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Research Article
Discovery of Core Herbal Ingredients for Allergic Rhinitis: Based on Data Mining and Network Pharmacology

Lei Zhao, Jianwang Yang, Tao Liu, Huan Cao and Baoshan Wang

Department of Otorhinolaryngology, The Second Hospital of Hebei Medical University, Shijiazhuang, Hebei 050005, China

Abstract

Background and Objective: The complexity and specificity of Chinese herbal medicine (CHM) has limited its wide application, despite presenting outstanding contributions to allergic rhinitis (AR). This study aimed to identify the core CHM and its active components, hoping to promote the accurate treatment of AR and the wide application of CHM. **Materials and Methods:** A rigorous scientific and logical research thought was designed by authors. Then, a series of public databases and bioinformatic tools were employed to conduct the present analysis according to the user guidelines. The data statistics involved in the relevant public databases and tools were automatically completed by their system background. Notably, $p<0.05$ indicated significant differences. **Results:** This study retrieved 76 eligible studies and excavated 74 effective prescriptions, which focused on discussing the efficacy of CHM on AR. Based on the 74 effective prescriptions, this study mined 153 herbs and constructed the formula-herb-ingredient-AR target network. Eventually, this study identified 10 core herbs and the valuable active ingredients of CHM for AR, including spathulenol, caryophyllene oxide and dibutyl phthalate. Additionally, this study confirmed the molecular mechanism of the active ingredients on AR, that is, the three active ingredients could concurrently regulate the calcium signaling pathway by targeting HTR2A, CHRM2, CHRM3 and NOS3, which in turn modulated AR. **Conclusion:** This study identified the core herbal ingredients, including spathulenol, caryophyllene oxide and dibutyl phthalate for AR and discussed the molecular mechanism of them modulating the calcium signaling pathway. This finding marked the place of CHM in AR pharmacotherapy.

Key words: Allergy, traditional Chinese medicine, Chinese herbal drug, network pharmacology, molecular docking

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Corresponding Author: Baoshan Wang, Department of Otorhinolaryngology, The Second Hospital of Hebei Medical University, Shijiazhuang, Hebei 050005, China

Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Allergic rhinitis (AR), driven by allergen exposure and mediated by Immunoglobulin E (IgE), is assigned to type I hypersensitivity in the nasal mucosa of sensitized individuals[1]. The prevalence of AR reported in diverse studies ranges from 5 to 50% worldwide, which showed great variability and resulted from different diagnostic approaches and participants[1]. Added, influenced by environmental exposure, climatic shift and lifestyle transformation, the prevalence of AR is increasing steadily and imposing an aggravated burden on people's health and social economy[1,2]. To alleviate the burden originating from AR, numerous researchers devoted themselves to exploring its pathophysiology and mechanisms of it, involving immunologic cascade mediated by IgE[1], innate immunity supported by nasal epithelial barrier[3], inflammatory infiltration induced by diverse inflammatory cells[4] and regulatory cytokine and mediator released by mast cells[5] and the like. For the management of AR, avoiding allergen exposure and improving the environment are effective measures, yet it is difficult to implement effectively in some cases[6,7]. Consequently, more studies are concerned on discussing other effective measures for AR, covering pharmacotherapy[8], immunotherapy[9] and intranasal operative therapy[10]. In addition, certain non-traditional therapies also exerted gratifying therapeutic effects on AR, including acupuncture[11], Chinese herb or herb-derived active ingredients[12,13], which only exhibited mild adverse effects. Noteworthily, among the non-traditional treatments, traditional Chinese medicine (TCM) or Chinese herbal medicine (CHM) has exerted significant roles on the treatments of multitudinous diseases, including the management of AR[14,15].

Benefit from the remarkable efficacy and dependable security, CHM has captured the recognition and acceptance of TCM and Western medicine during the long-standing practical application history[14-17]. Encouragingly, studies indicated that CHM prescriptions, single herbs, or active ingredients all exhibited satisfactory effects on AR. For instance, a clinical trial reported that San-Feng-Tong-Qiao-Di-Wan could alleviate the sneezing, rhinorrhea and nasal congestion of AR patients, especially for severe AR patients[18]. Tuo-Min-Zhi-Ti-Decoction could ameliorate the nasal allergy symptoms through decreasing IgE and histamine release and regulating Th1/Th2/Th17 balance[19]. Apart from herbal prescriptions, single herbs or active components also produced significant effects on AR. Typically, *Xanthium strumarium* L. (Cang-er-zi) could present positive effects on AR through changing cytokine levels, mucosa inflammation and arachidonic acid metabolism[20]. Hamaudol and emodin, the active components extracted from Guo-Min-Kang-Formula, could inhibit the Syk and Lyn contrapuntally, further play powerful effects on AR[15]. Tanshinone IIA, the extract of *Salvia miltiorrhiza* Bunge (Danshen), could inhibit the Th2 cytokines production and histamine release and ultimately alleviate AR symptoms[21]. All the above-mentioned studies indicated that CHM or herb-derived active components have performed significant roles in the treatment of AR.

The CHM has been extensively applied to ameliorate AR clinical manifestations and has achieved gratifying efficacy through diverse CHM prescriptions[22-24]. Noticeably, among the prescriptions, certain herbs frequently appeared in different formulas, which prompted that these herbs may be of great importance in the therapy of AR patients. *Herba ephedrae* (Ma-huang), for instance, simultaneously appeared in Bi-Min-Decoction[25], Xiao-Qing-Long-Decoction[26] and Qing-Fei-Jian-Pi-Decoction[27]. Analogously, *Radix astragali* (Huang-qi), coexisted in Bi-Min-Decoction[25], Jade-Wind-Barrier-Powder[28] and Bu-Zhong-Yi-Qi-Decoction[29]. Aforementioned findings prompt us to speculate that screening the key herbs and core active ingredients in different formulas may promote the precise treatment of AR while reducing the adverse effects of the formulas.

Based on above-mentioned analyses, the present study attempt to identify the CHM network, key herbs and core active ingredients, which may ameliorate the allergy symptoms of AR patients, through multiple methodologies, including literature review, bioinformatic analysis, network pharmacology and molecular docking. Herein, this study provides a reliable theoretical foundation for the precise treatment and real-world research of AR.

MATERIALS AND METHODS

This study was carried out at the Department of Otorhinolaryngology, The Second Hospital of Hebei Medical University, Shijiazhuang, Hebei, China, from January to July, 2023.

Retrieve documents and assess the studies: The literature was searched from database creation to December 31, 2022, in five databases. The detailed search strategy for each database was as follows:

- China National Knowledge Infrastructure (CNKI), the search term was topic: "Allergic Rhinitis" (precise) and "Peking University Core Periodical Catalogue" and "Clinical Observational Study or Clinical Study". The studies focused on the treatment of AR with the use of TCM or CHM

- WANFANG data, the search term was "Allergic Rhinitis" and "Traditional Chinese Medicine" or "Chinese Herbal Medicine" and "Peking University Core Periodical Catalogue" and "Clinical Controlled Trial"
- PubMed[30], the search term was "Allergic Rhinitis" and "Traditional Chinese Medicine" or "Chinese Herbal Drugs" and "Clinical Trial" or "Randomized Controlled Trial"
- Web of Science Core Collection[31], the search term was "Allergic Rhinitis" and "Traditional Chinese Medicine" or "Chinese Herbal Drugs"
- MEDLINE[32], the search term was "Allergic Rhinitis" and "Traditional Chinese Medicine" or "Chinese Herbal Drugs" (Topic) and "Randomized Controlled Trial" or "Clinical Trial" or "Comparative Study" or "Clinical Study" or "Equivalence Study" or "Equivalence Trial" or "Multicenter Study" (Publication Type)

The inclusion criteria for eligible studies were as follows: (1) Clinical controlled trials concerned with the evaluation of the effects of CHM on AR patients, not animal models or cell lines, (2) Studies focused on evaluating the efficacy of Chinese herbal prescriptions, not a single herb or herb-derived active component, (3) The CHM was given orally, not nasal spray or drop and (4) Prescriptions and herbs contained therein were available. Meanwhile, the following studies should be excluded: (1) Review, Systematic review, Meta-analysis, Comment, Case report, or Network pharmacology and (2) Studies focused on discussing the roles of acupuncture, acupoint herbal patching, acupoint catgut implantation, moxibustion.

