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Mechanisms and molecular targets of the Yu-Ping-Feng powder for allergic rhinitis, based on network pharmacology

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Abstract

In traditional Chinese medicine (TCM), Yu-Ping-Feng powder (YPFP) has been used to treat allergic rhinitis (AR) for centuries. However, the mechanisms underlying its effects or its molecular targets in AR treatment are yet to be elucidated. Therefore, the active compounds of YPFP and their targets were collected and identified from the Traditional Chinese Medicine Systems Pharmacology database. Moreover, AR-associated targets were acquired from the GeneCards and Online Mendelian Inheritance in Man database. Proteins interactions network of YPFP presumed targets and AR-associated targets were examined and merged to reveal the candidate YPFP targets against AR.

Cytoscape software and BisoGenet Database were employed to perform the Visualization and Integrated Discovery (Cluster Profiler R package, version: 3.8.1). Kyoto Encyclopedia of Genes and Genomes and genome pathway analyses. To identify the key target genes, a gene-pathway network has been constructed.

We identified 44 effective active compounds and 622 YPFP targets. Also 1324 target genes related to AR were identified. Twenty pathways, including those of AGE-RAGE signaling, fluid shear stress, atherosclerosis, PI3K-Akt signaling, and tumor necrosis factor signaling was enriched significantly. MAPK1 was identified as the core gene, while others including RELA, AKT1, NFKBIA, IL6, and JUN, were also important in the gene-pathway network. Clearly, network pharmacology can be applied in revealing the molecular targets and mechanisms of action of complex herbal preparations.

These findings suggested that YPFP could treat AR by regulating immunological functions, diminishing inflammation, and improving immunity through different pathways.

Abbreviations: AR = allergic rhinitis, BC = betweenness centrality, BP = biological process, CC = cellular component, DC = degree centrality, DL = drug-likeness, FSS = fluid shear stress, KEGG = Visualization and Integrated Discovery (Cluster Profiler R package, version: 3.8.1). Kyoto Encyclopedia of Genes and Genomes, MF = molecular function, NF-κB = nuclear factor-kappa B, OB = oral bioavailability, OMIM = "Online Mendelian Inheritance in Man" (ttp://omim.org/), PPI = protein–protein interaction, TCM = traditional Chinese medicine, TNF = tumor necrosis factor, YPFP = Yu-Ping-Feng powder.

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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1. Introduction

Allergic rhinitis (AR) is a common chronic disease that affects both adults and children. Its salient symptoms include sneezing, itching, nasal congestion, and watery rhinorrhea. AR is an immunoglobulin E (IgE)-mediated respiratory illness, characterized by Th2-driven prominent allergic inflammation, which can affect the quality of life and productivity, as well as exacerbate several other conditions such as asthma, obstructive sleep apnea.[1,2] Being a common disease, AR affects about 40% of people globally, resulting in a huge economic burden. Treatment involves administration of medicines that reduce the symptoms of rhinitis to ensure that the patient is comfortable.[3,4] The drugs include antihistamines, intranasal corticosteroids, and midodrine. Although these drugs can increase peripheral vascular resistance, promote blood reflux, stabilize blood volume, and improve insufficient circulatory volume, these medications are usually associated with side effects, including drowsiness, hormone resistance, and sedation.[5] Above all, an effective drug against AR remains a major unmet medical need.

Allergic rhinitis (AR) is still considered a chronic disease that can be alternatively treated by traditional Chinese medicine (TCM). In China, chronic diseases, including AR, have been treated and prevented by using TCM for thousands of years. Shenqi has been reported to exert its anti-allergic effect through the inhibition of mast cell-mediated allergic response and reduction of Th1/Th2 ratio imbalance in AR.[6] Yu-Ping-Feng powder (YPFP) has been widely used in Asia over many years for treating the symptoms of cold, nasal congestion, and especially AR. Some related research reported that a modified Yu-Ping-Feng powder can significantly relieve the symptoms of perennial or seasonal allergic rhinitis.[7–9] Zhou et al[10] reported that YPFP inhibits the expression of Bcl2L12 and increases IL-10 expression in AR Bregs. YPFP can efficiently inhibit experimental airway allergy[11] and has been used in the treatment of human allergic rhinitis in China.[12] YPFP may promote CD4+ CD25+Foxp3+ Treg to cell differentiation and other mechanisms to regulate the body's immune response by improving the symptoms of allergic rhinitis.[13] In addition, YPFP could strengthen immunity and relieve cold and asthma.[14] YPFP could also exert the functions of immune regulation, anti-inflammatory, bacteriostasis, microecological environment stabilization and anti-tumor through various mechanisms, and has prevention and treatment effects on diseases in the respiratory system, digestive system, pediatrics, dermatology, ENT, and other fields.[15] Thus, it is especially suitable for physically weak people, such as children and the elderly. YPFP is composed of 3 herbs, namely Huangqi (*Astragalus membranaceus* (Fisch.) Bunge.), Fangfeng (*Saposhnikovia divaricata* (Turcz.) Schischk.), and Baizhu (*Atractylodes macrocephala* Koidz.). Modern pharmacological research shows that Huangqi (*A membranaceus* (Fisch.) Bunge.) can improve the function of the mononuclear phagocyte system, promote the production of immune factors, improve humoral and cellular immunity, and also exhibits anti-asthmatic and anti-aging effects.[16] Fangfeng (*S divaricata* (Turcz.) Schischk.) has anti-inflammatory, sedative, anti-allergic effects.[17] Baizhu (*A macrocephala* Koidz.) can help digestion, enhance human immunity, and also has sedative and antibacterial effects.[18] In TCM, "Qi" circulates through the body all times, and YPFP is commonly utilized in the treatment of deficiency of the lung Qi and weakness of the exterior body, which is associated with many symptoms, such as weakness, dizziness, colds, fatigue, sweating, hives, and pallor. YPFP is suggested to be able to prevent cold, repeated respiratory tract infections, asthma, allergic rhinitis, etc. However, how YPFP exerts its therapeutic effects on patients with AR is unclear. Besides, few studies have reported on the active ingredients, targets, and pathways of YPFP.

In TCM, complex herbal formulations contain numerous active ingredients and may have multiple targets, including diverse genes, proteins, and pathways, leading to an integrated biochemical and physiological effect, suitable for treating complex diseases. Network pharmacology is a novel method, mainly based on system biology. It combines multidirectional pharmacology, which makes it applicable in exploring the mechanisms underlying TCM prescriptions. Based on the approach, multiple networks are constructed to aid in understanding the interactions between various compounds, proteins, genes, and diseases.[19] Thus, the application of network pharmacology can offer new insights into the molecular mechanism of YPFP in AR treatment, and provide information that is crucial in the future development and application of YPFP. The idea of employing the Network Pharmacology approach to resolve the mysteries surrounding some TCM was initially suggested by Liu et al.[20] Using the same approach, Liu et al[16] examined the potential mechanism of the Yiqi Shexue formula on primary immune thrombocytopenia.[21] The potential mechanism of *Flos magnoliae* and *Centipeda minima* for treating AR was also deciphered on the basis of the pharmacology network.[22] Lastly, Hu et al[23] employed network pharmacology to reveal the mechanism underlying the efficacy of Xiang Ju tablets in the treatment of AR.

