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Exploring the mechanism of Xiaoqinglong decoction in the treatment of infantile asthma based on network pharmacology and molecular docking

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Abstract

To explore the mechanism of Xiaoqinglong decoction (XQLD) in the treatment of infantile asthma (IA) based on network pharmacology and molecular docking. The active ingredients of fdrugs in XQLD were retrieved from Traditional Chinese Medicine Systems Pharmacology database and then the targets of drug ingredients were screened. The disease targets of IA were obtained from OMIM and Gencards databases, and the intersection targets of XQLD in the treatment of IA were obtained by Venny 2.1 mapping of ingredient targets and disease targets. Cytoscape software was used to construct active ingredient-intersection target network. The potential targets of XQLD in the treatment of IA were analyzed by protein-protein interaction network using STRING platform, and the Gene Ontology function and Kyoto Encyclopedia of Genes and Genomes enrichment analysis were obtained by R Studio software. AutoDock was used to perform molecular docking for verification. In this study, 150 active ingredients of XQLD were obtained, including quercetin, kaempferol, β-sitosterol, luteolin, stigmasterol, and so on. And 92 intersection targets of drugs and diseases were obtained, including interleukin 6 (IL6), cystatin 3, estrogen receptor 1, hypoxia inducible factor 1A, HSP90AA1, epidermal growth factor receptor and so on. There were 127 items of Gene Ontology enrichment analysis and 125 Kyoto Encyclopedia of Genes and Genomes enrichment results, showing that apoptosis, IL-17 signaling pathway, tumor necrosis factor signaling pathway, P13K-Akt signaling pathway and other pathways may play a key role in the treatment of IA by XQLD. The results of molecular docking showed that the key active ingredients including quercetin, kaempferol, β-sitosterol, luteolin, stigmasterol, and the core targets including IL6, cystatin 3, estrogen receptor 1, hypoxia inducible factor 1A, HSP90AA1, and epidermal growth factor receptor had good binding activity. Through network pharmacology and molecular docking, the potential targets and modern biological mechanisms of XQLD in the treatment of IA were preliminarily revealed in the study, which will provide reference for subsequent animal experiments and clinical trials.

Abbreviations: CASP3 = cystatin 3, DL = drug-likeness, EGFR = epidermal growth factor receptor, ESR1 = estrogen receptor 1, GO = Gene Ontology, HIF1A = hypoxia inducible factor 1A, IA = infantile asthma, IL = interleukin, KEGG = Kyoto Encyclopedia of Genes and Genomes, OB = oral bioavailability, PPI = protein-protein interaction, TCMSP = Traditional Chinese Medicine Systems Pharmacology, Th2 = T helper cell type 2, TNF = tumor necrosis factor, XQLD = Xiaoqinglong decoction.

Keywords: infantile asthma (IA), molecular docking, network pharmacology, Xiaoqinglong decoction (XQLD)

1. Introduction

Infantile asthma (IA) is a lung disease with recurrent wheezing and coughing in childhood, which can cause wheezing, shortness of breath, and prolonged breathing during acute flare-ups, and in severe cases can lead to dyspnea and inability to lie down, although it could be relieved by itself or improved after treatment.[1] According to the relevant epidemiological studies, the number of asthma patients in the world has exceeded 300 million, while the number in China has exceeded 30 million,[2] among which the prevalence rate of children has increased from 1.09% in 1990 to 3.02% in 2010, showing a rapid growth trend. At present, the main clinical drug treatments for the acute stage of the IA are hormones and bronchodilators, etc, but

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The datasets generated during and/or analyzed during the current study are publicly available.

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the therapeutic effect is not ideal due to poor compliance and heavy economic burden, and long-term use of hormones is not conducive to the healthy growth and development of children. Therefore, the combination of traditional Chinese medicine in the treatment of IA can effectively solve the shortcomings of Western medical routine therapy.

IA belongs to the category of wheezing syndrome and asthma syndrome in traditional Chinese medicine. Traditional Chinese medicine is effective in the treatment of asthma, among which Xiaoqinglong decoction (XQLD) is particularly effective. Asthma was first defined in *Danxi's Mastery of Medicine*,[3] and XQLD was first recorded in Zhongjing Zhang's *Treatise on Cold Pathogenic and Miscellaneous Diseases*. In XQLD, Mahuang and Guizhi can relieve exterior syndrome as well as dispel cold, and Mahuang can profoundly relieve asthma; Ganjiang and Banxia can dispel cold and resolve phlegm; Wuweizi and Baishao are to collect yin and promoting fluid; all herbs are used together to warm the lung and dissipate cold, resolve phlegm and settle asthma. That's the reason why XQLD is widely used in the Chinese population for the treatment of cold asthma. In clinical application and randomized clinical trials,[4–6] XQLD has been proved to be effective in the treatment of asthma. In order to further explore the mechanism of XQLD in the treatment of IA, this study analyzed its mechanism through network pharmacology and molecular docking. And the corresponding workflow was shown in Figure 1.

2. Materials and methods

2.1. Screening of active ingredients and targets of XQLD

Ganjiang (*Zingiberis Rhizoma*), Guizhi (*Cinnamomi Ramulus*), Mahuang (*Ephedrae Herba*), Baishao (*Paeoniae Radix Alba*), Gancao (*Licorice*), Xixin (*Asari Radix Et Rhizoma*), Banxia (*Arum Ternatum Thunb*), and Wuweizi (*Schisandrae Chinensis Fructus*) were searched from Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP, https://tcmsp-e.com/tcmsp.php). TCMSP database incorporates key absorption, distribution, metabolism, and excretion-related properties such as human oral bioavailability (OB), drug-likeness (DL) and so on, which can be used for active compound screening. The active ingredients of XQLD were screened according to the absorption, distribution, metabolism, and excretion screening criteria with OB ≥ 30% and DL ≥ 0.18, and the corresponding predicted protein targets of the active ingredients were collected.

2.2. Acquisition of intersection targets for XQLD treating IA

The keyword "Infantile Asthma" was searched in OMIM (http://www.omim.org/) database and Gencards (https://www.genecards.org/) database respectively, and the disease targets of IA were obtained after deleting repetitive genes. The intersection targets of XQLD in the treatment of IA was obtained by merging the ingredient targets of XQLD and the disease targets of IA by Venny 2.1 (https://bioinfogp.cnb.csic.es/tools/venny/).

2.3. Construction of active ingredient-intersection target network

By using Cytoscape 3.7.2 software, the active ingredients and intersection targets of XQLD in the treatment of IA were collected, and the active ingredient-intersection target network was constructed. The nodes represent the active ingredients or intersection targets, and the edges represent the interaction between the active ingredients and the intersection targets.

2.4. Construction of protein-protein interaction (PPI) network

STRING online platform (https://string-db.org) was used to construct PPI network of XQLD in the treatment of IA, and the PPI network was obtained to directly reflect the interaction between proteins. The interaction genes obtained from PPI network were introduced into Cytoscape 3.7.2 for topological analysis, and the proteins that played an important role in the network were screened out.

2.5. Gene Ontology (GO) function and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis

The potential target set of XQLD for the treatment of IA was imported into DAVID database for GO analysis and KEGG pathway enrichment analysis, which were carried out visually by R Studio software.

