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Original Article

Common mechanism of *Citrus Grandis Exocarpium* in treatment of chronic obstructive pulmonary disease and lung cancer

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ABSTRACT

Objective: "Same treatment for different diseases" is a unique treatment strategy in traditional Chinese medicine. Two kinds of malignant respiratory diseases endanger human health-chronic obstructive pulmonary disease (COPD) and lung cancer. *Citrus Grandis Exocarpium* (Huajuhong in Chinese, HJH), a famous herbal, is always applied by Chinese medicine practitioners to dispersion the lung to resolve phlegm based on "syndrome differentiation and treatment" theory. However, the common mechanism for HJH's treatment of COPD and lung cancer is not clear.

Methods: In this study, based on network pharmacology and molecular docking technology, the common mechanism of HJH in the treatment of COPD and lung cancer was studied. The active ingredients and related targets of HJH were integrated from TCMSP, BATMAN-TAM, STP, and Pubchem databases. The standard names of these targets were united by UniProt database. Targets of COPD and lung cancer were enriched through GeneCards, NCBI (Gene), Therapeutic Target Database, and DisGeNET (v7.0) databases. Then the intersection targets of HJH and diseases were obtained. The STRING network and the Cytoscape 3.7.2 were used to construct PPI network, the DAVID database was used to perform GO and KEGG analysis. Then Cytoscape 3.6.1 was used to build "ingredient-target-signal pathway" network. Finally, AutoDock 1.5.6 software was used to perform molecular docking of key proteins and molecules.

Results: Eleven active ingredients in HJH were obtained by searching the database, corresponding to 184 HJH-COPD-lung cancer targets intersection. The results of biological network analysis showed that naringenin, the active component in HJH, could mainly act on target proteins such as AKT1, EGFR. Then through positive regulation of vasoconstriction and other biological processes, naringenin could regulate estrogen signaling pathway, VEGF signaling pathway, HIF-1 signaling pathway, ErbB signaling pathway, PI3K-Akt signaling pathway to play an important role in the treatment of both COPD and lung cancer.

Conclusion: Network pharmacology was employed to systematically investigate the active ingredients and targets of HJH in treatment of COPD and lung cancer. And then, the common pharmacodynamic network of HJH for the two malignant respiratory diseases was firstly described. Furthermore, naringenin was proved to strongly bind with AKT1 and EGFR. It may provide the scientific basis for understanding the "Same treatment for different diseases" strategy in traditional Chinese medicine and inspirit subsequent drug discovery for COPD, lung cancer and other malignant lung diseases.

1. Introduction

According to the World Health Organization's reports, serious respiratory diseases such as chronic obstructive pulmonary disease (COPD) and lung cancer are the main causes of death in adults (especially men) Giovanni, Sara, Salvatore, and Sandra (2020). Clinical studies show that lung cancer and COPD, suffered from many common risk factors (such as smoking), are closely related and have many commonalities. According to reports, 90% of lung cancers are induced by smoking, which is also the main risk factor for COPD. Both lung cancer and COPD are characterized by chronic lung inflammation, airway remodeling and lung parenchyma destruction (Stellman et al., 2001), even 50%–80% of patients with lung cancer suffer from COPD (Young et al., 2009). COPD is always

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considered as important comorbidity of lung cancer. They also have multiple common pathological features, such as cough, sputum, premature lung failure, airway leukocyte infiltration, increased levels of oxidative stress, and some inflammatory-related features (De la Garza et al., 2018; T. De et al., 2011; Le et al., 2006; Semenza, 2014; Young et al., 2009). In particular, cough and sputum are common and important clinical manifestations of lung cancer and COPD patients. At present, the treatment for lung cancer and COPD mainly focus on reducing the symptoms and the frequency ofrecrudescence. Since chronic inflammation is a common mechanism of action for lung cancer and COPD, epidermal growth factor receptor (EGFR) inhibitors can be used to suppress inflammation in lungs and airways. However, there are many side effects and drug resistance problems (Xie et al., 2019; Zhou et al., 2016). It is imperative to find new treatment strategies.

In traditional Chinese medicine, "Same treatment for different diseases" is a unique treatment strategy based on "Syndrome differentiation and treatment". *Citrus Grandis Exocarpium* (Huajuhong in Chinese, HJH), a famous herbal for resolving phlegm, suppressing cough and calming panting (Wang, Chen, & Zhang, 2014), has a long history of clinical application and outstanding curative effect in traditional Chinese medicine for lung cancer and COPD. Some researches show that HJH exerts pharmacological activity (resolving phlegm, suppressing cough, calming panting, diminishing inflammation) mainly by acting on the respiratory system, affecting immune function (dissipating cold, enhancing immunity), regulating endocrine (Dong, Jiang, & Zhu, 2010; Dong et al., 2015; Guo et al., 2016; Hou, Shen, Xu, Wu, & Wang, 2012; Wang, 2017; Zhang, Chen, & Lin, 2004; Zhu, Wu, Su, Shi, & Li, 2019). However, HJH's effective ingredients and their detailed mechanism are not clear.

