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

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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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

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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. Although there have been rare reports of FUZI as a single herb for treating AR, its effect for treating AR in formula has been verified clinically and experimentally. 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, and it brings highlights TCM herbs using modern standards. Accordingly, network pharmacology was employed in this study to analyze the active compounds and targets of FUZI, and the mechanism of its treatment of AR was revealed at the molecular level (Figure 1).

Material and Methods

Active compounds of FUZI

We used BATMAN-TCM (Bioinformatics Analysis Tool for Molecular Mechanism 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 collated. 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,

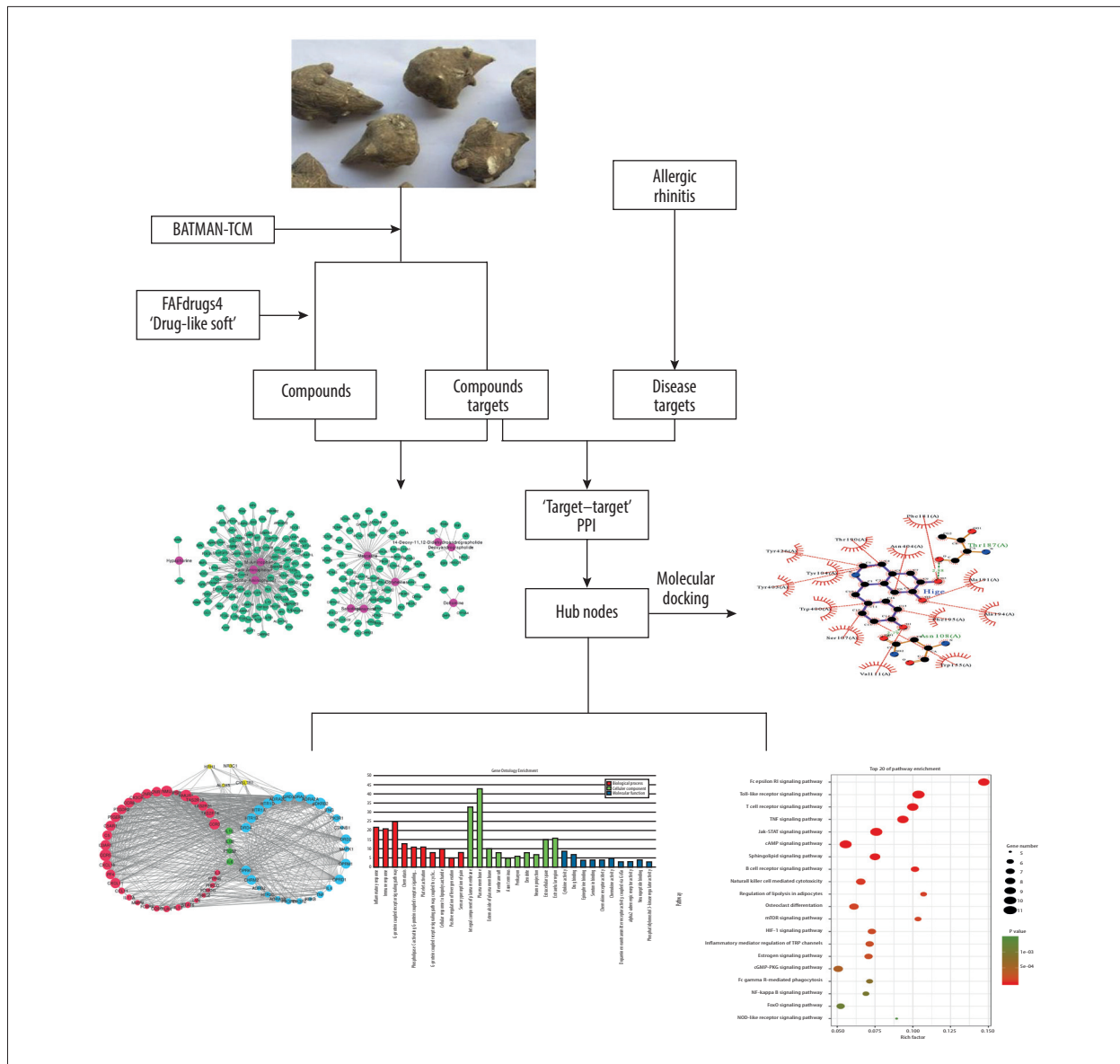


Figure 1. The technical strategy of this research. Exploration of molecular mechanism of FUZI for allergic rhinitis treatment based on network pharmacology.