2.6. Molecular docking

The key ingredients and core targets of XQLD in the treatment of IA were verified by molecular docking. The mol2 format files of the key ingredients of XQLD were downloaded in the TCMSP database, and the pdb format files of the core targets were downloaded in the RSCB PDB (http://www.rcsb.org/) database. The force field used to minimize the ligand energy is MMFF94, and the Chem3D is used to minimize the ligand energy of small molecules. The macromolecules were dehydrated, the ligand was removed and hydrogenated by PyMOL 2.4, and then the non-polar hydrogen was combined with AutoDock 1.5.6, and the macromolecular charge was calculated and converted into pdbqt format. Because the binding sites between proteins and small molecules were unknown in this study, we used blind docking. The binding pocket coordinates is generated with the protoligand of crystal structure as the center, and the input configuration file set as size_x = 126, size_y = 126, size_z = 126. Finally, the key ingredients and core targets will be docked with Autodock, and the docking parameters are set to genetic algorithm. Dexamethasone is currently recognized as one of the drugs for the treatment of asthma. We will dock dexamethasone and core targets in the same way for further verification. The docking result will be visualized through PyMOL 2.4.

3. Results

3.1. The active ingredients and corresponding targets of XQLD

According to the standard of OB ≥ 30%, DL ≥ 0.18 to screen in TCMSP database, there were 5 active ingredients in *Zingiberis Rhizoma*, 7 in *Cinnamomi Ramulus*, 23 in *Ephedra Herba*, 13 in *Paeoniae Radix Alba*, 92 in *licorice*, 8 in *Asari Radix Et Rhizoma*, 13 in *Arum Ternatum Thunb*, and 8 in *Schisandrae Chinensis Fructus*. After deduplicating, there were 150 active ingredients in total, Supplemental Digital Content 1, http://links.lww.com/MD/1333.

3.2. Disease target genes and intersection target genes

After searching the OMIM and Gencards databases with "Infantile Asthma" as the keyword, a total of 2241 disease target genes were obtained after merging and deduplicating. By mapping the intersection targets of the active ingredients of XQLD with the disease target genes of IA, 92 intersection targets were obtained (Fig. 2), Supplemental Digital Content 2, http://links.lww.com/MD/1334

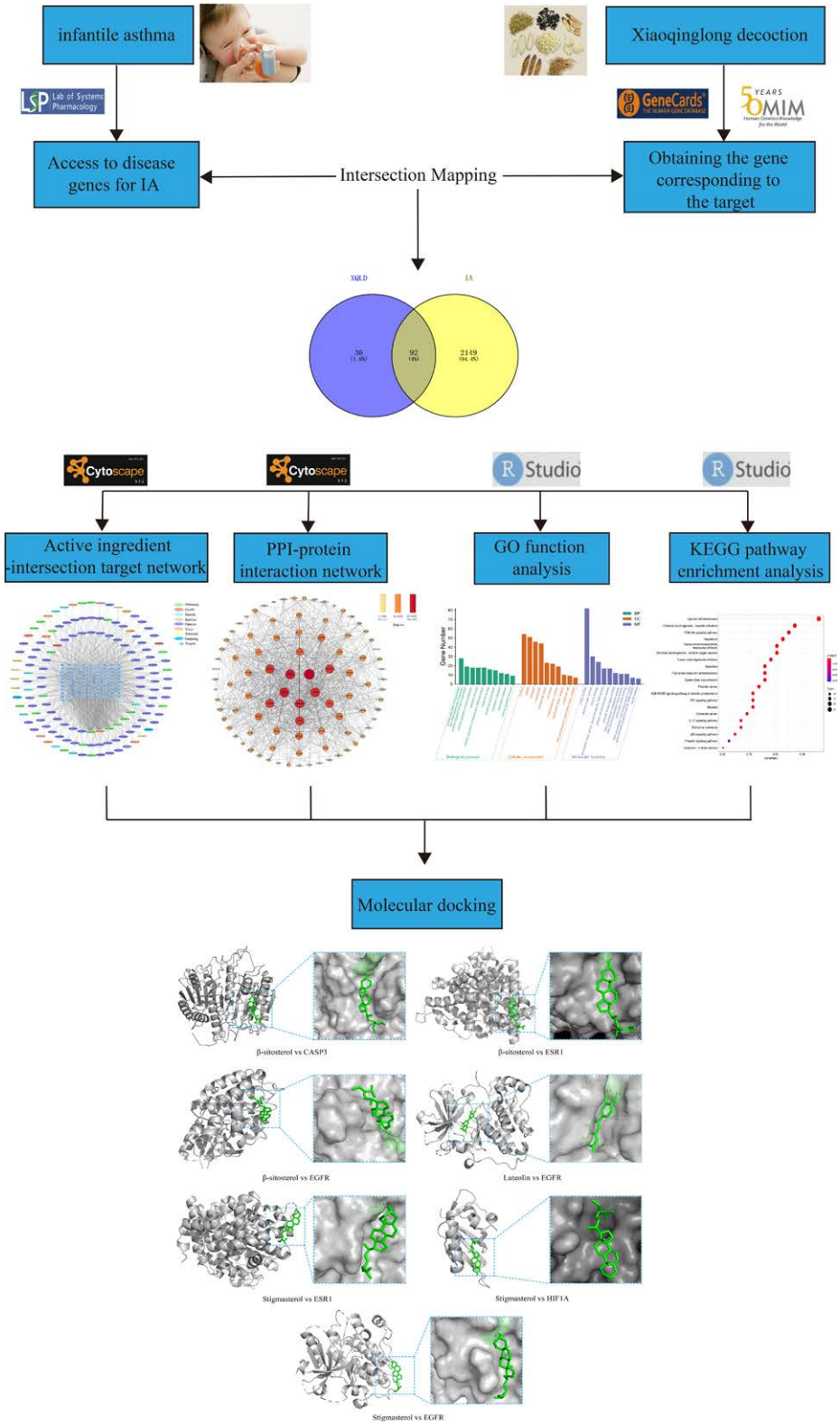

Figure 1. Workflow of network pharmacology and molecular docking.

3.3. Active ingredient-intersection target network

The active ingredient-intersection target network of XQLD was constructed by utilizing Cytoscape 3.7.2 software (Fig. 3), with a total of 226 nodes and 1330 edges. By Network Analyzer analysis, the top 5 key active ingredients were quercetin, kaempferol, β-sitosterol, luteolin, and stigmasterol (Table 1).

3.4. Construction of the PPI network and core targets screening

The 92 intersection targets of XQLD in the treatment of IA were introduced into STRING database to analyze the protein interaction of the potential targets of XQLD in the treatment of IA, and the results were introduced into Cytoscape 3.7.2 for visualization (Fig. 4). The average degree, betweenness centrality and closeness centrality were 20.696, 0.010, and 0.521 respectively,

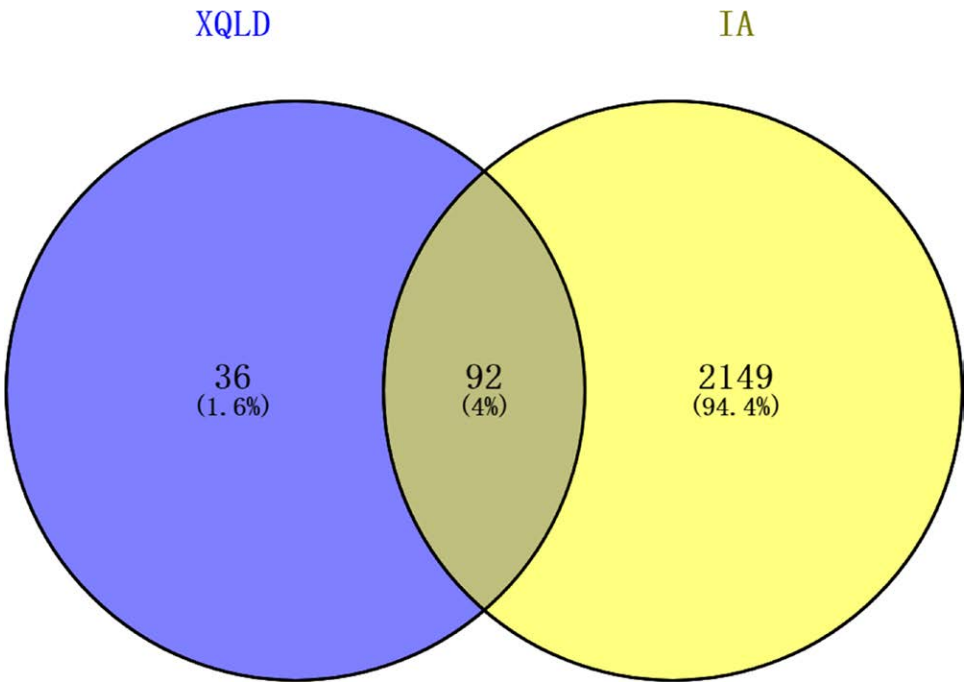

Figure 2. Venn diagram of the intersection targets of XQLD and IA. IA = infantile asthma, XQLD = Xiaoqinglong decoction.