Extract and analyze prescriptions, acquire herbs from prescriptions: Prescriptions were extracted from the included studies and the prescription-derived herbs were analyzed according to the following rules step by step. The details were as follows: (1) Extract formulas from each included literature, (2) Extract the herbs from each formula and unify the herb names with HERB[33] and Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP) (for herbs nor included in HERB)[34] and (3) Arrange the prescriptions and herbs to form formula-herb pairs for further analysis.

Construct the formula-herb network and identify the key herbs for AR: Based on previously formed formula-herb pairs, this study constructed a formula-herb network with Cytoscape (3.9.1) software[35]. Further, the top herbs with the highest frequency of occurrence in different formulas were extracted and defined as key herbs for AR treatment.

Extract the active ingredients from the key herbs and predict the targets for core ingredients: The active ingredients of key herbs were extracted from TCMSP according to the suggested parameters and criteria in TCMSP (Oral bioavailability $\geq$20%, Drug-likeness $\geq$0.1, Topological polar surface area $\leq$60 Angstroms squared, Rotatable bonds number $\leq$10 and 180$\leq$ Molecular weight (Dalton) $\leq$500)[34]. Secondly, the herb-ingredient network was constructed with Cytoscape (3.9.1) software and the top ingredients with the highest frequency of occurrence in different herbs were defined as core ingredients for AR treatment. After that, the names of the core ingredients were unified with PubChem[36]. Additionally, the targets for each core ingredient were predicted from TCMSP and were unified as gene symbol with GeneCards[37].

Predict and identify the crucial targets of AR: The specific targets of AR were predicted with GeneCards and Comparative Toxicogenomics Database (CTD)[38]. Furtherly, the intersections of targets predicted from TCMSP, GeneCards and CTD were calculated with EVenn online tool[39] and defined as the crucial targets of AR.

Construct the protein-protein interaction network and perform the functional enrichment analysis for the crucial AR targets: After acquired the crucial targets of AR, the protein-protein interaction (PPI) network was constructed with Search Tool for Recurring Instances of Neighbouring Genes (STRING)[40] for exploring the interactions among the targets. Furthermore, gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analyses were performed with the database for annotation, visualization and integrated discovery (DAVID)[41,42]. Added, the GO and KEGG pathway were visualized and presented with ChiPlot.

Select the potent pathway and identify the potential CHM target of AR: Considering the KEGG pathways associated with AR comprehensively, the top ranked pathway was selected. Afterwards, the molecules involved in the top ranked pathway were further screened by the manner of molecular docking to finally identify the molecular targets of CHM in AR. The molecular docking was performed with Cavity-Detection Guided Blind Docking (CB-Dock2)[43]. In preparation for molecular docking, the Three-Dimensional (3D) structures of interesting proteins were obtained from the Protein Data Bank (PDB) archive[44] and Universal Protein Resource (UniProt) (for proteins nor included in PDB)[45]. And, the 3D structures of molecular ligands were provided by PubChem.

Statistical analysis: This study was based on data mining and bioinformatics analyses. All the analyses were completed with online databases or tools, which did not directly involve statistical analysis. The statistical analysis involved in specific tools was carried out automatically by the tools in the system background, according to the user manual or default parameters. Notably, $p<0.05$ indicated a significant difference.

RESULTS

Total of 76 eligible literatures concerned on evaluating the efficacy of CHM on AR were retrieved from the five databases: Following the retrieval strategy, inclusion and exclusion criteria, a total of 76 eligible literatures concerned on evaluating the therapeutic efficacy of CHM on AR were finally enrolled in the present study. The details were as follows: (1) A total of 169 studies were first retrieved according to the search term in CNKI and 39 eligible studies were included in the subsequent analyses (retrieved January 8, 2023), (2) Of the 251 studies that met the search term in WANFANG were first retrieved and only 27 eligible studies were included in followed analyses (retrieved January 8, 2023), (3) In PubMed, of the 361 retrieved literatures that consistent with the search term, 17 eligible studies were finally enrolled in the present project (retrieved January 9, 2023), (4) Of the 124 retrieved literatures in Web of Science Core Collection, only six studies were eligible and were used for followed study (retrieved January 10, 2023) and (5) Of the 13 retrieved literatures in MEDLINE, only four eligible studies were included in further analyses (retrieved January 10, 2023). Of the 93 eligible studies, 17 studies were simultaneously included in different databases or reported in both English and Chinese. Accordingly, 76 eligible studies (18 studies in English and 58 studies in Chinese) were finally incorporated in the present project.

In all, 74 eligible prescriptions for the treatment of AR were extracted from the qualified studies: After obtained the 76 eligible studies, a total of 79 available prescriptions contained in them were extracted through purposefully reading papers one by one. Noticeably, the composition of the prescriptions in five studies could not be determined. Hence, the five studies were further excluded from this project. Consequently, a total of 74 prescriptions derived from 71 studies were finally enrolled in the present project and used for subsequent analyses.

Formula-herb network was constructed and the key herbs for the treatment of AR were identified: Through carefully analyzing the 74 previously screened prescriptions, all of the herbs contained in the prescriptions were extracted and collated manually. And then, the herb names were unified with HERB and TCMSP. Furthermore, the formula-herb pairs were manually matched and the formula-herb network was constructed with Cytoscape based on the formula-herb pairs. Due to the fact that different studies may have focused on discussing the same prescription and various prescriptions may contain the same herb, altogether 57 prescriptions (Supplementary data S1) and 153 herbs were ultimately located in the formula-herb network (Fig. S1). From a holistic perspective, it could be observed that different herbs participated in the composition of the formula-herb network at distinct frequencies (node size). Eventually, the top 10 herbs with the highest frequency were purposefully identified as the key herbs and were applied to subsequent study (Fig. S1). The key herbs included *Radix Saposhnikoviae divaricata* (Fang-feng), *Magnoliae flos* (Xin-yi), *Radix astragali* (Huang-qi), *Radix glycyrrhizae* (Gan-cao), *Rhizoma Atractylodis macrocephalae* (Bai-zhu), Herba Asari (Xi-xin), *Schisandra chinensis* (Wu-wei-zi), Radix *Angelicae dahuricae* (Bai-zhi), *Ramulus cinnamomi* (Gui-zhi), *Fructus Xanthii sibirici* (Cang-er-zi).

Herb-ingredient network was constructed and the core ingredients for the treatment of AR were identified: For exploring the molecular mechanism of herbs in treating AR, the pharmacokinetic properties and active ingredients of the key herbs were firstly acquired from TCMSP following the above-mentioned parameters and criteria in the methodology (retrieved February 26, 2023). Afterwards, the herb-ingredient pairs were matched manually and the herb-ingredient network was constructed with Cytoscape (Fig. S2). Similar to the formula-herb network, the herb-ingredient network indicated from an overall perspective that the ingredients appeared in diverse herbs and participated in the formation of the network at different frequencies (node size). Purposefully, the top three active ingredients, consisting of MOL002153, MOL000474 and MOL000676, were identified as the core ingredients with the highest frequency (Fig. S2). Then, the names of the three core ingredients were unified with PubChem and the details were as follows: (1) MOL002153 (1H-Cycloprop(e)azulen-7-ol, decahydro-1, 1, 7-trimethyl-4-methylene-, (1aR-(1aalpha, 4aalpha, 7beta, 7abeta, 7balpha))-, Spathulenol, PubChem CID 92231), (2) MOL000474 ((-)-Epoxycaryophyllene, Caryophyllene oxide, PubChem CID 1742210), (3) MOL000676 (DBP, Dibutyl Phthalate, PubChem CID 3026). Purposefully, for exploring the AR targets of the CHM ingredients, the potential targets of the three core ingredients were predicted in TCMSP and the name of targets were unified as gene symbol with GeneCards (Table 1) (retrieved February 27, 2023).