As a new approach in pharmacological research, network pharmacology makes a breakthrough. This method illustrates the mechanism of drug efficacy from the perspective of multiple targets and multiple pathways. It is the effective research method for studying the potential active ingredients, targets and mechanism of action of traditional Chinese medicine (TCM) (Yuan et al., 2017). In order to understand the connotation of HJH for COPD and lung cancer, we conducted network pharmacology and molecular docking to explore the possible substance basis, protein targets and mechanism. We are eager to unveil the common pharmacodynamic mechanism of HJH for the two malignant respiratory diseases, with hoping to provide inspiration to further treatment and drug discovery. Furthermore, our research may provide the scientific basis for understanding the "Same treatment for different diseases" strategy in traditional Chinese medicine.

2. Materials and methods

2.1. Materials

TCMSP (http://tcmspw.com/tcmsp.php), a pharmacological analysis platform for Chinese medicine systems. BATMAN-TCM (http://bionet.ncpsb.org/batman-tcm/), a bioinformatics analysis tool for molecular mechanism of TCM. GeneCards database (https://www.genecards.org/). PUBCHEM database (https://pubchem.ncbi.nlm.nih.gov/). STP database (http://www.swisstargetprediction.ch/). UnitProt database (http://www.unitprot.org/). NCBI (Gene) database (https://www.ncbi.nlm.nih.gov/gene). Therapeutic Target Database (TTD) database (http://db.idrblab.net/ttd/). DisGeNET (v7.0) database (https://www.disgenet.org/). STRING 11.0 database (http://string-db.org/). Biological information analysis tool Cytoscape 3.6.1. DAVID database (https://david.ncifcrf.gov/). Venn diagram construction platform (http://bioinformatics.psb.ugent.be/webtools/Venn/). ZINK database (http://zinc15.docking.org/). Protein Data Bank (RCSB PDB) database (http://www.rcsb.org/). AutoDock1.5.6 software, OpenBabelGUI software, Pymol1.1 software.

2.2. Screening of active ingredients in HJH

The TCMSP database was used to search for active ingredients with the keyword "Huajuhong"/ "*Citrus Grandis Exocarpium*", and OB (oral bioavailability) $\geq$ 30% and DL (drug-like) $\geq$ 0.18 were used as conditions to screen out the active ingredients in HJH. OB is an important parameter in pharmacokinetic studies and is often used in new drug research to evaluate the drug formation of oral drugs; DL refers to the similarity of an ingredient to a known drug and is an evaluation index for whether an ingredient can become a drug (Yao et al., 2020).

In the BATMAN-TAM database, "Huajuhong"/ "*Citrus Grandis Exocarpium*" was used as the keyword, and default score value (Score cutoff $\geq$ 20) and *P*-value (Adjusted *P*-value $\leq$ 0.05) were used as the screening conditions to obtain the effective chemical ingredients of HJH.

2.3. Identification of target proteins and their genes query of HJH

The target proteins corresponding to each active ingredient were obtained from TCMSP. Some proteins were not included in TCMSP, then we copied the CAS number of the ingredient to find the SMILES number in the PUBCHEM database, and then copied the SMILES number to get the target protein name in the STP database. Then UniProt database was used to query the gene name corresponding to the target protein.

In the BATMAN database, the targets were found corresponding to the active ingredients.

2.4. Obtaining drug-disease intersection targets

"Chronic obstructive pulmonary disease" and "Lung cancer" were used as search terms. The relevant targets related to COPD and lung cancer were obtained from the GeneCards database, NCBI (Gene) database, TTD database, and DisGeNET database. The target gene names of the two diseases were integrated and the repeated occurrence ones were removed.

The ingredient-disease intersection targets were taken from the Venn online tool. HJH might cure COPD or lung cancer by acting on these intersection targets. The analyses bellow was about the intersection targets.

2.5. Construction of protein–protein interaction network

Protein-Protein Interactions (PPI) were the basic ingredients in biomolecular networks, which played an important role in basic life activities such as DNA synthesis, protein translation, and cell signaling (Jiang, Jiang, & You, 2017).

The intersection proteins were imported into the STRING 11.0 database to obtain the PPI network. The nodes represented the gene names of the target proteins, the edges represent the interactions between the nodes, and the line thickness represented the degree of node correlation (Shi et al., 2020). The table (TSV format) of PPI information was obtained from the STRING database. Then the above TSV table was imported into Cytoscape 3.6.1 software to obtain a visual PPI network with degree value. The degree value of each node characterized the number of nodes interacting with it.

2.6. Target gene annotation analysis and pathway analysis

In order to further analyze the function of the target protein gene and its role in the signaling pathway, the intersected targets were imported into the DAVID database to make gene annotation

analysis (Gene Ontology, GO) and Kyoto Encyclopedia of Gene and Genomes (KEGG) pathway analysis, restricting the list of target gene names and the background to Homo sapiens. GO analysis includes biological process (BP), cellular composition (CC), and molecular function (MF) analysis. KEGG analysis showed the role of intersection targets in signaling pathways. Items were ranked by *P*-value from the smallest to the largest, $P < 0.05$ items were screened out. The front 10 GO items and 20 KEGG items were displayed in the result part.

2.7. Construction of "ingredient-target-signal pathway" network

Eleven ingredients in HJH, the intersection targets gene, and the KEGG signal pathways enriched above were imported into the Cytoscape 3.6.1 software to construct the "ingredient-target-signal pathway" network to show their relationships.