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

Table 1. The selected compounds of FUZI and their major physical-chemical properties.

| 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 |

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. It is well known that decongestants are standard drugs for treating AR; they can reduce the congestion and swelling of nasal mucosa and ameliorate

the symptoms of nasal congestion by 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- κ B [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. By searching PubChem, we found that Deltamine has the effect of sympathetic nerve excitation by accelerating the release of norepinephrine 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]. The compounds targets network is shown in Figure 2.

AR-associated genes

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

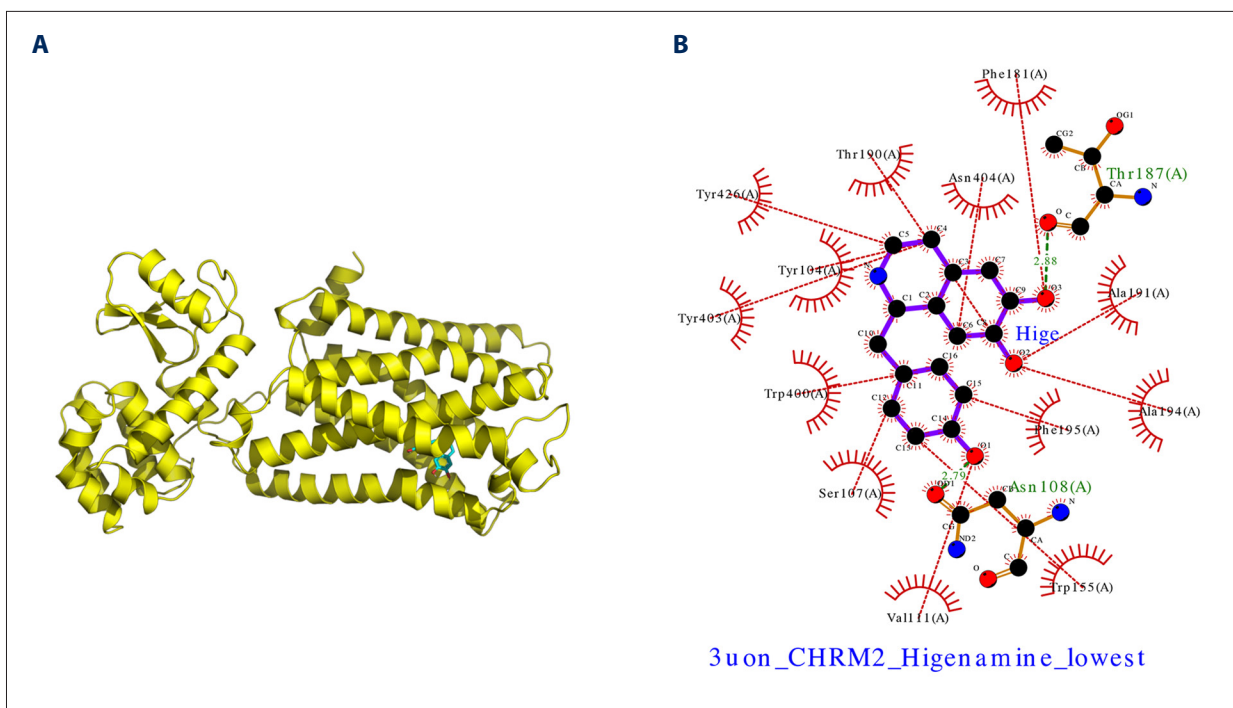


Figure 3. The molecular docking result of CHRM2 and Higenamine. (A) The 3D structure of protein receptor is illustrated as a ribbon model, and the 3D structure of the compound is presented as a stick model. (B) 2D diagram shows the interaction between protein CHRM2 and compound Higenamine.

