Exploration of the Molecular Mechanism of FUZI (Aconiti Lateralis Radix Praeparata) in Allergic Rhinitis Treatment Based on Network Pharmacology

FUZI (Aconiti Lateralis Radix Praeparata) is a traditional Chinese medicine herb used extensively for nourishing yang (regarded as the positive, male universal force), which is critical in treatment of allergic rhinitis. In this paper, FUZI was explored based on network pharmacology. The active components of FUZI were screened out, its protein targets were assessed, and the protein interaction network map was built with the differential protein of allergic rhinitis, as an attempt to determine the critical targets of FUZI for treating allergic rhinitis. Subsequently, DAVID was employed to explore the biological function and pathway enrichment to determine the biological pathway of FUZI for treating allergic rhinitis. As suggested by the results, FUZI is likely to affect the inhibition of inflammation and the regulation of immunity, probably reducing the incidence of allergic rhinitis, or alleviating nasal discomfort attributed to allergic inflammation. The targets and pathways of FUZI for treating allergic rhinitis assessed by network pharmacology provided a direction for our subsequent studies and may be a novel therapeutic target.

MeSH Keywords: Allergic Rhinitis • FUZI • Network Pharmacology
Background

Allergic rhinitis (AR) refers to an inflammatory disease of nasal mucosa mediated by IgE. The cumulative costs of drug treatment can be significant over time since AR is capable of recurrence and can seriously impair human health and adversely affect patient quality of life [1]. Western medicine is relatively ineffective in treating AR. Patients with mite allergy can try sublingual immunotherapy to eradicate the disease, but AR treatment primarily aims at alleviating symptoms.

Traditional Chinese Medicine (TCM) has safeguarded our health for thousands of years, it is a treasure for discovering potential treatments. TCM can act as a supplement or substitute during the treatment of AR. According to the knowledge of TCM, the occurrence of AR results from the deficiency of yang qi. The major approach to treat AR is to warm and tonify yang qi. FUZI refers to a traditional Chinese medicine herb, which is commonly used for warm and tonify yang qi, and is also extensively applied for treating AR in clinical practice. It is capable of inhibiting the inflammation activated by IgE, regulating the imbalance between Th1 and Th2, and reducing the clinical symptoms of AR rats by working in combination with other herbs in the formula [2,3]. Recent studies have shown that FUZI has definite anti-inflammatory and immunomodulatory effects [4,5].

Similar to all TCM herbs, FUZI contains many kinds of compounds, and its targets are sophisticated. For this reason, it is very difficult to analyze from a general perspective. To gain insights into the mechanism of FUZI for treating AR, a more systematic and modern study is required. Network pharmacology can effectively deepen the understanding of TCM, treatments. TCM can act as a supplement or substitute during the treatment of AR. According to the knowledge of TCM, the occurrence of AR results from the deficiency of yang qi. The major approach to treat AR is to warm and tonify yang qi. FUZI refers to a traditional Chinese medicine herb, which is commonly used for warm and tonify yang qi, and is also extensively applied for treating AR in clinical practice. It is capable of inhibiting the inflammation activated by IgE, regulating the imbalance between Th1 and Th2, and reducing the clinical symptoms of AR rats by working in combination with other herbs in the formula [2,3]. Recent studies have shown that FUZI has definite anti-inflammatory and immunomodulatory effects [4,5].

Material and Methods

Active compounds of FUZI

We used BATMAN-TCM (Bioinformatics Analysis Tool for Molecular mechanANism of TCM, http://bionet.ncpsb.org/batman-tcm/), a molecular mechanism analysis tool based on TCM ingredients’ target prediction and network pharmacology analyses [6]. To determine the active compounds and targets of FUZI, the herb name FUZI was submitted to BATMAN-TCM analysis and the ‘Score_cutoff’ was set to 20. Subsequently, the active compounds were screened out according to the ADME (Adsorption, Distribution, Metabolism, Excretion) parameters. First, the compounds were acquired in PubChem (https://pubchem.ncbi.nlm.nih.gov) [7], which is the world’s largest library of chemical information. Second, ADME parameters of the compounds were acquired in FAFdrugs4 (http://fafdrugs4.mti.univ-paris-diderot.fr) according to the SMILES query. FAFdrugs4 is a free ADME-Tox filtering tool which is conducive to screening our compounds. Subsequently, compounds were sifted following the standard ‘Drug-Like Soft’. Based on ‘Drug-Like Soft’, standard compounds were screened by combining their physical and chemical properties [8–12]. The molecular weight, hydrophobicity, rotatable bonds, and H-bonds donors were all considered in the assessment criteria. The compounds accepted by the standard ‘Drug-Like Soft’ were the active compounds of FUZI.