2.8. Molecular docking of key active ingredients with key targets

The results of this study and the literatures were combined to screen out the key active ingredients and key targets. 3D structures of the key active ingredients were obtained from the TCMSP and ZINC databases and were saved as MOL2 format. 3D structures of the target proteins were obtained from RCSB-PDB database and were saved as PDB format. The molecules and proteins were preprocessed and docked by Autodock1.5.6 software. After that, the format of the docking result was adapted by OpenBabel GUI software. Finally, the docking results were shown by Pymol2.2.0 software. The binding energy was used to evaluate the tightness of binding. The smaller the binding energy is, the stronger the binding ability and tighter binding of small molecules to proteins is.

3. Results

3.1. Screening of active ingredients in HJH

A total of 44 active ingredients of HJH were obtained from the TCMSP database, and 10 ingredients with OB $\geq$ 30% and DL $\geq$ 0.18 were obtained through screening. Three ingredients were obtained after screening in the BATMAN database. As shown in Table 1, 11 ingredients were obtained after excluding duplicates.

3.2. Exploration of target intersections HJH and diseases

"Huajuhong"/ "*Citrus Grandis Exocarpium*" was the search term to get the ingredients and target in the TCMSP, UniProt, BATMAN, PUBCHEM, and STP databases, finally 240 targets were obtained.

"Chronic obstructive pulmonary disease" and "Lung cancer" were the search terms to get the disease targets in the GeneCards database, NCBI (Gene) database, TTD database, and DisGeNET (v7.0) database. Finally, 6382 COPD targets and 22,474 lung cancer targets were obtained.

Then the intersection targets of HJH and two diseases' targets were obtained in the Venn Online tool. Fig. 1 showed 227 lung cancer-HJH ingredient intersection genes and 184 COPD-HJH intersection targets, and the 184 targets were contained in the 227 genes. Later, the 184 targets were mainly analyzed.

3.3. PPI network construction and analysis

A total of 184 targets were imported into STRING 11.0 database respectively to obtain PPI network and TSV results; Then TSV results were imported into Cytoscape 3.6.1 software to obtain a visual PPI network with Degree Value. In Fig. 2, the nodes represented the gene names of the target protein, and the connections between the nodes indicate the possible interactions between the proteins. The nodes with higher Degree were closer to the center of the circle and showed larger and darker nodes.

3.4. Annotation and pathway analysis of intersection targets

A total of 184 intersection target genes were imported into the DAVID database for GO analysis and KEGG analysis. In Fig. 3 and Fig. 4, the top 20 GO entries, including 72% Biological Process (BP), 10% Cellular Components (CC), and 18% Molecular Function (MF) entries, and the top 20 KEGG entries were displayed.

3.5. Construction of "ingredient-target-signal pathway" network

Eleven HJH active ingredients, related intersection targets, and top 20 signal pathways were imported into Cytoscape 3.6.1 software to construct the "ingredient-target-signal pathway" network. The network was shown in Fig. 5.

3.6. Screening of key targets and key ingredients and molecular docking

We focused on pathways related to COPD and lung cancer (estrogen signaling pathway, VEGF signaling pathway, HIF-1 signaling pathway, ErbB signaling pathway, PI3K-Akt signaling pathway, small cell lung cancer, non-small cell lung cancer, Ras signaling pathway), and counted the occurrences of each target in the pathways. AKT1, AKT3, EGFR, MAPK1, MAPK3, MAP2K1 and PIK3CG were the most frequently appeared targets in these pathways. In addition, in the PPI network and the "ingredient-target-signal pathway" network, all the above-mentioned seven targets had top degree values. In summary, this study designated AKT1, AKT3, EGFR, MAPK1, MAPK3, MAP2K1, PIK3CG as the key targets.

For the 11 active ingredients, naringin was the quality indicator of HJH in the Chinese Pharmacopoeia 2015 (Commission, 2015). Moreover, naringenin and naringin have been reported to have pharmacological activities in the respiratory system, mainly in the following aspects: peripheral antitussive effect (Li, Zhu, Jiao, He, & Liao, 2015), phlegm-dispelling effect (Chen et al., 2014), anti-pulmonary inflammation effect (Kyeom et al., 2018; Y. Zhang, Wang, Dong, Wei, & Niu, 2013), etc. After entering the intestine, most of naringin was metabolized by intestinal flora into naringenin, then naringenin was absorbed into the blood and played biological activities (Li et al., 2020). Therefore, naringenin and naringin can be transformed in body. This study focused on the study of the pharmacodynamic mechanism of naringenin and naringin on COPD and lung cancer.

In this study, naringenin was the key active ingredient of HJH; Naringin and naringenin were metabolites that can be converted mutually in body. In order to explore their binding ability with the key target proteins, the 3D structures of naringenin and naringin and the key targets were obtained, and molecular docking was performed with Autodock1.5.6 software to predict the possible binding mode and mechanism between small molecules and proteins. The docking results were shown in Table 2.

Table 2 showed that naringenin had lower binding energy and was easier to bind to important target proteins than naringin. In the targets docked with naringenin, AKT1 had the smallest binding energy, followed by EGFR, indicating that these two proteins may have strong binding ability to naringenin. Fig. 6 showed the docking result of naringenin with AKT1 and EGFR. LYS875, VAL876, TRP880 and THR22, LYS41, and GLU53 were important amino acid residues in AKT1 and EGFR proteins that can bind to naringenin molecules, respectively.