Table 1: Targets of the 3 core ingredients in TCMSP

Molecule ID	Target name	Gene symbol
MOL002153	Muscarinic acetylcholine receptor M3	CHRM3
MOL002153	Muscarinic acetylcholine receptor M1	CHRM1
MOL002153	Muscarinic acetylcholine receptor M2	CHRM2
MOL002153	Gamma-aminobutyric acid receptor subunit alpha-1	GABRA1
MOL002153	Gamma-aminobutyric-acid receptor subunit alpha-6	GABRA6
MOL000474	Muscarinic acetylcholine receptor M3	CHRM3
MOL000474	Thrombin	F2
MOL000474	Muscarinic acetylcholine receptor M1	CHRM1
MOL000474	Prostaglandin G/H synthase 2	PTGS2
MOL000474	Acetylcholinesterase	ACHE
MOL000474	Muscarinic acetylcholine receptor M2	CHRM2
MOL000474	Alpha-1B adrenergic receptor	ADRA1B
MOL000474	Gamma-aminobutyric acid receptor subunit alpha-1	GABRA1
MOL000474	Dipeptidyl peptidase IV	DPP4
MOL000474	Gamma-aminobutyric-acid receptor subunit alpha-6	GABRA6
MOL000676	Muscarinic acetylcholine receptor M3	CHRM3
MOL000676	Muscarinic acetylcholine receptor M1	CHRM1
MOL000676	Sodium-dependent noradrenaline transporter	SLC6A2
MOL000676	Sodium-dependent dopamine transporter	SLC6A3
MOL000676	Beta-2 adrenergic receptor	ADRB2
MOL000676	Sodium-dependent serotonin transporter	SLC6A4
MOL000676	Prostaglandin G/H synthase 1	PTGS1
MOL000676	Prostaglandin G/H synthase 2	PTGS2
MOL000676	Nitric-oxide synthase, endothelial	NOS3
MOL000676	Retinoic acid receptor RXR-alpha	RXRA
MOL000676	Glycogen synthase kinase-3 beta	GSK3B
MOL000676	Heat shock protein HSP 90	HSP90AB1
MOL000676	Beta-lactamase	DPEP1
MOL000676	mRNA of PKA Catalytic Subunit C-alpha	PRKACA
MOL000676	CGMP-inhibited 3',5'-cyclic phosphodiesterase A	PDE3A
MOL000676	Alpha-1A adrenergic receptor	ADRA1A
MOL000676	Muscarinic acetylcholine receptor M2	CHRM2
MOL000676	Ig gamma-1 chain C region	IGHG1
MOL000676	5-hydroxytryptamine 2A receptor	HTR2A
MOL000676	Gamma-aminobutyric acid receptor subunit alpha-1	GABRA1
MOL000676	Neuronal acetylcholine receptor protein, alpha-7 chain	CHRNA7
MOL000676	Gamma-aminobutyric-acid receptor subunit alpha-6	GABRA6

TCMSP: Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform, Targets of the 3 core ingredients were predicted in TCMSP (https://old.tcmsp-e.com/tcmsp.php) and unified as gene symbol with GeneCards (https://www.genecards.org/)

Total of 17 pivotal targets of CHM in the treatment of AR were identified: For understanding the molecular mechanism of AR, the specific targets of AR were predicted with CTD and GeneCards and altogether 29219 targets and 2382 targets were obtained after removing duplicate values in CTD and GeneCards, respectively (retrieved April 18, 2023). In order to more accurately explore the molecular targets of CHM for treating AR, the intersection of the predicted targets in CTD and GeneCards and the targets of the core ingredients of CHM for treating AR were identified as the pivotal targets and finally used for subsequent analyses (Fig. 1). Ultimately, a total of 17 specific targets were screened, including HTR2A, ACHE, ADRA1A, ADRA1B, ADRB2, DPEP1, DPP4, GSK3B, IGHG1, CHRM2, CHRM3, CHRNA7, NOS3, PTGS1, PTGS2, SLC6A2 and SLC6A4.

Functional enrichment analyses suggested the relationships among the 17 targets and the biological roles they participated in: Through constructing PPI regulatory network and k-means clustering among the 17 targets, this study revealed the interactional mechanism and the clusters of targets that may have the same or approximate roles in the pathogenesis of AR (Fig. 2). The GO analysis indicated that the 17 targets, as different cellular components, participated in multiple biological processes in the pathogenesis of AR through different molecular functions. And, KEGG pathway analysis showed that the 17 targets mainly enriched in six signaling pathways (Fig. 3 and Table S1). For instance, CHRM2 and CHRM3, as the cellular component of integral component of plasma membrane (GO:0005887), participated in the biological process of chemical synaptic transmission

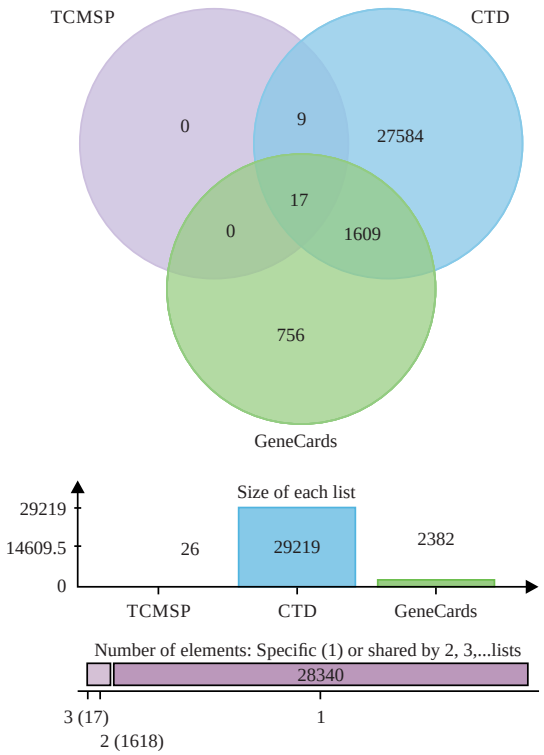

Fig. 1: Venn-diagram of allergic rhinitis associated targets

Diagram presented the predicted targets and the intersectional targets of allergic rhinitis, which derived from TCMSP, CTD and GeneCards, TCMSP: Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform and CTD: Comparative toxicogenomics database

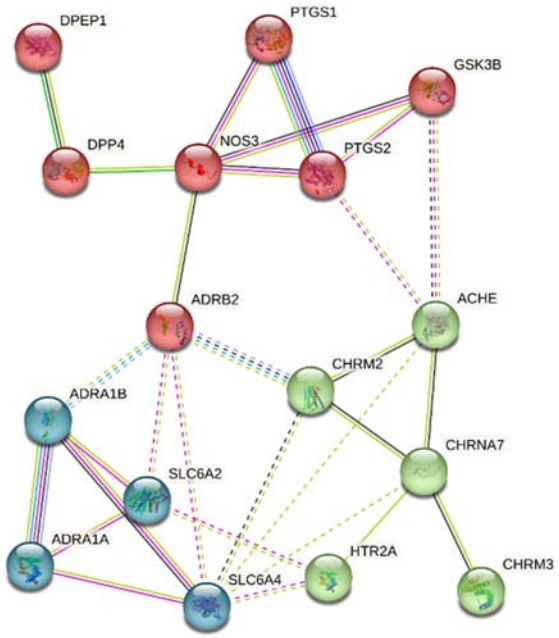

Fig. 2: Protein-protein interaction network for the 17 pivotal targets of allergic rhinitis

Network presented the interaction among the pivotal targets of allergic rhinitis and provided the four clusters that the 17 pivotal targets were clustered into with k-mean clustering, nodes represented the proteins and node colors represented the different clusters, edges represented the interactions among proteins and edge colors represented the interaction types, the light blue and purple mean known interactions, green, red and blue mean predicted interactions

