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Target Prediction of Xinyi San for Nasal Polyposis Based on Network Pharmacology

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Abstract

Objective: To analyze the potential mechanism of Xinyi San in treating nasal polyposis through network pharmacology. **Methods:** We Screened the active components and targets of Xinyi San by TCMSP database, and disease targets through GeneCards database. We constructed "disease-single drug-component-target" network through software Cytoscape 3.7.2 and constructed PPI network through STRING database. GO function and KEGG pathway enrichment were analyzed to predict its mechanism. **Results:** We got 162 components, 69 therapeutic targets, 88 GO items and 135 pathways. The main pathways include Lipid and atherosclerosis, Chemical carcinogenesis-receptor activation, Kaposi sarcoma-associated herpesvirus infection, Hepatitis B, Human cytomegalovirus infection, etc. **Conclusion:** This study preliminarily revealed the active components, targets and pathways of Xinyi San in treating nasal polyposis.

Keywords

Nasal Polyposis, Network Pharmacology, Xinyi San

1. Introduction

Nasal polyposis is a nasal disease with high incidence rate. The main clinical manifestations are nasal obstruction, runny nose, dizziness, headache and diminished olfaction. It seriously affects the quality of life of patients and is difficult to treat. It is easy to relapse [1]. The occurrence of nasal polyposis is closely related to allergy, bacterial infection, fungal infection, aspirin intolerance, genetics and other factors, but the related pathogenesis is not clear [2] [3]. Modern medicine mainly treats nasal polyposis with drugs and surgery. It is easy to repeat after stopping drugs, and the side effects of drugs are large. Traditional Chinese medicine has great advantages in treating nasal polyposis.

Xinyi San is a classic famous prescription, which originates from Yan's Jisheng prescription [4] written by Yan Yonghe in the Song Dynasty. The whole prescription is composed of 10 drugs such as xinyi, xixin, gaoben, shengma, chuanxiong, mutong, fangfeng, qianghuo, gancao and baizhi. It has the function of evacuating wind cold and dredging nose orifices. The clinical pathology of nasal polyposis is complex, but the mechanism of Xinyi San in treating nasal polyposis is not clear. Network pharmacology can construct a complex network between drug component target disease to explore the mechanism of drug action. Therefore, based on network pharmacology, this study explored the pharmacodynamic material basis and potential mechanism of Xinyi San in treating nasal polyposis, so as to provide reference for clinical application.

2. Materials and Methods

2.1. Screened for Active Components and Targets of Xinyi San

The active components and targets were screened with xinyi, xixin, gaoben, shengma, chuanxiong, mutong, fangfeng, qianghuo, gancao and baizhi as keywords through TCMSP (http://tcmspw.com/tcmsp.php), in which OB ≥ 30% and DL ≥ 0.18 (OB: oral bioavailability; DL: drug properties). Then converted the target proteins to gene name through UniProt (https://www.uniprot.org/).

2.2. Screened Disease Targets

We searched for disease targets with "nasal polyposis" as the keyword through genecards (https://www.genecards.org). The total targets were obtained by eliminating the repeated targets.

2.3. Constructed Disease-Single Drug-Ingredient-Target Network

Based on the above results, Cytoscape 3.7.2 software builded the network model of "disease-single drug-component-target". Nodes represented diseases, single drugs, components and targets, and edges were used to show the relationship between them.

2.4. Constructed PPI Network

The active component targets of Xinyi San and the disease targets of nasal polyposis were introduced into Venny analysis platform (https://bioinfogp.cnb.csic.es/tools/venny/) to obtain the potential targets of Xinyi San in treating nasal polyposis. Imported intersection targets into String (https://string-db.org), the species was limited to "Homo sapiens", the isolated targets were removed, and the PPI network was constructed with a confidence of 0.4 as the screening condition.

2.5. Gene Enrichment Analysis

GO functional enrichment analysis and KEGG pathway enrichment analysis were performed on R4 1.1 software for the main components of Xinyi San (P ≤

0.05). The top 20 biological processes and pathways were selected.

