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 (Notop-
terygii 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 addi-
tion, 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 clinicopa-
thology of rhinitis and more chemical components contained in Xinyi San, the
mechanism of its treatment of rhinitis at the molecular level is not clear. Net-
work pharmacology is a branch of pharmacology that uses network methods to
analyze the “multi-component, multi-target and multi-channel” synergistic rela-
tionship between drugs, diseases and targets. It can build a complex network
between drugs, components, targets and diseases to explore the action mecha-
nism 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 ob-
tained 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  |
| Name     | Compound Name   | Molecular Formula | m/z      | pIC50  | Error  |
|----------|-----------------|-------------------|----------|--------|--------|
| 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-Cardanol      | 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 | 0.7512  |
| 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 | MOL000069       | methyl palmitate  | 270.51   | 18.08756 | 0.11594 |
| mutong   | 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 | 0.7512  |
Continued

| MOL Code | Compound         | Retention Time (min) | Purity (%) | Identity |
|----------|------------------|----------------------|------------|----------|
| MOL000114 | vanillic acid    | 168.16               | 41.90444   | EIC      |
| MOL000359 | sitosterol       | 414.79               | 36.91391   | DBP      |
| MOL000118 | (+/-)-Isoborneol | 154.28               | 86.98413   | DBP      |
| MOL00122  | 1, 8-cineole     | 154.28               | 39.72922   | EIC      |
| MOL000140 | sitosterol       | 414.79               | 36.91391   | DBP      |
| MOL00114  | vanillic acid    | 168.16               | 41.90444   | EIC      |
| MOL000198 | (R)-linalool     | 154.28               | 39.8043    | DBP      |
| MOL00133  | myristic acid    | 228.42               | 21.18117   | EIC      |
| MOL00069  | palmitic acid    | 256.48               | 19.29656   | EIC      |
| MOL00066  | stearic acid     | 284.54               | 17.82543   | EIC      |
| MOL005402 | Methyl margarate | 284.54               | 17.40885   | EIC      |
| MOL000131 | EIC              | 280.5                | 41.90444   | EIC      |
| MOL000198 | (R)-linalool     | 154.28               | 39.8043    | DBP      |
| MOL00114  | vanillic acid    | 168.16               | 41.90444   | EIC      |
| MOL000198 | (R)-linalool     | 154.28               | 39.8043    | DBP      |
| MOL00133  | myristic acid    | 228.42               | 21.18117   | EIC      |
| MOL00069  | palmitic acid    | 256.48               | 19.29656   | EIC      |
| MOL00066  | stearic acid     | 284.54               | 17.82543   | EIC      |
| MOL000131 | EIC              | 280.5                | 41.90444   | EIC      |
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
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-LO 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-inflammatory 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. PPARγ can regulate the inflammatory response of macrophages, mast cells, T cells and eosinophils, PPARγ 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.

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Conflicts of Interest

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