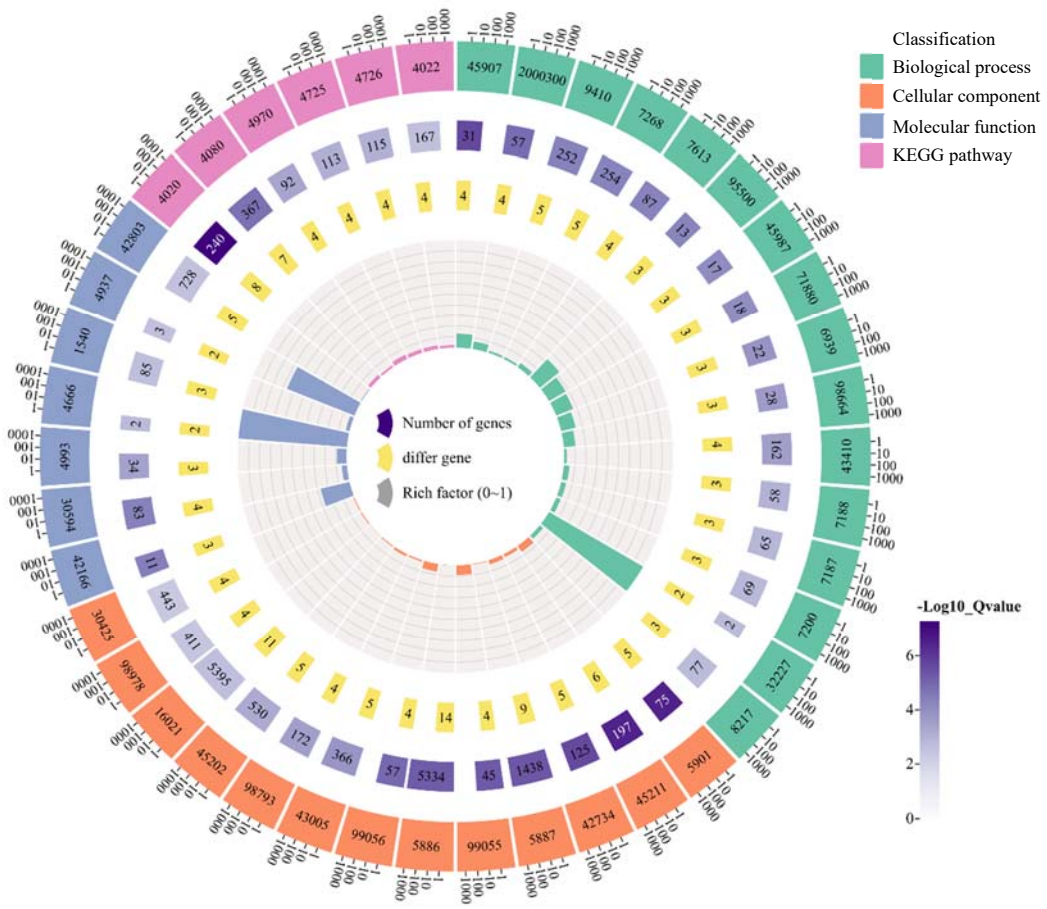

Fig. 3: Functional enrichment analyses for the pivotal targets of allergic rhinitis
Circle enrich plot presented the GO terms and KEGG pathways of the 17 targets enriched in, GO: Gene ontology and KEGG: Kyoto Encyclopedia of Genes and Genomes

(GO:0007268) through the molecular function of neurotransmitter receptor activity (GO:0030594) and even engaged in calcium signaling pathway (hsa04020) (Table S1).

Molecular docking verified that calcium signaling pathway may have mediated the therapeutic effect of CHM on AR: Comprehensive analysis and judgement from the KEGG pathways, calcium signaling pathway was regarded as the most meaningful and potential pathway with the smallest P-value in AR, which consist of CHRM2, CHRM3, NOS3, CHRNA7, ADRB2, HTR2A, ADRA1B, ADRA1A (Table S1). As previous studies demonstrated that Ca^{2+} mobilization and influx were associated with mast cells degranulation, which could initiate AR. Accordingly, the present authors speculated that the three core ingredients spathulenol, caryophyllene oxide and dibutyl phthalate, may regulate the calcium signaling pathway and effect on AR through targeting some or all of the eight current members of calcium signaling pathway. Molecular docking manifested that the same ligand (the core ingredient) could bind to different pockets of one or more proteins and different ligands could also bind to the same protein through diverse pockets (Table S2). For identifying the specific targets of the core ingredients more accurately, the molecular docking results were further filtered and the final targets of the core ingredients were defined as the target with the smallest vina score and score $\leq$-7 (Table 2). What was particularly striking to the present authors was that all the three core ingredients of CHM simultaneously bind to HTR2A, CHRM2, CHRM3 and NOS3. This finding suggested that HTR2A, CHRM2, CHRM3 and NOS3 may synchronously mediate the therapeutic effects of Spathulenol, Caryophyllene oxide and Dibutyl Phthalate on AR (Fig. 4).

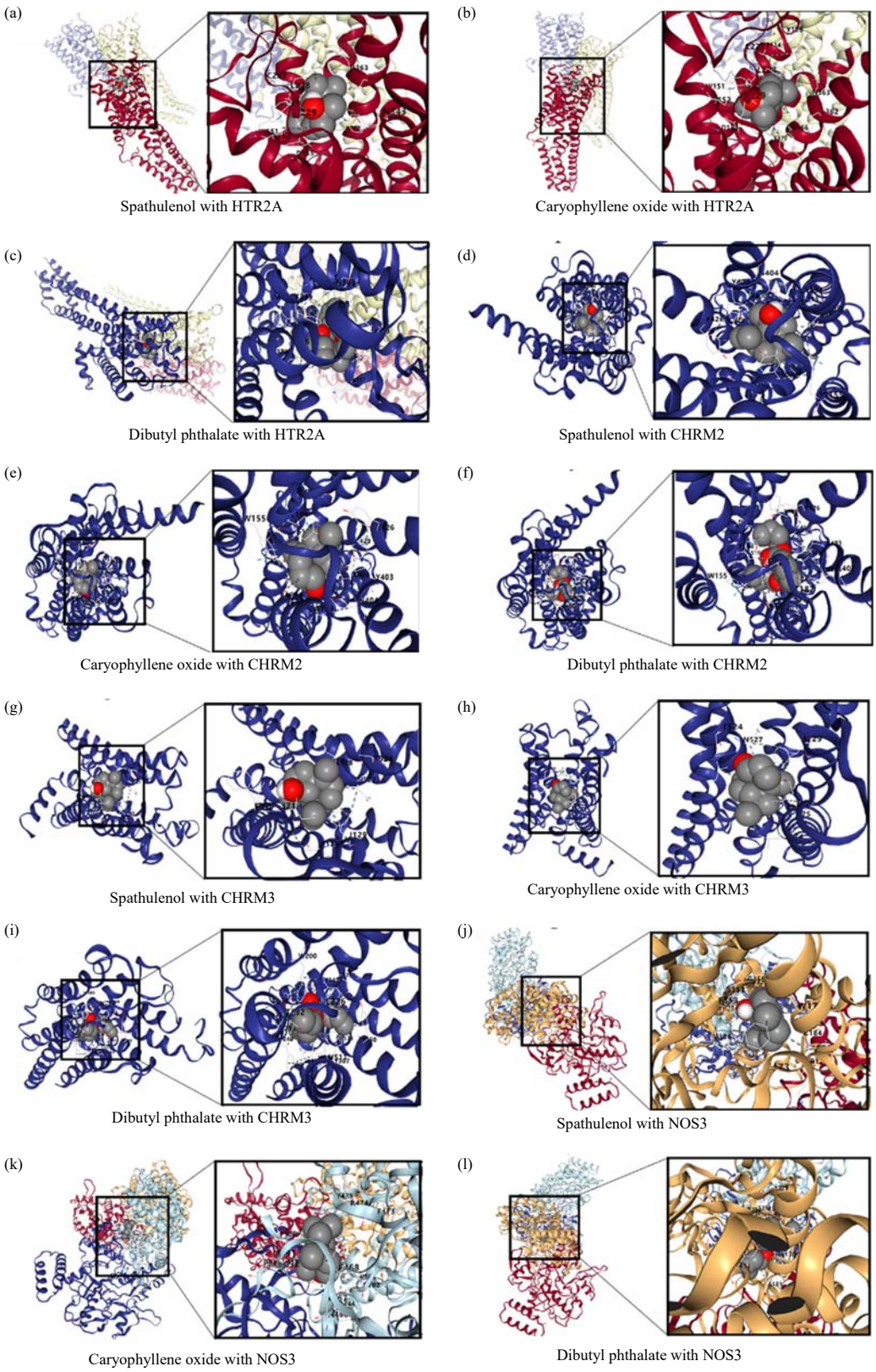

Fig. 4(a-l): Molecular docking

Three-Dimensional (3D) structure of molecular docking presented the detected cavities and predicted ligand-binding poses through structure-based blind docking and the cartoon represented the receptor style and space fill represented the ligand style

Spathulenol, caryophyllene oxide and dibutyl phthalate, concurrently targeted on HTR2A, CHRM2, CHRM3 and NOS3 and finally ameliorated AR: Systematic and holistic analyses demonstrated that the core active ingredients, consisting of spathulenol, caryophyllene oxide and dibutyl phthalate, derived from diverse herbs of multiple formulas, synergistically regulated the calcium signaling pathway through concurrently effecting on HTR2A, CHRM2, CHRM3 and NOS3 and finally ameliorated AR (Fig. 5 and 6).