Table 1
Key compounds in HJH.

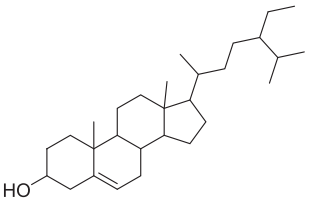
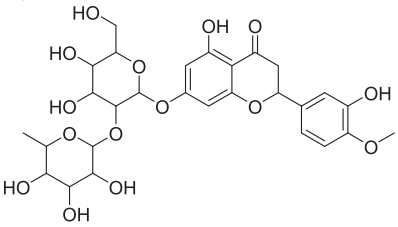
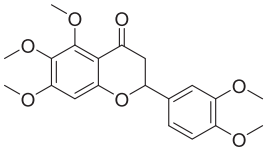
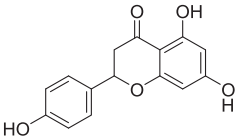
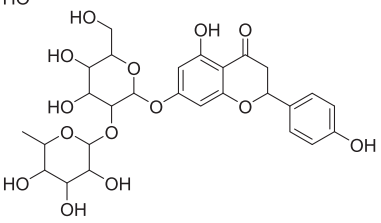
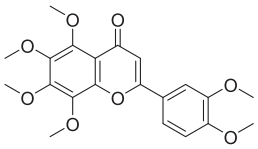
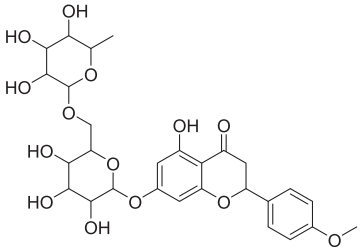
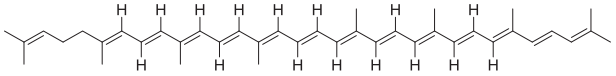
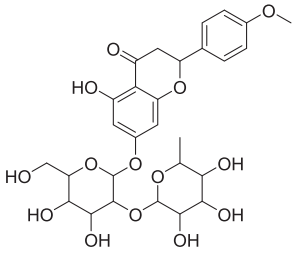
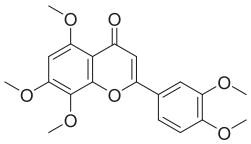
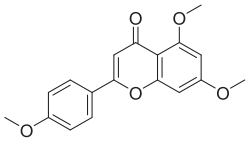
No.	Ingredient names	MOL Number	OB (100%)	DL	Chemical structures
1	beta-Sitosterol	MOL000358	36.91	0.75	
2	Neohesperidin	MOL001798	71.17	0.27	
3	Sinensetin	MOL001803	50.56	0.45	
4	Naringenin	MOL004328	59.29	0.21	
5	Naringin	MOL005812	6.92	0.78	
6	Nobiletin	MOL005828	61.67	0.52	
7	Didymin	MOL005849	38.55	0.24	
8	Lycopene	MOL010267	32.57	0.51	
9	Poncirin	MOL013276	36.55	0.74	

Table 1 (*continued*)

No.	Ingredient names	MOL Number	OB (100%)	DL	Chemical structures
10	Isosinensetin	MOL013277	51.15	0.44	
11	5,7,4′-Trimethylapigenin	MOL013279	39.83	0.30	

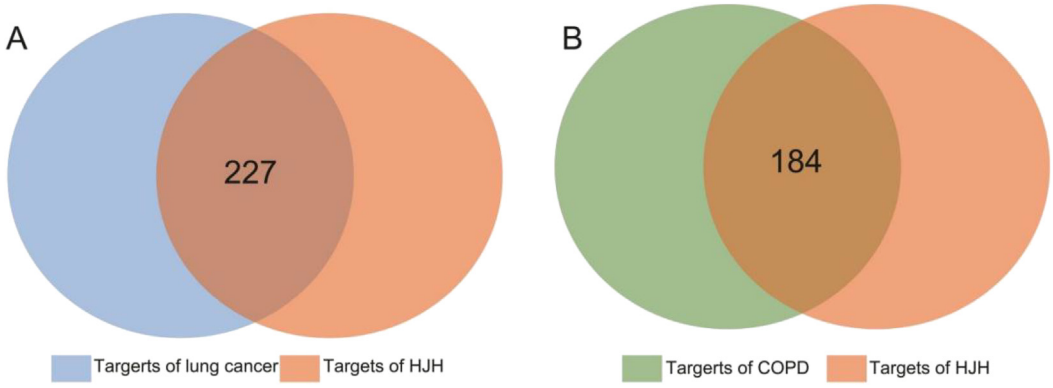


Fig. 1. Venn diagram of intersection targets of HJH and diseases.