Candidate targets of FUZI’s active compounds

The compounds accepted by FAFdrugs4 and the targets obtained from the results of BATMAN-TCM database were collected. Subsequently, the compounds and targets were used to construct an interaction network to describe their relationship. To facilitate subsequent analysis, the target names were converted to uniform standard Uniprot IDs via the Uniprot website (https://www.uniprot.org), a universal protein database.

AR-associated genes

AR-associated genes were collected as the disease targets from the OMIM (Online Mendelian Inheritance in Man, https://omim.org, updated May 2019) and DrugBank (https://www.drugbank.ca). The OMIM database is an authoritative database of human genes. DrugBank covers chemical data and drug targets or protein data [13–15]. AR-associated genes were searched in the above databases with ‘Allergic Rhinitis’ as the key word. The target genes were labeled by Uniprot IDs.

Construction of a protein–protein interaction (PPI) network

The interaction network between the compounds targets and disease targets was built using STRING version 11.0 (https://string-db.org/). Then, the built network was imported into Cytoscape version 3.7.1 for visualization and topology analysis. In line with the topological index Degree, the nodes’ connectivity centrality was sifted. The node with the value greater than twice the median degree of all nodes was defined as the hub node.

Molecular docking is capable of revealing the molecular mechanism of drug treatment of diseases, enhancing the pharmacological effects to the molecular level, and materially underpinning the study of drug mechanism. To verify our predicted targets,
molecular docking was performed using the compounds and their targets with high degree in the hub nodes. The three-dimensional structures of the target proteins were obtained in the Protein Data Bank (http://www.rcsb.org/pdb/home/home.do) [16]. Next, the obtained proteins were decomposed into protein receptors and small molecular ligands for storage. The 3D structures of the active compounds originated from PubChem (https://pubchem.ncbi.nlm.nih.gov) were stored as molecular docking ligand after corresponding processing. The obtained protein receptors and ligands were docked by autodock4.

The drugs used to treat AR and their targets were collected in DrugBank. Subsequently, the PPI network was built with the hub nodes and the known targets to treat AR using STRING version 11.0. A novel network was obtained. Next, the network was imported into Cytoscape version 3.7.1 for visualization.

**Enrichment analysis of the hub nodes of FUZI acting on AR**

The Database for Annotation, Visualization and Integrated Discovery (DAVID, https://david.ncifcrf.gov/home.jsp) is a functional annotation tool that can provide insights into the biological significance of genes [17,18]. The DAVID 6.8 database was used for Gene Ontology enrichment (GO enrichment) and Pathway enrichment analysis of hub nodes harvested. The directed Biological Process, Cellular Component, and Molecular

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**Figure 1.** The technical strategy of this research. Exploration of molecular mechanism of FUZI for allergic rhinitis treatment based on network pharmacology.
Function were employed to analyze the biological process. The KEGG pathway was selected to analyze the active pathway of FUZI for treating AR (P<0.01).

Results

Active compounds of FUZI

The BATMAN-TCM database was searched. We found 58 compounds of FUZI, of which 46 compounds had potential targets when the ‘Score_cutoff’ was set to 20. The SMILES query of the 46 compounds was performed in PubChem. Subsequently, according to SMILES query of the compounds, ADME parameters were queried in the FAFdrugs4 database, and only 44 compounds were matched in the FAFdrugs4 database. Lastly, 11 compounds were accepted when compounds were screened according to the ‘Drug-Like Soft’ standard (Table 1).

Targets of FUZI’s Active Compounds

Target proteins of the 11 accepted compounds were screened out from the search results in the BATMAN-TCM database. After removing duplicate targets, 194 targets were obtained in total. The compounds targets network was constructed using Cytoscape 3.7.1. After clustering analysis was conducted on the obtained compounds targets network, 5 clusters were obtained. The first cluster covers 4 compounds and their targets, which were Mescaline, Coryneine, Salsolinol, and Higenamine. By searching for the properties of these compounds in PubChem, it was found that they all have the effect of constricting blood vessels. Moreover, Higenamine is a natural non-steroidal anti-inflammatory drug that can inhibit inflammation by interfering with the synthesis of prostaglandins. The second cluster covers 2 compounds and their targets, which were 14-Deoxy-11,12-Didehydroandrographolide, and Deoxyandrographolide. Both 2 compounds are andrographolides and exhibit anti-inflammatory functions, which are probably associated with the inhibition of NF-κB [19,20]. The allergic reaction process of AR is relatively short-lived, and it is the subsequent inflammation in the later stage that primarily affects the quality of life of patients. Thus, anti-inflammation is the top priority for treating AR. The third cluster covers 3 compounds and their targets, which were M-Aminophenol, Ortho-Aminophenol, and Para-Aminophenol. These are toxic compounds, and their clinical effects have been rarely studied. Thus, the mechanism of their action remains unclear. The fourth cluster covers only 1 compound, Hypaphorine, and 2 targets. Hypaphorine is capable of exerting its anti-inflammatory properties by regulating Toll-like receptor 4 and peroxisome proliferator-activated receptor γ via the PI3K/Akt/mTOR signaling pathway [21]. The fifth cluster covers only 1 compound, Deltamine, and 4 targets. Deltamine has the effect of sympathetic nerve excitation by accelerating the release of noradrenaline and dopamine. Studies have confirmed that sympathetic depression and parasympathetic excitation are common in immune-mediated inflammatory diseases. Regulation of sympathetic nerves can effectively treat these diseases [22].