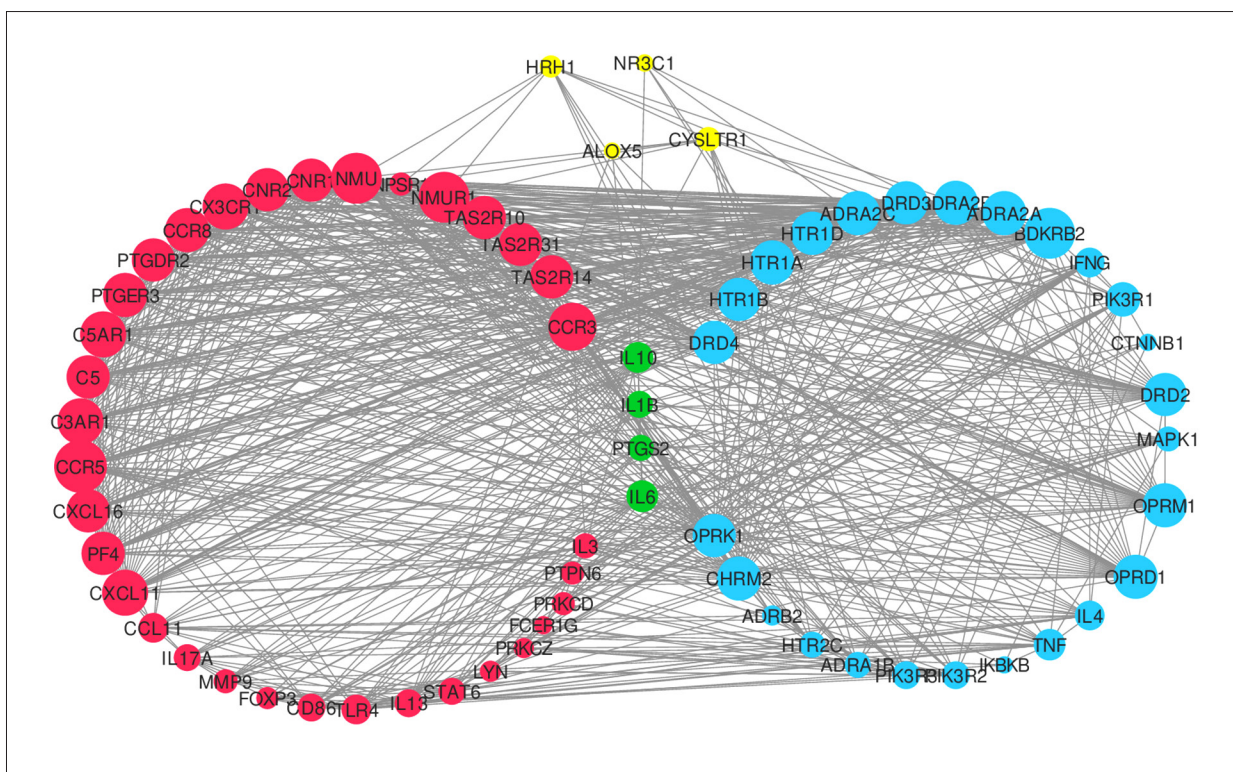


Figure 4. ‘Target-target’ interaction network. The red nodes, the blue nodes, the green nodes, and the yellow nodes acted as the disease targets, the targets of FUZI, the targets both of disease and FUZI, and the known therapeutic targets, respectively. The size of the nodes in the figure are associated with the degree of the target in the network.