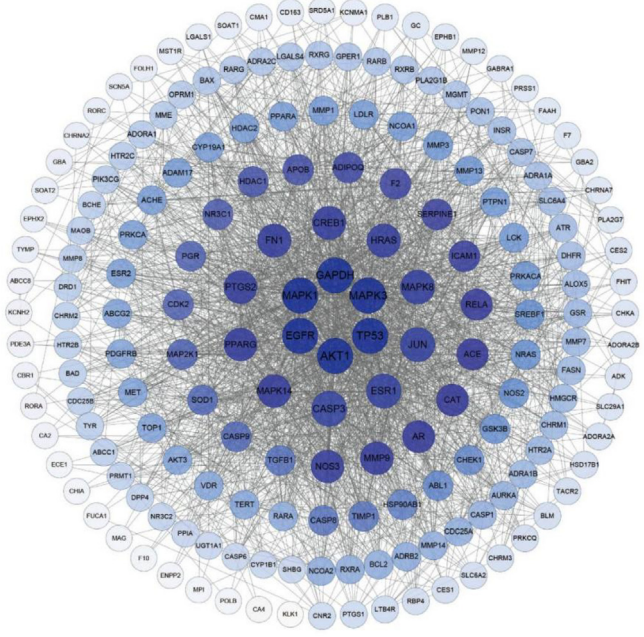


Fig. 2. PPI network of 184 intersection targets.

4. Discussion

"Same treatment for different diseases" is one of the unique treatment strategies of TCM based on the theory of "syndrome differentiation and treatment". In different stages of disease development, even in different diseases, similar pathological changes were observed, which is called "Syndrome". According to "syndrome differentiation and treatment", the treatment strategy is similar even in different diseases with the same "syndrome" (Zhang, 2011). Actually, the view of "same treatment for different diseases" originates from "*Books Related to the Internal Classic*" (Neijing in Chinese), which is the classic of traditional medicine. In later medical works-"*Treatise on Cold Damage Diseases*" (ShanghanLun in Chinese) and "*Synopsis of Prescriptions of the Golden Chamber*" (JinkuiYaolue in Chinese), 31 formulas and 99 entries were related to the "same treatment for different diseases" (Yang, 2013). At present, this concept has been inherited by Chinese medicine practitioners and innovatively used in lung diseases, encephalopathy, cardiovascular disease, digestive system disease, and urinary system diseases (Zhang, 2011). Lung cancer and COPD have some common clinical manifestations, and COPD is an important comorbidity of lung cancer. Especially, cough and sputum are common and important clinical manifestations of lung cancer and COPD patients. For lung cancer and COPD, it is feasible to adopt the same treatment strategy for different diseases. In TCM, the principle of treatment for lung cancer and COPD is both to fortify spleen and purge lung (Yuan & Tan, 2008). Because of HJH's magical and unique medicinal effect, it has been listed as a royal medicine since the Ming Dynasty. HJH acts out purge-lung and resolve-phlegm effects (Yang & Ma, 2014), and formulas with HJH have definite effect in the prevention and treatment of lung cancer and COPD. Such as Pingchuan Guben Decoction, Sujin Xiaozheng Decoction and Daotan Decoction (Zuo, 2014). However, the common mechanism of HJH in the treatment of lung cancer and COPD is not clear.

Network pharmacology builds a network based on the databases, and predicts the relevance of different nodes (Hopkins, 2008; K. Zhao et al., 2018). Its main advantage is to predict the

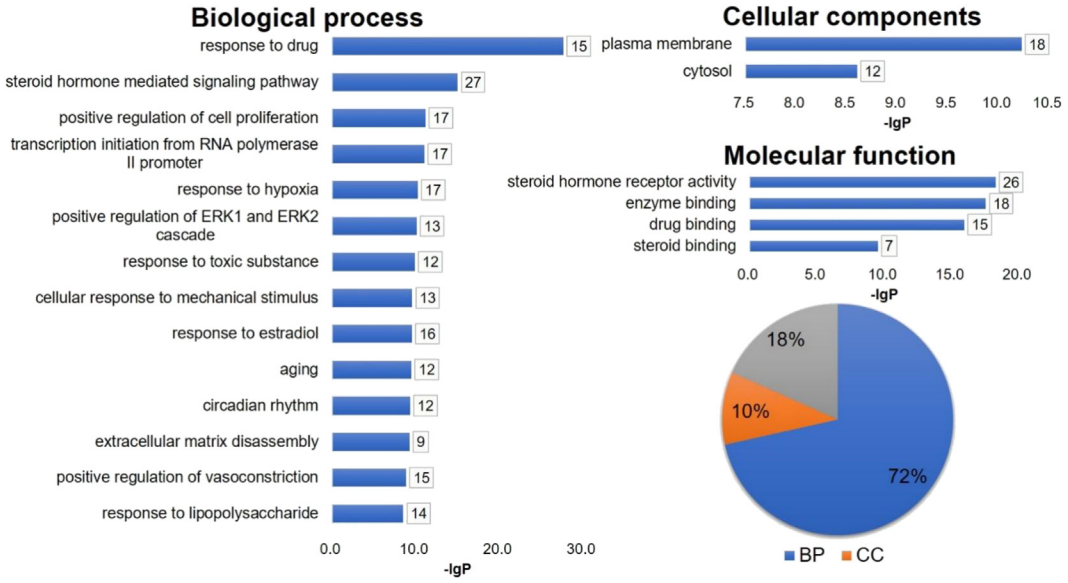


Fig. 3. GO analysis of 184 intersection targets.