AR-associated genes

To harvest the AR-associated disease targets, the OMIM and DrugBank databases were searched. We obtained 151 targets

| Compounds | MW    | logP | Rotatable Bonds | HBD |
|-----------|-------|------|-----------------|-----|
| 14-deoxy-11,12-didehydroandrographolide | 332.43 | 3.23 | 3               | 2   |
| Deltamine | 176.17 | 0.90 | 1               | 2   |
| Salsolinol | 179.22 | 1.02 | 0               | 3   |
| Coryneine  | 196.27 | 0.01 | 3               | 2   |
| M-aminophenol | 109.13 | 0.21 | 0               | 3   |
| Hypaphorine | 247.31 | 2.22 | 4               | 2   |
| Ortho-aminophenol | 109.13 | 0.62 | 0               | 3   |
| Para-aminophenol | 109.13 | 0.04 | 0               | 3   |
| Deoxyandrographolide | 334.45 | 2.90 | 4               | 2   |
| Mescaline   | 211.26 | 0.78 | 5               | 2   |
| Higenamine  | 271.31 | 2.25 | 2               | 4   |
genes in the OMIM database, and 16 targets genes were acquired in the DrugBank database. All the targets genes were labeled by Uniprot IDs. After duplicate targets were removed, 161 targets genes were harvested.

Selection of hub nodes of FUZI acting on AR and construction of a PPI network

A ‘Target–target’ interaction network was constructed with the compounds’ targets and disease targets though the STRING database. To construct a network with high confidence, the STRING with threshold value greater than or equal to 0.7 was sifted. The network consisted of 338 nodes and 1902 edges. Cytoscape was used to visualize and analyze the topological features of the network. After the nodes with values greater than twice the median degree of all nodes were screened out, 65 hub nodes were harvested, 31 nodes of which originated from compounds targets, 38 nodes were from disease targets, and 4 nodes were both compounds targets and disease targets. The 4 nodes were IL10, IL1β, PTGS2, and IL6. We found that the 31 compounds targets were predicted from 7 compounds. They were Coryneine, Higenamine, M-Aminophenol, Mescaline, Ortho-Aminophenol, Para-Aminophenol, and Salsolinol.

To verify the screened compounds and targets, they were analyzed. The result was that most of the targets with the highest degree values corresponding to the 7 active components were neurotransmitter receptors. Molecular docking was performed using the active compounds as well as the target proteins with the highest degree corresponding to compounds. Since the crystal proteins could not be found, the 3 proteins ADRA2B, ADRA2C, and HTR1A were no longer analyzed. According to the results of molecular docking analysis, all of them were satisfactory except for protein BDKRB2. The optimal binding was protein CHRM2 and compound Higenamine. The results are shown in Figure 3.

AR-associated drugs and their targets were harvested in DrugBank. We found that the first-line drugs for treating AR were glucocorticoids, H1 receptor antagonists, and Leukotriene receptor antagonist. Their targets were NR3C1, HRH1, ALOX5, and CYSLTR1. In other words, these 4 targets are known targets for treating AR. Subsequently, another network was built using the 65 hub nodes and the 4 known therapeutic targets. The threshold value remained set to 0.7. The network consisted of 68 nodes and 787 edges. GABRG2 was separated from the network for the reliability of the connection. The network was visualized by Cytoscape. The results are shown in Figure 4.

In this PPI network, FUZI could act as an indirect therapy (blue nodes) or exert a direct therapeutic effect (green nodes) through its potential target. The blue nodes in the network were the targets of the compounds, whereas they interacted with the targets of the disease (red nodes). For this reason, by regulating these proteins, FUZI can regulate the disease proteins indirectly. The 4 green nodes in the network were targets of both compounds and diseases, so FUZI can play a therapeutic role by directly regulating the expression of these proteins. Our review of the literature revealed that these 4 targets are critical to AR. IL1β and IL6 are 2 vital inflammatory factors.