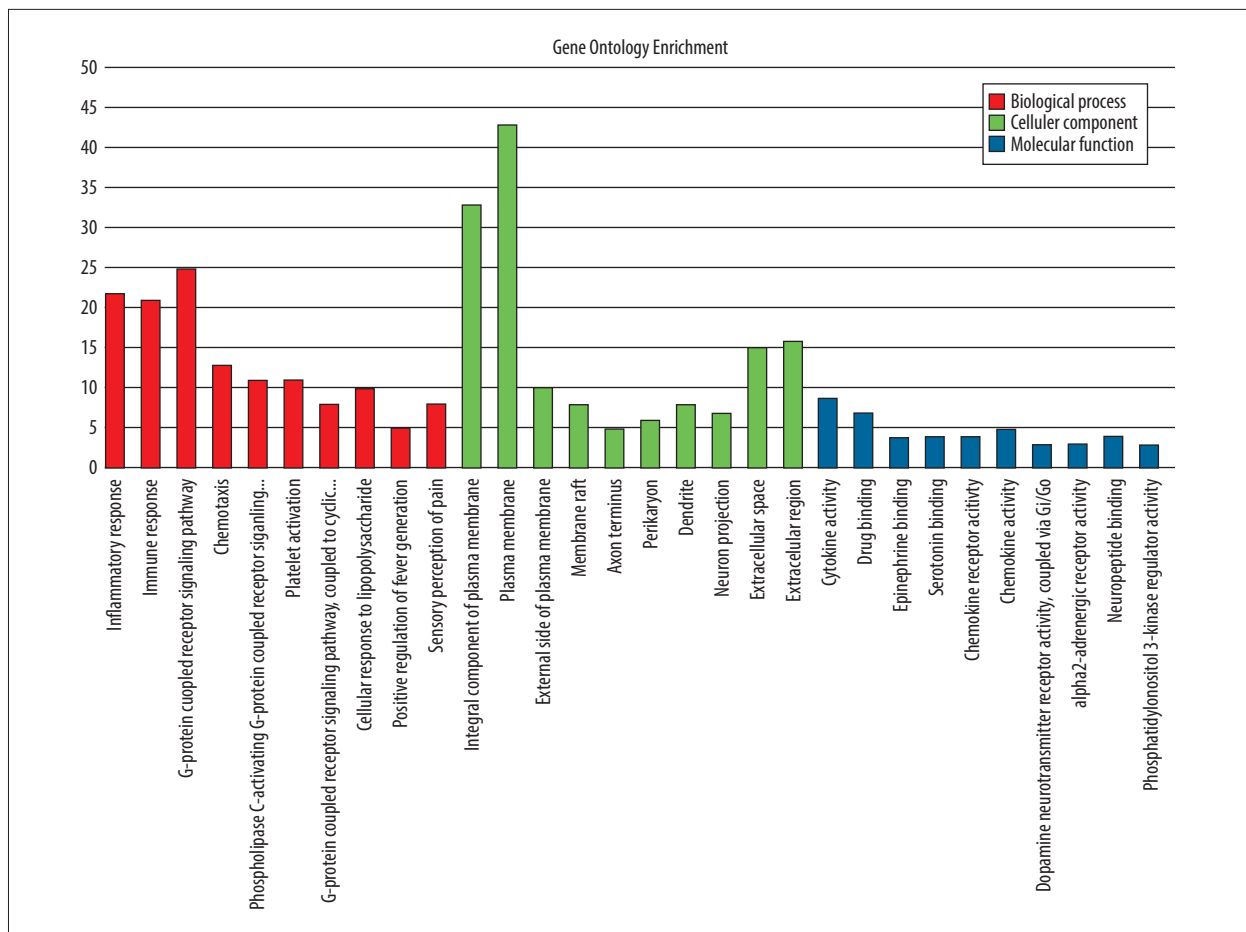


Figure 5. Gene ontology enrichment. The red columns, the green columns, and the blue columns are Biological process, Cellular component, and Molecular function, respectively. The height of the column is associated with the target number. The P value of the column is smaller than the right one in each module.

The expression levels of IL1 β 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