Herein, we utilized the network pharmacology method to predict targets, elucidate the mechanisms underlying the efficacy of YPFP in AR treatment. Drugbank database was used to select YPFP active compounds plus their targets. Subsequently, we obtained R-associated targets from the GeneCards and Online Mendelian Inheritance in Man (OMIM) database. Finally, we performed gene ontology (GO) and pathway analyses to identify the enriched pathways. This is the first study to contemplate the mechanism of action of YPFP in the treatment of AR, which provides the theoretical basis for the further development and utilization of YPFP. However, clinical outcomes such as "efficacy" and "effectiveness" in this study are speculative analysis according to special soft-ware data.

2. Methods

Network pharmacology is a novel approach that combines system network analysis and pharmacology. It could be used to elucidate the synergistic effects among compounds and potential mechanisms of multicomponent and multiple target drugs at the molecular level through the networks of the compound–compound, compound–target, and target–disease. Network pharmacology would facilitate the understanding of the interactions among the compounds, genes, proteins, and diseases and is suitable for the study of complex TCM formulations.[24,25]

2.1. Reagents

Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP, http://tcmspw.com/tcmsp.php, Version 2.3); DrugBank database (https://www.drugbank.ca/),[21] Gene Cards (http://www.genecards.org/), OMIM (http://www.omim.org/), UniProt (http://ctdbase.org/, updated in 2019–12–18); STRING Database (https://string-db.org/, Version 11.0); Cytoscape Software (version 3.7.1), its tool: Network Analyzer, and its apps: BisoGenet, CytoNCA; Bioconductor (http://www.bioconductor.org/) and its packages: org.Hs.eg. db, enrichplot, ggplot2, DOSE, colorspace, clusterProfiler (version 3.8.1); The R Programming Language (RGUI); Visualization and Integrated Discovery (Cluster Profiler R package, version: 3.8.1). Kyoto Encyclopedia of Genes and Genomes (KEGG) Pathway Database (https://www.kegg.jp/k egg/pathway.html, updated in 2020–01–14).

2.2. Collection of YPFP active ingredients and their targets

All components of the 3 Chinese medicinal herbs in YPFS were retrieved from the Traditional Chinese Medicine Systems Pharmacology (TCMSP) database (http://tcmspw.com/). In drug development, 2 crucial parameters are usually considered when selecting candidate compounds, namely, Oral Bioavailability (OB) and Drug-likeness (DL). In absorption, distribution, metabolism, and excretion (ADME) processes, OB is one of the most significant pharmacokinetic parameters.[26] High OB is usually an essential indicator to determine the druglikeness (DL) index of active substances. The substances with OB $\geq$30% were regarded as high OB. As a qualitative concept applied in drug design to estimate the druggability of a molecule, the DL index is useful for rapid screening of active substances.[26] In the DrugBank database, the average DL index is 0.18. The substances with DL index $\geq$0.18 were regarded to have high druggability. These 2 considerations determine how the drug will be absorbed and distributed in the human circulatory system, and therefore, dictate whether a compound is suitable to be used as a drug. Additionally, they reveal how the property of the chemicals correspond to most of the existing drugs.[27] With this premise, we screened for YPFP active ingredients as well as their matching targets from TCMSP to satisfy both OB $\geq$30% and DL $\geq$0.18.[28] As mentioned earlier, YPFP is a mixture of 3 Chinese medicines, including huangqi (*A membranaceus* (Fisch.) Bunge.), Fangfeng (*S divaricata* (Turcz.) Schischk.), and Baizhu (*A macrocephala* Koidz.). Their active ingredients were selected from TCMSP. Moreover, we indirectly obtained data on their targets from the DrugBank database via the TCMSP database. Forty-four eligible compounds were obtained in total after removing the duplications: 19 in Huangqi (*A membranaceus* (Fisch.) Bunge.), 18 in Fangfeng (*S divaricata* (Turcz.) Schischk.), 7 in Baizhu (*A macrocephala* Koidz.). The corresponding 3658 targets of YPFP were obtained in total, of which 622 targets were finally selected after removing 3036 duplications; they consisted of 405 in Huangqi (*A membranaceus* (Fisch.) Bunge.), 197 in Fangfeng (*S divaricata* (Turcz.) Schischk.), 20 in Baizhu (*A macrocephala* Koidz.).

2.3. Collection of AR-related targets

AR-related targets were retrieved from Gene Cards and OMIM database through the following instructional steps: open the web page of Gene Cards and OMIM databases, in the search engine "Keyword Search," choose "Disease," and input "Allergic rhinitis," then click on the result, and look over "Genes" related human genes of AR, and remove the duplications. In the end, a total of 1324 target genes associated with AR were identified.

2.4. Network construction and analysis

The "Disease-components-targets" network was then constructed by using the Cytoscape 3.7.1 software, importing the information of column "network" and "Node Properties" of the file in text (TXT) format, mapping style including shape, color, edge, and so on. The final network was edited and exported as an image. We then employed the Cytoscape software to merge the YPFP putative and AR-associated targets to obtain a preliminary protein–protein interaction (PPI) network. We analyzed it with the Apps BisoGenet 3.0.0, which included the Biological General Repository for Interaction Datasets, Database of Interacting Proteins, Human Protein Reference Database, Biomolecular Interaction Network Database, Molecular INTeraction database, and IntAct Molecular Interaction Database. The resultant PPI relationship was saved in PNG format.

2.5. Network merge

The PPI networks covered a multitude of genes. In order to expose the key target genes, the Cytoscape plugin CytoNCA was used and degree centrality (DC) and betweenness centrality (BC) were analyzed. The 2 parameters represent topological importance and reflect the tightness of gene nodes.[29] We set the conditions of DC $>$ 61 and BC $>$ 600.

2.6. Bioinformatic analysis

These analyses were performed by using the Cluster Profiler R package, v 3.8.1. GO annotation and KEGG pathway enrichment analysis involving biological process (BP), molecular function (MF), and cellular component (CC) was done using the Database for Annotation, Visualization and Integrated Discovery. Functional categories were enriched within genes (P adjust $<$.05). We selected the top 20 GO functional categories. The genes that were significantly ($P < .05$) enriched were analyzed further. The genes that played significant roles in pathway regulation were identified and used to construct the gene-pathway network, which was then applied in the screening of the key target genes associated with YPFP effects against AR.

3. Results

3.1. Identification of bioactive components in YPFP

We performed HPLC to conduct a fingerprinting analysis of the YPFP decoction extract. The phytochemical profile of YPFP comprised about 14 chromatographic peaks (Supplement 1, http://links.lww.com/MD2/A326); out of these, 9 compounds were recognized by their UV spectra and retention times; they were: prim-O-glucosylcimifugin, psoralen, cimifugin, calycosin-7-O-β-D-glucoside, 4′-O-β-glucopyranosyl-5-O-methylvisamminol, atractylon, calycosin, sec-O-glucosylhamaudol, and formononetin.

