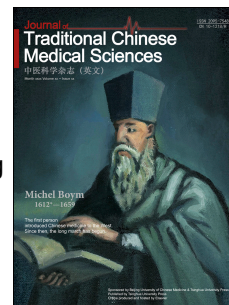


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**Mechanisms of traditional Chinese medicines in the treatment of allergic rhinitis
using a network biology approach**

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Abstract

Objective: To apply network biology to systematically explore the effect and mechanism of traditional Chinese herbs in the treatment of allergic rhinitis.

Methods: Magnolia flower, xanthium fruit, astragalus root, paniculate cynanchum, scutellaria root, cicada molting, stephania root, small centipeda herb, and licorice root as traditional Chinese herbs are widely used to treat allergic rhinitis. Using multiple database integration and entity grammar systems, a model molecular interaction network of traditional Chinese herbs for treating allergic rhinitis was established. Bioinformatics approaches were adopted to integrate relevant data and biologic information by multiple databases. Constructional molecular interaction network of Chinese herbs for treating allergic rhinitis was based on entity grammar systems model. The network was then used for elucidating the anti-allergic rhinitis mechanism of the Chinese herbs holistically and on the molecular level. The subnetworks were also extracted to explicitly display the pathway where effective components acted on the related targets of allergic rhinitis.

Results: Traditional Chinese herbs could adjust various pathologic aspects in allergic rhinitis including the production of pro-inflammatory substances, such as histamine and cytokine IL-4, IL-13, lowering IgE level or blocking antigen binding, altering the structure of IgE, modulating the balance of Th or other cells by cell proliferation and differentiation, mediating cell-cell signaling and second-messenger-mediated signaling, stabilizing the cell membrane, and affecting regulation of cellular defense response.

Conclusion: The research theoretically confirms the mechanism of anti-allergic rhinitis by traditional Chinese herbs, provides important fundamental research information for treatment of allergic rhinitis, and may serve as a reference for new drug development and effective ingredients of compatibility.

Key words: Traditional Chinese medicine; Allergic rhinitis; Entity grammar systems, Mechanisms

1.0 Introduction

In 2001, the World Health Organization (WHO) released a report on allergic

rhinitis and its impact on asthma and defined allergic rhinitis as a chronic airway inflammatory disease.¹ It is currently thought that allergic rhinitis is an IgE-mediated allergic response in the nasal mucosa that occurs from allergen exposure. Research on the pathogenesis of allergic rhinitis is mainly focused on neurotransmitters, cytokines, substance P, receptors, and eosinophil cationic proteins. Allergic rhinitis affects quality of life and its economic burden is great. Worldwide, the incidence of allergic rhinitis is rising and the condition has become a public health concern.²

In traditional Chinese medicine (TCM), allergic rhinitis is known as nasal blockage (*bi qiu*). Its etiology is deficiency of lung *qi*, such that pathogenic cold invades the nose, resulting in symptoms of nasal congestion, sneezing, and rhinorrhea.³ In China, herbal medicines are commonly used to treat allergic rhinitis. Research has shown that certain herbs can modify biological mechanisms involved in allergic rhinitis, such as IgE regulation, eosinophil cell apoptosis, regulation of Th1/Th2 imbalance, adhesion molecule regulation, mast cell production, concentration of nuclear transcription factors and chemokines, at an overall efficacy of 80%–90%.⁴ Herbs commonly used to treat allergic rhinitis include magnolia flower (*Magnolia biondii* Pamp.), xanthium fruit (*Xanthium strumarium* subsp. *Sibiricum* (Patrin ex Widder) Greuter), astragalus root (*Astragalus membranaceus* (Fisch.) Bunge), paniculate cynanchum (*Cynanchum paniculatum* (Bunge) Kitag. ex H.Hara), scutellaria root (*Scutellaria baicalensis* Georgi), cicada molting (*Cryptotympana atrata* Fabr.), stephania root (*Stephania tetrandra* S. Moore), small centipeda herb (*Centipeda minima* (L.) A.Braun & Asch.), and licorice root (*Glycyrrhiza uralensis* Fisch.). These herbs are typically the main ingredients in herbal prescriptions that combine with other Chinese herbs.⁴ According to literature research and statistics, astragalus root is the most frequently used Chinese herb for the treatment of allergic rhinitis, at a rate of 75.7%, followed by magnolia flower and xanthium fruit at 70.4% and 53.9%, respectively.⁵ Astragalus has been shown to regulate the immune response and enhance cellular and humoral immunity by elevating serum levels of IgA and IgM,⁶ as well as increase human lymphocyte proliferation, cytotoxic T cell responses, and IgG