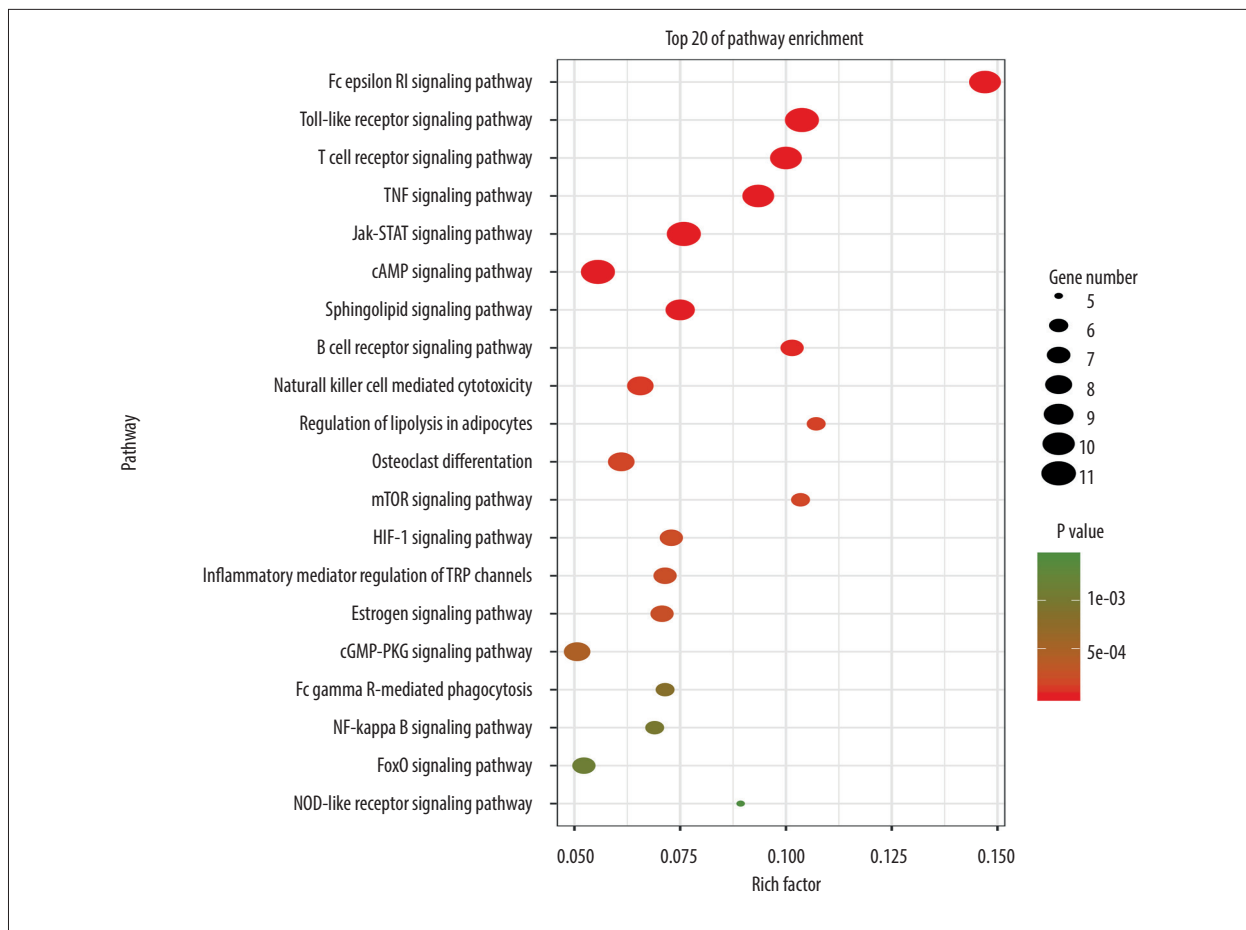


Figure 6. KEGG pathway enrichment. The color of the bubble is associated with the P value, and the size is related to the number of targets.

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.

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 individual 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 transduction 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.

References:

