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Mechanism of Jiawei Sanzi Yangqin Decoction in the Treatment of Asthma Based on Network Pharmacology and Molecular Docking

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Abstract: *This study investigated the effectiveness of Jiawei Sanzi Yangqin Decoction (JSYD) in asthma treatment, utilizing network pharmacology and molecular docking methods. The key components of JSYD and their targets were pinpointed using the TCMSP database, while specific asthma-related targets were collated from the GeneGards and Disgenet databases. We constructed interaction networks between JSYD components and biological targets using Cytoscape 3.9.1 and the STRING database. This was followed by gene ontology and pathway analysis via Metascape. Selected targets and ingredients underwent molecular docking, were analyzed using AutoDockTools Vina, and visualized with Pymol. Our findings emphasize that the constituents of JSYD, especially kaempferol, interact with various molecules, such as IL-6, and affect key pathways, including Th17 cell differentiation. This research highlights the comprehensive potential of JSYD in asthma management and paves the way for more in-depth studies.*

Keywords: *Asthma, Jiawei Sanzi Yangqin Decoction, Network Pharmacology, Molecular Docking*

1. Introduction

Asthma is a refractory heterogeneous disease of the respiratory tract that poses a serious threat to public health, involving a variety of immune cells (e.g., eosinophils, helper T-cells, and intrinsic lymphocytes) and cellular components, and clinically manifesting itself in recurrent episodes of wheezing, coughing, shortness of breath, and chest tightness, which can be severe and life-threatening[1]. Epidemiologic survey results show that the prevalence of asthma in adults over 20 years of age in China is as high as 4.2%, the number of people with asthma has reached 45.7 million, and the prevalence of asthma is still showing a trend of sustained growth, which has brought a heavy medical, economic and psychological burden to society and patients[2]. For thousands of years, Chinese medicine has a wealth of experience in the treatment of asthma, Chinese medicine believes that asthma belongs to the category of "croup", "phlegm" as the mechanism of its disease, with the clinical characteristics of "wheezing caused by blood stasis", and the treatment should be used to "resolve phlegm and activate the blood method"[3]. Sanzi Yangqin Decoction is one of the representative expectorant formulas, commonly used in the treatment of asthma, composed of three medicines: BaiJieZi, ZiSuZi, and LaiFuZi, which has the effects of lowering qi and moving phlegm, relieving cough and asthma, and eliminating food and stagnation, and clinically, through the addition and subtraction of changes in the formula in the prevention and control of asthma has achieved significant therapeutic effects[4]; TaoRen and HongHua are one of the classic pairs of medicines to activate blood circulation and remove blood stasis. Through the principle of "resolve phlegm and activate the blood method" for the treatment of asthma, Sanzi Yangqin Decoction was combined with TaoRen and HongHua to form Jiawei Sanzi Yangqin Decoction (JSYD), which has not been reported in the literature on the mechanism of action of this formula for the treatment of asthma. Therefore, the present study adopts network pharmacology and molecular docking methods to predict the active components and disease targets of JSYD in the treatment of asthma, and to

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excavate the related mechanism of its action, in order to provide ideas for the research on the mechanism of action of the formula for the treatment of asthma.

2. Information and Methods

2.1. Collection and screening of the active ingredients and corresponding targets of JSYD

TCMSP(https://temspw.com/tcmsp.php) was used to search for the active ingredients of the drugs in JSYD: TaoRen, TongHua, BaiJieZi, ZiSuZi, and LaiFuZi, respectively, and screened for the active ingredients with pharmacokinetic profile (ADME) oral bioavailability (OB) ≥30%, drug-like properties (DL) ≥0.18, the target proteins corresponding to the screened active ingredients were transformed into target genes via UniPort (https://www. uniprot.org/), and the "active ingredient-target" visualization network was constructed on the Cytoscape 3.9.1 software platform. Visualizing networks using the Cytoscape 3.9.1 software platform.

2.2. Collection and Screening of Disease Corresponding Targets

The GeneCards database (http://www.genecards.org/) and DisGeNET database (www.disgenet.org/) were used to search for asthma-related disease targets using the keyword "asthma", and the two databases were combined to remove duplicates. The targets retrieved from the two databases were combined and duplicates were removed.