3.2. Ingredient-target network analysis

Through our query of TCMSP, we identified 315 active ingredients and 3658 targets for the 3 components of YPFP, that is, Huangqi (*A membranaceus* (Fisch.) Bunge.), Fangfeng (*S divaricata* (Turcz.) Schischk.), and Baizhu (*A macrocephala*

Table 1

The final selected compounds in YQSX for analysis.

ID	Name	OB (%)	DL	Drug
MOL000392	Formononetin	69.67	0.21	Huangqi (*A membranaceus* (Fisch.) Bunge.)
MOL000422	Kaempferol	41.88	0.24	Huangqi (*A membranaceus* (Fisch.) Bunge.)
MOL000417	Calycosin	47.75	0.24	Huangqi (*A membranaceus* (Fisch.) Bunge.)
MOL000438	(3R)-3-(2-hydroxy-3,4-dimethoxyphenyl) chroman-7-ol	67.67	0.26	Huangqi (*A membranaceus* (Fisch.) Bunge.)
MOL000098	Quercetin	46.43	0.28	Huangqi (*A membranaceus* (Fisch.) Bunge.)
MOL000239	Jaranol	50.83	0.29	Huangqi (*A membranaceus* (Fisch.) Bunge.)
MOL000398	Isoflavanone	109.99	0.3	Huangqi (*A membranaceus* (Fisch.) Bunge.)
MOL000378	7-O-methylisomucronulatol	74.69	0.3	Huangqi (*A membranaceus* (Fisch.) Bunge.)
MOL000354	Isorhamnetin	49.6	0.31	Huangqi (*A membranaceus* (Fisch.) Bunge.)
MOL000380	(6aR,11aR)-9,10-dimethoxy-6a,11a-dihydro-6H-benzofurano[3,2-c]chromen-3-ol	64.26	0.42	Huangqi (*A membranaceus* (Fisch.) Bunge.)
MOL000371	3,9-di-O-methylnissolin	53.74	0.48	Huangqi (*A membranaceus* (Fisch.) Bunge.)
MOL000442	1,7-Dihydroxy-3,9-dimethoxy pterocarpene	39.05	0.48	Huangqi (*A membranaceus* (Fisch.) Bunge.)
MOL000439	Isomucronulatol-7,2′-di-O-glucosiole	49.28	0.62	Huangqi (*A membranaceus* (Fisch.) Bunge.)
MOL000387	Bifendate	31.1	0.67	Huangqi (*A membranaceus* (Fisch.) Bunge.)
MOL000374	5′-hydroxyiso-muronulatol-2′,5′-di-O-glucoside	41.72	0.69	Huangqi (*A membranaceus* (Fisch.) Bunge.)
MOL000433	FA	68.96	0.71	Huangqi (*A membranaceus* (Fisch.) Bunge.)
MOL000296	Hederagenin	36.91	0.75	Huangqi (*A membranaceus* (Fisch.) Bunge.)
MOL000211	Mairin	55.38	0.78	Huangqi (*A membranaceus* (Fisch.) Bunge.)
MOL000033	"(3S,8S,9S,10R,13R,14S,17R)-10,13-dimethyl-17-[(2R,5S)-5-propan-2-yloctan-2-yl]-2,3,4,7,8,9,11,12,14,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-3-ol"	36.23	0.78	Huangqi (*A membranaceus* (Fisch.) Bunge.)
MOL000379	9,10-dimethoxypterocarpan-3-O-β-D-glucoside	36.74	0.92	Huangqi (*A membranaceus* (Fisch.) Bunge.)
MOL000173	Wogonin	30.68	0.23	Fangfeng (*S divaricata* (Turcz.) Schischk.)
MOL011740	Divaricatol	31.65	0.38	Fangfeng (*S divaricata* (Turcz.) Schischk.)
MOL011747	Ledebouriellol	32.05	0.51	Fangfeng (*S divaricata* (Turcz.) Schischk.)
MOL001941	Ammidin	34.55	0.22	Fangfeng (*S divaricata* (Turcz.) Schischk.)
MOL003588	Prangenidin	36.31	0.22	Fangfeng (*S divaricata* (Turcz.) Schischk.)
MOL000359	Sitosterol	36.91	0.75	Fangfeng (*S divaricata* (Turcz.) Schischk.)
MOL000358	Beta-sitosterol	36.91	0.75	Fangfeng (*S divaricata* (Turcz.) Schischk.)
MOL011753	5-O-Methylvisamminol	37.99	0.25	Fangfeng (*S divaricata* (Turcz.) Schischk.)
MOL013077	Decursin	39.27	0.38	Fangfeng (*S divaricata* (Turcz.) Schischk.)
MOL007514	"methyl icosa-11,14-dienoate"	39.67	0.23	Fangfeng (*S divaricata* (Turcz.) Schischk.)
MOL002644	Phellopterin	40.19	0.28	Fangfeng (*S divaricata* (Turcz.) Schischk.)
MOL001494	Mandenol	42	0.19	Fangfeng (*S divaricata* (Turcz.) Schischk.)
MOL011749	Phelloptorin	43.39	0.28	Fangfeng (*S divaricata* (Turcz.) Schischk.)
MOL001942	Isoimperatorin	45.46	0.23	Fangfeng (*S divaricata* (Turcz.) Schischk.)
MOL011730	11-hydroxy-sec-o-beta-d-glucosylhamaudol_qt	50.24	0.27	Fangfeng (*S divaricata* (Turcz.) Schischk.)
MOL011732	Anomalin	59.65	0.66	Fangfeng (*S divaricata* (Turcz.) Schischk.)
MOL000011	(2R,3R)-3-(4-hydroxy-3-methoxy-phenyl)-5-methoxy-2-methylol-2,3-dihydropyrano[5,6-h][1,4] benzodioxin-9-one	68.83 0.66	68.83 0.66	Fangfeng (*S divaricata* (Turcz.) Schischk.)
MOL011737	divaricatacid	87	0.32	Fangfeng (*S divaricata* (Turcz.) Schischk.)
MOL000072	8β-ethoxy atractylenolide III	35.95	0.21	Baizhu (*A macrocephala* Koidz.)
MOL000033	"(3S,8S,9S,10R,13R,14S,17R)-10,13-dimethyl-[(2R,5S)-5-propan-2-yloctan-2-yl]-2,3,4,7,8,9,11,12,14,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-3-ol"	36.23	0.78	Baizhu (*A macrocephala* Koidz.)
MOL000028	α-Amyrin	39.51	0.76	Baizhu (*A macrocephala* Koidz.)
MOL000049	3β-acetoxyatractylone	54.07	0.22	Baizhu (*A macrocephala* Koidz.)
MOL000021	14-acetyl-12-senecioyl-2E,8E,10E-atractylentriol"	60.31	0.31	Baizhu (*A macrocephala* Koidz.)
MOL000020	12-senecioyl-2E,8E,10E-atractylentriol	62.4	0.22	Baizhu (*A macrocephala* Koidz.)
MOL000022	14-acetyl-12-senecioyl-2E,8Z,10E-atractylentriol	63.37	0.3	Baizhu (*A macrocephala* Koidz.)