- Cox LS: Sublingual immunotherapy for allergic rhinitis: Is 2-year treatment sufficient for long-term benefit? *JAMA*, 2017; 317: 591–93
- Ren M, Tang Q, Chen F et al: Mahuang Fuzi Xixin decoction attenuates Th1 and Th2 responses for treating ovalbumin-induced allergic inflammation in a rat model of allergic rhinitis. *J Immunol Res*, 2017; 2017: 8254324
- Tang F, Tang Q, Tian Y et al: Network pharmacology-based prediction of the active ingredients and potential targets of Mahuang Fuzi Xixin decoction for application to allergic rhinitis. *J Ethnopharmacol*, 2015; 176: 402–12
- Sun F, Huang Y, Li L et al: PKA/beta2-AR-Gs/Gi signaling pathway is associated with anti-inflammatory and pro-apoptotic effects of Fuzi and Banxia combination on rats subjected to pressure overload. *J Ethnopharmacol*, 2019; 235: 375–84
- Zhou G, Tang L, Zhou X et al: A review on phytochemistry and pharmacological activities of the processed lateral root of *Aconitum carmichaelii* Debeaux. *J Ethnopharmacol*, 2015; 160: 173–93
- Liu Z, Guo F, Wang Y et al: BATMAN-TCM: A Bioinformatics Analysis Tool for Molecular mechANism of Traditional Chinese Medicine. *Sci Rep*, 2016; 6: 21146
- Kim S, Chen J, Cheng T et al: PubChem 2019 update: Improved access to chemical data. *Nucleic Acids Res*, 2019; 47: D1102–9
- Lipinski CA, Lombardo F, Dominy BW, Feeney PJ: Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv Drug Deliv Rev*, 2001; 46: 3–26
- Oprea TI: Property distribution of drug-related chemical databases. *J Comput Aided Mol Des*, 2000; 14: 251–64
- Irwin JJ, Shoichet BK: ZINC – a free database of commercially available compounds for virtual screening. *J Chem Inf Model*, 2005; 45: 177–82
- Oprea TI, Davis AM, Teague SJ, Leeson PD: Is there a difference between leads and drugs? A historical perspective. *J Chem Inf Comput Sci*, 2001; 41: 1308–15
- Pihan E, Colliandre L, Guichou JF, Douguet D: e-Drug3D: 3D structure collections dedicated to drug repurposing and fragment-based drug design. *Bioinformatics*, 2012; 28: 1540–41
- Wishart DS, Feunang YD, Guo AC et al: DrugBank 5.0: A major update to the DrugBank database for 2018. *Nucleic Acids Res*, 2018; 46: D1074–82
- Wishart DS, Knox C, Guo AC et al: DrugBank: A comprehensive resource for in silico drug discovery and exploration. *Nucleic Acids Res*, 2006; 34: D668–72
- Wishart DS, Knox C, Guo AC et al: DrugBank: A knowledgebase for drugs, drug actions and drug targets. *Nucleic Acids Res*, 2008; 36: D901–6
- Berman HM, Westbrook J, Feng Z et al: The Protein Data Bank. *Nucleic Acids Res*, 2000; 28: 235–42
- Huang da W, Sherman BT, Lempicki RA: Systematic and integrative analysis of large gene lists using DAVID bioinformatics resources. *Nat Protoc*, 2009; 4: 44–57
- Huang da W, Sherman BT, Lempicki RA: Bioinformatics enrichment tools: paths toward the comprehensive functional analysis of large gene lists. *Nucleic Acids Res*, 2009; 37: 1–13
- Nguyen VS, Loh XY, Wijaya H et al: Specificity and inhibitory mechanism of andrographolide and its analogues as antiasthma agents on NF-kappaB p50. *J Nat Prod*, 2015; 78: 208–17
- Cai W, Chen S, Li Y et al: 14-Deoxy-11,12-didehydroandrographolide attenuates excessive inflammatory responses and protects mice lethally challenged with highly pathogenic A(H5N1) influenza viruses. *Antiviral Res*, 2016; 133: 95–105
- Sun H, Zhu X, Cai W, Qiu L: Hypaphorine attenuates lipopolysaccharide-induced endothelial inflammation via regulation of TLR4 and PPAR-gamma dependent on PI3K/Akt/mTOR signal pathway. *Int J Mol Sci*. 2017; 18: pii: E844
- Bellinger DL, Lorton D: Sympathetic nerve hyperactivity in the spleen: Causal for nonpathogenic-driven chronic immune-mediated inflammatory diseases (IMDs)? *Int J Mol Sci*, 2018; 19: pii: E1188
- Shen Y, Ke X, Yun L et al: Decreased expression of interleukin37 and its anti-inflammatory effect in allergic rhinitis. *Mol Med Rep*, 2018; 17: 1333–39