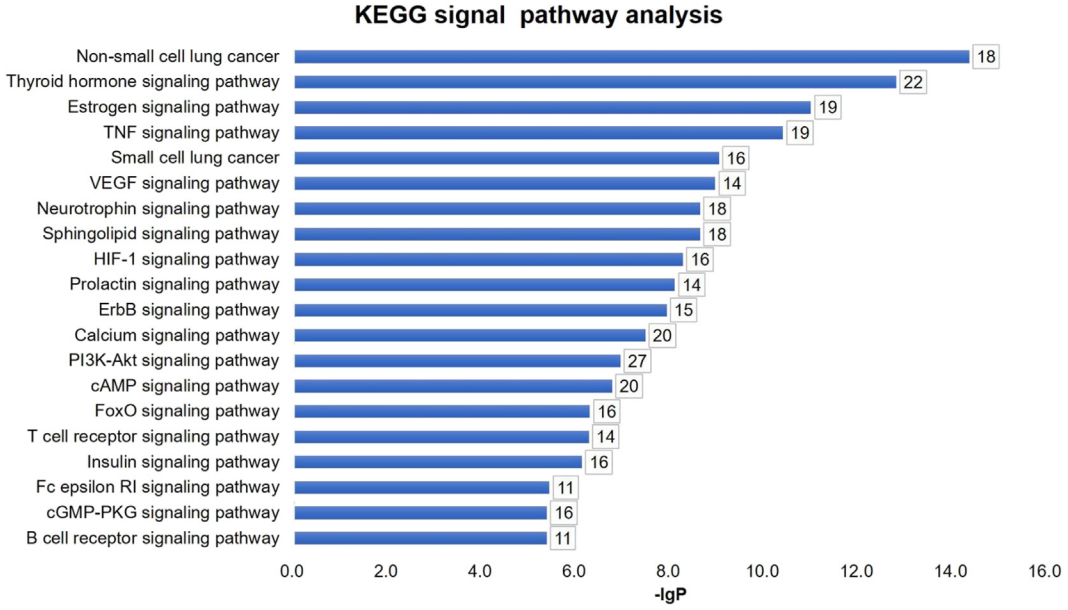


Fig. 4. Pathway analysis of 184 intersection targets.

association of biological active ingredients, drug targets, and disease targets. Considering of multi-target, multi-pathway and multi-level strategy, it is the holistic system theory of TCM and is widely used in the mechanism research of TCM. This study explored the possible targets and mechanisms of HJH in the treatment of COPD and lung cancer. After inquiries and screenings, 11 active ingredients and 240 targets were obtained in HJH, 6382 COPD targets, and 22,474 lung cancer targets. By intersecting the disease targets with the key targets of HJH, it was found that the 184 therapeutic targets of HJH for COPD were included in the treatment of lung cancer. Compared with COPD, HJH had 43 more targets in the treatment of lung cancer, however, they could not be enriched in a biological pathway. We constructed PPI network, performed annotation and pathway analyses, and constructed the "ingredient-target-signal pathway" network to annotate the 184 intersection targets. Enriched biological processes such as positive regulation of vasoconstriction, response to estradiol, response to hypoxia, estrogen signaling pathway, VEGF signaling pathway, HIF-1 signaling pathway, ErbB signaling pathway, PI3K-Akt signaling pathway, small cell lung cancer, non -small cell lung cancer, Ras signaling pathway all can be found in the literatures related to the pathogenesis and treatment mechanism of lung cancer and COPD.

Among pathways enriched in this study, the EGFR signaling pathway can induce ErbB, PI3K-Akt, MAPK, and HIF-1 signaling pathways (Lu et al., 2019; Z. Zhao, Zhang, Zhou, & Zhang, 2014). Fig. 7 showed the expression mechanism of EGF-induced MUC5AC, a highly expressed protein in malignant lung disease. Epidermal