Koidz.). The screening threshold was: OB ≥ 30% and DL ≥ 0.18. Forty-four ingredients of YPFP were finally selected as the candidates, which consisted of 20, 18, and 7 potentially active ingredients of Huangqi (*A membranaceus* (Fisch.) Bunge.), Fangfeng (*S divaricata* (Turcz.) Schischk.), and Baizhu (*A macrocephala* Koidz.), respectively (Table 1). After removing duplicate targets, 622 YPFP-related targets were identified from the Drug Bank database: 405 in Huangqi (*A membranaceus* (Fisch.) Bunge.), 197 in Fangfeng (*S divaricata* (Turcz.) Schischk.), 20 in Baizhu (*A macrocephala* Koidz.). AR-related

Table 2

The intersection of YPFP and AR targets for analysis.

No.	Symbol name	No.	Symbol name
1	PTGS2	45	EGFR
2	PGR	46	VEGFA
3	CHRM3	47	BCL2L1
4	AR	48	PLAU
5	ACHE	49	MMP2
6	ADRA1A	50	MMP9
7	ADRB2	51	MAPK1
8	DPP4	52	EGF
9	NOS2	53	NFKBIA
10	ESR1	54	SOD1
11	KDR	55	HIF1A
12	PTGS1	56	ERBB2
13	PPARG	57	MYC
14	ESR2	58	GJA1
15	GSK3B	59	IL1B
16	ADRA1B	60	BIRC5
17	MAPK14	61	NOS3
18	RELA	62	IL2
19	AKT1	63	PLAT
20	BCL2	64	SERPINE1
21	CASP9	65	IFNGR1
22	JUN	66	IL1A
23	IL6	67	MPO
24	CASP3	68	ABCG2
25	MMP1	69	NFE2L2
26	CCL2	70	PARP1
27	PRKCD	71	CXCL11
28	PTGER3	72	CXCL2
29	CHRM2	73	SSP1
30	SLC6A4	74	CD40LG
31	PRKCA	75	ERBB3
32	PON1	76	ADRA2C
33	IGHG1	77	ADRA1D
34	ADH1B	78	MET
35	PPARA	79	IL4
36	CRP	80	MAPK8
37	CXCL10	81	STAT1
38	CHUK	82	HMOX1
39	AKR1B1	83	CYP3A4
40	ALOX5	84	CYP1A1
41	GSTP1	85	ICAM1
42	AHR	86	SELE
43	GSTM1	87	VCAM1
44	SLPI	/	/

AR = allergic rhinitis, YPFP = Yu-Ping-Feng powder.

target genes were collected from Gene Cards database and OMIM database. After removing duplicate genes, a total of 1324 targets related to AR were obtained by integrating the retrieval results of each database, which included Interleukin-13, Interleukin-4 receptor, tumor necrosis factor (TNF), eosinophil peroxidase, ribonuclease A family member 3, and others. The intersections of YPFP and AR targets are shown (Table 2).

We constructed the ingredient-target network of YPFP using the screened ingredients and their targets (Fig. 1). The network consisted of 123 nodes (36 YPFP compounds and 87 target compounds) plus 309 edges, indicating the interactions between the proteins and their targets. Thirty-six candidate compounds had a median of 8°, indicating that most YPFP compounds affected several targets. Quercetin, kaempferol, and wogonin acted on 141, 56, and 42 targets, respectively. The OB of quercetin, kaempferol, and wogonin was 46.43%, 41.88%, and 30.68%, respectively. According to the positions they occupy in the network, these compounds could represent the key active YPFP compounds.

3.3. Analysis of PPI network

PPI is a major aim of system biology, as it integrates many biological processes, including metabolic regulation, cell-to-cell interactions, and developmental regulation.[30] We, therefore, constructed a PPI network to visualize the YPFP putative and AR-associated targets. The PPI network of YPFP putative targets comprised 4159 nodes and 113,210 edges, representing 4159 interacting protein, as well as 113,210 interactions, whereas that of AR-associated targets comprised 412 nodes plus 107,564 edges.

3.4. Identification of candidate targets of YPFP against AR

To expose the mechanisms underlying the anti-AR effects of YPFP, we joined the 2 PPI networks in a bid to select the candidate YPFP targets. The new network comprised 4571 nodes and 111,448 edges (Fig. 2A). Subsequently, we constructed a network of significant YPFP targets comprising 1044 nodes and 45,975 edges (Fig. 2B). The DC and BC median values were 61, and 600, respectively. We screened the candidate targets further and identified 87 targets with $DC > 61$, $BC > 600$ (Fig. 2C). Eighty-seven genes were finally identified as YPFP targets against AR.

3.5. GO and pathway enrichment analysis

In total, 321 GO terms were considerably enriched ($P < .05$), 260 in BP, 21 in cellular component, and 40 in molecular function (see Table S1–S3, Supplemental Digital Content, http://links.lww.com/MD2/A326, http://links.lww.com/MD2/A327, http://links.lww.com/MD2/A328 , which illustrate GO enrichment analysis data, including BP, cellular component, and molecular function —BP CC, BP MF, BP); Fig. 3 shows the top 20 terms. The highly enriched GO terms in the 3 GO domains were gene expression and silencing regulation, protein binding, nucleus, nucleoplasm, ubiquitin protein ligase binding, and protein binding.

According to KEGG pathway analysis, 20 overtly enriched pathways ($P < .05$) were identified, including AGE-RAGE signaling pathway in diabetic complications, TNF signaling pathway, fluid shear stress and atherosclerosis, kaposi sarcoma-associated herpesvirus infection, and PI3K-Akt signaling pathway (Fig. 4; see Table S4, Supplemental Digital Content, http://links.lww.com/MD2/A329, which illustrates data of KEGG pathway analysis).