3. Results

3.1. Screened Active Components of Xinyi San

We screened 97 potential active components of Xinyi San by TCMSP platform, including 12 xinyi, 6 xixin, 1 gaoben, 7 shengma, 6 chuanxiong, 8 mutong, 14 fangfeng, 10 qianghuo, 85 gancao and 13 baizhi. The basic information of some active components was as follows (see Table 1).

3.2. Constructed "Disease-Single Drug-Ingredient-Target" Network

The disease, single drug, active ingredients and targets were introduced into Cytoscape to construct the "disease-single drug-component-target" network (see Figure 1), including 222 nodes (1 disease node, 10 drug nodes, 142 active

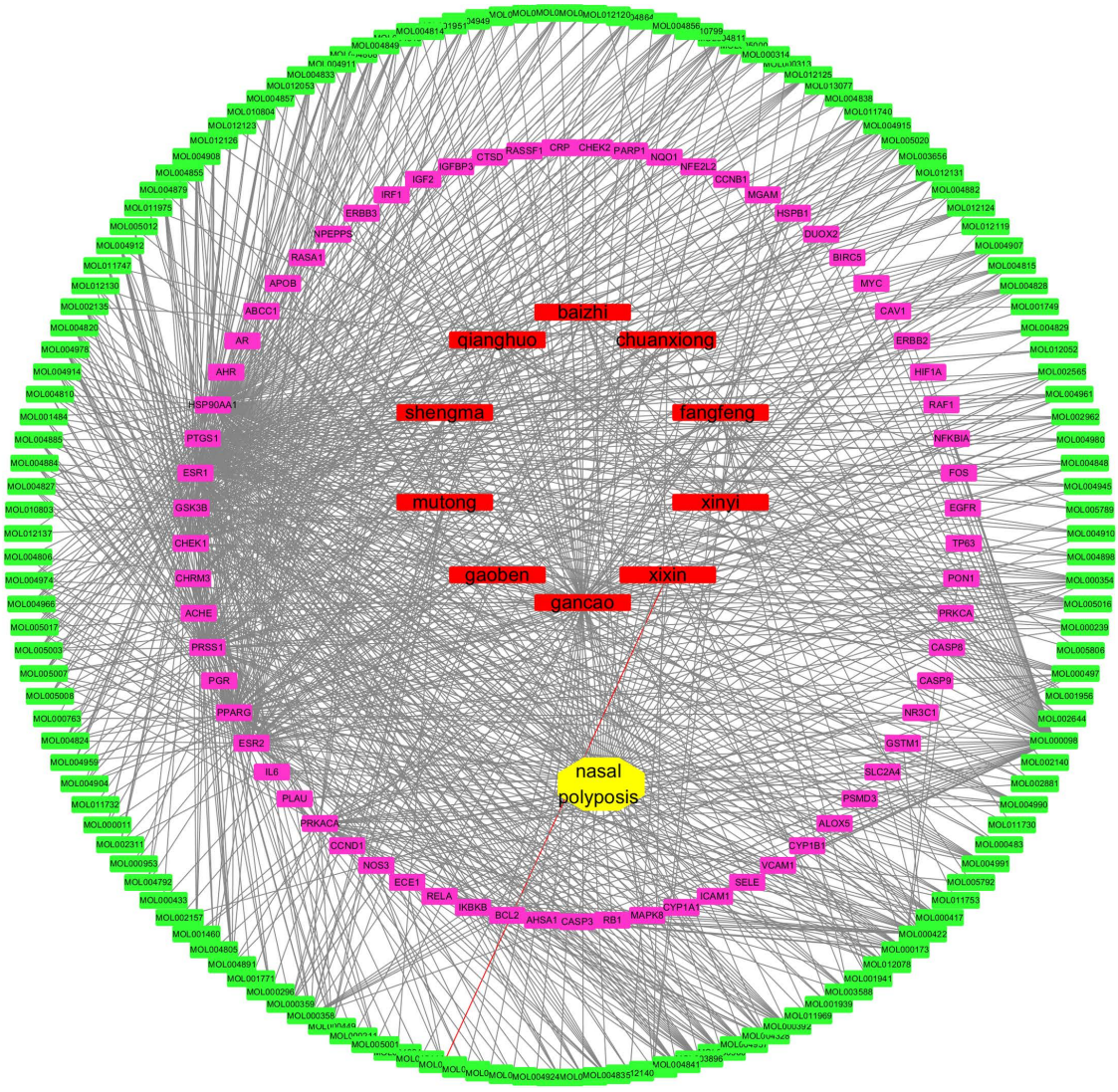

Figure 1. Network diagram of "disease-single drug-component-target".

Table 1. The basic information of some 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
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

Continued

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
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

Continued

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
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

ingredient nodes and 69 action target nodes) and 995 edges. The degree value of the node represents the number of the edges connected with the node, and the

compound nodes with large degree value were screened. These compounds may be the key compounds of Xinyi San in treating nasal polyposis. The results showed that the top 7 compounds were quercetin, kaempferol, wogonin, beta-sitosterol, 7-Methoxy-2-methyl isoflavone, licochalcone a and isorhamnetin, which could connect with 56, 24, 17, 15, 12, 12 and 12 targets respectively.

3.3. Constructed PPI Network

Searched "nasal polyposis" in Genecards database to obtain 2062 disease targets, and mapped the intersection with 120 potential active component targets through Venn analysis, that was, 69 targets of Xinyi San in treating nasal polyposis (see Figure 2). Imported the 69 intersection targets into the String database to build the PPI network (see Figure 3). The top 30 targets were processed with R language to obtain the core target map (see Figure 4). The corresponding targets of these proteins with a large degree value may be the key targets of Xinyi San in treating nasal polyposis.

3.4. GO Enrichment Analysis

A total of 88 functional enrichments were obtained through R software analysis, and the top 20 with the greatest significance were made into a bar graph (see