production.⁷ Animal research showed that intraperitoneal injection of 6 species of astragalus root augmented anti-histamine function and the permeability of capillary induced by 5-hydroxytryptamine (5-HT).⁴ Baicalein is a chemical isolated from the Chinese scutellaria root and has been found to inhibit production of inflammatory cytokines by blocking nuclear factor kappa B cells (NF- κ B) activation and kappa light polypeptide gene enhancer in B-cells inhibitor, alpha (I κ B α) phosphorylation and degradation in human mast cells (HMC).⁸ Cicada molting appears to have an inhibitory effect on allergic reactions.⁹ Tetrandrine, an active component in stephania root, has been found to prevent or decrease the severity of anaphylaxis in animal studies.¹⁰ Hot water extract of small centipeda herb was found to reduce severity of passive cutaneous anaphylaxis and lower histamine release from rat peritoneal mast cells induced by compound 48/80 or concanavalin A.¹¹ Magnolia flower extract administered to guinea pigs reduced histamine-induced spasm of the trachea and ileum.¹² The effective rate of allergic rhinitis treated with xanthium fruit was 32.4%. Xanthium fruit alleviated rhinitis symptoms by inhibiting the release of histamine and ovalbumin-specific (OVA-specific) IgE and reducing the infiltration of eosinophils. Xanthium fruit had anti-inflammatory activity via suppression of TNF- α , IL-1 β , IL-5 and IL-6 production. In addition, Xanthium fruit significantly inhibited the phosphorylation of NF- κ B and I κ B- α in HMC-1, and alleviated the allergic responses in ovalbumin-sensitized mouse allergic rhinitis model.¹³ A complex (LX) extracted from licorice root contained protein, polysaccharide nucleic acids and glycyrrhizic acid, had a good anti-allergic effect. Glycyrrhizin at the concentration of 0.46 mM, as one active ingredient of licorice root, could inhibit mast cells from removing particles induced by compound 48/80 leading to histamine release, thereby preventing the release of allergic substances.⁴

Though much research has been done on allergic rhinitis, there are many components, targets, and pathways involved in the mechanism of allergen-induced inflammatory disorders, and because of the complexity, only symptomatic treatment or integrated medication and immunotherapy has been successful thus far. In terms of TCM, since the aforementioned herbs have been shown to be efficacious against

allergic rhinitis, a systematic analysis of their anti-allergic rhinitis mechanisms based on published scientific results has never been performed. Accordingly, we undertook this study to explore the mechanisms of Chinese herbal medicines in the treatment of allergic rhinitis using a network biology approach. This study was based on existing research data, and applied a TCM auxiliary analytical system established by our research team that used an entity grammar system to construct a molecular interaction network between Chinese herbs and allergic rhinitis.

With the development of network pharmacology, data analysis is a critical methodology for ascertaining the mechanisms of Chinese herbs. Network models and network analysis are useful for translating genomic information, identifying potential targets¹⁴⁻¹⁵ and enriched pathways involved in the function of Chinese herbs.¹⁶⁻¹⁸ For example, phenotype network-biological network-herb network was implemented to explore the underlying network systems of TCM syndromes and herbal formulas.¹⁹ Although computational systems biology is in its initial stage of application in the broader field of TCM, its use in the analysis of TCM formulas is feasible through integrating the biological network and the empirical knowledge of herbal medicines.

The aim of this study was to elucidate whether or not application of network biology can be applied toward finding the bioactive ingredients in Chinese herbs that can act on the different processes of allergic rhinitis through proteins, molecules, or pathways. This will confirm the TCM effect in the treatment of allergic rhinitis from a theoretical level, provide a basis for clinical study of allergic rhinitis, and help to find a more effective treatment for the disease.

2.0 Data sources

The chemical constituents of the Chinese herbs in this study and their molecular targets were taken from the Traditional Chinese Medicine Systems Pharmacology (TCMSP) database (<http://lsp.nwsuaf.edu.cn/tcmsp.php>)²⁰ and the Search Tool for Interactions of Chemicals (STITCH) database (<http://stitch.embl.de>).²¹ Biological reaction and signaling pathway data were from the Human Integrated Pathway Database (hiPathDB; <http://hipathdb.kobic.re.kr>).²² Allergic rhinitis-related targets

were taken from the Therapeutic Targets Database (TTD; <http://bidd.nus.edu.sg/BIDD-Databases/TTD/TTD.asp>).²³ Information from these databases allowed us to build a molecular network between the herbs and allergic rhinitis, with *link* (X, Y, Z, W) as the node form. Visualization of the molecular networks was accomplished with Cytoscape version 2.8.3 (The Cytoscape Consortium, San Diego, CA).