2.3. Target screening for the treatment of asthma with JSYD

The active ingredient targets of JSYD and asthma disease targets were imported into the Venny 2.1.0 (https://bioinfogp.cnb.csic.es/tools/venny/) platform, and the intersection was taken, which is the potential target of JSYD for the treatment of asthma. The intersecting targets were imported into Cytoscape 3.9.1 software, and the drug components without corresponding targets were deleted to construct a network diagram of the JSYD-Asthma targets.

2.4. Constructing protein interaction (PPI) networks

The targets obtained in 2.3 for the treatment of asthma by JSYD were imported into the STRING database (https://www.string-db.org/), the species parameter was set to "Homo sapiens", the minimum required interaction score was set to high confidence (0.700), and the protein interaction PPI network was constructed, followed by exporting the protein interaction results in STV format, and then pour the results into Cytoscape 3.9.1 software for PPI visualization.

2.5. GO functional enrichment and KEGG pathway enrichment analysis

The proteins with interactions exported from the STRING database were imported into the Metascape (http://metascape.org/gp/index.html) platform, and the species parameter was set to human (H. sapiens) with the significance of $P<0.01$, and GO and KEGG analyses were carried out, respectively, in which the GO analysis included 3 aspects of biological process (BP), cellular component (CC), and molecular function (MF), and part of the data were visualized by bar charts and bubble charts.

2.6. Molecular docking

The key targets with the top 8 degree values in the PPI network were screened as receptor proteins, and the 3D structures of the screened receptor proteins were downloaded from the PDB database (http://www.rcsb.org/); the active ingredients with the top 8 degree values in the "JSYD - Asthma Target Network" were selected as ligand small molecules, and the MOL2 files of the screened ligand small molecules were downloaded from TCMSP. The 3D structure of the receptor protein was hydrogenated and dehydrogenated using PyMOL software, and molecular docking of the receptor protein and ligand small molecules was carried out using AutoDock Vina software, and the corresponding binding energies were recorded, and some of the results of the docking were visualized using PyMol.

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3. Results

3.1. The active ingredients and corresponding targets of JSYD

Using the TCMSP database platform, with the oral utilization OB set at greater than or equal to 30% and the drug-like property DL greater than or equal to 0.18, the five traditional Chinese medicines in JSYD were screened, and a total of 61 active ingredients were obtained in the formula, of which 22 were TaoRen, 17 were HongHua, 3 were LaiFuZi, 3 were BaiJieZi and 11 were ZiSuZi, and there was one ingredient common to TaoRen, HongHua and ZiSuZi, and four ingredients common to HongHua and ZiSuZi, the results are shown in Table 1. The active ingredients and targets corresponding to each traditional Chinese medicine were imported into Cytoscape 3.9.1 software, and the "active ingredient-target" network was constructed, as shown in Figure 1, which contained 183 drug targets, 233 nodes and 505 edges.

Table 1: Information on the active ingredients of JSYD.

Molecule Number	Compound Name	OB (%)	DL	Source
MOL001323	Sitosterol alpha1	43.28	0.78	TaoRen
MOL001328	2,3-didehydro GA70	63.29	0.5	TaoRen
MOL001329	2,3-didehydro GA77	88.08	0.53	TaoRen
MOL001339	GA119	76.36	0.49	TaoRen
MOL001340	GA120	84.85	0.45	TaoRen
MOL001342	GA121-isolactone	72.7	0.54	TaoRen
MOL001343	GA122	64.79	0.5	TaoRen
MOL001344	GA122-isolactone	88.11	0.54	TaoRen
MOL001348	gibberellin 17	94.64	0.49	TaoRen
MOL001349	4a-formyl-7alpha-hydroxy-1-methyl-8-methylidene-4aalpha,4bbeta-gibbane-1alpha,10beta-dicarboxylic acid	88.6	0.46	TaoRen
MOL001350	GA30	61.72	0.54	TaoRen
MOL001351	Gibberellin A44	101.61	0.54	TaoRen
MOL001352	GA54	64.21	0.53	TaoRen
MOL001353	GA60	93.17	0.53	TaoRen
MOL001355	GA63	65.54	0.54	TaoRen
MOL001358	gibberellin 7	73.8	0.5	TaoRen
MOL001360	GA77	87.89	0.53	TaoRen
MOL001361	GA87	68.85	0.57	TaoRen
MOL001368	3-O-p-coumaroylquinic acid	37.63	0.29	TaoRen
MOL001371	Populoside_qt	108.89	0.2	TaoRen
MOL000296	hederagenin	36.91	0.75	TaoRen
MOL000493	campesterol	37.58	0.71	TaoRen
MOL001771	poriferast-5-en-3beta-ol	36.91	0.75	HongHua
MOL002680	Flavoxanthin	60.41	0.56	HongHua
MOL002694	4-[(E)-4-(3,5-dimethoxy-4-oxo-1-cyclohexa-2,5-dienylidene)but-2-enylidene]-2,6-dimethoxycyclohexa-2,5-dien-1-one	48.47	0.36	HongHua
MOL002695	lignan	43.32	0.65	HongHua
MOL002698	lupeol-palmitate	33.98	0.32	HongHua
MOL002706	Phytoene	39.56	0.5	HongHua
MOL002707	phytofluene	43.18	0.5	HongHua
MOL002710	Pyrethrin II	48.36	0.35	HongHua
MOL002712	6-Hydroxykaempferol	62.13	0.27	HongHua
MOL002714	baicalein	33.52	0.21	HongHua
MOL002717	qt_carthamone	51.03	0.2	HongHua
MOL002719	6-Hydroxynaringenin	33.23	0.24	HongHua
MOL002721	quercetagetin	45.01	0.31	HongHua
MOL002757	7,8-dimethyl-1H-pyrimido[5,6-g]quinoxaline-2,4-dione	45.75	0.19	HongHua