3.6. Gene-pathway network analysis

We established the gene-pathway network according to the significantly enriched pathways and their associated genes (Fig. 5). BC was used to analyze the 20 pathways and 59 genes topologically. In the network, the squares denote target genes, whereas the V-shapes denote pathways. According to the network diagram, MAPK1 emerged as the core target gene and possessed the maximum BC. Many other genes also showed large BC, and these include RELA, AKT1, NFKBIA, IL6, and

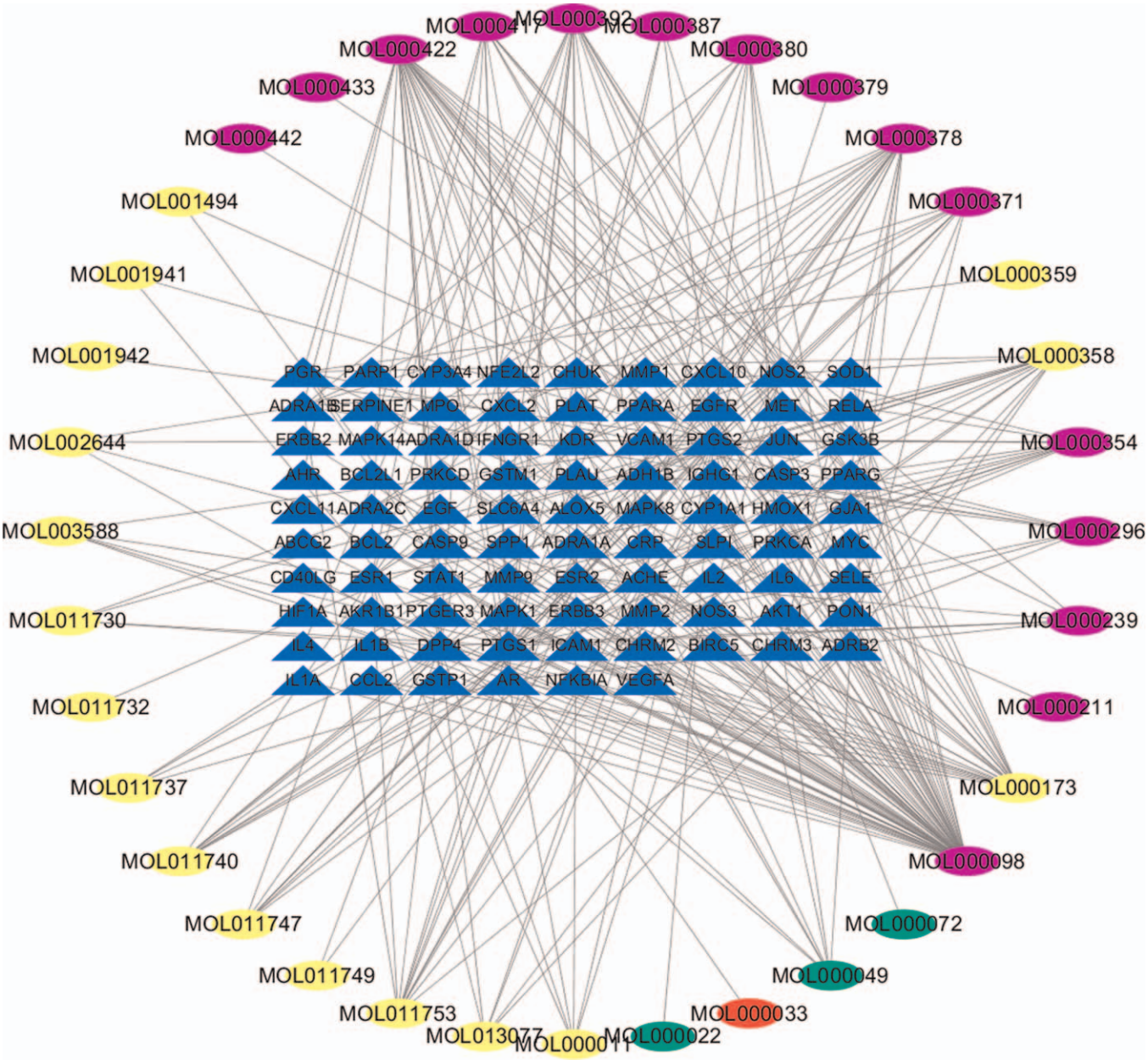

Figure 1. The Ingredient-target network of YPFP with the screened ingredients and their targets. YPFP = Yu-Ping-Feng powder.

JUN, suggesting that they could be major target genes in the anti-AR effects of YPFP.

4. Discussion

YPFP originally came from "Jian Yi Fang," widely prescribed formulations for the therapy and prevention of AR. In TCM, it is believed that AR occurs because of a deficiency and cold of lung-qi. The uniqueness of TCM theory is that it involves the use of a blend of several herbal products against a condition. The mixture is believed to work synergistically to cure the illness.[31] Notably, this is in line with the network pharmacology approach that uses various databases and software to explore the mechanisms underlying the therapeutic effects of sophisticated TCM herbal formulations. Herein, we examined the mechanisms behind the anti-AR effects of YPFP.

Firstly, we constructed a compound-target network of YPFP using 44 compounds and 724 target compounds. Based on the results, most YPFP compounds influenced several targets. For instance, wogonin, kaempferol, and quercetin impacted 45, 63, and 154 targets, respectively, and therefore, were likely the most vital pleiotropically active compounds in YPFP. Despite variations in the putative target number of each herb, there were several overlapping targets in various herbs. Thus, several YPFO compounds could have one target, and this meant that there was synergy in their effects. Wogonin is a flavonoid with several biochemical activities, which includes anti-allergic, antioxidant, anti-apoptotic, anti-inflammatory effects, and

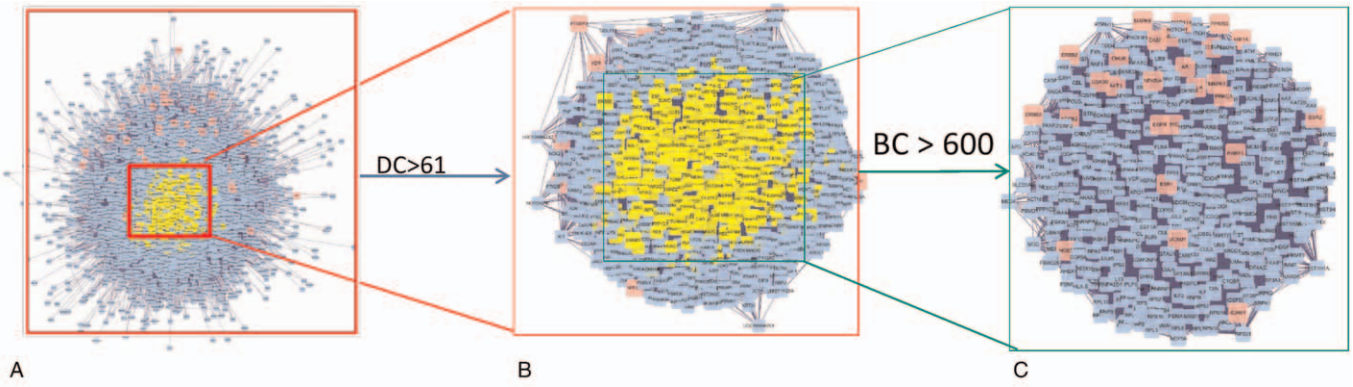

Figure 2. Identification of candidate targets of YPFP against AR. (A) The interactive PPI network of YPFP putative targets and AR-related targets. (B) PPI network of significant proteins extracted from A. (C) PPI network of candidate YPFP targets for AR treatment extracted from B. AR = allergic rhinitis, BC = betweenness centrality, DC = degree centrality, PPI = protein–protein interaction, YPFP = Yu-Ping-Feng powder.