3.0 Molecular network construction based on entity grammar systems

3.1 Entity grammar systems

Entity grammar systems are proposed for modeling of biological systems as well as studying the hierarchical structures of biological systems. These are expressed by $G = (V_N, V_T, F, P, S)$, where V_N is a non-terminal character set, V_T is a terminal character set, F is a set of operators, P is the production rule set, and S is the axiom. When there is no difference between the terminal characters and non-terminal characters, entity grammar systems can be represented as $G = (V, F, P, S)$, where $V = V_N \cup V_T$.²⁴ Entity grammar systems have been used to analyze mechanisms of Chinese herbs²⁵ and to discover their bioactive components.²⁶

3.2 Network construction

In this study, V represents a node in the network of each type, which can be the Chinese herb, their chemical compositions, molecular targets, a disease and its related proteins, or small molecules and other related proteins. F represents various types of relationships between the network nodes, such as “includes” “interacts with” “activates” or “inhibits”. P is a set of rules or herbal formulas that is used for deducing the relationship between the herb targets and allergic rhinitis targets. For example, if A to B and B to C are both either positive or negative, then the regulatory effect of A to C is positive, otherwise it is negative, and the action distance of A to C is the sum of distances from A to B and B to C.

The above-mentioned formula *link* (X, Y, Z, W) can be described as an action mode of source node X with Z (activation represents forward and positive effect;

inhibition represents reverse and negative effect) by a W -step reaction by influencing target node Y . W represents the sum of the transitional steps of positive or negative regulation between the nodes in the network. In this study, W was set to 5, and the results were not considered if $W \geq 6$. The source node and target node were labeled by setting W to find all signal paths starting at point X , ending at point Y with Z as the mode of action and the pathway when the value of W was the minimum. Finally, the molecular biological network results of the effectiveness of compound C (from the Chinese herb) to the allergic rhinitis-related protein D can be visualized using Cytoscape.

4.0 Results and discussion

4.1 Association of TCM herbs for allergic rhinitis with their protein targets

Because of a lack of reliable data for the Chinese herb cicada molting, we do not discuss it further in this paper. As shown in Fig. 1, after visualization the remaining 8 herbs were found to be associated with allergic rhinitis, with a total of 712 nodes and 2685 edges.