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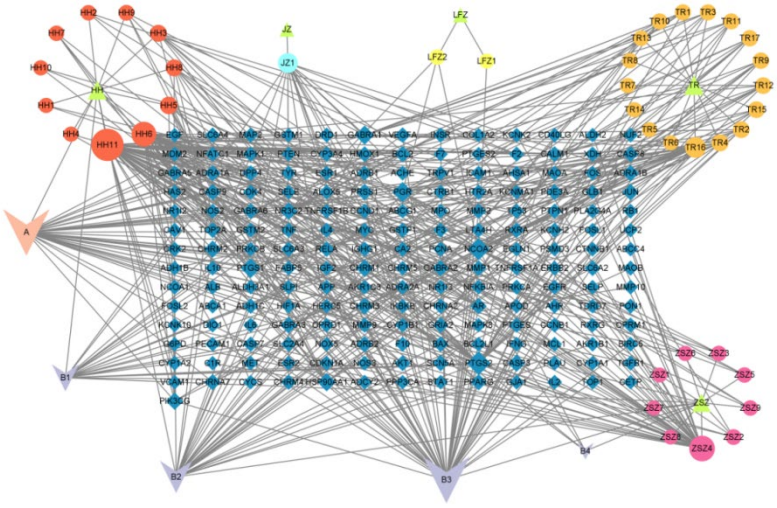
MOL002776	Baicalin	40.12	0.75	HongHua
MOL000422	kaempferol	41.88	0.24	HongHua
MOL000098	quercetin	46.43	0.28	HongHua
MOL010672	icosa-8,11,14-trienoic acid methyl ester	44.81	0.23	LaiFuZi
MOL000359	sitosterol	36.91	0.75	LaiFuZi
MOL003975	icosa-11,14,17-trienoic acid methyl ester	44.81	0.23	LaiFuZi
MOL010690	Uniflex BYO	30.13	0.25	BaiJieZi
MOL013037	2-(2-phenylethyl)-6-[[(5S,6R,7R,8S)-5,6,7-trihydroxy-4-keto-2-(2-phenylethyl)-5,6,7,8-tetrahydrochromen-8-yl]oxy]chromone	31.31	0.61	BaiJieZi
MOL001697	Sinoacutine	63.39	0.53	BaiJieZi
MOL012888	citrostadienol	43.28	0.79	ZiSuZi
MOL012891	(2E,4E,6E)-icosa-2,4,6-trienoic acid	41.64	0.2	ZiSuZi
MOL012893	(E)-(4-methylbenzylidene)-(4-phenyltriazol-1-yl)amine	57.87	0.19	ZiSuZi
MOL001439	arachidonic acid	45.57	0.2	ZiSuZi
MOL004355	Spinasterol	42.98	0.76	ZiSuZi
MOL005030	gondoic acid	30.7	0.2	ZiSuZi
MOL005043	campest-5-en-3beta-ol	37.58	0.71	ZiSuZi
MOL005481	2,6,10,14,18-pentamethylicosa-2,6,10,14,18-pentaene	33.4	0.24	ZiSuZi
MOL007449	24-methylidenelophenol	44.19	0.75	ZiSuZi
MOL009653	Cycloeucalenol	39.73	0.79	ZiSuZi
MOL009681	Obtusifoliol	42.55	0.76	ZiSuZi
MOL000358	beta-sitosterol	36.91	0.75	HongHuaTaoRenZiSuZi
MOL002773	beta-carotene	37.18	0.58	HongHuaZiSuZi
MOL000449	Stigmasterol	43.83	0.76	HongHuaZiSuZi
MOL000006	luteolin	36.16	0.25	HongHuaZiSuZi
MOL000953	CLR	37.87	0.68	HongHuaZiSuZi