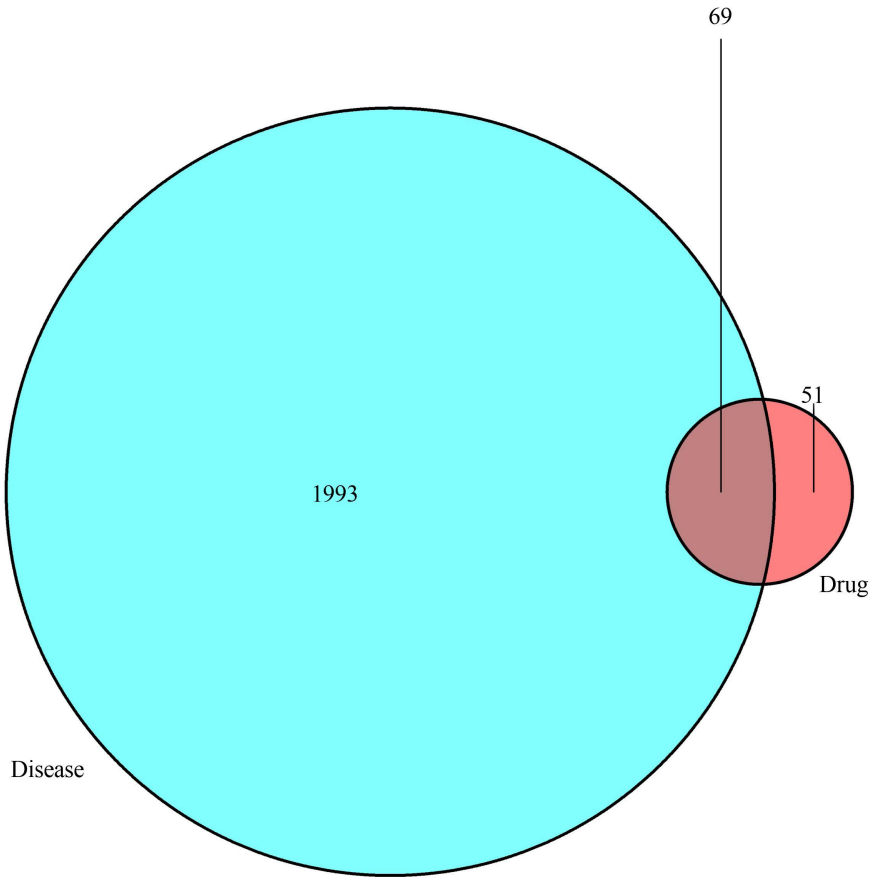

Figure 2. Venn diagram of intersection target of Xinyi San and nasal polyposis.