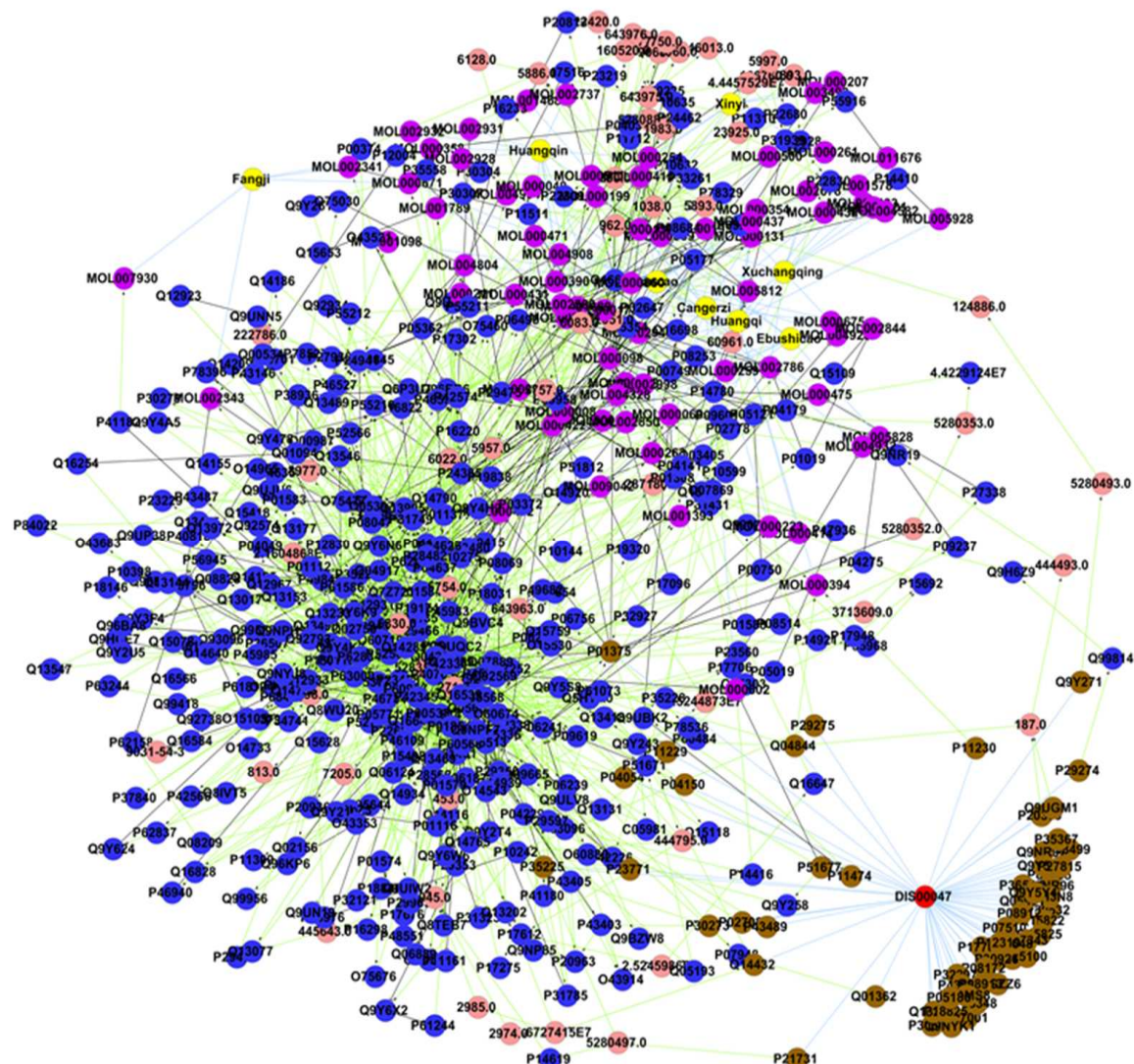


Figure 1 Molecular network of Chinese herbs for treating allergic rhinitis. Yellow nodes: the traditional Chinese herbs; purple nodes: the chemical constituents of the plant; blue nodes: proteins; pink nodes: small molecules; brownish-yellow nodes: disease targets, and the red node: allergic rhinitis disease. Arrows represent the direction of action, with a triangular arrow and light green lines representing a positive moderating role, T-shaped arrow and black lines representing as negative effect, and blue lines indicating there is a correlation between two nodes, for example whether one node includes the other or they are related. The number of connections reflects its importance in the network. Bioactive components of herbs are involved in multiple targets and pathways.

The Chinese herbs in this study can affect different allergic rhinitis-related proteins through multiple proteins and small molecules (Table 1).

Table 1 Effect of allergic rhinitis-related proteins by multiple proteins and small molecules from components of Chinese herbs

Chinese herb	Selected components	Selected proteins	Allergic rhinitis-related
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			targets
Magnolia flower	Safrol, eugenol, myristicin, naphthalene	CYP3A4, CYP2C19, HRAS, CYP3A7, CASP9, CASP3, CYP1A2, PTGS2, GSTP1	TNF, CHRNE, MS4A2, TNFRSF4, GATA3, PLA2G1B, IL13, NR3C1, ESRRA, CHRNA1, FCER1G, PDE3A, ADORA2B, CHRM1, TBXA2R
Xanthium fruit	Lecithin, caffeic acid, sitosterol, aloe-emodin, hydroquinone, fumaric acid, stearic acid, palmitic acid and oleic acid	NFKB1, RelA, MAPK8, MAPK1, STAT3, PPARA, TNF, CASP3, IL1B, CASP9, JAK2, IL1A, MMP2, PTGS2, CCR3	TNF, PDE3A, CCR3, TBXA2R, FCER1G, CHRNA1, PLA2G1B, ESRRA, MS4A2, CHRM1, GATA3, ADORA2B, CHRNE, NR3C1, IL13, TNFRSF4
Stephania root	Hesperidin, hesperetin, tetrandrine, beta-sitosterol	BCL6, NFKBIA, SMAD2, CCNB1, CDK6, CASP3	TNF, TNFRSF4, PLA2G1B, GATA3, FCER1G, PDE3A, IL13
Small centipeda herb	Lupeol, nobiletin, sitosterol, apigenin, helenalin	AKT1, RelA, MAPK8, PPARA, CASP3, TNF, PTK2, NFKBIA, MMP9, CYP19A1, PTGS2, NOS1, VCAM1	FCER1G, CHRNE, ESRRA, TNFRSF4, GATA3, PDE3A, TNF, TBXA2R, ADORA2B, PLA2G1B, CHRM1, IL13, CHRNA1, NR3C1
Astragalus root	Heriguard, isorhamnetin, lupeol, isoferulic acid, choline, daidzein, caffeate, hirsutrin, coumarin, quercetin	Jun, RelA, TNF, CASP3, CASP7, MAPK8, AKT1, IL1B, STAT1, BCL2, INS, JAK1, ICAM1, CDK1, PTGS2, MMP9	TNF, GATA3, FCER1G, CHRNE, CHRM3, ADORA2B, TNFRSF4, ESRRA, CHRNA9, MS4A2, IL13, TBXA2R, CCR3
Scutellaria root	Acacetin, wogonin, eugenol, oroxylin-A, chrysin, baicalein, scutellarein, scutellarin, panicolin	Jun, PTGS2, TNF, CCND1, HMOX1, CASP3, MMP9, NOS1, AKT1, PTK2, CYP1B1,	NR3C1, MS4A2, CHRNA1, PLA2G1B, ADORA2A, CHRNE, IL13, ADORA2B, TNFRSF4, CHRM1, ESRRA,