Note: TR: TaoRen; HH: HongHua; LFZ: LaiFuZi; JZ: BaiJieZi; ZSZ: ZiSuZi; A: common ingredient of HongHua, TaoRen and ZiSuZi; B: common ingredient of HongHua and ZiSuZi.

Figure 1: Active ingredient-target network of JSYD.

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3.2. Targets related to the treatment of asthma with JSYD

By searching GeneCards and DisGeNET databases with "asthma" as the keyword, 750 disease targets were obtained by merging the retrieved data and removing duplicates. Using Venny 2.1.0, the targets corresponding to the active ingredients of JSYD were merged with the asthma-related targets, and a total of 73 intersecting targets were obtained, which are the potential targets for the treatment of asthma by JSYD, as shown in Figure 2. The active ingredients of JSYD and the 73 intersecting targets were imported into Cytoscape 3.9.1 software, and the drug ingredients without corresponding targets were deleted to construct a network of JSYD-asthma targets, as shown in Figure 3, in which the ingredients with the first 8 degrees of degree value were kaempferol, luteolin, beta-sitosterol, baicalein, arachidonic acid, beta-carotene, Stigmasterol, 6-Hydroxykaempferol.

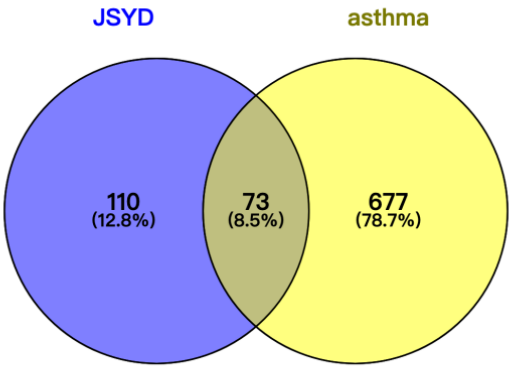
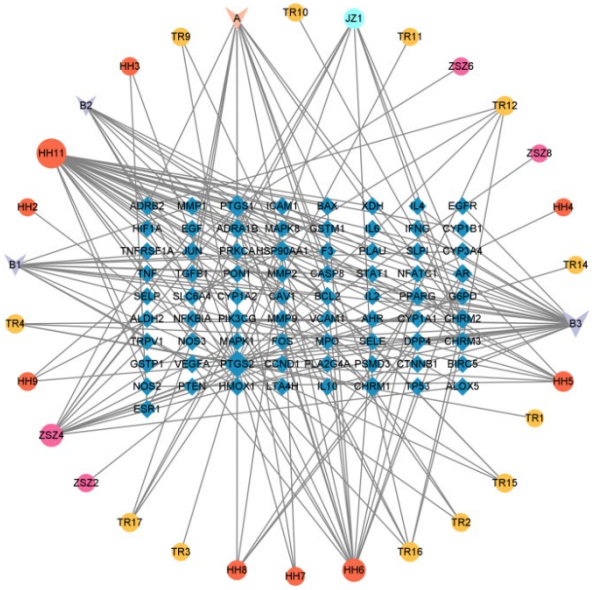


Figure 2: Venn diagram of the common target points of JSYD and Asthma.



Note: TR: TaoRen; HH: HongHua; LFZ: LaiFuZi; JZ: BaiJieZi; ZSZ: ZiSuZi; A: common ingredient of HongHua, TaoRen and ZiSuZi; B: common ingredient of HongHua and ZiSuZi.

Figure 3: JSYD-Asthma targets network.