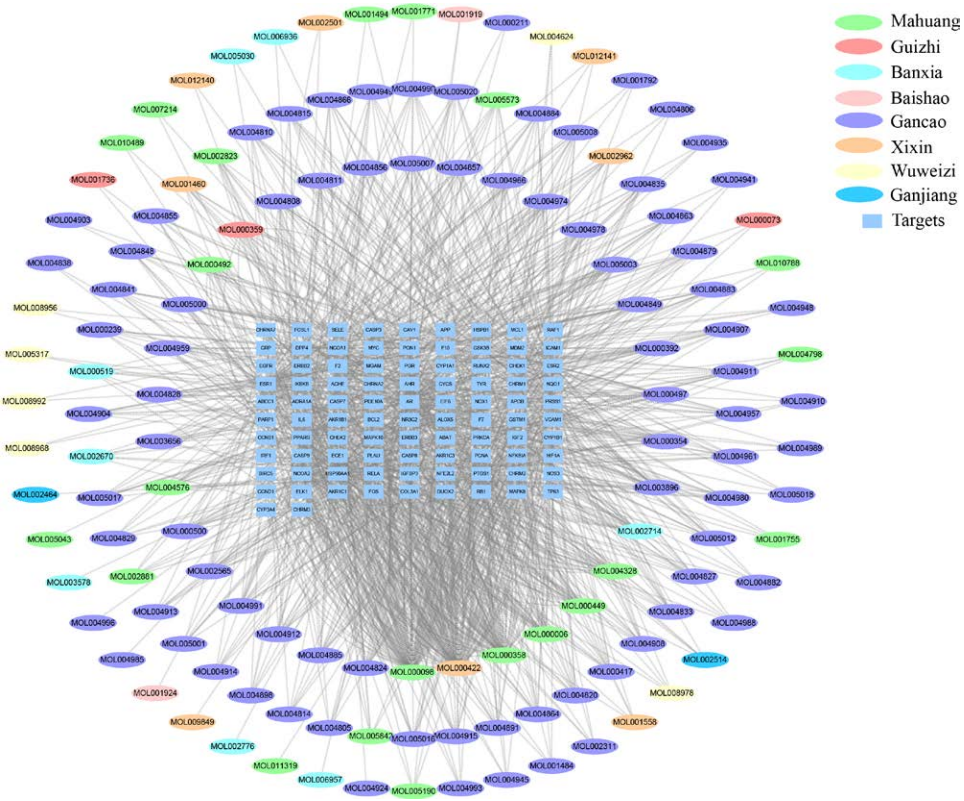

Figure 3. Active ingredient-intersection target network. The ovals represent active compounds, and the rectangles represent targets.

among which 40 parameters of targets were above the average, and the topologic parameters of the top 10 key proteins were shown in Table 2. Therefore, we speculated that targets such as interleukin 6 (IL6), cystatin 3 (CASP3), estrogen receptor 1 (ESR1), hypoxia inducible factor 1A (HIF1A), HSP90AA1 and epidermal growth factor receptor (EGFR) play a significant regulatory role in XQLD treating IA.

3.5. GO enrichment analysis and KEGG enrichment analysis

The R software was used to analyze the GO function and KEGG pathway enrichment of the intersection targets. There were 127 items of GO enrichment analysis, including 405 biological processes, 63 cellular components, and 107 molecular functions,

Table 1

Top 5 key active ingredients by degree value.

MOL ID	Active ingredient	Degree	Affiliated herbs
MOL000098	Quercetin	122	*Ephedrae herba*, *Licorice*
MOL000422	Kaempferol	116	*Ephedrae herba*, *Paeoniae radix alba*, *Licorice*, *Asari radix et rhizoma*
MOL000358	β-sitosterol	80	*Zingiberis rhizoma*, *Cinnamomi ramulus*, *Ephedrae herba*, *Paeoniae radix alba*, *Arum ternatum thunb*
MOL000006	Luteolin	26	*Ephedrae herba*
MOL000449	Stigmasterol	24	*Ephedrae herba*, *Arum ternatum thunb*

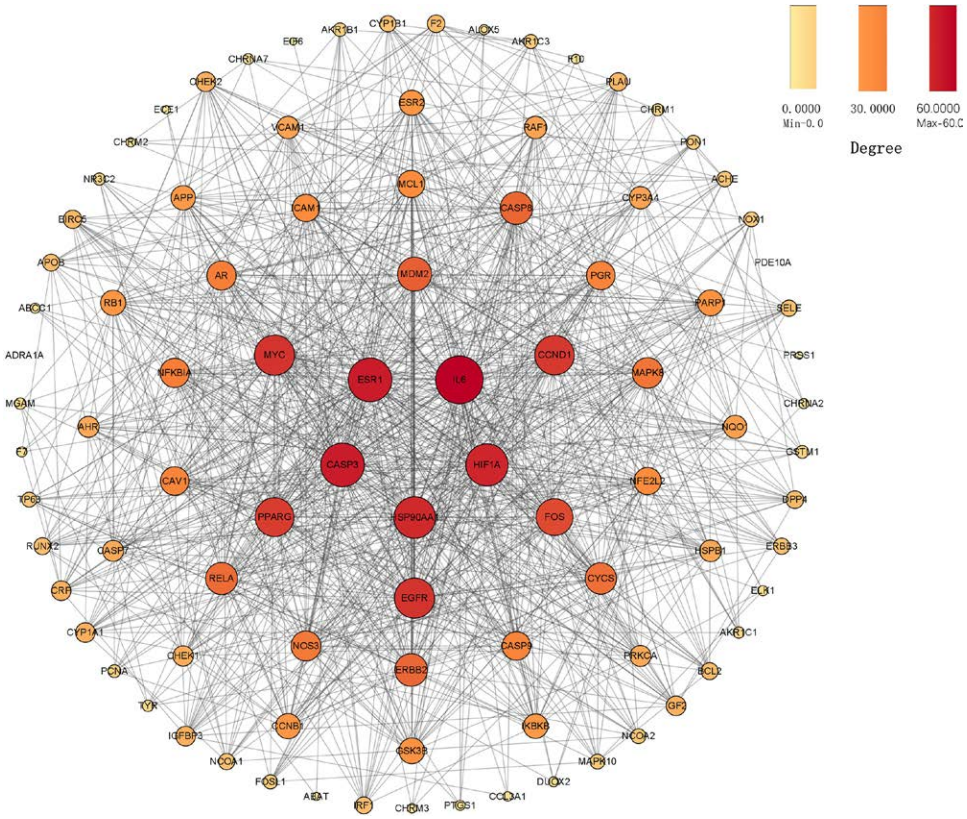

Figure 4. PPI network of XQLD in the treatment of IA. The size and color of the nodes indicate the different degree. IA = infantile asthma, PPI = protein-protein interaction, XQLD = Xiaoqinglong decoction.

