study also had some limitations, some of the results still needed to be verified by further laboratory tests and clinical studies.

Funding

Conflicts of Interest

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

References

[1] Hu, C., Li, H.W., Wu, L.J., *et al.* (2020) Mechanism of Cang'er San in Treatment of Rhinitis Based on Network Pharmacology. *Chinese Archives of Traditional Chinese Medicine*, **38**, 64-71.

[2] Yan, Y.H. (1980) Redraft Yan's Jisheng Recipe. People's Health Publishing House, Beijing, 137.

[3] Wang, Y.H., Xu, Y., Cheng, Z.J., *et al.* (2008) Clinical Observation on 80 Cases of Children's Sinusitis Treated with Xinyi San. *Zhejiang Journal of Traditional Chinese Medicine*, **43**, 42.

[4] Liu, L.J. (2017) Observation on 25 Cases of Rhinitis Treated with Modified Xinyi San and Xiaoqinglong Decoction. *Nei Mongol Journal of Traditional Chinese Medicine*, **1**, 24.

[5] Xie, J., Gao, S., Li, L., *et al.* (2019) Research Progress and Application Strategy on Network Pharmacology in Chinese Materia Medica. *Chinese Traditional and Herbal Drugs*, **50**, 2257-2265.

[6] Peng, W., Wang, W., Zhao, A.J., *et al.* (2018) Effects of Quercetin on Expressions of Th1/Th2 Cytokines in Serum of Experimental Allergic Rhinitis in Rats. *Chinese Journal of Otorhinolaryngology-Skull Base Surgery*, **24**, 557-560.

[7] Sagit, M., Polat, H., Gurgen, S.G., Berk, E., Guler, S. and Yasar, M. (2017) Effectiveness of Quercetin in an Experimental Rat Model of Allergic Rhinitis. *European Archives of Oto-Rhino-Laryngology*, **274**, 3087-3095. https://doi.org/10.1007/s00405-017-4602-z

[8] Mlcek, J., Jurikova, T., Skrovankova, S., *et al.* (2016) Quercetin and Its Anti-Allergic Immune Response. *Molecules*, **21**, Article No. 623. https://doi.org/10.3390/molecules21050623

[9] Jafarinia, M., Hosseini, M.S., Kasiri, N., *et al.* (2020) Quercetin with the Potential Effect on Allergic Diseases. *Allergy, Asthma & Clinical Immunology*, **16**, Article No. 36. https://doi.org/10.1186/s13223-020-00434-0

[10] Choi, J.N., Choi, Y.H., Lee, J.M., *et al.* (2012) Anti-Inflammatory Effects of β-Sitosterol-β-D-Glucoside from *Trachelospermum jasminoides* (Apocynaceae) in Lipopolysaccharide-Stimulated RAW 264.7 Murine Macrophages. *Natural Product Research*, **26**, 2340-2343. https://doi.org/10.1080/14786419.2012.654608

[11] Sabeva, N.S., McPhaul, C.M., Li, X.G., *et al.* (2011) Phytosterols Differentially Influence ABC Transporter Expression, Cholesterol Efflux and Inflammatory Cytokine Secretion in Macrophage Foam Cells. *The Journal of Nutritional Biochemistry*, **22**, 777-783.

[12] Tang, F., Chen, F.L., Ling, X., *et al.* (2015) Inhibitory Effect of Methyleugenol on IgE-Mediated Allergic Inflammation in RBL-2H3 Cells. *Mediators of Inflammation*, **2015**, Article ID: 463530. https://doi.org/10.1155/2015/463530

[13] Li, X.J. (2015) Toll-Like Receptors in the Research Progress of Rhinitis Nasal Polyps. *Journal of Clinical and Pathological Research*, **35**, 1852-1856.

[14] Zhao, N.J., Wang, D.Q., Rong, Q.F., *et al.* (2013) Palmitate Enhances Toll-Like Receptor 4 Expression and Signaling in Porcine Vascular Endothelial Cells. *Journal of Southern Medical University*, **33**, 1775-1777.

[15] Gong, G.W., Wang, H.Y., Kong, X.P., *et al.* (2018) Flavonoids Are Identified from the Extract of Scutellariae Radix to Suppress Inflammatory-Induced Angiogenic Responses in Cultured RAW 264.7 Macrophages. *Scientific Reports*, **8**, Article No. 17412. https://doi.org/10.1038/s41598-018-35817-2

[16] Luo, J.H., Liao, F.G. and Liao, Z.P. (2010) Association the Polymorphism of Inter-

leukin-6 in Patients with Allergic Rhinitis. *Progress of Anatomical Sciences*, **16**, 442-444.

[17] Wang, B., Shu, Y., Liang, J., *et al*. (2016) Expression and Significance of Interleukin-6 in Children with Chronic Sinusitis. *Chongqing Medicine*, **45**, 19-23.

[18] Han, R., Zheng, P.Y., Wang, J.Q., *et al*. (2019) Desmoglein 3 Gene Mediates Epidermal Growth Factor/Epidermal Growth Factor Receptor Signaling Pathway Involved in Inflammatory Response and Immune Function of Anaphylactic Rhinitis. *Biomedicine & Pharmacotherapy*, **118**, Article ID: 109214.

[19] Guo, Q., Zou, S.Y., Xu, S.J., *et al*. (2020) The Histopathologic Changes and the Protein Expression of Vascular Endothelial Growth Factor in the Nasal Mucosa of Allergic Rhinitis. *Journal of Harbin Medical University*, **54**, 546-548.

[20] Baek, K.J., Cho, J.Y., Rosenthal, P., *et al*. (2013) Hypoxia Potentiates Allergen Induction of HIF-1α, Chemokines, Airway Inflammation, TGF-β1, and Airway Remodeling in a Mouse Model. *Clinical Immunology*, **147**, 27-37.

[21] Li, Y., Zhang, J.F. and Wang, D.Y. (2018) Effects of Qingbi Pills on the Expression of IL-8 mRNA and TNF-α mRNA of Nasal Mucosa Tissue in the Rabbits of Rhinosinusitis. *World Journal of Integrated Traditional and Western Medicine*, **13**, 1095-1098.

[22] Klis, K. and Wronka, I. (2017) Association of Estrogen-Related Traits with Allergic Rhinitis. In: Pokorski, M., Ed., *Influenza and Respiratory Care*, Springer, Cham, 71-78. https://doi.org/10.1007/5584_2016_190

[23] Lee, J.E., Zhang, Y.L., Han, D.H., *et al*. (2015) Antiallergic Function of KR62980, a Peroxisome Proliferator-Activated Receptor-γ Agonist, in a Mouse Allergic Rhinitis Model. *Allergy, Asthma & Immunology Research*, **7**, 256-264.

[24] Guo, X.J., Cheng, Z.Q. and Jin, H.T. (2017) Expression of c-myc and Ki-67 and Their Significance in Extranodal NK/T-Cell Lymphoma, Nasal Type. *Chinese Journal of Diagnostic Pathology*, **24**, 517-520.

[25] Xiao, L.F., Jiang, L., Hu, Q., *et al*. (2018) MiR-302e Attenuates Allergic Inflammation Model by Targeting RelA. *Bioscience Reports*, **38**, Article ID: BSR20180025. https://doi.org/10.1042/BSR20180025

[26] Guan, H.J., Sun, G.F. and Xie, H.F. (2019) Genetic Loci in the NF-κB Pathway and Lung Cancer Susceptibility: A Meta-Analysis. *Chinese Journal of Evidence-Based Medicine*, **19**, 1430-1435.