anti-cancer properties.[32,33] Kaempferol is a polyphenol compound that regulates the immune system by modulating the immune cells, synthesis of proinflammatory cytokines, as well as gene expression. They are also involved in the inactivation of MAPK, NF-κB, and arachidonic acids pathways. Polyphenolic compounds are known to suppress phosphatidylinositide 3-kinases/protein kinase B (PI3K/AkT), as well as kappa kinase/c-Jun amino-terminal kinases (IKK/JNK).[34] Quercetin, another flavonoid, also shows anti-inflammatory, anti-proliferative, and anti-angiogenic activities, and regulatory effects on immune responses.[35] It is a common knowledge that the efficacy of TCM against various ailments depends on the synergistic effect that results from the combined action of various components. However, there is no straightforward way to identify the total effective components of TCM. Researchers have, therefore, attempted to verify the effective chemical components of TCM via a network pharmacology method. Herein, wogonin, quercetin, and kaempferol were found to modulate the majority of the targets related to AR, and all exhibited immunomodulatory properties. Even though wogonin, kaempferol, and quercetin are ubiquitous and commonly known, some studies have revealed that they possess immunomodulatory effects. In addition, they exhibit high oral bioavailability, and are extracts of 2 herbs that yield YPFP. Thus, Fangfeng (*S divaricata* (Turcz.) Schischk.) and Huangqi (*A membranaceus* (Fisch.) Bunge.) could be considered as the characteristic and active YPFP compounds.

We constructed and joined the PPI networks of YPFP putative targets and AR-associated targets to obtain the candidate YPFP targets against AR. To obtain more precise targets, we utilized 6 parameters that included DC, BC, and CC for node screening and establishment a new network. Finally, we identified 183 targets which were further analyzed using bioinformatics to explore the mechanisms behind the anti-AR effects of YPFP. The YPFP targets against AR were enriched in all 3 GO domains (i.e., BP, CC, and MF). The results indicated that YPFP modulated specific biological processes, including regulation of inflammatory response, control of apoptotic signaling pathway, cellular response to oxidative stress, and response to lipopolysaccharide. AR is characterized by mucosal inflammation as a result of an influx of basophils and eosinophils in the tissues.[36] The expression of IFN-γ was decreased, while sIgE and IL-4 expression were increased in AR patients.[37] p38MAPK signaling pathway was shown to affect olfactory mucosal function and apoptosis of olfactory sensory neurons (OSNs) in AR mice.[38] Passive smoking was found to exacerbate arterial dysfunction and oxidative stress induced by nicotinamide-adenine dinucleotide phosphate oxidase isoform 2 in children suffering from chronic AR.[39] TLR4 upregulation enhances cytokine release in the nasal tissues of AR patients triggered by lipopolysaccharide.[40] There is evidence that YPFP regulates several cellular components, such as intrinsic component of synaptic membrane, nuclear envelope, nuclear chromatin, receptor, membrane region. In the standard pathway of active immunity, the allergen is taken up by dendritic and B cells, then converted to small peptides that bind to certain class II molecules of the major histocompatibility complex, which also could stimulate B-cells to differentiate into plasma cells that produce antibodies.[41] Some immune cells such as the natural killer cells and plasmacytoid dendritic cells could be crucial in triggering the production of Th2 cytokine.[42] In innate immunity Toll-like receptors recognize foreign antigens, such as allergens, and induce immune responses that may lead to inflammation.[43] The nuclear factor-kappa B (NF-κB) actively participates in AR; the NF-κB p65 subunit resides primarily in the cytoplasm in its basal state, but translocates to the nucleus when activated, and transcriptionally induces a large number of immunological important genes. ICAM-1 is one such gene that is overtly upregulated in the nasal mucosa of patients with AR when NF-κB is activated.[44]

Collectively, our results indicate that YPFP regulates critical molecular functions, such as protein phosphatase binding, cytokine receptor binding. The Th2/Th1 paradigm and SHP-1 enzyme have been suggested to have a crucial function in controlling AR and maintaining nasal immune homeostasis. It has been found that MiR-202–5p/MATN2 were related to the differentiation of regulatory T-cells and participate in AR.[45] Circulating microRNAs indeed served as biomarkers in patients with allergic rhinitis and asthma.[46] Thus, YPFP could regulate immunological functions by suppressing these biological or pathological processes. In particular, YPFP might regulate strategic pathways in AR pathogenesis, which could impact specific BP, CC, and MF, including inflammatory response, regulation of apoptotic signaling pathway, oxidative stress,