Supplemental Digital Contents 3 and 4, http://links.lww.com/MD/1335; http://links.lww.com/MD/1336. Biological process was mainly related to positive regulation of transcription from ribonucleic acid polymerase II promoter, positive regulation of gene expression, and positive regulation of cell proliferation. Cellular component was associated with nucleus, cytosol, and cytoplasm. Molecular function was mainly connected with protein binding, identical protein binding, and enzyme binding (Fig. 5). One hundred twenty-five pathways were obtained by KEGG enrichment analysis, among which the top 20 KEGG pathways were screened out according to *P* value (Fig. 6). The results of KEGG enrichment showed that it was related to

Table 2

Topology parameters of the top 10 key targets in the PPI network.

Target	Betweenness centrality	Closeness centrality	Degree
IL6	0.138512	0.754237	60
CASP3	0.054739	0.717742	54
ESR1	0.050779	0.700787	54
HIF1A	0.030726	0.689922	52
HSP90AA1	0.04699	0.684615	51
EGFR	0.032718	0.679389	49
MYC	0.021697	0.674242	49
CCND1	0.019305	0.654412	48
PPARG	0.05526	0.669173	47
FOS	0.029722	0.659259	44

CASP3 = cystatin 3, EGFR = epidermal growth factor receptor, ESR1 = estrogen receptor 1, HIF1A = hypoxia inducible factor 1A, IL6 = interleukin 6, PPI = protein-protein interaction.

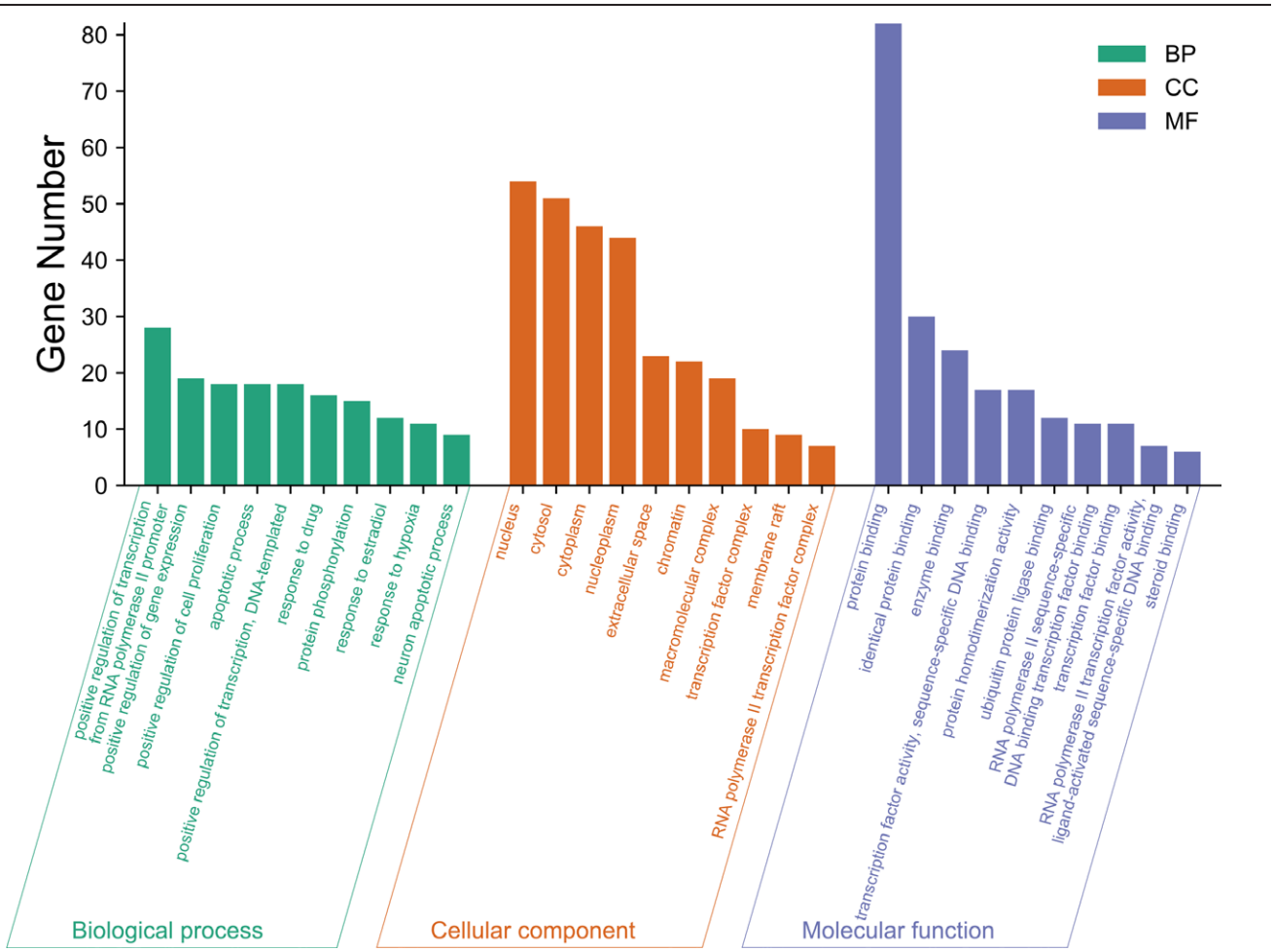

Figure 5. GO function enrichment analysis. GO = Gene Ontology.

apoptosis, IL-17 signal pathway, tumor necrosis factor (TNF) signal pathway and P13K-Akt signal pathway. The R software was used to analyze the target pathways, and the mechanism of apoptosis and TNF signal pathway was shown in Figures 7 and 8, among which the red mark was the potential target of XQLD in treating IA.

3.6. Molecular docking

According to the results of network pharmacology, the top 5 key active ingredients including quercetin, kaempferol, β-sitosterol, luteolin, and stigmasterol were docked with the top 6 core targets including IL6, CASP3, ESR1, HIF1A, HSP90AA1, and EGFR. The result of molecular docking was represented by heat map (Fig. 9), and the unit of docking result was kcal·mol^{-1}. If the binding energy is <0, it means that ligand and receptor can spontaneously bind, and the smaller the value, the higher the binding activity. The deeper the color was, the better the binding activity between the ingredients and the targets was. The result showed that most of the key active ingredients of XQLD had better binding activity with key targets in the treatment of IA. After selecting the binding energy <−6 kcal mol^{-1}, the simulation diagram of molecular docking was constructed by PyMOL software (Fig. 10).

Combined with the docking and PyMOL visualization results, the docking accuracy between the key active ingredients and its key target proteins was calculated. Luteolin bound to EGFR by 7 hydrogen bonds between it and LYS-745, GLN-791, MET-793, ASN-842, and ASP-855. Other forces including π-π stacked bonds between it and ALA-743, LEU-718 and LEU-844 were also found. The β-sitosterol was attracted to CASP3, ESR1 and EGFR by alkyl, π-alkyl, van der Waals forces and hydrogen bond, while the hydrogen bonding as the main force of interaction. Stigmasterol was attracted to EGFR by 6 π-alkyl between it and LYS-806, PHE-910 and MET-987, as well as hydrogen bond between it and THR-909. When encountered to HIF1A, it formed 1 hydrogen bond with ARG-51 and alkyl.

4. Discussion

IA is a common chronic respiratory disease characterized by airway hyperresponsiveness, chronic airway inflammation, and airway remodeling.[7] The functions of children are not yet perfect, so the defensive qi instability results in being invaded by external evils, unclean diet breeds turbid phlegm, which mutually accumulate to induce asthma.[8] Compared with the treatment of Western medicine, syndrome differentiation and treatment of traditional Chinese medicine considers from the perspective of overall concept, featuring its unique advantages and characteristics. Based on network pharmacology and molecular docking, this study revealed the mechanism of XQLD in the treatment of IA from multi-targets and multi-pathways, and discussed the key active ingredients, potential targets and pathways of XQLD in the treatment of IA.