Table 2: Final targets of the core ingredients in allergic rhinitis

	CurPocket ID	Vina score	Cavity volume (Å3)	Center (x, y, z)	Docking size (x, y, z)
MOL000676 and HTR2A	C3	-7.2	3471	26, -39, 57	28, 20, 26
MOL000676 and CHRM2	C1	-7.4	1730	183, 28, 523	27, 20, 28
MOL000676 and CHRM3	C3	-8.5	249	129, 121, 154	20, 20, 20
MOL000676 and NOS3	C2	-8.1	11424	69, 16, -170	31, 35, 35
MOL002153 and HTR2A	C2	-8.1	4086	22, 36, 57	18, 31, 27
MOL002153 and ADRB2	C1	-8.2	3965	2, 6, 56	27, 29, 25
MOL002153 and CHRM2	C1	-8.5	1730	183, 28, 523	27, 18, 28
MOL002153 and CHRM3	C4	-8.3	195	114, 127, 160	18, 18, 18
MOL002153 and NOS3	C2	-8	11424	69, 16, -170	31, 35, 35
MOL000474 and HTR2A	C2	-8.3	4086	22, 36, 57	18, 31, 27
MOL000474 and ADRA1A	C2	-7	2952	24, 0, -17	35, 18, 35
MOL000474 and ADRA1B	C2	-7.8	1257	-19, 0, 16	30, 18, 18
MOL000474 and ADRB2	C1	-7.3	3965	2, 6, 56	27, 29, 25
MOL000474 and CHRM2	C1	-8.7	1730	183, 28, 523	27, 18, 28
MOL000474 and CHRM3	C4	-7.2	195	114, 127, 160	18, 18, 18
MOL000474 and CHRNA7	C5	-7.6	1860	49, -13, -3	32, 18, 18
MOL000474 and NOS3	C1	-7	11839	99, -22, -211	31, 35, 35

Molecular docking was performed with Cavity-Detection Guided Blind Docking (CB-Dock2) (https://cadd.labshare.cn/cb-dock2/) and the final targets of the core ingredients were defined as the target with the smallest vina score and score $\leq$-7

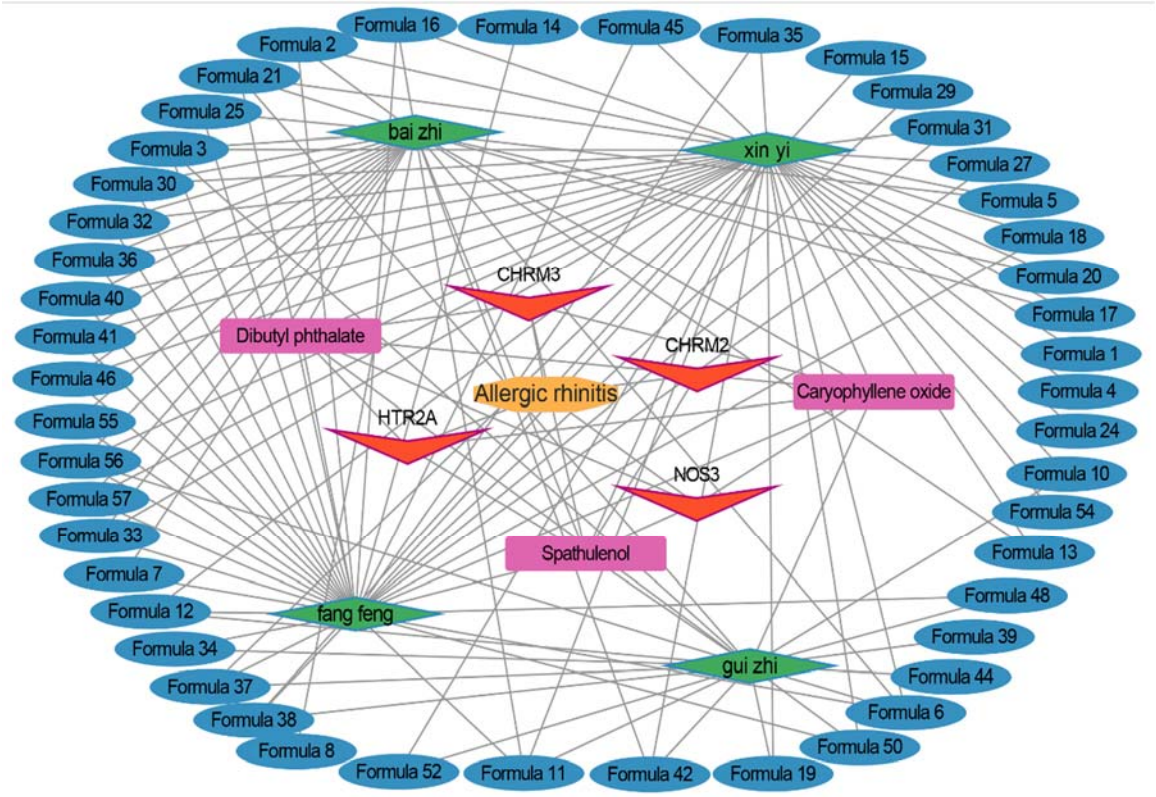

Fig. 5: Formula-herb-active ingredient-allergic rhinitis network

Network presented the core herbs, active ingredients and pivotal targets of allergic rhinitis, blue ellipses represented the formulas, green diamonds represented the core herbs, purple rectangles represented the core active ingredients and red triangles represented the specific targets of allergic rhinitis