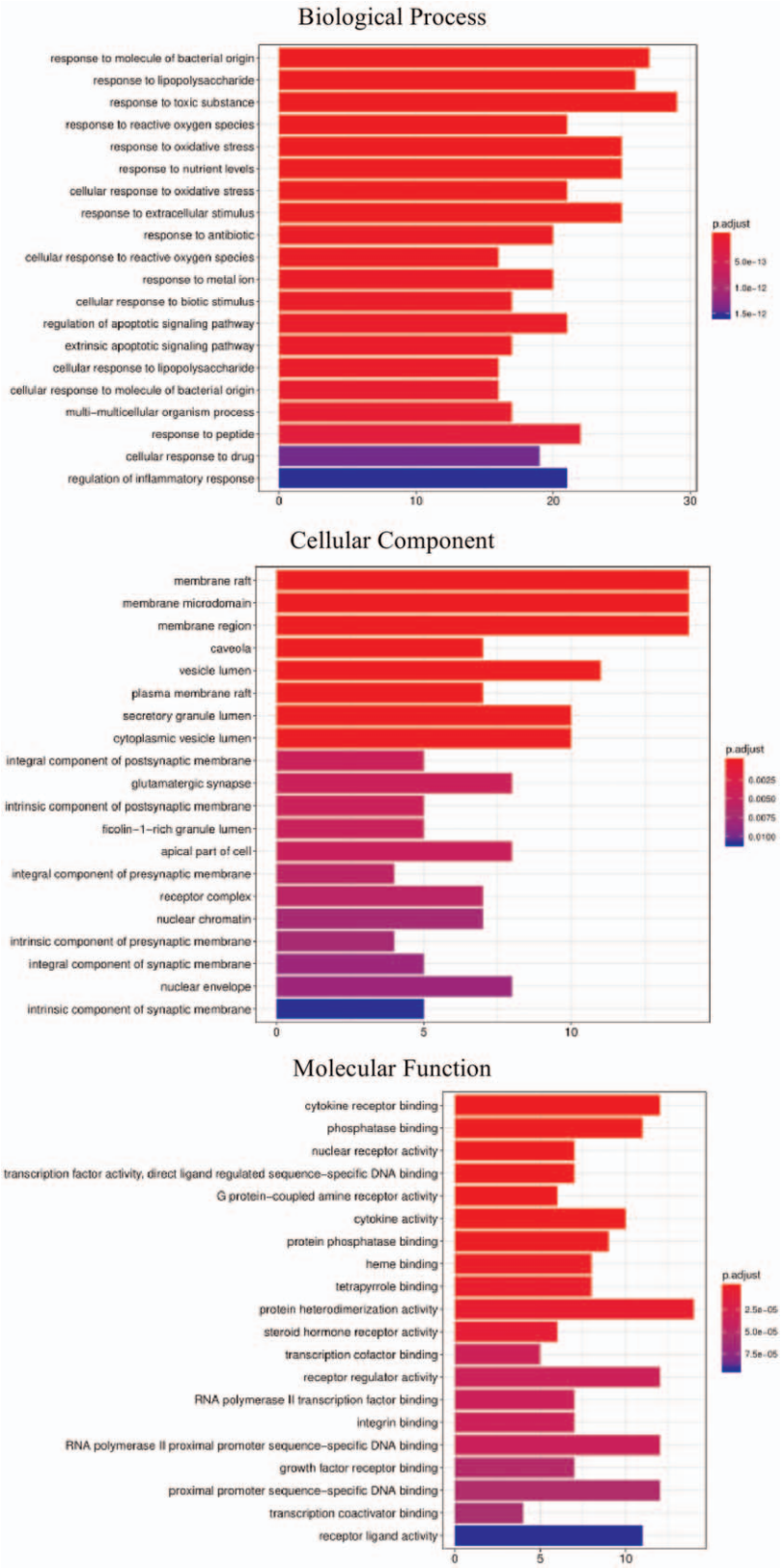

Figure 3. Gene ontology terms of candidate targets of YPFP against AR. The top 20 GO functional categories with *P* (adjust) < .05 were selected. (A) Top: biological process. (B) Middle: cellular component. (C) Bottom: molecular function. AR = allergic rhinitis, YPFP = Yu-Ping-Feng powder.

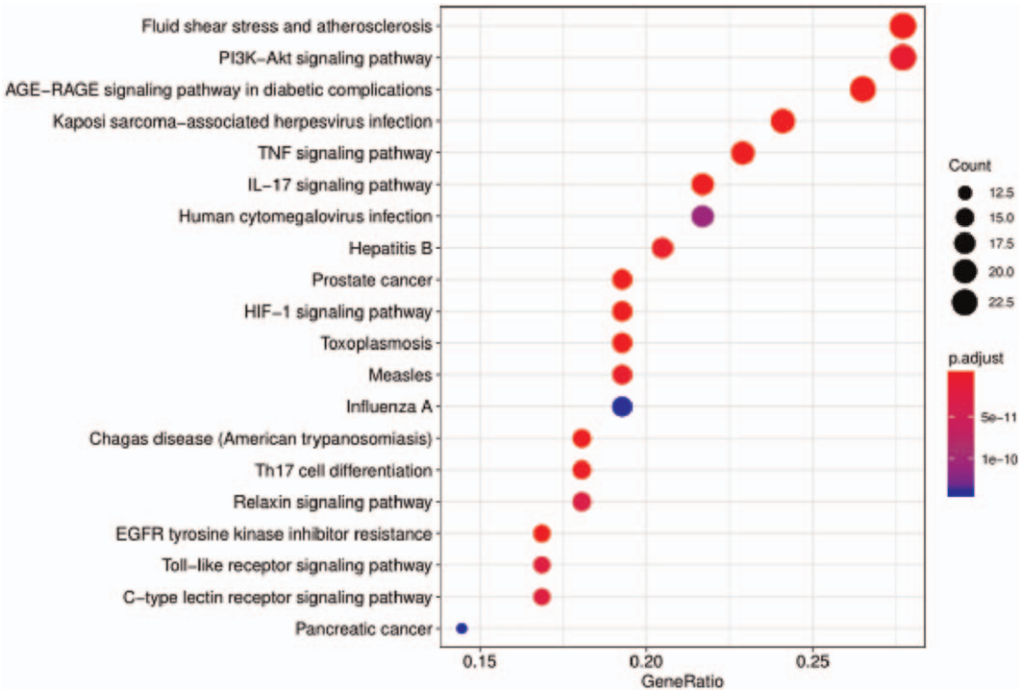

Figure 4. KEGG pathway enrichment of candidate targets of YPFP against AR. Pathways that had significant changes of *P*.adjust <.05 were identified. Size of the spot represents number of genes and color represents *P*.adjust value. AR = allergic rhinitis, KEGG = Visualization and Integrated Discovery (Cluster Profiler R package, version: 3.8.1). Kyoto Encyclopedia of Genes and Genomes, YPFP = Yu-Ping-Feng powder.

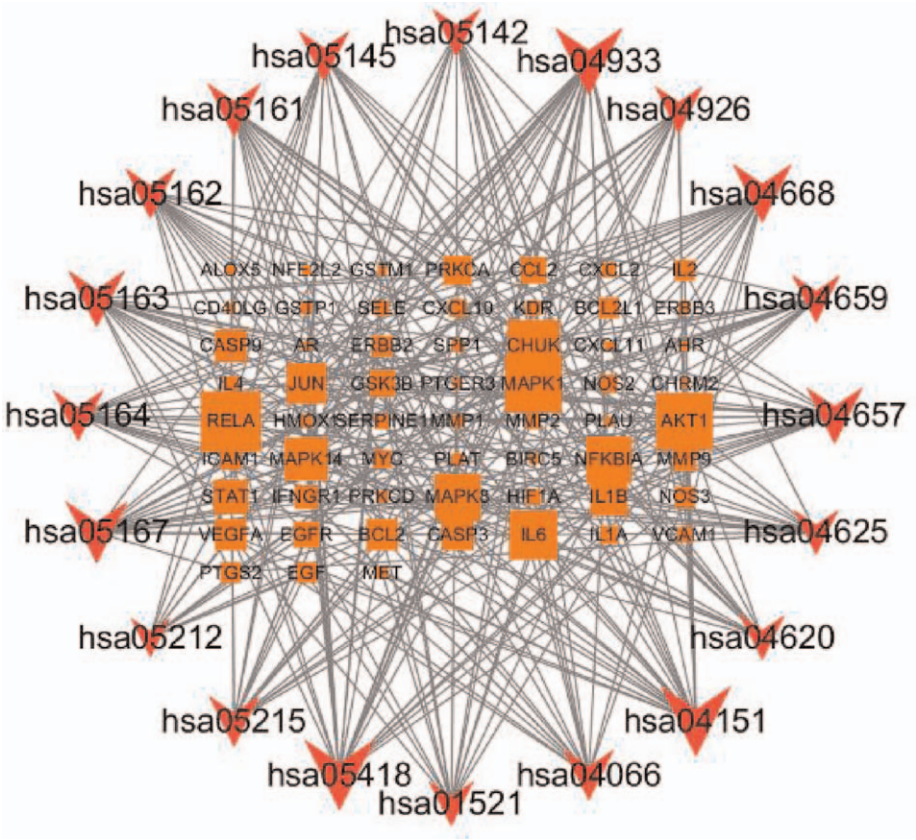

Figure 5. Gene-pathway network of YPFP against AR. The topological analysis of 20 pathways and 59 genes were carried out with betweenness centrality. The brown squares represent target genes and the red V-shapes represent pathways. Bigger size indicates larger betweenness centrality. AR = allergic rhinitis, YPFP = Yu-Ping-Feng powder.

cytosolic and nuclear processes, enzyme binding, protein binding, and DNA binding in AR therapy.