Active ingredients of XQLD were searched and screened through database, and the active ingredient-intersection target network was further constructed and analyzed, which obtained top 5 key active ingredients including quercetin, kaempferol, β-sitosterol, luteolin, and stigmasterol. Studies have

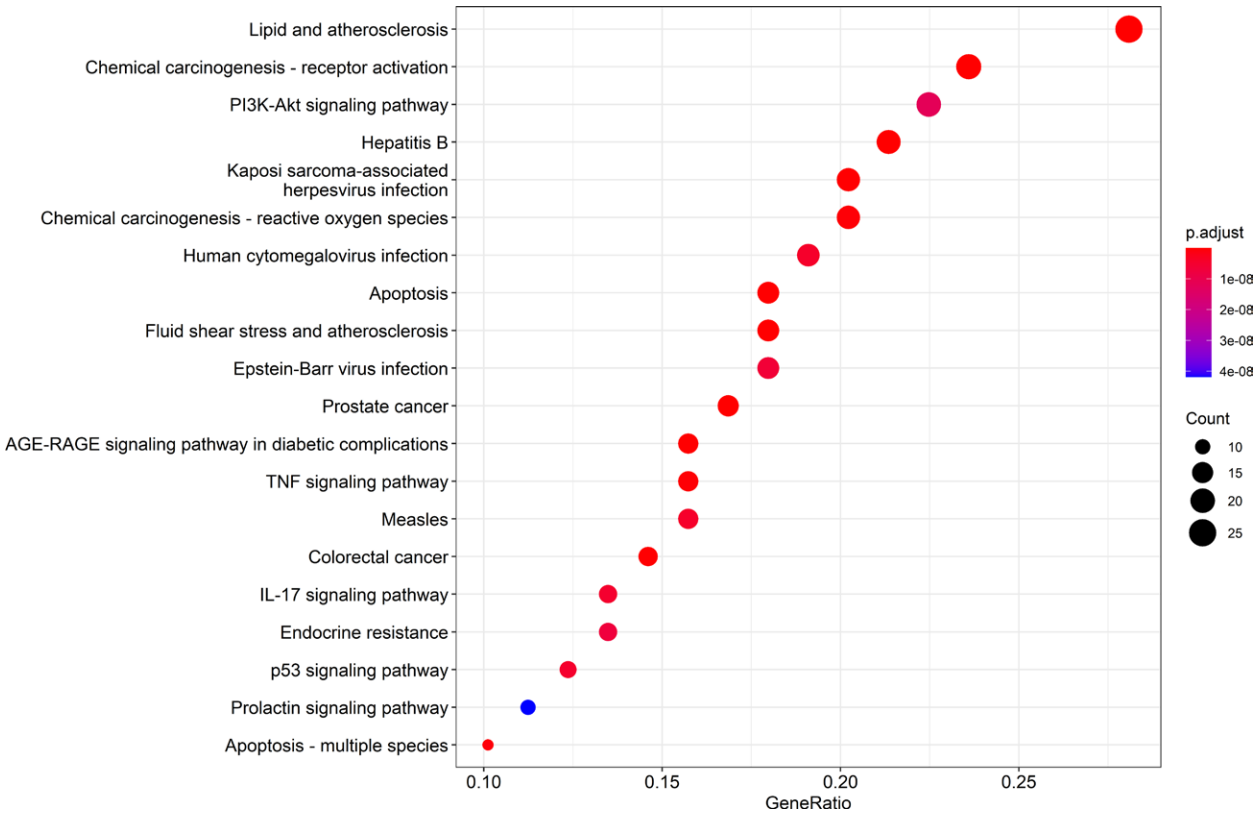

Figure 6. KEGG pathway enrichment analysis. KEGG = Kyoto Encyclopedia of Genes and Genomes.

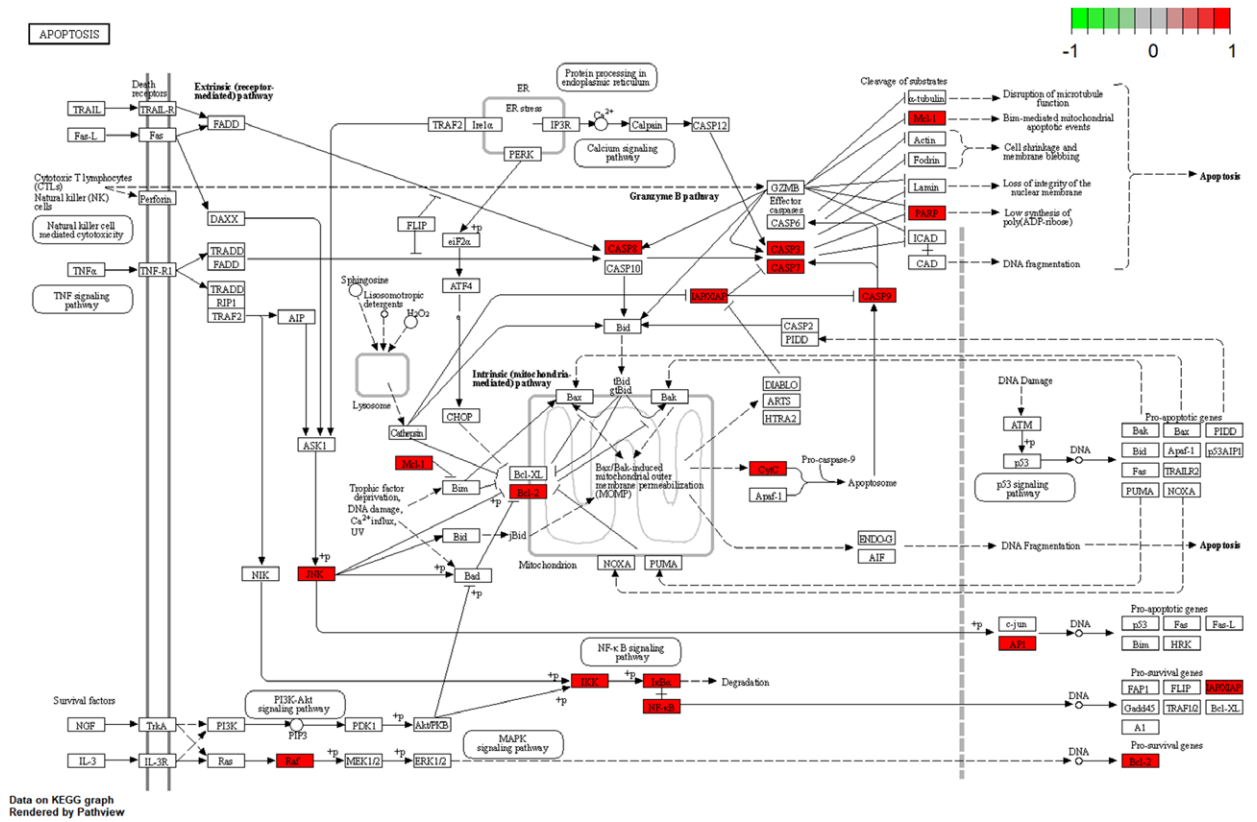

Figure 7. Mechanism of apoptosis signal pathway. Core targets are marked in red.

shown that airway epithelial cell activation may lead to airway hyperresponsiveness and airway remodeling, while kaempferol can inhibit eosinophil infiltration and airway inflammation by blocking NF-κB signal transduction.[9] In guinea pig asthma