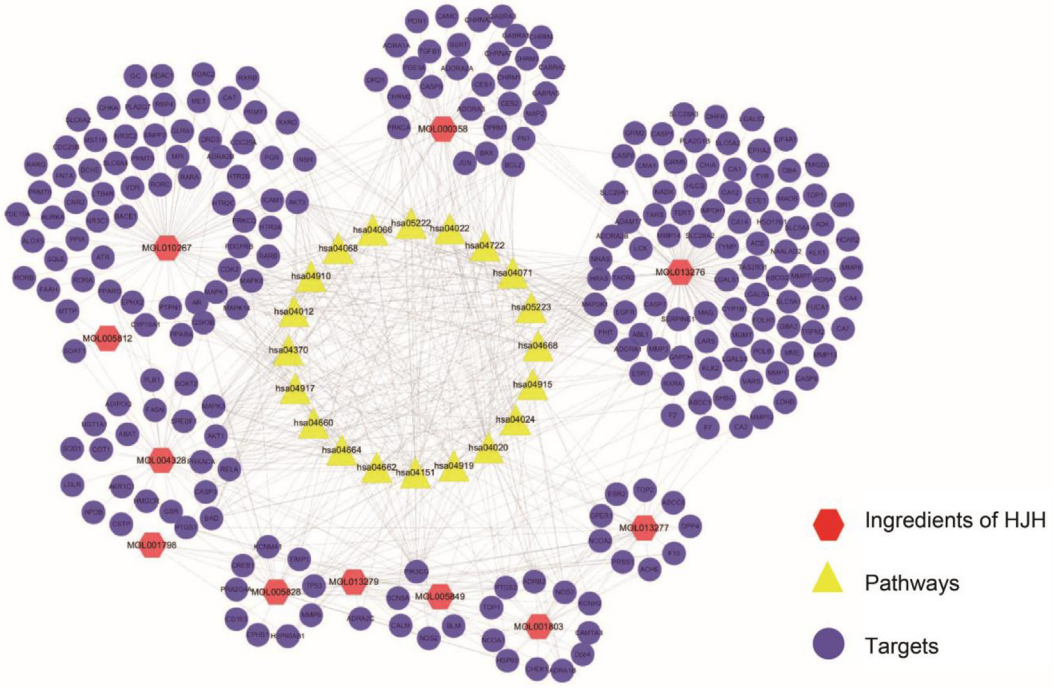


Fig. 5. "Ingredient-target-signal pathway" network of HJH.

Table 2
Binding energy of naringenin and naringin to key targets.

Naringenin	Binding energy/ (Kcal·mol^{-1})	Naringin	Binding energy/ (Kcal·mol^{-1})
AKT1	−5.31	AKT1	−2.83
EGFR	−3.79	EGFR	−1.7
MAPK1	−3.66	PIK3CG	−-1.18
PIK3CG	−3.23	MAP2K1	−1.06
MAP2K1	−2.82	MAPK1	−0.99
AKT3	−1.96	AKT3	−0.93
MAPK3	−1.92	MAPK3	0.92

growth factor (EGF) binds to EGFR to activate the EGFR signaling pathway. Then the ErbB signaling pathway is activated to regulate cell proliferation and promote inflammation (Rahman et al., 2019; Roskoski, 2014); The PI3K-Akt and Ras/ERK/MAPKs/AP-1 pathways are activated to regulate cell proliferation, pathological and physiological processes (Shi, Wang, Lei, Cong, & Zhou, 2019); The HIF-1 pathway is activated to promote inflammation and the expression of VEGF, to regulate the use of oxygen. In the downstream of the PI3K-Akt and RAS /ERK/MAPKs/AP-1 pathways, the NF-κB signaling pathway is activated, and NF-κB and AP-1 enter the nucleus, thereby promoting MU5AC transcription (Wang, 2012; C. Yang et al., 2019). Therefore, inhibition of EGFR can inhibit the progression of lung cancer and COPD. AKT is an oncogene and plays an important node of the AKT signaling pathway. AKT includes three subtypes: AKT1, AKT2, and AKT3. Among them, the expression of AKT1 in non-small cell lung cancer tissues is significantly higher than the former two (Wang, Lv, Xu, Han, & Zhu, 2016), indicating that AKT1 can promote the development of lung cancer. The MAPK family is a class of serine/threonine protein kinases that can regulate intracellular signaling pathways. MAPK1 is of the MAPK family and it participates in pathological processes such as malignant transformation of cells and induces the development of non-small cell lung cancer (Sinoi, Toplak, & Miloti, 2011; Y. Zhao et al., 2020). PIK3CG is a PI3K enzyme inhibitor. Many patients with lung cancer have mutations in the PIK3CG gene compared with normal people (Liu et al., 2012), indicating that PIK3CG may treat lung cancer by inhibiting PI3K-Akt pathway.

Recently, naringenin and naringin have been found to possess various pharmacological effects on respiratory diseases such as anti-sputum-production, anti-cough, anti-inflammatory, and anti-pulmonary injury. Naringin and its aglycone naringenin are dihydroflavonoids. Naringin has an antitussive effect on experimental cough, chronic airway inflammation and cough induced by airway neurogenic inflammation under physiological conditions. It is worth noting that naringin belongs to peripheral antitussive drugs (Gao, Li, Yang, Fang, & Su, 2011). Naringin can significantly inhibit the EGF-induced increase in MUC5AC mRNA and protein expression, and its mechanism may be related to its inhibition of MAPKs/AP-1 and NF-κB signaling pathway (Nie et al., 2012). After entering the intestine, most of naringin is metabolized by intestinal flora into naringenin, then naringenin is absorbed into the blood by passive diffusion and plays biological activities (Li et al., 2020; Zeng et al., 2020). Naringenin has been proved to be able to regulate the EGFR-PI3K-Akt signaling pathway and ERK/MAPK signaling pathway to inhibit the production of reactive oxygen species (ROS) and the activation of NF-κB, which finally inhibits the expression of MUC5AC (J. Yang, Li, Zhou, Kolosov, & Perelman, 2011). In our results, molecular docking suggested that naringenin present better binding ability to the target proteins AKT1 and EGFR than naringin. So, study on structure activity relationship among naringenin, naringin and other dihydroflavonoidsmay provide inspiration to subsequent drug discovery for COPD, lung cancer and other malignant lung diseases.