3.3. PPI network analysis

The 73 potential targets of JSYD for asthma treatment in 3.2 were imported into the STRING database for protein interactions analysis, and the protein interactions data in TSV format were downloaded, and the TSV file was imported into Cytoscape 3.9.1 software to construct the PPI network, as shown in Figure

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4, and the degree value is calculated. The greater the degree value of the target indicates the greater the correlation between the target and other proteins.The top 8 core targets with the highest degree values were screened, which were IL-6, TNF, TP53, EGFR, JUN, MMP9, prostaglandin oxidative cyclase 2 (PTGS2) and IL-10.

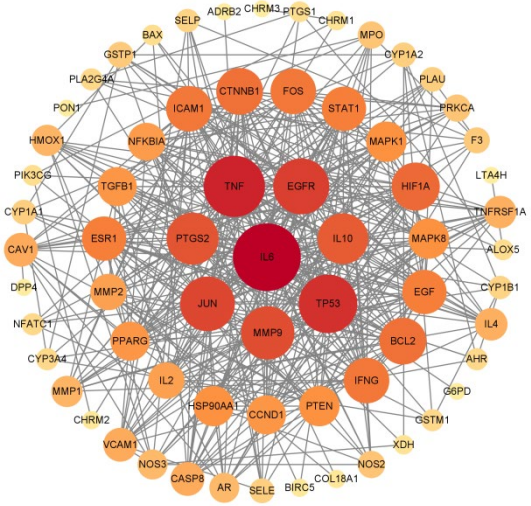

Figure 4: PPI network.

3.4. GO analysis and KEGG pathway enrichment analysis

By importing the screened proteins with interactions into the Metascape platform for analysis, a total of 1,413 GO biological entries were obtained, of which 1,237 were BP, 61 were CC, 115 were MF, and the top 10 entries were selected to draw a bar chart, as shown in Figure 5. The results of the KEGG enrichment analysis included a total of 179 entries, which were ranked according to the count value from the largest to the smallest, and the top 20 entries with count value were selected to draw a bubble chart to show the enrichment situation, as shown in Figure 6, in which the pathways involved in asthma mainly include Th17 cell differentiation pathway, TNF signaling pathway, IL-17 signaling pathway, T cell receptor signaling pathway, Th1 and Th2 cell differentiation pathway, etc.

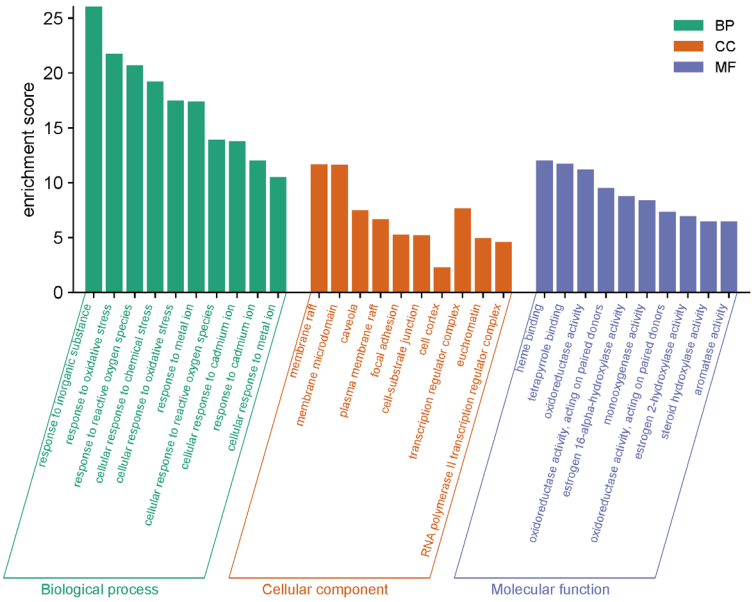

Figure 5: Histogram of GO function enrichment analysis

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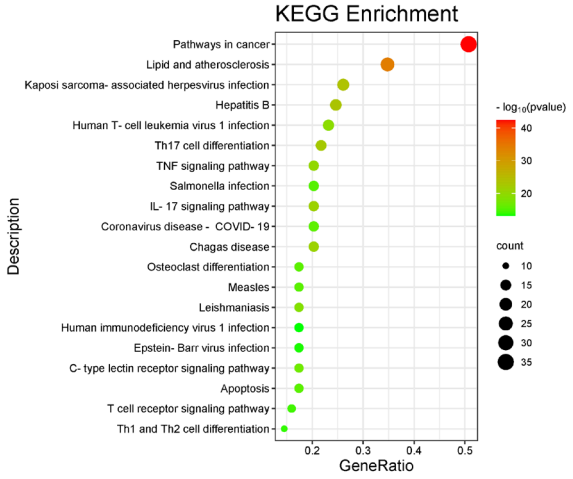


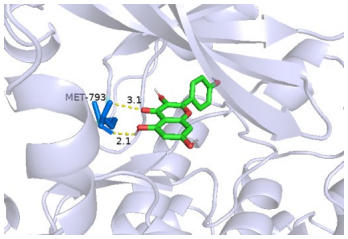
Figure 6: Bubble map for KEGG pathway enrichment analysis.