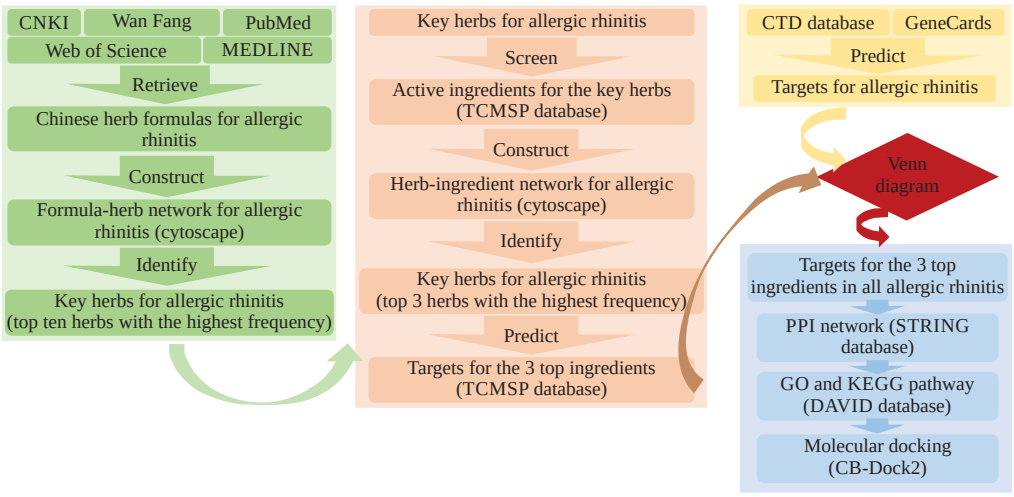

Fig. 6: Flow chart for the present study

Flow chart detailed the methodology and logic of the study

DISCUSSION

Proverbially, AR could incur intermittent or persistent clinical symptoms, consisting of frequent sneezing, rhinocnesmus, watery rhinorrhea and nasal congestion, even induce or aggravate asthma. Owing to the aforementioned symptoms, AR has troubled a good many of people on earth and wasted enormous wealth. In most cases, the allergic symptoms or discomfort could be alleviated or controlled by certain managements, for instance, avoiding allergen exposure, local or systemic glucocorticoid application, oral or intranasal antihistamines, leukotriene receptor antagonists and the combined application of multiple measures[1]. Unsatisfactorily, after systematic treatment, many patients, whose symptoms could not be effectively controlled or alleviated, still suffered enough from the long-standing torment of AR. Some patients are insensitive to treatment or require long-term medication, resulting in poor adherence to treatment or irregular medications[46,47]. Typically, AR-related glucocorticoid insensitivity deserved extra effort to explore the pathogenesis and effective pharmacotherapy[48,49]. Added, allergen immunotherapy has been recognized as an effective measure for AR treatment, while its long-term efficacy benefitted from continuous treatment for at least three years, which making adherence and persistence become the primary obstacles of allergen immunotherapy[50]. Hence, numerous studies have been conducted to explore more effective measures for AR treatments. Among the multiple therapeutic approaches, acupuncture and herb therapies presented outstanding contributions to the treatment of AR with mild adverse effects[1]. The TCM or CHM have exerted positive effects on all sorts of medical conditions, consisting of improving endothelial cell function[51], reducing inflammatory factor level[52], alleviating mitochondrial injury[53], inhibiting pyroptosis[54], ameliorating airway allergic inflammation[55], or even administrating olfactory function and minimal persistent inflammation of AR[56,57]. To our knowledge, numerous studies have provided substantial evidence for the positive efficacy of TCM or CHM in the treatment of AR. Yu-Ping-Feng-San, a prescription frequently used in the treatment of allergic diseases, could alleviate AR symptoms through decreasing the levels of inflammatory related factors[58]. Xiao-Qing-Long-Decoction, a classic prescription, has presented noteworthy, permanent and secure effects on the treatment of AR[26,59]. However, due to the particularity and complexity of TCM or CHM, the widespread application of TCM or CHM in the treatment of AR was constrained. Thereupon, how to expand the extensive application of TCM or CHM in the management of AR was of great significance. Through comprehensive analyses, the authors found that different formulas have been used for AR treatment and these formulas may contain one or more identical herbs, indicating that these identical herbs or their active ingredients may play pivotal roles in AR treatment. Herein, the current study identified 10 core herbs used in diversity formulas for AR through constructing formula-herb networks. For instance, Fang-feng, Xin-yi and Huang-qi were all involved in the treatment of AR in more than 40 prescriptions, which indicated that the core herbs may provide novel options for AR treatment. Furtherly, from the perspective of precision medicine, screening key herbs, especially exploring their active ingredients are of great significance for pharmacotherapy of AR and previous studies

have proved the efficacy of active ingredients of herbs on AR[12,21]. Accordingly, the present study has successfully identified three core active ingredients, including spathulenol, caryophyllene oxide and dibutyl phthalate, which may mediate the positive effects of herbs on AR. The followed series of analyses manifested that the three core active ingredients could regulate multiple AR-related targets and administrate the associated molecular functions, biological processes and signaling pathways. Significantly, the calcium signaling pathway, which could initiate AR[60-62], were concurrently regulated by spathulenol, caryophyllene oxide and dibutyl phthalate through targeting on HTR2A, CHRM2, CHRM3 and NOS3. And, this finding was verified by molecular docking, which provided a gratifying prospect for the study of AR treatment.

All the findings in this study were based on data mining and bioinformatics analyses and provided meaningful references for exploring new drugs for AR. However, to further confirm these findings, real-word studies should be conducted in the future study.

CONCLUSION

This study came through the advance of TCM or CHM on the treatment of AR, constructed the formula-herb-ingredient-AR target network and identified the core herbs and novel active ingredients for the treatment of AR through network pharmacology, bioinformatics, molecular docking and other methodology. Satisfactorily, the present study identified the potential values of spathulenol, caryophyllene oxide and dibutyl phthalate for AR and further marked the place of TCM or CHM in the pharmacotherapy of AR.

SIGNIFICANCE STATEMENT

Despite demonstrating valuable effects on diseases, the complexity of traditional Chinese medicine has limited its wide application. Screening and identification of the core components of Chinese herbal medicine (CHM) will be of great significance for the accurate diagnosis and treatment of diseases and the wide application of CHM. Through scientific and systematic analyses, this study discovered the core herbal components for the treatment of allergic rhinitis (AR), including spathulenol, caryophyllene oxide and dibutyl phthalate. Furtherly, the present study identified that the three active ingredients could concurrently regulate the calcium signaling pathway through targeting HTR2A, CHRM2, CHRM3 and NOS3. This finding marked the pivotal place of CHM on AR and brought light to the research on novel drugs for treating AR.

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Table S1: GO and KEGG pathway analyses

Term	Genes	p-value	FDR
Biological process			
GO:0045907~positive regulation of vasoconstriction	HTR2A, ADRA1B, PTGS2, ADRA1A	2.05E-06	7.64E-04
GO:2000300~regulation of synaptic vesicle exocytosis	CHRM2, GSK3B, HTR2A, ADRA1A	1.32E-05	2.45E-03
GO:0009410~response to xenobiotic stimulus	HTR2A, PTGS2, SLC6A2, ADRA1A, SLC6A4	4.51E-05	3.08E-03
GO:0007268~chemical synaptic transmission	CHRM2, CHRM3, CHRNA7, HTR2A, SLC6A2	4.65E-05	3.08E-03
GO:0007613~memory	CHRNA7, HTR2A, PTGS2, SLC6A4	4.71E-05	3.08E-03
GO:0095500~acetylcholine receptor signaling pathway	ACHE, CHRM3, CHRNA7	4.97E-05	3.08E-03
GO:0045987~positive regulation of smooth muscle contraction	CHRM3, PTGS2, ADRA1A	8.65E-05	4.52E-03
GO:0071880~adenylate cyclase-activating adrenergic receptor signaling pathway	ADRB2, ADRA1B, ADRA1A	9.73E-05	4.52E-03
GO:0006939~smooth muscle contraction	CHRM3, ADRB2, ADRA1A	1.47E-04	6.06E-03
GO:0098664~G-protein coupled serotonin receptor signaling pathway	CHRM2, CHRM3, HTR2A	2.39E-04	8.90E-03
GO:0043410~positive regulation of MAPK cascade	CHRNA7, ADRB2, ADRA1B, ADRA1A	2.97E-04	0.01
GO:0007188~adenylate cyclase-modulating G-protein coupled receptor signaling pathway	CHRM2, ADRB2, ADRA1B	1.03E-03	0.03
GO:0007187~G-protein coupled receptor signaling pathway, coupled to cyclic nucleotide second messenger	CHRM2, CHRM3, HTR2A	1.29E-03	0.04
GO:0007200~phospholipase C-activating G-protein coupled receptor signaling pathway	HTR2A, ADRA1B, ADRA1A	1.45E-03	0.04
GO:0032227~negative regulation of synaptic transmission, dopaminergic	PTGS2, SLC6A4	1.65E-03	0.04
GO:0008217~regulation of blood pressure	NOS3, PTGS2, PTGS1	1.81E-03	0.04
Cellular component			
GO:0005901~caveola	NOS3, HTR2A, ADRA1B, PTGS2, ADRA1A	2.86E-07	1.16E-05
GO:0045211~postsynaptic membrane	CHRM2, CHRM3, CHRNA7, HTR2A, ADRA1A, SLC6A4	3.06E-07	1.16E-05
GO:0042734~presynaptic membrane	CHRM2, HTR2A, SLC6A2, ADRA1A, SLC6A4	2.23E-06	5.64E-05
GO:0005887~integral component of plasma membrane	CHRM2, CHRM3, CHRNA7, ADRB2, HTR2A, ADRA1B, SLC6A2, ADRA1A, SLC6A4	4.31E-06	7.31E-05
GO:0099055~integral component of postsynaptic membrane	CHRM2, HTR2A, ADRA1A, SLC6A4	5.36E-06	7.31E-05
GO:0005886~plasma membrane	CHRM2, ACHE, CHRM3, GSK3B, NOS3, CHRNA7, ADRB2, HTR2A, ADRA1B, SLC6A2, ADRA1A, SLC6A4, DPP4, DPEP1	5.77E-06	7.31E-05
GO:0099056~integral component of presynaptic membrane	CHRM2, HTR2A, ADRA1A, SLC6A4	1.10E-05	1.19E-04
GO:0043005~neuron projection	CHRNA7, PTGS2, SLC6A2, SLC6A4, PTGS1	1.51E-04	1.43E-03
GO:0098793~presynapse	GSK3B, HTR2A, SLC6A2, SLC6A4	2.96E-04	2.50E-03
GO:0045202~synapse	CHRM2, ACHE, CHRM3, CHRNA7, SLC6A4	6.18E-04	4.70E-03
GO:0016021~integral component of membrane	CHRM2, DPP4, GSK3B, ACHE, IGHG1, CHRNA7, ADRB2, ADRA1B, SLC6A2, ADRA1A, SLC6A4	2.41E-03	0.02
GO:0098978~glutamatergic synapse	CHRM2, GSK3B, HTR2A, ADRA1A	3.65E-03	0.02
GO:0030425~dendrite	CHRM2, GSK3B, CHRM3, HTR2A	4.50E-03	0.03
Molecular function			
GO:0042166~acetylcholine binding	ACHE, CHRM3, CHRNA7	3.67E-05	2.08E-03
GO:0030594~neurotransmitter receptor activity	CHRM2, CHRM3, CHRNA7, HTR2A	4.38E-05	2.08E-03
GO:0004993~G-protein coupled serotonin receptor activity	CHRM2, CHRM3, HTR2A	3.71E-04	0.01
GO:0004666~prostaglandin-endoperoxide synthase activity	PTGS2, PTGS1	1.69E-03	0.04
GO:0001540~beta-amyloid binding	ACHE, CHRNA7, ADRB2	2.30E-03	0.04
GO:0004937~alpha1-adrenergic receptor activity	ADRA1B, ADRA1A	2.54E-03	0.04
GO:0042803~protein homodimerization activity	DPP4, ACHE, CHRNA7, ADRB2, PTGS2	2.74E-03	0.04
KEGG pathway			
hsa04020~calcium signaling pathway	CHRM2, CHRM3, NOS3, CHRNA7, ADRB2, HTR2A, ADRA1B, ADRA1A	4.84E-08	4.31E-06
hsa04080~neuroactive ligand-receptor interaction	CHRM2, CHRM3, CHRNA7, ADRB2, HTR2A, ADRA1B, ADRA1A	1.70E-05	7.57E-04
hsa04970~salivary secretion	CHRM3, ADRB2, ADRA1B, ADRA1A	4.54E-04	0.01
hsa04725~cholinergic synapse	CHRM2, ACHE, CHRM3, CHRNA7	8.29E-04	0.02
hsa04726~serotonergic synapse	HTR2A, PTGS2, SLC6A4, PTGS1	8.72E-04	0.02
hsa04022~cGMP-PKG signaling pathway	NOS3, ADRB2, ADRA1B, ADRA1A	2.56E-03	0.04