Figure 2. Compounds targets network. The pink nodes are the active compounds of FUZI, and the green nodes are the targets of the active compounds.
Figure 3. The molecular docking result of CHRM2 and Higenamine. (A) The 3D structure of protein receptor is illustrated as a ribbon model, and the 3D structure of the compound is presented as a stick model. (B) 2D diagram shows the interaction between protein CHRM2 and compound Higenamine.

Figure 4. ‘Target–target’ interaction network. The red nodes, the blue nodes, the green nodes, and the yellow nodes acted as the disease targets, the targets of FUZI, the targets both of disease and FUZI, and the known therapeutic targets, respectively. The size of the nodes in the figure are associated with the degree of the target in the network.
The expression levels of IL1β and IL6 were upregulated in the nasal mucosa of AR mice and in the peripheral blood of AR patients [23,24]. PTGS2 refers to various bioactive lipid mediators that participate in both normal homeostasis and inflammatory conditions [25]. IL10 acts as a negative immunoregulatory factor, as expressed in nasal endothelial cells. IL-10 exerts an anti-inflammatory effect by inhibiting the activation of various leukocytes and the secretion of inflammatory cytokines [26–28]. These 4 targets are closely involved in the occurrence and development of AR.

Enrichment analysis of the hub nodes of FUZI acting on AR

To analyze the function and biological processes involved for treating AR with FUZI, the DAVID database was used for Gene Ontology enrichment (GO enrichment) and Pathway enrichment analysis of hub nodes (P<0.01). We found 148 items of biological process, 24 items of molecular function, and 14 items of cell component when the GO enrichment was performed. The first 10 items of each functional item are shown in Figure 5. We used the DAVID database for KEGG pathway enrichment and found 67 pathways (P<0.01). Bubble maps were made of the first 20 pathways, after removing extensive and false-positive pathways. The results are shown in Figure 6.

Discussion

The result of GO enrichment suggests that FUZI is likely to be involved in inflammatory response, immune response, G-protein-coupled receptor signaling pathway, and other processes for the treatment of AR. After analyzing the results of KEGG pathway enrichment, we found that the major pathways that FUZI was involved in were largely associated with inflammation and immunity.

The Fc epsilon RI signaling pathway was the first pathway we found. Fc epsilon RI is the key to induce and maintain allergic reaction. In mast cells, Fc epsilon RI can activate a range of signal transduction pathways and regulate the activation...
of inflammatory cells such as mast cells and basophils after cross-linking with the Fc terminal of IgE. Subsequently, mast cells can release histamine [29]. It has been reported that the pharmacological mechanism of allergen immunotherapy for AR and asthma may cover the downregulation of high-affinity IgE Fc receptors on basophils and mast cells [30]. Allergen immunotherapy is capable of blocking the production of IgG antibody. IgG antibody can suppress allergic response by inhibiting the link of Fc epsilon RI and the Fc terminal of IgE [31]. Whether FUZI has an effect similar to allergen immunotherapy, and whether it can effectively block the combination of Fc epsilon RI and IgE, warrants further study.

The second pathway harvested was the Toll-like receptor signaling pathway (TLRs). The major role of TLRs is to participate in the identification of allergens. TLRs mediates the recognition and response of pathogens and their ligands such as endotoxins, lipoproteins, viruses, and bacteria [32]. It has been reported that the innate immunity of nasal mucosa can be activated by extract of house dust mites via TLR4 to trigger AR [33]. FUZI may be able to mitigate allergic symptoms or reduce the incidence of allergies by downregulating the sensitivity of TLRs to allergens.

The third pathway we found was the T cell receptor (TCRs) signaling pathway. TCRs is essential for T cells to exert immune functions. It links T cells and antigen-presenting cells (APC). By the activation of TCRs, a range of immune- and inflammation-related signal pathways can be activated. A study found that the strength of TCR signals is closely associated with the degree of atopic disease in patients [34]. Weak TCR specificity can enable primitive T cells to obtain the Th2 phenotype in response to specific antigens [35]. It is well known that AR is IgE-mediated Th2 inflammation. After APC transmits allergens to Th cells, Th cells begin to differentiate into Th1 or Th2. When Th2 dominates, a range of allergic symptoms will occur. In theory, the treatment of AR can reverse the production of the Th2 phenotype by balancing the damaged TCR signals. FUZI might be able to enhance TCR signals that are initially defective or weakened.