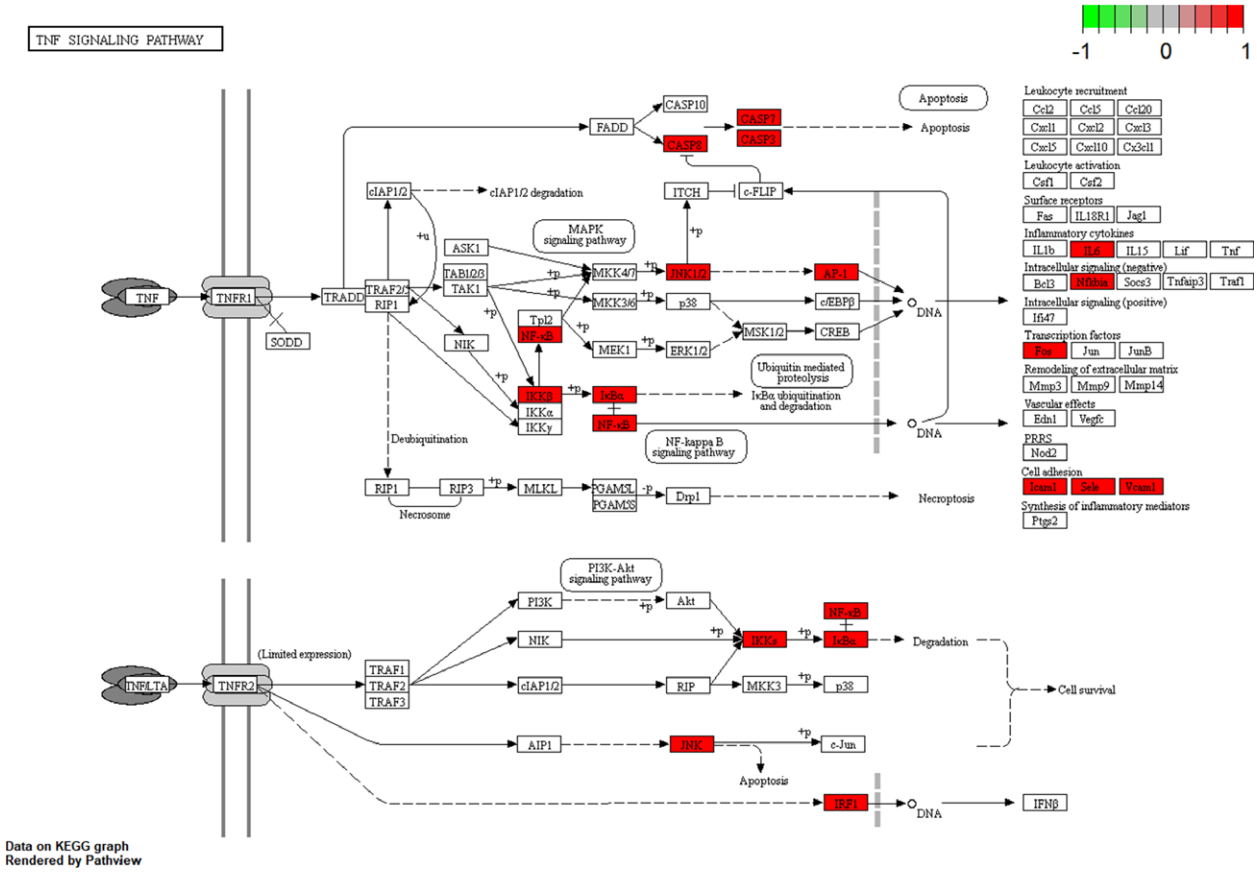

Figure 8. Mechanism of TNF signal pathway. Core targets are marked in red. TNF = tumor necrosis factor.

model, β-sitosterol exerted its anti-asthma effect by inhibiting the reaction of T helper cell type 2 (Th2) and the synthesis and release of Th2 cytokines, significantly increasing the tidal volume and decreasing the respiratory rate, which was about the same level as the control group.[10] Luteolin can effectively reduce the expression of IgE, alleviate pulmonary inflammation and asthma symptoms by inhibiting the synthesis and excessive secretion of pro-inflammatory cytokines such as IL-6 and TNF-α.[11] Through the topology analysis of the PPI network, the core targets including IL6, CASP3, ESR1, HIF1A, HSP90AA1 and EGFR were screened. IL-6 is an inflammatory factor, which participates in many pathological processes such as inflammatory response and cellular immunity. Clinical experiments have found that overexpression of IL-6 in asthma patients induces compensatory hyperplasia such as alveolar walls thickening and lung interstitium increasing, and also stimulates a variety of inflammatory factors, which finally leads to pulmonary fibrosis.[12] ESR1 is an estrogen receptor expressed in pulmonary myofibroblasts. When ESR1 is activated by estrogen, it will lead to phosphorylation of Raf1 and extracellular signal-regulated kinase, and inhibit the proliferation of pulmonary myofibroblasts. Therefore, estrogen can be used as a replacement therapy for female patients with asthma.[13] EGFR can downregulate the expression of Claudin1 in bronchial epithelial cells, destroy the function of respiratory epithelial barrier and lead to excessive mucus secretion.[14]

KEGG pathway enrichment analysis shows that XQLD in the treatment of IA is related to apoptosis, IL-17 signal pathway, TNF signal pathway, P13K-Akt signal pathway, etc. The main pathological features of asthma patients are excessive cellular response of Th2 and specific IgE driven airway hyperresponsiveness.[15] Asthma can be pathologically divided into Th2-high type (eosinophil) and Th2-low type (non-eosinophil) according to the content of eosinophils in sputum.[16] Th17 cells are the key participants of Th2-low type, which are differentiated by T lymphocyte precursors stimulated by a variety of cytokines, and can secrete a variety of inflammatory cytokines, among which IL-17 is the most iconic effector.[17] When IL-17 is activated in airway smooth muscle cells, it releases a variety of bioactive substances such as elastase, which leads to lung tissue destruction and mucus oversecretion, and induces airway hyperresponsiveness, playing an important role in airway remodeling in asthma patients.[18,19] P13K-Akt signaling pathway participates in the regulation of Th17 cells, which can affect the development of proliferation, aggregation, activation, and apoptosis of inflammatory cells, so as to inhibit the dominant differentiation of Th17 as well as decrease the level of inflammatory factor IL-17.[20] The activation of TNF pathway plays a role through NF-κB signal pathway, resulting in the overexpression of IL-1, IL-6, IL-8, TNF-α, and chemokines, thus aggravating inflammatory and immune responses.[21] Among them, TNF-α is released by Th2 and neutrophils, which can accelerate the aggregation of inflammatory cells such as neutrophils and vascular endothelial cells, and stimulate immune cells to release IL-1β and IL-6.[22]

We performed molecular docking to verify whether the key active ingredients of XQLD have good binding activity with the core targets of IA. When the binding energy is <0, the small molecular ligand can bind to the protein receptor spontaneously, and the smaller the number is, the stronger the binding ability is.[23] The results of molecular docking showed that most of the binding energies of 30 pairs of results performed by simulation docking are <−5.0 kcal·mol^{-1}, which means that the active ingredients of XQLD have a good affinity with the targets. The binding energies of β-sitosterol with CASP3, ESR1 and EGFR are all <−6.0 kcal·mol^{-1}, and the binding energy of stigmasterol with HIF1A is the lowest: −6.9 kcal·mol^{-1}. Studies