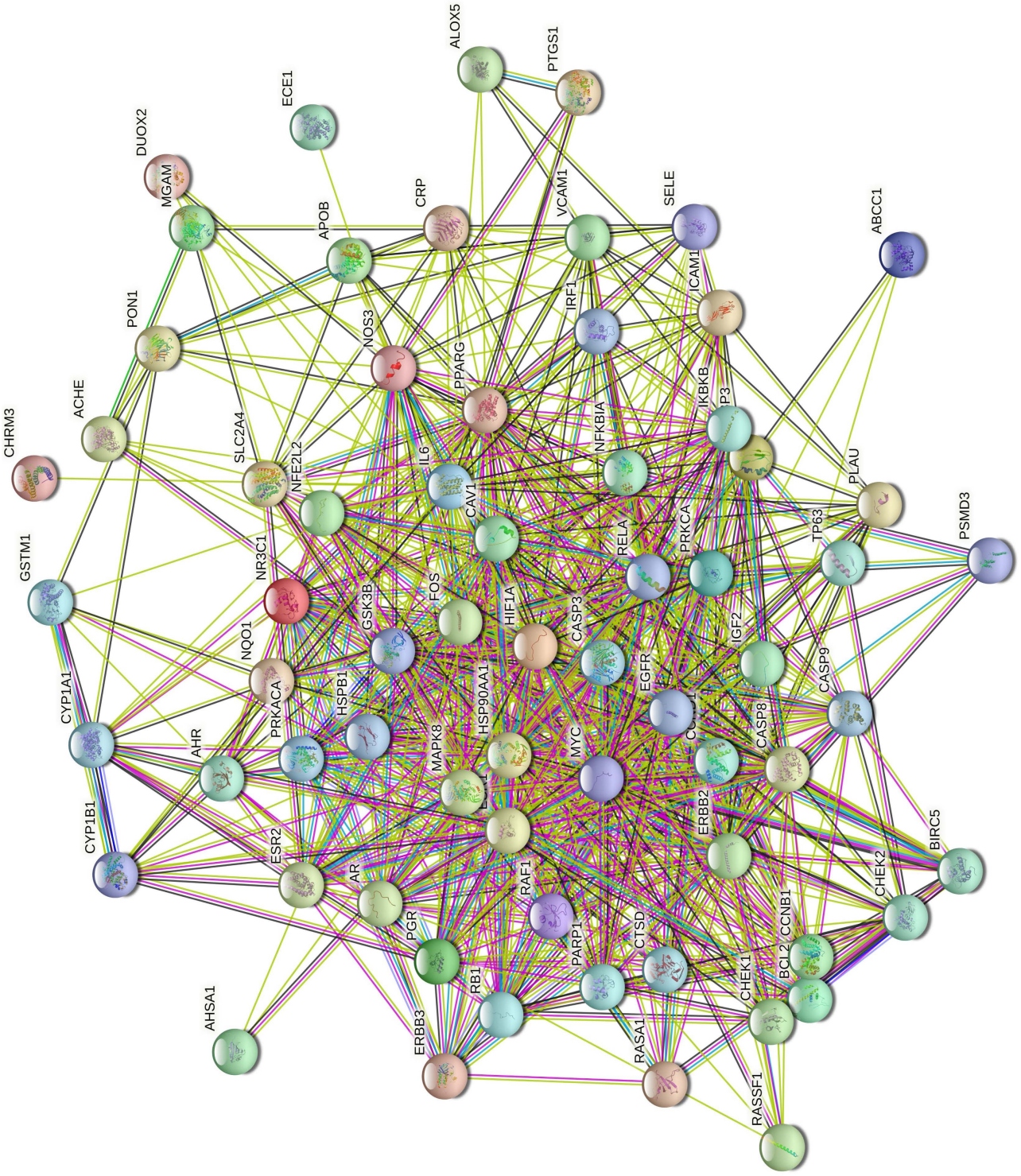

Figure 3. PPI network of Xinyi San in treating nasal polyposis.

Figure 5). DNA-binding transcription factor binding, ubiquitin-like protein ligase binding, ubiquitin protein ligase binding, nuclear receptor activity, ligand-activated transcription factor activity, RNA polymerase II-specific DNA-binding transcription factor binding, etc.

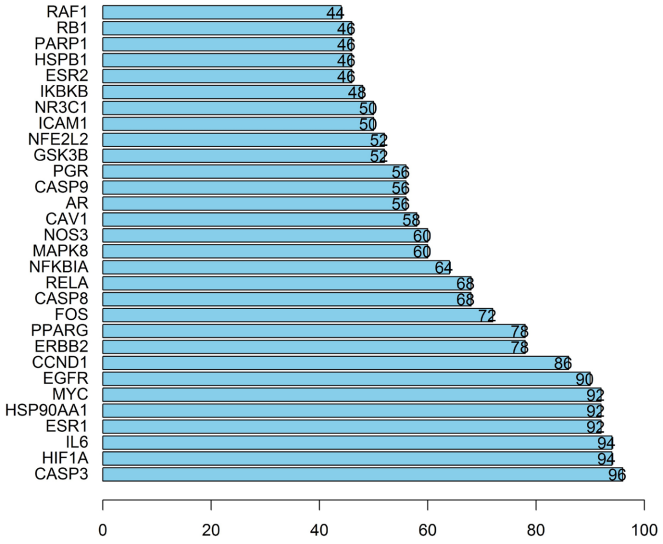

Figure 4. The key targets of Xinyi San.