3.5. Docking results of core active ingredients with key protein molecules

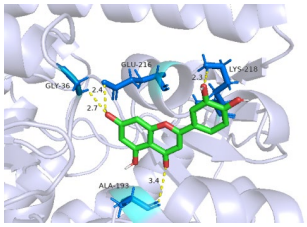
The core components with the top 8 degree values in 3.2 and the key proteins with the top 8 degree values of PPI interaction analysis in 3.3 were molecularly docked by AutoDock Vina software to verify the binding activities of the active components with the target proteins. The docking results are shown in Table 2, and the binding energies of each active ingredient with the target proteins were less than -5.0 kcal/mol, suggesting a good binding activity, and some of the docked conformations that produced hydrogen bonds were visualized as shown in Figure 7.

Table 2 Binding energies of the key active ingredients of JSYD with core targets

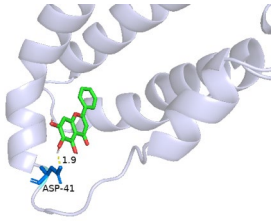
Targets / Components	IL-6	TNF	TP53	EGFR	JUN	MMP9	PTGS2	IL-10
kaempferol	-6.6	-6.8	-7.6	-8.3	-6.3	-9.9	-9.6	-6.7
luteolin	-7.5	-7.2	-7.5	-8.6	-6.4	-10.8	-9.3	-6.8
beta-sitosterol	-7	-7.4	-8.0	-9.6	-6.9	-8.6	-7.9	-8.7
baicalein	-7.5	-7.2	-7.6	-8.3	-6.4	-10	-9.3	-6.8
arachidonic acid	-5.4	-5.3	-5.1	-6.7	-5.2	-7.5	-5.9	-5.6
beta-carotene	-6.8	-7.3	-8.4	-8.6	-7	-9.4	-9.7	-10
Stigmasterol	-7.5	-6.5	-6.6	-8.9	-6.1	-8.9	-7.7	-7.5
6-Hydroxykaempferol	-6.7	-6.3	-7.5	-7.9	-5.8	-9.6	-8.1	-6.2



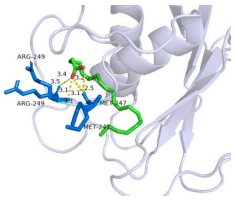
EGFR and Kaempferol



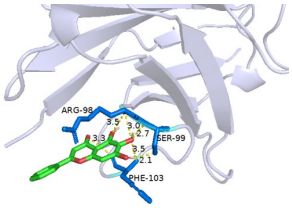
IL-6 and luteolin



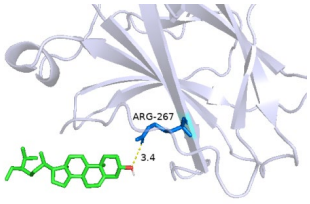
IL-10 and baicalein



MMP9 and arachidonic acid



TNF and baicalein



TP53 and beta-sitosterol

Figure 7: Molecular docking diagram.