		GSK3B, NOTCH1, PTGS1, CDK1, SERPINE1, PLA2, MMP2	PDE3A, TNF, GATA3, FCER1G
Licorice root	Mairin, pinocembrin, kaempferol, scopoletol, naringenin, hirsutrin, anethole, naringin, glabridin, vitexin, vestitol, ursolic acid	MAPK14, IL1A, RelA, Jun, CASP3, STAT1, MAPK8, HMGCR, IL1B, NFKB1, AKT1, NOS1, PTGS2, CYP1A2, PTGIS, BCL2, JAK3	TNF, TBXA2R, FCER1G, CHRNE, CHRM3, ADORA2B, ESRRA, IL13, TBXA2R, NR3C1, ADORA2A, PLA2G1B, CYSLTR1, PDE3A, TNFRSF4
Paniculate cynanchum	Myristic acid, hypnon, 2-methylnaphthalene, methyl salicylate, paeonol, oleic acid, stearic acid, palmitic acid	PPARA, HMGCR, IL2, CASP3, PPARGC1A, CYP3A4, CYP1A2, PTGS2, VCAM1, ESR1, ERBB2, MMP2, CCND1, HMOX1, ACADM, NOS1, GSTP1	TNF, NR3C1, PDE3A, ESRRA, ADORA2B, CHRNA1, GATA3, PLA2G1B, IL13, TNFRSF4, FCER1G, CHRM1, CHRNE, TBXA2R

In the molecular network diagram (Fig. 1), it is evident that many herbal compounds are active on more than one protein, indicating that they participate in multiple pathways to regulate the body in order to treat allergic rhinitis. Some molecular targets of the herbs in this study are also directly involved in the pathogenesis of allergic rhinitis. Two such targets are C-C chemokine receptor type 3 (CCR3) and tumor necrosis factor (TNF). CCR3 belongs to family 1 of G protein-coupled receptors. It is highly expressed in eosinophils²⁷ and is also detected in Th1 and Th2 cells, as well as in airway epithelial cells. And it may contribute to the accumulation and activation of eosinophils and other inflammatory cells in the allergic airway. TNF is a cytokine protein that functions to signal other cells. TNF is one of the cytokines that is involved in the acute phase reaction, including allergic

rhinitis, and has a variety of biological effects. TNF plays a primary role in regulating the functions of immune cells. Though it is mainly produced by activated macrophages, it is also manufactured by a variety of cell types including natural killer (NK) cells, mast cells, eosinophils, and neurons.²⁸

4.2 Association of herbal compounds with their protein targets

The ultimate effects of TCM compounds are their protein targets, which can be used to find the active ingredients for allergic rhinitis. The network shown in Fig. 2 was constructed based on herbal compounds and protein targets from the entire network shown in Fig. 1. The purple nodes represent compounds of the Chinese herbs in this study and the other nodes represent targets of allergic rhinitis, with many targets modulated by multiple compounds. For example, GATA3 can be regulated by tetrandrine, glycyrrhizin, coumarin, o-thymol and other compounds. IL13 can be regulated by compounds such as baicalin, safrole, quercetin, and daidzein. Although there are some allergic rhinitis-related targets in the network that have not yet been confirmed by other studies, we used the enrichment analysis tool DAVID 6.7 (National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD, USA) and found these targets have some similar effects with the targets that are already known for allergic rhinitis. These targets affect cell signaling, biosynthesis, inflammatory response, among other physiologic functions. Thus, the herbs in this study appear to have a comprehensive effect on modulating the body's response in allergic rhinitis.