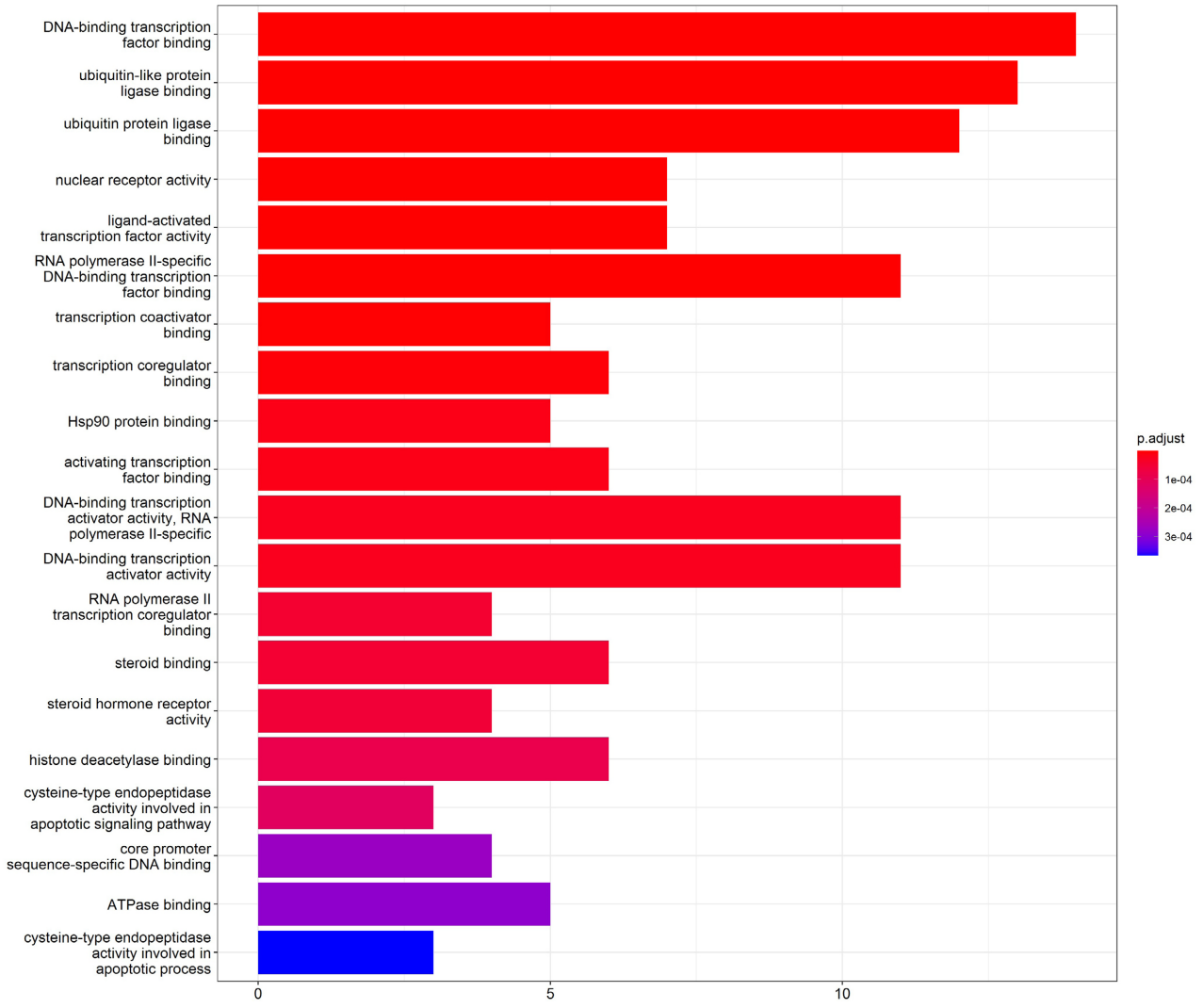

Figure 5. GO enrichment analysis of Xinyi San.

3.5. KEGG Pathway Analysis

We got 135 KEGG pathways ($P < 0.05$), the top of 20 were plotted as a bar graph (see Figure 6). The results showed that the effective mechanism of Xinyi San in treating nasal polyposis mainly involves Lipid and atherosclerosis, Chemical carcinogenesis-receptor activation, Kaposi sarcoma-associated herpesvirus infection, Hepatitis B, Human cytomegalovirus infection and other pathways.

4. Discussion

Although the pathogenesis of nasal polyposis is not clear, the current etiological theory believes that the root cause of nasal polyposis is the inflammatory reaction caused by environmental or allergic stimuli or nasal infection [5].

The construction results of "disease-single drug-component-target" network showed that quercetin, kaempferol, wogonin, beta sitosterol, 7-methoxy-2-methyl isoflavone, Licochalcone a and isorhamnetin may be the key compounds of Xinyi San in treating nasal polyposis. It was found that [6] quercetin could significantly inhibit the infiltration of eosinophils in nasal mucosa of rhinitis rats, and significantly improved nasal mucosal edema, vasodilation and gland hyperplasia. Kaempferol could inhibit TNF in nasal mucosa-α and the expression level of IL-4, reducing the infiltration of eosinophils in nasal mucosa [7]. Chalcone had many pharmacological activities, such as anti-inflammatory, antifungal, anti ulcer, anti-oxidation, anti-virus and anti-tumor. Especially in terms