**Figure 6.** KEGG pathway enrichment. The color of the bubble is associated with the P value, and the size is related to the number of targets.
The fourth pathway we found was the TNF signaling pathway. Tumor necrosis factor (TNF) is a vital cytokine that can induce apoptosis, inflammation, and immunity. It has been found that TNF can promote the development of Th2 cells and type 2 innate lymphoid cells (iLC2) in allergic airway response [36]. For the recruitment of neutrophils and eosinophils in the airway during immune challenge, TNF is required as well. Involvement in the development of Th2 cells and allergic airway inflammation may be the result of a range of genes expression in airway epithelial cells induced by TNF. The TNF receptors TNFR1 and TNFR2 have the opposite effect, so by TNF blocking, the symptoms of some patients can be ameliorated, whereas some individuals are also at risk of aggravating allergic inflammation. Nevertheless, this does not affect the TNF signaling pathway and might become a new target of intervention therapy. If the relative effects of these 2 receptors on individual diseases are further clarified, the protective effect of blocking TNF signaling pathway on some individuals might play an important role in clinical applications. There may be some active components in FUZI that block the TNF signaling pathway, and further experiments are needed to determine them.

The fifth pathway obtained was the JAK/STAT signaling pathway. The JAK/STAT signaling pathway is a simple and extensive pathway. JAK acts as a non-receptor protein tyrosine kinase, which is activated by the binding of tyrosine kinase-associated receptor to ligands. The intracellular segment of the tyrosine kinase-associated receptor has the binding site of JAK. After binding to the ligand, the receptor phosphorylates STAT, the “signal transducer and transcriptional activator”, through the activation of JAK bound to it, and the signal is transmitted from extracellular to intracellular sites. The JAK/STAT signaling pathway is critical to the functional differentiation of immune cells and immune regulation [37]. There are various members of the JAK family and STAT family, and cytokines have certain selectivity to activated molecules. The JAK/STAT signaling pathway is capable of facilitating the differentiation of different Th subsets. For example, IL-2/STAT5 and IL-4/STAT6 signaling pathways are capable of activating Th2 differentiation, and IL-6-activated STAT3 can enhance mast cell degranulation, leading to allergic reactions [38–40]. The JAK/STAT signaling pathway has become a target for treating various immune diseases. JAK inhibitors have been tested in clinical trials of immune diseases [37]. It is suggested that the inhibition of JAK has a therapeutic effect on patients with AR [41]. JAK/STAT signal transduction interruption may reveal the mechanism of inhibiting the development of allergic diseases. The results of our enrichment suggest that FUZI interferes with the transmission of the JAK/STAT signaling pathway, but its specific target remains unclear.

The sixth pathway found was the cAMP signaling pathway. Cyclic adenosine monophosphate (cAMP) acts as the second messenger of extracellular signal transmission to intracellular sites. cAMP is produced by regulatory T cells, and cAMP participates in the regulation of effector T cells. Deficiency of cAMP can lead to an imbalance of immune regulation and the occurrence of allergic diseases [42]. The major effect of the cAMP signaling pathway is to activate cyclic-AMP dependent protein kinase A (PKA) to phosphorylation of downstream target proteins and continues to transmit information. Studies have suggested that cAMP balances immune signals via PKA [41]. Intracellular cAMP can inhibit the production of inflammatory cytokines such as TNF and IL-12, and promote the production of IL-10, an anti-inflammatory cytokine [43]. According to the results of both in vitro and in vivo experiments, low cAMP levels in dendritic cells induce a Th2 bias response, while high cAMP level suppress this response [44]. It has been reported that activation of the cAMP/PKA signaling pathway in mast cells can mitigate its degranulation and inhibit allergic reaction [45]. Elevated cAMP levels can exert immunosuppressive and anti-inflammatory effects in cells, which is a potential treatment for autoimmune diseases [46]. Phosphodiesterase 4 (PDE4) refers to an enzyme degrading cAMP. PDE4 inhibitor blocks the hydrolysis of cAMP in cells, and the accumulated cAMP can weaken the release of inflammatory cytokines; thus, PDE4 inhibitor has become a novel method to treat AR [41]. It is theoretically feasible to inhibit the cAMP signaling pathway in other targets to reduce allergic reaction and inflammation. Our results suggest that FUZI affects one or some aspects of cAMP signaling pathway, but the specific mechanism remains unclear.

Conclusions

In conclusion, FUZI has a sophisticated therapeutic mechanism for treating AR, and network pharmacology can provide insights into the critical targets of its therapeutic mechanism. By the analysis, FUZI was found to play a regulatory role in the critical inflammatory pathway of AR. Interpretation of the results of network pharmacology suggest a future research direction.
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