GO: Gene ontology, KEGG, Kyoto Encyclopedia of Genes and Genomes, FDR: False discovery rate, all the terms were filtered with the criteria of $p<0.05$ and $FDR<0.05$

Table S2: Results of molecular docking

	CurPocket ID	Vina score	Cavity volume (Å3)	Center (x, y, z)	Docking size (x, y, z)
MOL000676 and HTR2A	C3	-7.2	3471	26, -39, 57	28, 20, 26
	C2	-7	4086	22, 36, 57	20, 31, 27
	C1	-5.7	5455	28, 46, 17	31, 30, 27
	C5	-5.7	2175	13, -36, 9	20, 20, 35
	C4	-5.1	2602	0, 8, 7	20, 20, 35
MOL000676 and ADRA1A	C4	-6.2	894	-11, -10, 19	20, 20, 31
	C3	-5.9	1069	-14, -4, 8	20, 20, 20
	C1	-5.1	6332	25, 19, -20	28, 34, 32
	C2	-5	2952	24, 0, -17	35, 20, 35
	C5	-4.4	528	48, 26, -24	20, 20, 20
MOL000676 and ADRA1B	C2	-6.3	1257	-19, 0, 16	30, 20, 20
	C1	-5.9	1739	12, 6, -13	27, 20, 20
	C4	-5.8	538	-10, -8, 21	20, 20, 20
	C3	-5.4	897	28, 13, -11	20, 20, 28
	C5	-4.8	380	12, 17, -5	20, 20, 20
MOL000676 and ADRB2	C1	-6.8	3965	2, 6, 56	27, 29, 20
	C3	-6.6	1241	3, 6, 22	28, 20, 20
	C2	-5.8	1412	23, 3, -1	20, 20, 20
	C5	-5.4	203	-6, -2, 47	20, 20, 27
	C4	-5.2	302	11, 3, 11	20, 20, 20
MOL000676 and CHRM2	C1	-7.4	1730	183, 28, 523	27, 20, 28
	C2	-6.4	1075	179, 26, 551	20, 20, 20
	C4	-5.6	229	167, 29, 521	20, 20, 20
	C3	-5.1	420	180, 15, 554	20, 20, 20
	C5	-3.9	174	164, 24, 566	20, 20, 20
MOL000676 and CHRM3	C3	-8.5	249	129, 121, 154	20, 20, 20
	C1	-6.7	808	125, 114, 165	20, 20, 20
	C5	-5.9	169	135, 140, 138	20, 20, 20
	C2	-5.7	316	131, 134, 131	20, 20, 20
	C4	-5.7	195	114, 127, 160	20, 20, 20
MOL000676 and CHRNA7	C4	-6.6	7550	41, -10, 34	35, 30, 33
	C5	-6.3	1860	49, -13, -3	32, 20, 20
	C3	-6.2	8076	29, 7, -9	35, 35, 20
	C1	-5.9	11745	17, 26, 16	35, 33, 33
	C2	-5.9	8198	24, 15, 42	35, 35, 20
MOL000676 and NOS3	C2	-8.1	11424	69, 16, -170	31, 35, 35
	C1	-7.7	11839	99, -22, -211	31, 35, 35
	C5	-7.1	1053	76, 16, -168	20, 20, 20
	C3	-5.5	1316	90, -1, -196	20, 31, 26
	C4	-5	1265	90, -15, -235	20, 27, 20
MOL002153 and HTR2A	C2	-8.1	4086	22, 36, 57	18, 31, 27
	C3	-7.5	3471	26, -39, 57	28, 18, 26
	C1	-7.4	5455	28, 46, 17	31, 30, 27
	C4	-6	2602	0, 8, 7	18, 18, 35
	C5	-5.5	2175	13, -36, 9	18, 18, 35
MOL002153 and ADRA1A	C2	-6.6	2952	24, 0, -17	35, 18, 35
	C1	-6.3	6332	25, 19, -20	28, 34, 32
	C4	-6.2	894	-11, -10, 19	18, 18, 31
	C3	-6	1069	-14, -4, 8	18, 18, 18
	C5	-4.9	528	48, 26, -24	18, 18, 18
MOL002153 and ADRA1B	C1	-6.8	1739	12, 6, -13	27, 18, 18
	C2	-6.6	1257	-19, 0, 16	30, 18, 18
	C5	-6.4	380	12, 17, -5	18, 18, 18
	C3	-6.2	897	28, 13, -11	18, 18, 28
	C4	-5.7	538	-10, -8, 21	18, 18, 18
MOL002153 and ADRB2	C1	-8.2	3965	2, 6, 56	27, 29, 25
	C5	-7.3	203	-6, -2, 47	18, 18, 27
	C3	-6.8	1241	3, 6, 22	28, 18, 18
	C2	-6.6	1412	23, 3, -1	25, 18, 18
	C4	-6.3	302	11, 3, 11	18, 18, 18