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4. Discussion

Asthma belongs to the Chinese medicine "croup" category. Synopsis of the Golden Chamber - phlegm and cough disease article" pointed out that "the diaphragm on the disease phlegm, full of asthma, cough and vomit, hair is cold and hot, back pain and lumbago …… There must be ambrosia". Generations of medical doctors believe that "phlegm" is asthma recurrent attacks of the "long-standing root". In addition, Chinese medicine believes that the onset of asthma is also closely related to "blood stasis"[5,6]. Asthma patients often have shortness of breath and wheezing, limb cyanosis, cyanosis of the lips, facial blood vessels, tongue reddish-red or dark purple and other phlegm stasis and gas obstruction. As early as in the "Nei Jing" has been "wheezing from the stasis" of the discussion. Tang Rongchuan in the "blood evidence theory - blood stasis chapter" clearly pointed out that "blood stasis multiplied by the lung, coughing and wheezing", "internal blood stasis, airway obstruction, can not lift and wheeze". Therefore, "resolve phlegm and activate the blood method" is an important principle in the treatment of asthma in Chinese medicine[7,8]. JSYD is composed of the classic expectorant Sanzi Yangqin Decoction and the classic medicine pair of TaoRen and HongHua for removing blood stasis. Among them, Sanzi Yangqin Decoction consists of three medicines, namely, BaiJieZi, LaiFuZi, and ZiSuZi, in which white mustard seed warms the lungs and removes phlegm, and disperses qi and knots; perilla seed lowers qi and removes phlegm, stops coughing and calms wheezing; and lycopodium seed eliminates food and induces stagnation and lowers qi to dispel phlegm. The main effects of TaoRen are to activate blood circulation and remove blood stasis, laxative, relieving cough and asthma, and modern research has shown that it has the functions of anti-inflammatory, anti-allergy, and improving the immunity of the body[9]; The main effect of HongHua is to promote blood circulation and menstruation, dissipate blood stasis and relieve pain, and modern research has shown that it has a vasodilating and anti-inflammatory effect[10]. Therefore, in this study, based on the treatment principle of "resolve phlegm and activate the blood method" in Chinese medicine for asthma, we formed the JSYD, and investigated the potential targets and mechanisms of its action by using network pharmacology and molecular docking technology.

The results of network pharmacology showed that the main active ingredients of JSYD for asthma treatment are kaempferol, luteolin, beta-sitosterol, baicalein, and so on. Studies have shown that these components have important therapeutic roles in the development of asthma. Kaempferol binds NOX4 to exert therapeutic effects in allergic asthma[11]. luteolin inhibit autophagy in allergic asthma through activation of the PI3K/Akt/mTOR signaling pathway and inhibition of the Beclin-1-PI3KC3 complex[12]. beta-sitosterol is a common active ingredient in safflower, perilla seed and peach kernel, which can reduce inflammatory factors such as IL-6 and IL-13 in asthmatic rats, thereby inhibiting the development of asthma[13]. Baicalein can attenuate ova-induced allergic airway inflammation in mice by inhibiting the NF-κB signaling pathway thereby[14]. Therefore, JSYD may work together to achieve the effect of asthma suppression through different components in the treatment of asthma. In addition, this study obtained 750 asthma-associated targets by searching for disease targets in asthma, indicating that asthma development is influenced by multiple targets, suggesting the complexity of the mechanism of asthma. PPI interactions analysis of the relevant targets of action in this study revealed that the top 8 core targets ranked in the treatment of asthma by JSYD were IL-6, TNF, TP53, EGFR, JUN, MMP9, PTGS2, and IL-10. Among them, IL-6, which has the largest percentage of protein interactions in this study, is a common pro-inflammatory factor in the organism and one of the important factors in the immunological mechanism of asthma, which is mainly secreted by macrophages, dendritic cells, and Th2 and other cells[15]. Clinical trials have reported that the serum and sputum levels of IL-6 in asthma patients are significantly higher than those in normal subjects[16]. Through the pathway enrichment analysis of the targets with relevant effects, we obtained that the signaling pathways for the treatment of asthma by JSYD were mainly enriched in the Th17 cell differentiation pathway, the TNF signaling pathway, the IL-17 signaling pathway, the T-cell receptor signaling pathway, and the Th1 and Th2 cell differentiation pathways, which are the signaling pathways commonly used to study the pathogenesis of asthma[17-19]. It can be seen that the active ingredients related to the treatment of asthma by JSYD may be through multiple pathways and multiple targets to co-regulate each signaling pathway.

By molecularly docking the screened key active ingredients with the core targets, the results showed that the binding energies of each ingredient with the targets were less than -5.0 kcal/mol, indicating that they were able to bind stably[20], suggesting that JSYD was able to target-bind the relevant disease targets, thus exerting therapeutic effects.

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5. Conclusions

In summary, this study initially elucidated the potential active ingredients, core targets and main pathways of JSYD for the treatment of asthma by means of network pharmacology, and verified the key active ingredients and core targets using molecular docking technology on the sub-basis. The results showed that the treatment of asthma by JSYD works through multiple targets and pathways, which provides the basis and direction for further experimental research.

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