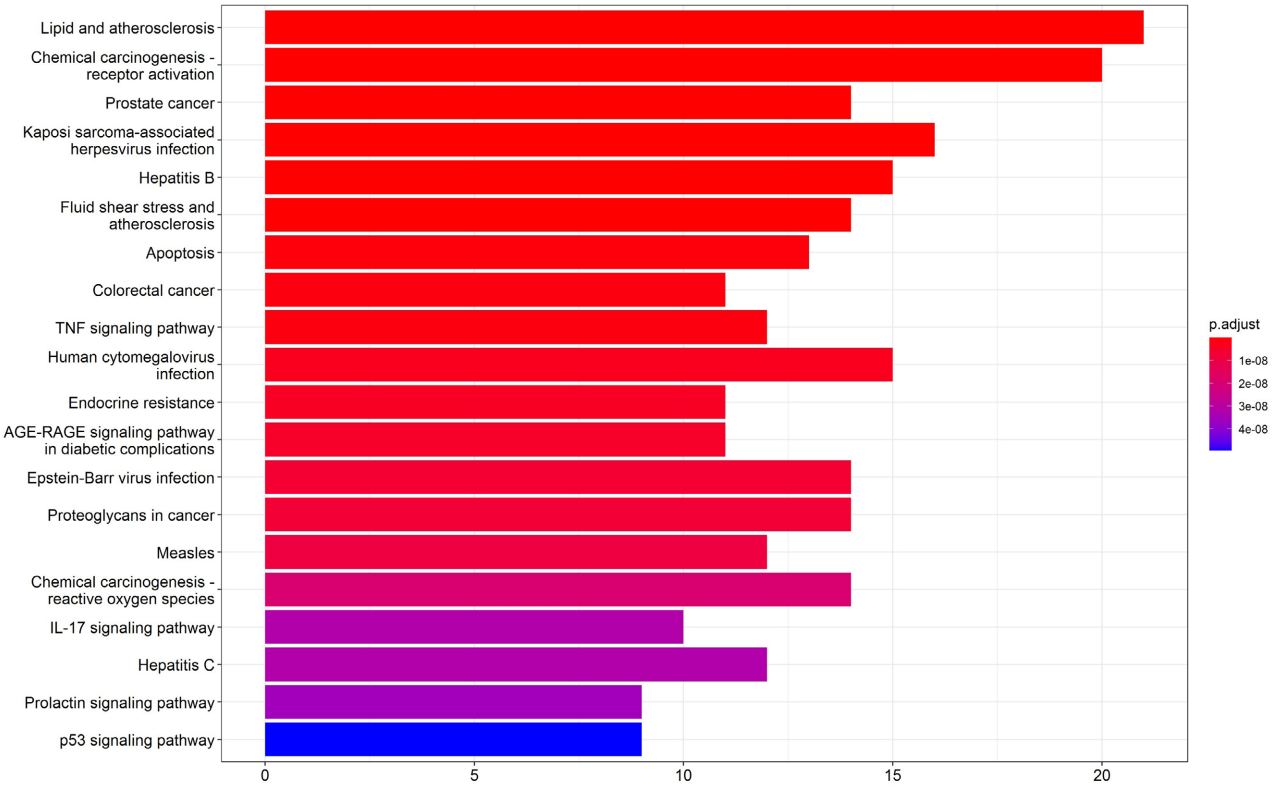

Figure 6. KEGG pathway enrichment analysis of Xinyi San.

of anti-inflammatory, some chalcone compounds had very significant biological activities [8].

The PPI network showed that the key targets of Xinyi San in treating nasal polyposis were RAF1, RB1, PARP1, HSPB1, ESR2, IKBKB, NR3C1, ICAM1, NFE2L2 and GSK3B. The results of GO analysis showed that the active components of Xinyi San mainly involved in biological processes such as cell response, inflammatory response and immune response, suggesting that Xinyi San might act on a variety of cytokines, anti-inflammatory and inhibit cytokine storm in treating nasal polyposis. KEGG pathway enrichment mainly involved Lipid and atherosclerosis, Chemical carcinogenesis-receptor activation, Kaposi sarcoma-associated herpesvirus infection, Hepatitis B, Human cytomegalovirus infection, etc.

5. Conclusion

The study used network pharmacology to analyze the action mechanism of Xinyi San in treating nasal polyposis, and confirmed the complex action mechanism of multi-component, multi-target and multi-channel of Xinyi San, which laid a foundation for its in-depth 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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