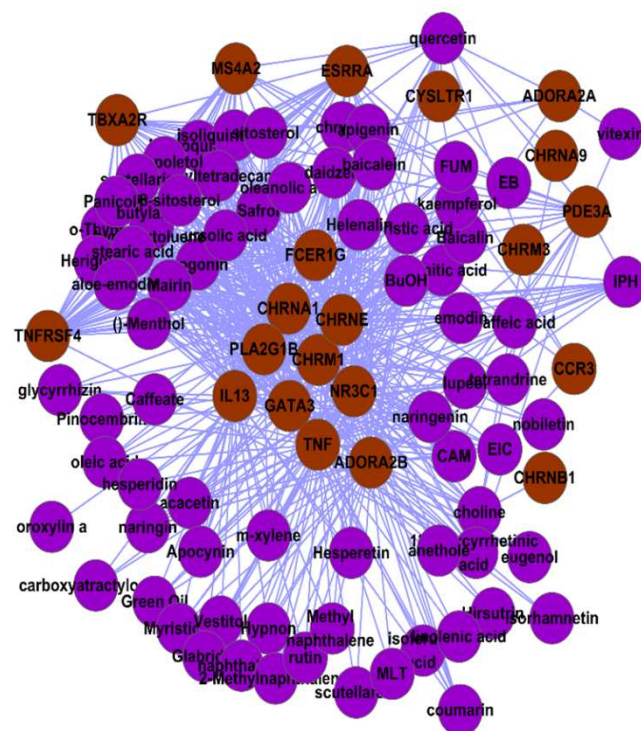


Figure 2 Associated network of herbal compounds and allergic rhinitis molecular targets, in which molecular targets can be modulated by multiple compounds.

Herbs in this study were found to act on different allergic rhinitis-related targets (Fig. 3). For example, astragalus root acts on CHRNA1, an acetylcholine receptor β -subunit. Acetylcholine is a neurotransmitter that helps in regulating the immune system. The network association depicted in Fig. 3 also found that all the herbs in this study can target TNF (brown node on the far right).

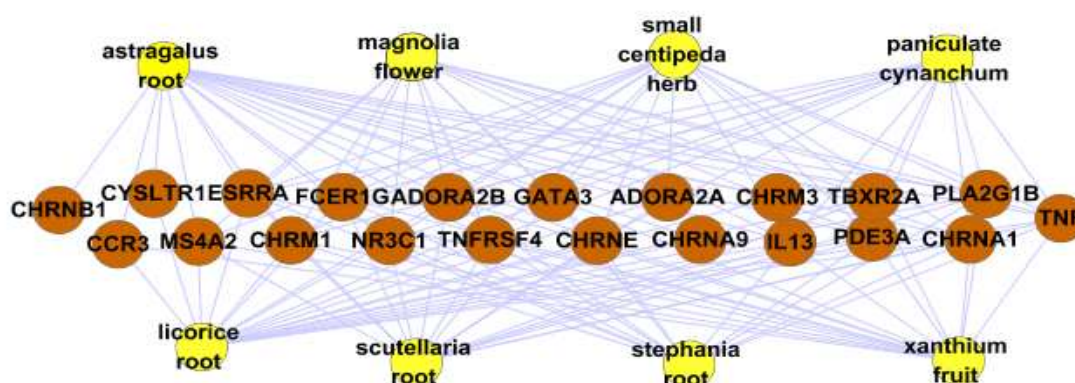


Figure 3 Associated network for the herbs in this study and allergic rhinitis. Yellow nodes: herbs; brown nodes: targets of allergic rhinitis; connecting lines between two nodes indicate the herb can act on the target.

The overall molecular network shown in Fig. 1 is complex. Therefore, we performed a more focused visualization by extracting TNF-related pathways to illustrate how the herbs affect TNF (Fig. 4). Compounds such as emodin, choline, and apigenin can modulate TNF directly or indirectly through activating protein-protein interactions or inhibiting expression of the proteins RelA, Jun, VCAM1, CASP3, NFATc2, MAPK14, which then results in changes in level of expression of TNF. Research has shown that these proteins are involved in immune or inflammatory system.