The material basis of TCM is complex. Moreover, TCM compounds exhibit features of multicomponent combination, multi-target, and long-term cumulative drug effect. As a TCM formulation, YPFP possesses similar features that can treat AR via 20 KEGG pathways, such as AGE-RAGE signaling pathway, Fluid shear stress and atherosclerosis, and PI3K-AKT signaling pathway, which were enriched remarkably. A significant body of literature reported that AGE-RAGEs were involved in neuro-vascular and endocrine pathways, focused on regeneration and repair of nerve and peripheral blood vessels.[47] In addition, AGE-RAGEs had an effect on apoptosis, cell proliferation, and oxidative stress response.[48] In diabetic nephropathy, RAGE activation could lead to the activation of different intracellular signaling pathways, such as PI3K/Akt, MAPK/ERK, and NF-κB.[49] Few studies reported AGE-RAGEs could regulate immune response, and yet, neuroimmunoendocrine regulatory networks work together to maintain homeostasis. We, therefore, speculate that AGE-RAGEs may modulate the immune system by regulating the nervous system and endocrine system, which may stimulate further investigation of the specific impact of YPFP on cells, to explore the molecular mechanisms in the treatment of AR. Fluid shear stress (FSS) is a major type of mechanical stress and can stimulate osteogenic differentiation of hPDLCs, and the ERK1/2 and p38MAPK signaling pathways were involved in this cellular process.[50] Besides, mechanical signals of FSS could regulate the function of macrophages, monocytes, and dendritic cells.[50,51] At the molecular level, FSS could activate Akt via a PI3-kinase-independent pathway and inhibit TNF-alpha-induced apoptosis in osteoblasts.[52] The PI3K-AKT signaling pathway indeed plays a key role in regulating immune response and inflammatory factors.[53] House dust mite extract induced the expression of growth factors in the nasal mucosa by activating the hif-1 PCR/PI3K/Akt pathway.[54] Studies also showed that miR-126 accelerated IgE-mediated MC degranulation associated with the PI3K/Akt signaling pathway by promoting Ca^{2+} influx.[55] Overall, YPFP may regulate immunological functions through these pathways in AR treatment. In this study, several pathways related to RelA were also significantly enriched. RelA belongs to a family of transcription factors (NF-κB complex) that play a fundamental role in inflammatory and immune responses. As mentioned earlier, activated NF-κB can promote the transcription of ICAM-1, which is related to the pathogenesis and development of AR.[56] Tonggyu-tang (TGT), a traditional Korean medicine, frequently used for treatment of patients with nasal disorder,[57] can suppress pro-inflammatory cytokine production through the suppression of MAPK and NF-κB activation in human mast cells and keratinocytes. It is composed of 12 different herbs that include 3 components of YPFP. Thus. inflammatory and immune responses may be regulated by YPFP through the aforementioned pathways. In addition, YPFP could regulate other pathways, including Kaposi sarcoma-associated herpes-virus infection, HIF-1 signaling pathway, IL-17 signaling pathway, TNF signaling pathway, Hepatitis B, and Toll-like receptor signaling pathway.

Gene-pathway network analysis suggested that MAPK1 (mitogen activated protein kinase 1) had the maximum BC and may be the key target along with the other top 5 genes (RELA, AKT1, NFKBIA, IL6, and CHUK). MAPKs in general, and MAPK1 in particular, plays a key role in the proliferation, differentiation, and production of inflammatory cells and was involved in the activation of allergic rhinitis.[57,58] RelA belongs to the family of NF-κB transcription factors noted earlier, and play a fundamental role in inflammatory and immune responses of AR.[56] NFKBIA protein was also a NF-κB p65 transcriptional target and can activate cell cycle checkpoints, promote DNA repair, downregulate apoptosis, and trigger a senescence-like growth arrested response, all of which play an important role in the network of DNA damage surveillance,[59] and interestingly, serve as a developmental marker of oocyte maturation and early embryogenesis.[53,60] Phosphorylated Akt positively regulates the function of the transcription factor NF-κB and mediates cytokine production.[61] When phosphorylation of AKT and the resultant AKT signaling is suppressed, IL-6 levels are downregulated and the allergic responses in AR is attenuated.[62] Regarding the role of IL-6, its polymorphism is associated with an increased risk of allergic rhinitis,[63,64] and IL-6 levels were increased in the exhaled breath condensates of children with AR.[64] CHUK (also known as NIK with IκB kinase α) is required for inflammatory responses. Endothelial inflammatory activation induced by synovial fluid from rheumatoid arthritis patients was significantly reduced by NIK knockdown, suggesting that NIK-mediated alternative activation of canonical NF-κB signaling is a key driver of pathological inflammation.[65]

5. Conclusion

In this study, we applied a network pharmacology method to predict the active ingredients and potential targets of YPFP for AR. To sum up, YPFP efficacy is likely manifested through its ability to regulate MAPK14, IL6, RELA, AKT1, BCL2, JUN, CASP3, CCL2, ICAM1, VCAM1, which in turn regulate AGE-RAGE, PI3K-Akt, fluid shear stress and atherosclerosis, TNF, and IL-17 signaling pathway. Collectively, all the targets and pathways could inhibit inflammation, regulate apoptosis, balance innate immunity, alleviate allergic inflammation of nasal mucosa, and finally achieve the goal of treating AR. In-depth experimental analysis of these interactions, the GO functions and KEGG pathway enrichment will certainly shed important light on the molecular mechanism underlying YPFP efficacy.

In conclusion, the pharmacological mechanism by which YPFP for treating AR was investigated with the combination of network pharmacology prediction. We demonstrated that YPFP may treat AR via the regulation of AGE-RAGE, PI3K-Akt, fluid shear stress and atherosclerosis, TNF, and IL-17 signaling pathway. But there are also some limitations in our study, there are no further experiments to verify the results. The interaction between compounds and main targets was unclear, so a molecular docking between compound and core target is needed. Therefore, these findings are expected to inform future research into AR treatments; and the network analysis method used is expected to be amenable to the study of other TCM formulas.

Author contributions

Shasha Yang, Qinwei Fu, Hua Deng performed main analysis and drafted the manuscript. Chuanhui Sun, Jing Wu, and Zhiqing Liu designed the research. Juan Zhong helped in the Introduction and Discussion sections. Qian Wang, Xiaoyu Zhu assisted in the preparation of the manuscript. All authors wrote, read, and approved the manuscript.

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Software: Shasha Yang, Juan Zhong.
Supervision: Hua Deng.
Validation: Hua Deng, Xiaoyu Zhu, Qian Wang.
Visualization: Juan Zhong.
Writing – original draft: Shasha Yang, Qinwei Fu, Hua Deng, Jing Wu.
Writing – review & editing: Shasha Yang, Hua Deng.

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