5. Conclusion

Network pharmacology was employed to systematically investigate the active ingredients and targets of HJH in treatment of COPD and lung cancer. And then, the common pharmacodynamic network of HJH for the two malignant respiratory diseases was firstly described. Furthermore, naringenin was proved to strongly bind with AKT1 and EGFR. So far, common pharmacodynamic

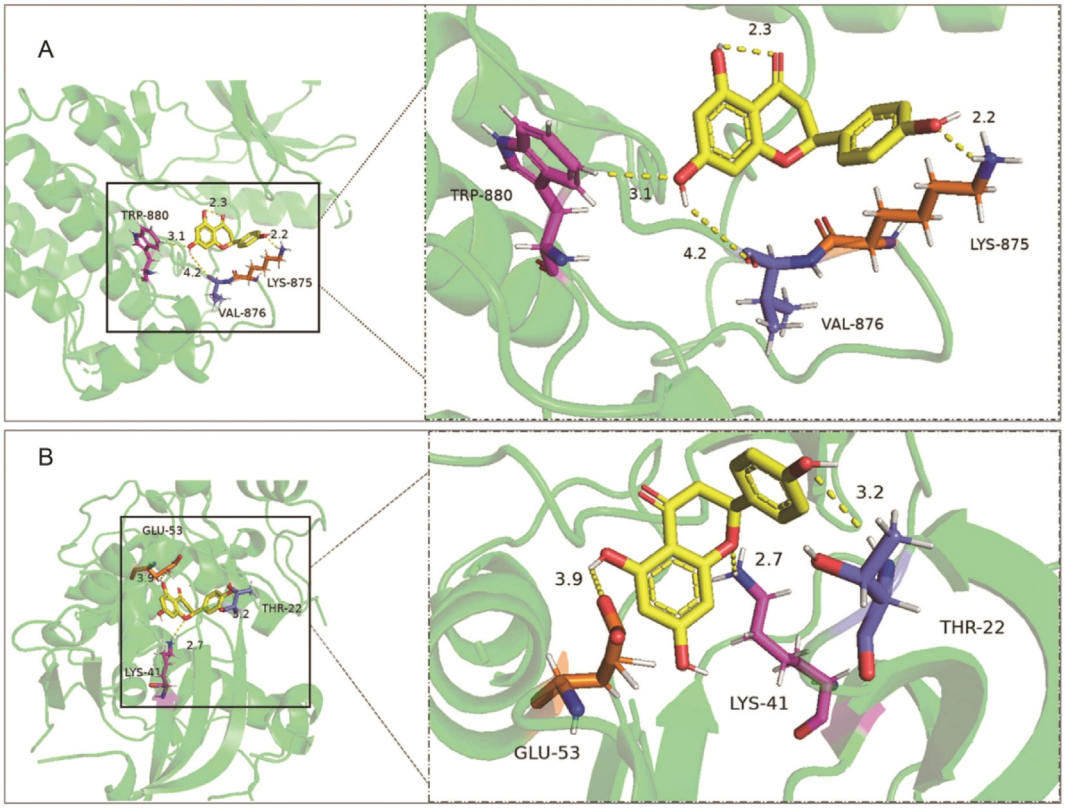


Fig. 6. Docking results of naringenin to AKT1 and EGFR.

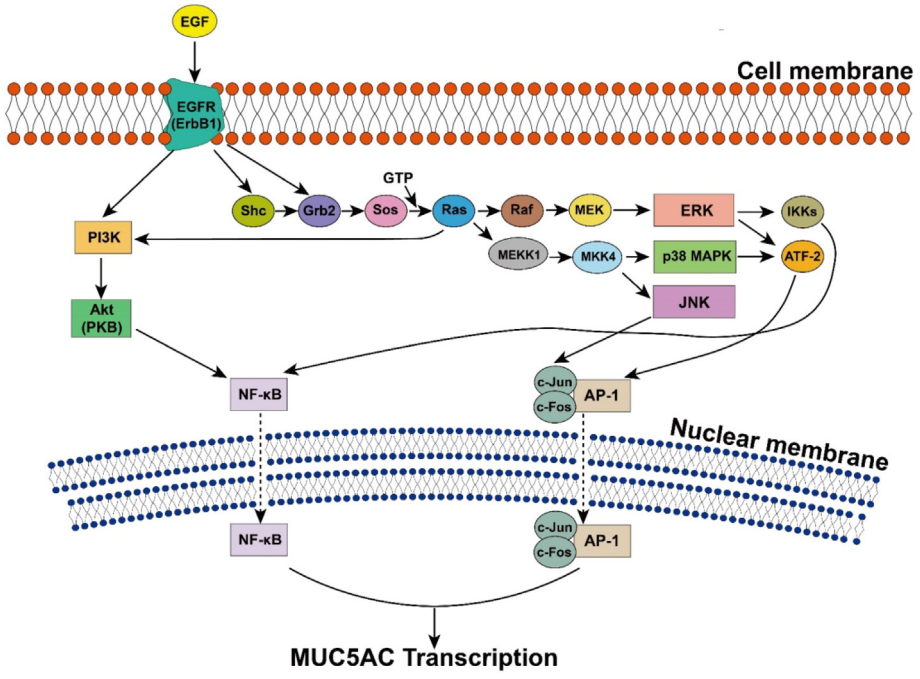


Fig. 7. Mechanism of EGF-induced MUC5AC expression.

mechanism of HJH for the two malignant respiratory diseases was firstly described, with hoping to provide inspiration to further treatment and drug discovery. Furthermore, our research may provide the scientific basis for understanding the "Same treatment for different diseases" strategy in traditional Chinese medicine.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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