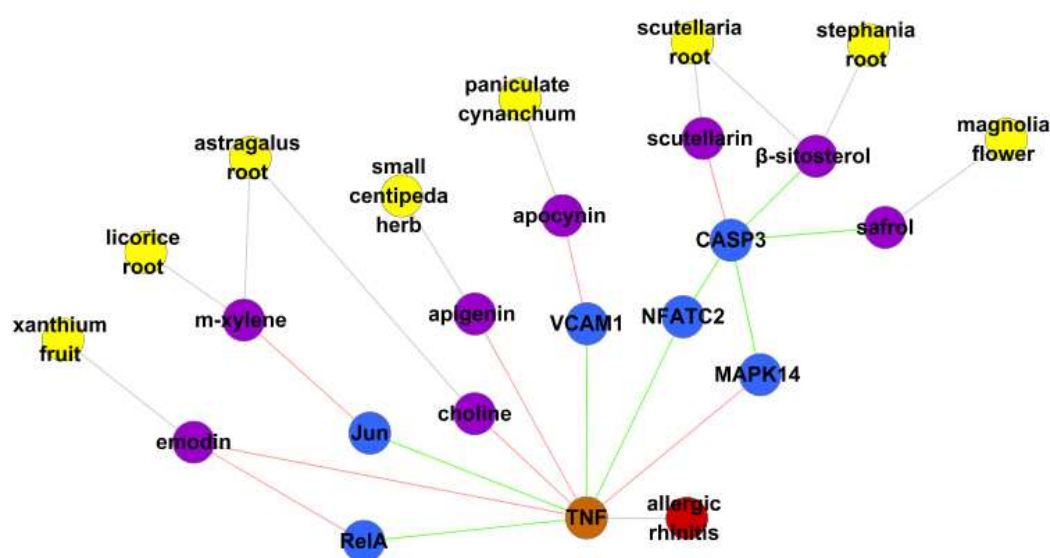


Figure 4 Pathways of actions of the herbs on TNF in allergic rhinitis.

Yellow nodes: the Chinese herbs; purple nodes: the chemical constituents of the plant; blue nodes: proteins; brownish-yellow nodes: disease targets; red node: allergic rhinitis disease. Light green lines show a positive moderating role and pink lines indicate a negative effect.

RelA (p65) has been shown to regulate immune response and response to invading pathogens via NF- κ B activation.²⁹ The fact that cytokines such as TNF- α and IL-1 can activate RelA further supports its participation in the immune response.²⁹⁻³⁰

Jun and its dimerization partners in AP-1 (activator protein 1) formation regulated by diverse extracellular stimuli, including peptide growth factors and pro-inflammatory cytokines. Together with NF- κ B, C-jun can prevent the apoptosis induced by TNF- α .³¹

The VCAM-1 (vascular cell adhesion molecule-1) protein regulates the adhesion of lymphocytes, monocytes, eosinophils, and basophils to vascular endothelium as well as leukocyte-endothelial cell signal transduction. Upregulation of VCAM-1 in endothelial cells by cytokines is a result of increased gene transcription (e.g., in response to TNF- α and IL-1 and through stabilization of messenger RNA (mRNA) (e.g. IL-4).³²

The CASP3 protein belongs to cysteine-aspartic acid protease (caspase) family.³³ Increased levels of pro-caspase-3 causes OVA-treated cells more to apoptosis is a potential factor in the fragility of epithelium in asthma. Also active caspase-3 can increase in the lamina propria within regions of accumulation of eosinophils.³⁴

NFATc2 is a member of the nuclear factor of activated T cells (NFAT) family. The product of this gene is a DNA-binding protein with a REL-homology region (RHR) and a NFAT-homology region (NHR). By T cell receptor (TCR) stimulation, the protein from cytosol can only translocate to the nucleus, where it turns into a member of the nuclear factors of activated T cell transcription complex. The complex is of great importance in inducing gene transcription during the immune response.³⁵

MAPK14 encodes p38 α mitogen-activated protein kinase (MAPK), and the latter is the prototypic member of the p38 MAPK family. Originally identified as a tyrosine phosphorylated protein, p38 α MAPK was detected in activated immune cell macrophages, and plays a key role in inflammatory cytokine induction, such as TNF- α .³⁶⁻³⁷

To comprehensively understand the relationship between the pharmacologic actions of bioactive compounds in the herbs and allergic rhinitis, the protein targets were used for enrichment analysis. Using DAVID, we found that the herbs appear to treat allergic rhinitis through a number of pathways including influencing the intracellular signaling cascade, and regulating immune effector processes, biosynthetic and metabolic processes, chemokines and cytokines, transcription, inflammatory responses, and cellular defense responses. The results of enrichment analysis essentially corresponded with the preceding biologic network analysis.