- Kim HY, Han NR, Kim HM, Jeong HJ: The iron chelator and anticancer agent Dp44mT relieves allergic inflammation in mice with allergic rhinitis. *Inflammation*, 2018; 41: 1744–54
- Cornejo-Garcia JA, Perkins JR, Jurado-Escobar R et al: Pharmacogenomics of prostaglandin and leukotriene receptors. *Front Pharmacol*, 2016; 7: 316
- Fang D, Zhu J: Molecular switches for regulating the differentiation of inflammatory and IL-10-producing anti-inflammatory T-helper cells. *Cell Mol Life Sci*, 2019 [Epub ahead of print]
- Sagar S, Morgan ME, Chen S et al: Bifidobacterium breve and Lactobacillus rhamnosus treatment is as effective as budesonide at reducing inflammation in a murine model for chronic asthma. *Respir Res*, 2014; 15: 46
- Muller B, van Egmond D, de Groot EJ et al: Characterisation of interleukin-10 expression on different vascular structures in allergic nasal mucosa. *Clin Transl Allergy*, 2014; 4: 2
- Mazuc E, Villoutreix BO, Malbec O et al: A novel druglike spleen tyrosine kinase binder prevents anaphylactic shock when administered orally. *J Allergy Clin Immunol*, 2008; 122: 188–94, 194.e1–3
- Chang TW: The pharmacological basis of anti-IgE therapy. *Nat Biotechnol*, 2000; 18: 157–62
- Shamji MH, Durham SR: Mechanisms of allergen immunotherapy for inhaled allergens and predictive biomarkers. *J Allergy Clin Immunol*, 2017; 140: 1485–98
- Xirakia C, Koltsida O, Stavropoulos A et al: Toll-like receptor 7-triggered immune response in the lung mediates acute and long-lasting suppression of experimental asthma. *Am J Respir Crit Care Med*, 2010; 181: 1207–16
- Ryu JH, Yoo JY, Kim MJ et al: Distinct TLR-mediated pathways regulate house dust mite-induced allergic disease in the upper and lower airways. *J Allergy Clin Immunol*, 2013; 131: 549–61
- Datta S, Milner JD: Altered T-cell receptor signaling in the pathogenesis of allergic disease. *J Allergy Clin Immunol*, 2011; 127: 351–54
- Milner JD: TCR signaling abnormalities in human Th2-associated atopic disease. *Front Immunol*, 2018; 9: 719
- Richard AC, Tan C, Hawley ET et al: The TNF-family ligand TL1A and its receptor DR3 promote T cell-mediated allergic immunopathology by enhancing differentiation and pathogenicity of IL-9-producing T cells. *J Immunol*, 2015; 194: 3567–82
- Lin JX, Leonard WJ: The common cytokine receptor γ chain family of cytokines. *Cold Spring Harb Perspect Biol*, 2018; 10: pii: a028449
- Ashino S, Takeda K, Li H et al: Janus kinase 1/3 signaling pathways are key initiators of TH2 differentiation and lung allergic responses. *J Allergy Clin Immunol*, 2014; 133: 1162–74
- Lyons JJ, Milner JD: The clinical and mechanistic intersection of primary atopic disorders and inborn errors of growth and metabolism. *Immunol Rev*, 2019; 287: 135–44
- Kelly-Welch AE, Hanson EM et al: Interleukin-4 and interleukin-13 signaling connections maps. *Science*, 2003; 300: 1527–28
- Howell MD, Fitzsimons C, Smith PA: JAK/STAT inhibitors and other small molecule cytokine antagonists for the treatment of allergic disease. *Ann Allergy Asthma Immunol*, 2018; 120: 367–75
- Teixeira HM, Alcantara-Neves NM, Barreto M et al: Adenylyl cyclase type 9 gene polymorphisms are associated with asthma and allergy in Brazilian children. *Mol Immunol*, 2017; 82: 137–45
- Arizmendi N, Kulka M: Adenosine activates Galphas proteins and inhibits C3a-induced activation of human mast cells. *Biochem Pharmacol*, 2018; 156: 157–67
- Lee J, Kim TH, Murray F et al: Cyclic AMP concentrations in dendritic cells induce and regulate Th2 immunity and allergic asthma. *Proc Natl Acad Sci USA*, 2015; 112: 1529–34
- Serra-Pages M, Olivera A, Torres R et al: E-prostanoid 2 receptors dampen mast cell degranulation via cAMP/PKA-mediated suppression of IgE-dependent signaling. *J Leukoc Biol*, 2012; 92: 1155–65
- Chevalier E, Lagente V, Dupont M et al: Lack of involvement of type 7 phosphodiesterase in an experimental model of asthma. *Eur Respir J*, 2012; 39: 582–88