Table S2: Continue

	CurPocket ID	Vina score	Cavity volume (Å3)	Center (x, y, z)	Docking size (x, y, z)
MOL002153 and CHRM2	C1	-8.5	1730	183, 28, 523	27, 18, 28
	C4	-6.4	229	167, 29, 521	18, 18, 18
	C3	-5.3	420	180, 15, 554	18, 18, 18
	C2	-4.8	1075	179, 26, 551	18, 18, 18
	C5	-4.3	174	164, 24, 566	18, 18, 18
MOL002153 and CHRM3	C4	-8.3	195	114, 127, 160	18, 18, 18
	C1	-7	808	125, 114, 165	18, 18, 18
	C5	-6	169	135, 140, 138	18, 18, 18
	C2	-5.6	316	131, 134, 131	18, 18, 18
	C3	-1.3	249	129, 121, 154	18, 18, 18
MOL002153 and CHRNA7	C1	-6.9	11745	17, 26, 16	35, 33, 33
	C5	-6.9	1860	49, -13, -3	32, 18, 18
	C4	-6.8	7550	41, -10, 34	35, 30, 33
	C2	-6.7	8198	24, 15, 42	35, 35, 18
	C3	-6.7	8076	29, 7, -9	35, 35, 18
MOL002153 and NOS3	C2	-8	11424	69, 16, -170	31, 35, 35
	C1	-7.7	11839	99, -22, -211	31, 35, 35
	C3	-6.3	1316	90, -1, -196	18, 31, 26
	C5	-6.3	1053	76, 16, -168	18, 18, 18
	C4	-4.8	1265	90, -15, -235	18, 27, 18
MOL000474 and HTR2A	C2	-8.3	4086	22, 36, 57	18, 31, 27
	C3	-8.2	3471	26, -39, 57	28, 18, 26
	C1	-7.2	5455	28, 46, 17	31, 30, 27
	C4	-5.1	2602	0, 8, 7	18, 18, 35
	C5	-5	2175	13, -36, 9	18, 18, 35
MOL000474 and ADRA1A	C2	-7	2952	24, 0, -17	35, 18, 35
	C1	-6.1	6332	25, 19, -20	28, 34, 32
	C4	-5.9	894	-11, -10, 19	18, 18, 31
	C3	-5.8	1069	-14, -4, 8	18, 18, 18
	C5	-5.4	528	48, 26, -24	18, 18, 18
MOL000474 and ADRA1B	C2	-7.8	1257	-19, 0, 16	30, 18, 18
	C1	-6.8	1739	12, 6, -13	27, 18, 18
	C4	-6.4	538	-10, -8, 21	18, 18, 18
	C5	-6.1	380	12, 17, -5	18, 18, 18
	C3	-5.7	897	28, 13, -11	18, 18, 28
MOL000474 and ADRB2	C1	-7.3	3965	2, 6, 56	27, 29, 25
	C3	-6.8	1241	3, 6, 22	28, 18, 18
	C2	-6.3	1412	23, 3, -1	25, 18, 18
	C4	-6.1	302	11, 3, 11	18, 18, 18
	C5	-6.1	203	-6, -2, 47	18, 18, 27
MOL000474 and CHRM2	C1	-8.7	1730	183, 28, 523	27, 18, 28
	C4	-6.8	229	167, 29, 521	18, 18, 18
	C3	-5.6	420	180, 15, 554	18, 18, 18
	C5	-4.7	174	164, 24, 566	18, 18, 18
	C2	-4.1	1075	179, 26, 551	18, 18, 18
MOL000474 and CHRM3	C4	-7.2	195	114, 127, 160	18, 18, 18
	C1	-6.6	808	125, 114, 165	18, 18, 18
	C5	-5.8	169	135, 140, 138	18, 18, 18
	C2	-5.2	316	131, 134, 131	18, 18, 18
	C3	-1.1	249	129, 121, 154	18, 18, 18
MOL000474 and CHRNA7	C5	-7.6	1860	49, -13, -3	32, 18, 18
	C3	-7.5	8076	29, 7, -9	35, 35, 18
	C4	-7.1	7550	41, -10, 34	35, 30, 33
	C1	-6.9	11745	17, 26, 16	35, 33, 33
	C2	-6.7	8198	24, 15, 42	35, 35, 18
MOL000474 and NOS3	C1	-7	11839	99, -22, -211	31, 35, 35
	C2	-6.5	11424	69, 16, -170	31, 35, 35
	C5	-6.4	1053	76, 16, -168	18, 18, 18
	C4	-5.6	1265	90, -15, -235	18, 27, 18
	C3	-5.5	1316	90, -1, -196	18, 31, 26

Molecular docking was performed with Cavity-Detection Guided Blind Docking (CB-Dock2) (https://cadd.labshare.cn/cb-dock2/)

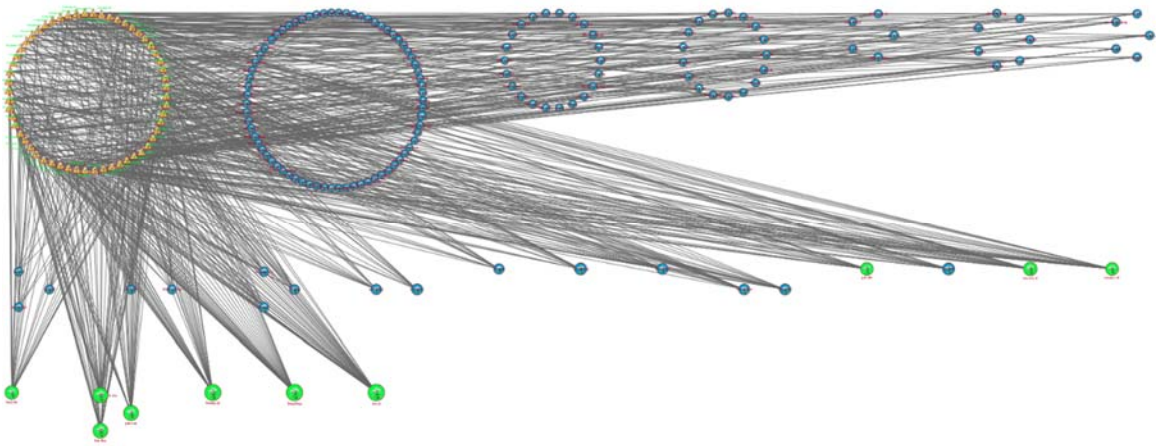

Fig. S1: Formula-herb network

Formula-herb network presented the pivotal herbs and the frequency of herbs used in different formulas, yellow triangles represented formulas, light blue dots represented herbs and green dots represented the core herbs, which showed the highest frequency

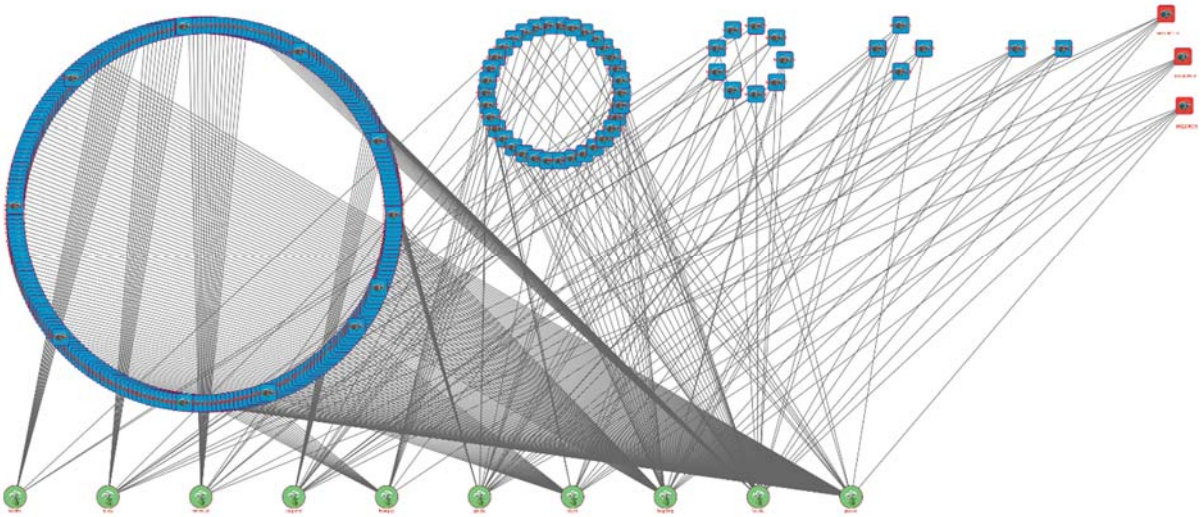

Fig. S2: Herb-ingredient network

Herb-ingredient network presented the core ingredients of herbs, which mediated the roles of herbs on allergic rhinitis, green dots represented the core herbs, light blue squares represented the active ingredients of herbs and red squares represented the core ingredients of herbs