The immune response mechanism in allergic rhinitis is well known (Fig. 5).³⁸⁻⁴¹

From the network construction and visualization that we performed in this study, we propose that the Chinese herbs in this study exert their effects on the immune response in various ways (Fig. 5).

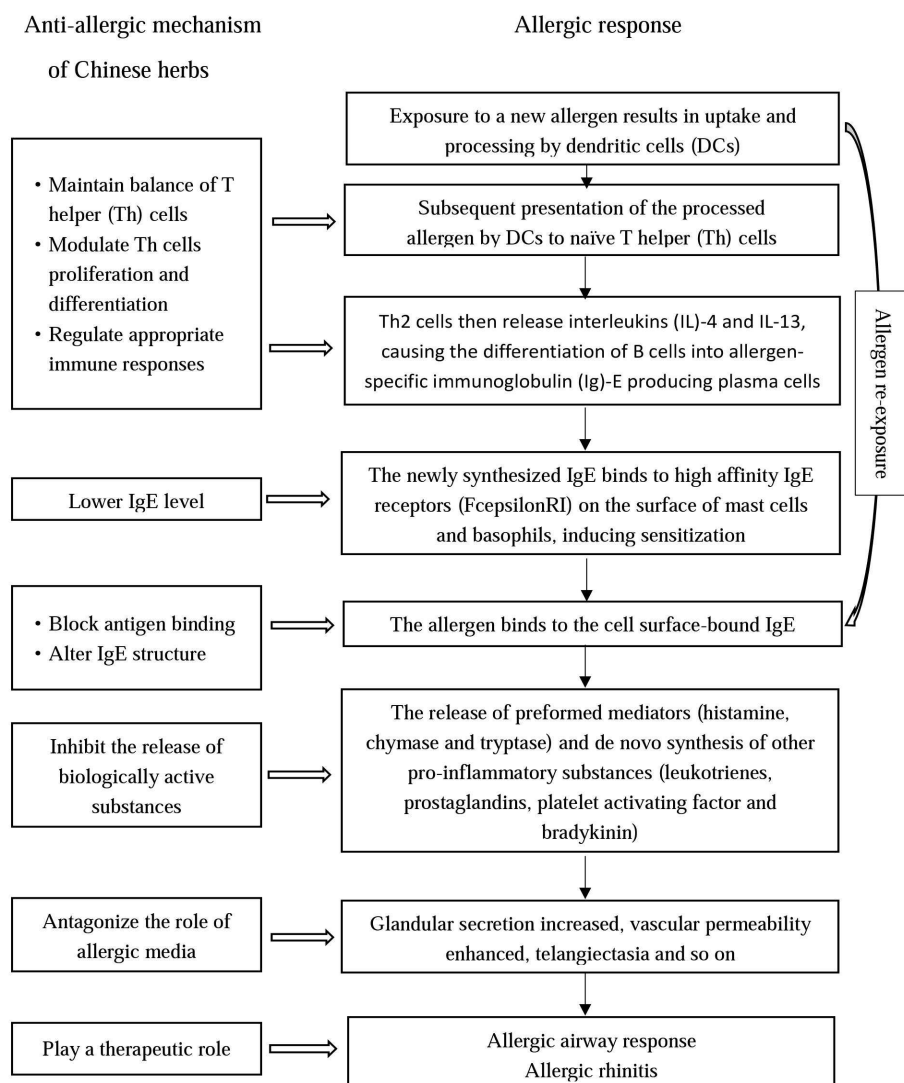


Figure 5 Allergic airway response and possible mechanism of actions of the herbs.

5.0 Conclusions

Based on existing databases and published literature, results of network analysis showed that the chemical compounds in common herbs for allergic rhinitis work through multiple targets and pathways. A limitation of our study is data integration. As databases become more complete, network analyses will in turn become more robust, allowing for a more thorough understanding of the mechanisms of Chinese herbs in the treatment of allergic rhinitis and other diseases. Such analyses will also

lead to development of novel herb-based drugs.

Acknowledgments

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Conflict of interest

The authors have no competing financial interests to declare.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the appendix.

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