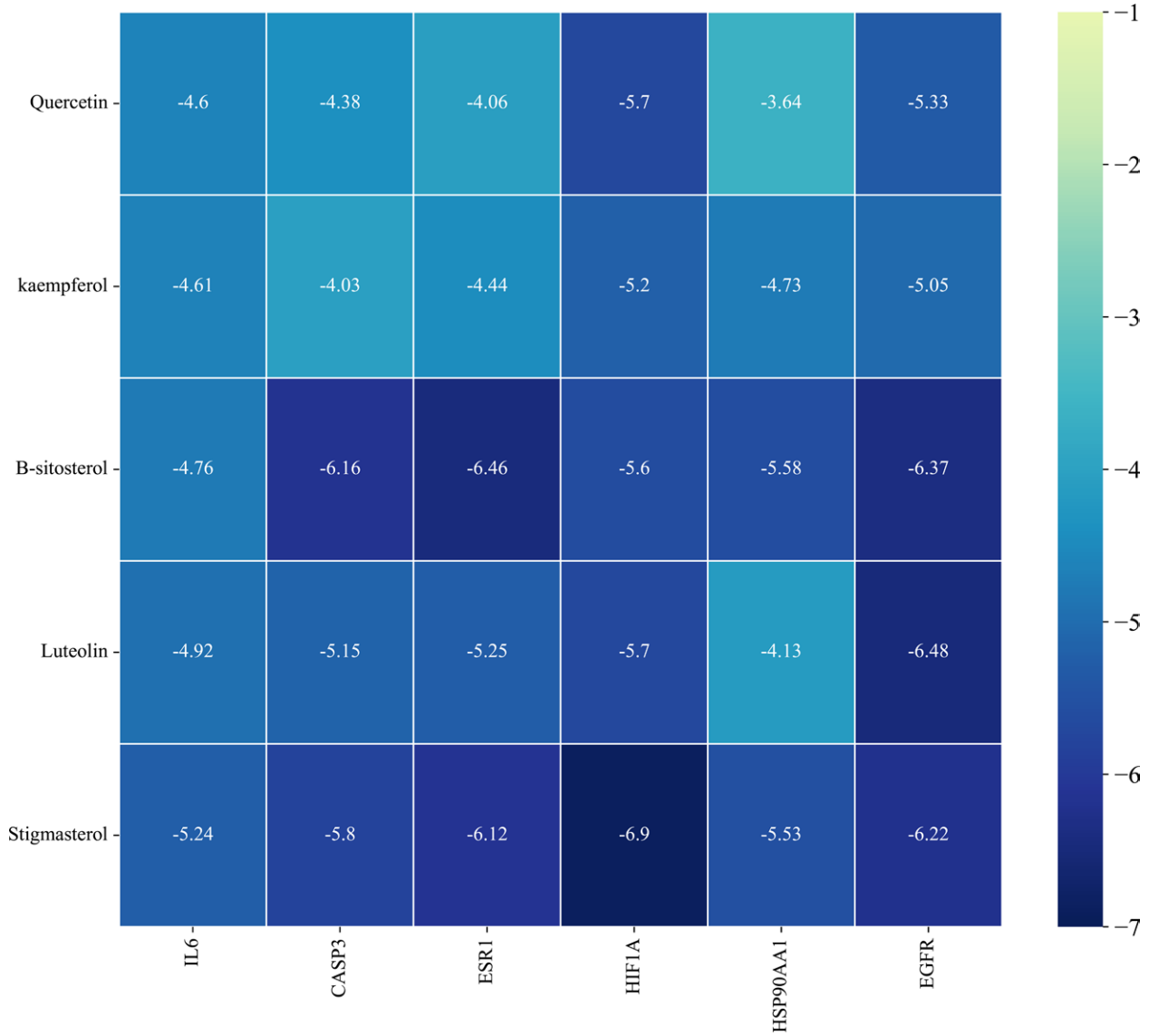

Figure 9. Binding energy heat map of core active ingredients and core targets.

found that β-sitosterol shows good pharmacological activities in anti-inflammation, antioxidation, reducing blood lipids and regulating immunity, which helps to treat IA.[24] Quercetin can reduce tracheal inflammatory reaction by downregulating the levels of IL-4, IL-5, and miR-155. Experiments showed that stigmasterol could significantly reduce eosinophils, lymphocytes and mononuclear cells in guinea pig model of asthma. It has a significant therapeutic effect on IA by reducing the infiltration of inflammatory cells around bronchi, blood vessels and alveoli.[25] The above combination may play an important role in the treatment of IA with XQLD.

5. Conclusion

Inhaled glucocorticoids are preferred in the asthma guidelines for the treatment of IA, which can improve chronic airway inflammation and reduce abnormal hypersecretion of airway mucus for asthma, as well as long-acting β2 agonists and leukotriene receptor antagonists.[26] However, when these drugs are used, they are prone to recurrence if discontinued, and their long-term use may affect the growth and development of children,[27] and compliance is poor.[28] Therefore, there is an urgent need to find a fully effective treatment for IA.

In Chinese medicine, XQLD has the efficacy of pungent warming to relieve superficial symptoms, warming the lung and resolving drinks, and is mainly used to treat external cold and internal drinks, but its pharmacological mechanism of action in treating IA is still unclear. The multi-component, multi-target and multi-pathway model of Chinese medicine is consistent with the systematic and holistic nature of network pharmacology. Therefore, this study explores the molecular mechanism of XQLD in the treatment of IA based on network pharmacology, which can lay a theoretical foundation for expanding its application in clinical practice and subsequent research.

The results of this study confirmed that key active ingredients such as quercetin, kaempferol, β-sitosterol, luteolin, stigmasterol in XQLD may act on potential core targets such as IL6, CASP3, ESR1, HIF1A, HSP90AA1, EGFR, participating in apoptosis, IL-17 signal pathway, TNF pathway, P13K-Akt signal pathway, and so on. This study has a certain feasibility and reliability, which provides a new idea for the treatment of IA, but the data in this study were mainly obtained from databases, which may be incomplete and need to be combined with literature search for screening and supplementation; the target prediction database is not perfect and has certain limitations,

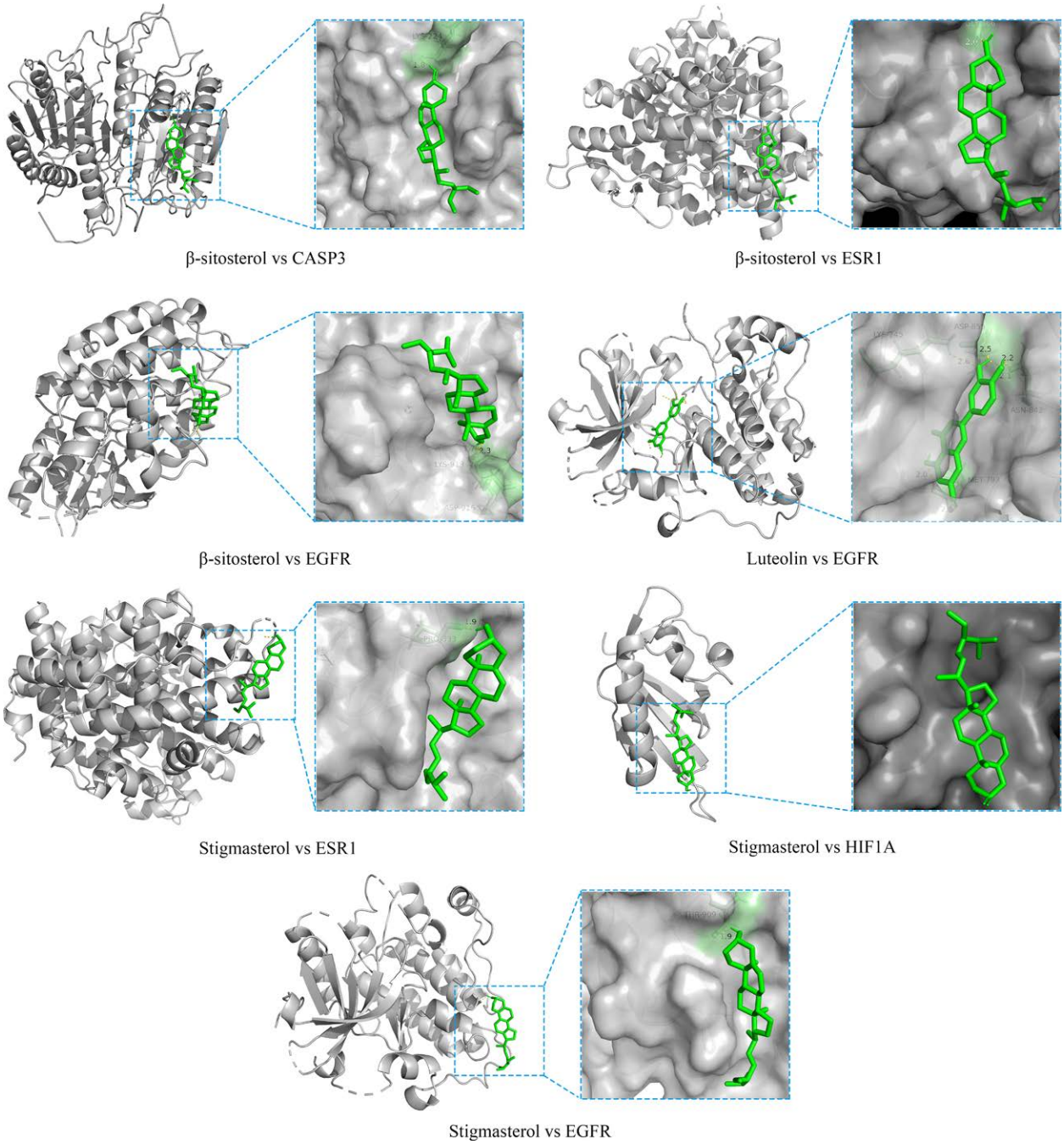

Figure 10. Visualization result of molecular docking.

and further animal experiments and clinical trials are needed to verify the prediction results.

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Writing – review and editing: Daman Chen, Qiqi Chen, Kaibo Zhao, Yongqi Guo, Xiaohong Lin.

References

[1] Zhao X, Qin YH, Wang YP, et al. TCM diagnosis and treatment guidelines of childhood asthma (Revised). J Nanjing Univ Trad Chin Med. 2022;38:476–82.
[2] Jozsa T, Papp A, Gonczi F, et al. [Studying the health behavior of asthmatic children regarding the dimensions of media and internet usage and self-esteem]. Orv Hetil. 2018;159:1971–80.
[3] Zhao BL. Discussion of the etiology and prescription understanding of asthma. Clin J Trad Chin Med. 2006;1:85–7.
[4] Song G, Zhang Y, Zhao K, et al. Regulatory effect of Xiaoqinglong decoction on thymic stromal lymphopoietin (TSLP) inflammation promoter in mice with cold asthma. Iran J Allergy Asthma Immunol. 2018;17:39–46.

[5] Wang L, Feng X, Wang B, et al. Adjuvant treatment with Xiaoqinglong formula for bronchial asthma in acute attack: a systematic review of randomized controlled trials. Evid Based Compl Alternat Med. 2020;2020:8468219.
[6] Zhang X, Wang L, Shi Q. [Effect of fluticasone inhalation combined with xiaoqinglong decoction on pulmonary function and serum interleukin-16 level in asthma patients]. Zhongguo Zhong Xi Yi Jie He Za Zhi. 2003;23:426–9.
[7] Papi A, Brightling C, Pedersen SE, et al. Asthma. Lancet. 2018;391:783–800.
[8] Zhao XB, Lai DY, Xiao Q, et al. Analysis on the effect of Ma soup on inflammatory factors and ACTH and CORT based on intestinal flora. China J Trad Chin Med. 2022;40:213–5.
[9] Gong JH, Shin D, Han SY, et al. Kaempferol suppresses eosionphil infiltration and airway inflammation in airway epithelial cells and in mice with allergic asthma. J Nutr. 2012;142:47–56.
[10] Mahajan SG, Mehta AA. Suppression of ovalbumin-induced Th2-driven airway inflammation by β-sitosterol in a guinea pig model of asthma. Eur J Pharmacol. 2011;650:458–64.
[11] Yu J, Peng Z, Xie T, et al. Effects and the mechanism study of luteolin on TNF-and IL-6 secretion of peripheral blood monocytes in children with asthma. Chin J Immunol. 2019;35:1580–3.
[12] Zhan HT, Fan ZQ, Chen XW, et al. Clinical significance of the changes in the serum levels of IL-6, IL-10, and TNF-in patients with bronchial asthma. Chin Exp Diagn. 2019;23:1741–3.
[13] Koppelman GH, Sayers I. Evidence of a genetic contribution to lung function decline in asthma. J Allergy Clin Immunol. 2011;128:479–84.
[14] Jia Z, Bao K, Wei P, et al. EGFR activation-induced decreases in claudin1 promote MUC5AC expression and exacerbate asthma in mice. Mucosal Immunol. 2021;14:125–34.
[15] Kuruvilla ME, Lee FE, Lee GB. Understanding asthma phenotypes, endotypes, and mechanisms of disease. Clin Rev Allergy Immunol. 2019;56:219–33.
[16] Wenzel SE, Schwartz LB, Langmack EL, et al. Evidence that severe asthma can be divided pathologically into two inflammatory subtypes with distinct physiologic and clinical characteristics. Am J Respir Crit Care Med. 1999;160:1001–8.
[17] Ramakrishnan RK, Al HS, Hamid Q. Role of IL-17 in asthma pathogenesis and its implications for the clinic. Expert Rev Respir Med. 2019;13:1057–68.
[18] Chesne J, Braza F, Mahay G, et al. IL-17 in severe asthma. Where do we stand? Am J Respir Crit Care Med. 2014;190:1094–101.
[19] Chen H, Zhou J, Wang SY. Progress in the role of Th17 and IL-17 in the development and development of neutrophilic asthma. J Jilin Univ. 2021;47:1331–6.
[20] Nie Y, Zhang WX, Chong L, et al. Regulation of PI3K signaling on the imbalance between regulatory T cells and Th17 in asthmatic mice. Chin J Pathophysiol. 2012;28:332–7.
[21] Wang X, Qian GY, Ling XY, et al. Network pharmacology study and experimental verification of Huanglong cough granules in asthma treatment. J Nanjing Univ Trad Chin Med. 2022;38:496–503.
[22] Zhang Y, Li X, Zhang L, et al. Effect of acute cold exposure on the expression of proinflammatory factors in rat lung tissue. Chin J Appl Physiol. 2015;31:6–9.
[23] Lian WJ, Hu J, Fu MW, et al. Based on network pharmacology and molecular docking technology to explore the mechanism of Cordyceps sinensis in the treatment of bronchial asthma and chronic renal failure. Chin J Exp Formul. 2022;28:184–91.
[24] Imaoka H, Hoshino T, Takei S, et al. Effects of thioredoxin on established airway remodeling in a chronic antigen exposure asthma model. Biochem Biophys Res Commun. 2007;360:525–30.
[25] Antwi AO, Darko Obiri D, Newman O, et al. Stigmas terol modulates allergic airway inflammation in Guinea Pig Model of Ovalbumin-induced asthma. Mediators Inflamm. 2017;2017:1–141.
[26] Bao YX, Chen AH, Fu Z, et al. Guidelines for the diagnosis and prevention of bronchial asthma in children (2016 edition). Chin J Pediatr. 2016;54:167–81.
[27] Xu CC, Lin RJ, Jin R, et al. Study on the effect of asthma on bone development in children. J Pract Clin Med. 2020;24:52–4.
[28] Xiao YN. Analysis of factors influencing adherence to inhaled glucocorticoid therapy in children with bronchial asthma. Henan Med Res. 2020;29:5983–6.