Exploring the Mechanism of Feilike Capsule in the Treatment of Chronic Obstructive Pulmonary Disease Based on Network Pharmacology, Transcriptomics and Molecular Docking Technology

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ABSTRACT

To explore the molecular mechanism of Chronic Obstructive Pulmonary Disease (COPD) based on network pharmacology, transcriptomics and molecular docking technology. Databases including TCMSP, SwissTarget Prediction, OMIM, Gene Cards, Drug bank, String, Metascape were used to search the active components and target proteins of feilike capsule, the target proteins shared with COPD were screened out, and the information of signal pathways and biological functions involved by these target proteins were obtained. 114 active ingredients of Feilike Capsule were obtained, including 214 potential targets for treating COPD. The protein interaction network was obtained through String database and Cytoscape software, and 14 potential core targets were obtained by network topology analysis, which were AKT1, TNF, SRC, MMP9, PTGS2, CASP3, EGFR, TP53, STAT3, MAPK3, GAPDH, MAPK1, IL2 and STAT1. Go function enrichment analysis and KEGG pathway enrichment analysis were carried out on the potential targets of Feilike Capsule in treating COPD by using Metascape database, and important biological processes, cell composition, molecular functions and signal pathways related to the targets were screened by R language. The results showed that the GO biological process was related to cellular response to nitrogen compound and inflammatory response the GO cell composition was related to perinuclear region of cytoplast, membrane raft and membrane micro-domain and the GO molecular function was related to protein kinase activity, phosphotransfer activity, alcohol group as acceptor, etc. In addition, the main signal pathways involved were PIK3 - Akt signal pathway, HIF - 1 signal pathway and MAPK signal pathway. Meanwhile, the gene chip data set related to COPD in GEO database was analyzed using transcriptome method, and the differentially expressed genes between COPD patients and healthy people were obtained, which were verified and compared with the target information predicted by network pharmacology, and new targets were obtained, namely BCHE, PLA2G7, MMP9, PLA2G4A, LGALS3, HSPA1A. Finally, the results of molecular docking confirmed that the active components had good binding ability with the target. Feilike capsule plays a role in treating COPD with multi -components, multi - targets, multi - signal channels and multi - biological functions.

KEYWORDS
Feilike capsule, Chronic obstructive pulmonary disease, Network pharmacology, Transcriptomics, Molecular docking

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INTRODUCTION

Chronic Obstructive Pulmonary Disease [COPD] is a common, preventable, and treatable disease characterized by persistent respiratory symptoms and airflow limitation due to airway and alveolar abnormalities.[1] COPD has a high case - fatality rate and seriously affect the quality of the patient's life, as well as imparts heavy economic burdens on the families of patients and society.[2] The mainstay of western medicine for COPD involves bronchodilators, glucocorticoids and so on. However, these drugs can only relieve the symptoms of some patients, the long - term results are still not satisfactory.[3] Along with the expanded usage of TCM in COPD, Chinese patent medicine for relieving cough and asthma and clearing away heat and toxic materials, represented by Feilike capsule, are gradually recognized for their therapeutic effects. To a certain extent, Chinese patent medicine can reduce the number of acute attacks of COPD and delay the deterioration of lung function. Feilike capsule is composed of *Scutellaria baicalensis Georgi, Peucedanum praeruptorum, Stemona Stemona, Gentiana scabra, Hedyotis diffusa* and *Rhubarb*. It has the functions of relieving cough and asthma, clearing away heat and toxic materials, reducing qi and eliminating phlegm. Among them, *Gentiana scabra* is a common medicinal material of Miao medicine in Guizhou Miao medicine name "Ruidingmou", which is mostly used for cough due to lung heat. As a traditional national medicine, Wutonggen is widely used in Miao, Tujia and other ethnic minorities, and is mostly used to treat asthma and acute bronchitis. Feilike capsule is an effective Chinese patent medicine for treating COPD, but its mechanism needs to be further explored. At present, the research on the mechanism of Chinese patent medicine in the treatment of diseases is mostly carried out by basic experiments, resulting in single information and unable to really clarify its action mechanism, and thus it cannot be widely applied in clinic. In the present study, network pharmacology, transcriptomics and molecular docking were used to analyze the complex network relationship among the multiple targets of Feilike Capsule in treating COPD, and to predict its potential targets and mechanism of action in preventing and treating COPD, thus providing a basis for clinical research and experimental research. The study was conducted in accordance with the basic and clinical pharmacology and toxicology policy for experimental and clinical studies.[4]

MATERIAL AND METHODS

Screening of Active Ingredients in Feilike Capsules

All components of the seven Chinese medicines in Feilike capsule were retrieved from the traditional Chinese medicine systems pharmacology database and analysis platform and related literatures.[5-8] The screening conditions were based on oral bioavailability (OB, ≥ 30 %) and drug - likeness (DL ≥ 0.18), so as to obtain the drug composition and targets. The resulting structures were saved in 3D SDF format. Next, the structured files were converted to the simplified molecular - input entry specification file using open Babel GUI software, and then imported into excel to filter the duplicate values. The common components of each traditional Chinese medicine were recorded.

Drug Targets and Construction of Traditional Chinese Medicine - Component - Target Network Diagram

The SDF of the active compounds were imported into the Swiss Target Prediction to obtain the target protein of the ingredient and download the csv file to screen the effective target protein of the active ingredient, with the standard of probability ≥ 0.1. The screened targets were combined, and the same target in each active ingredient of each traditional Chinese medicine was de - duplicated, and the unique value was retained. Finally, the target file was imported into Cytoscape software to construct the network diagram of traditional Chinese medicine - components - targets.

Acquisition of COPD targets

"Chronic obstructive pulmonary disease" was used as a keyword to search OMIM. Genecards Drugbank and other databases. The obtained targets were summarized and de duplicated to obtain the disease targets of COPD.

Mapping of the Target of Feilike Capsule and the Common Target of COPD

The drug target and disease target R language software were analyzed, the "Venn diagram" package of R language was used to draw the Wayne diagram, and the action target of Feilike capsule in the treatment of COPD was obtained.

PPI Analysis

The target of Feilike capsule in the treatment of COPD was imported into String database for protein - protein interaction [PPI]. The analysis results were calculated using R language, and the core targets of the PPI network were screened according to the median of the values of Betweenness, Closeness, Degree, Eigenvector, LAC, and Network of the targets, then the calculation results were imported into Cytoscape software for visualization.

Go Enrichment Analysis and Kegg Enrichment Analysis

Metascape platform has a comprehensive annotation function and updates the data of gene annotation every month.[8] the targets of Feilike capsules in treating COPD were imported into the Medscape database and the species was set to for gene ontology function enrichment analysis and Kyoto Encyclopedia of genes and Genomes Kyoto Encyclopedia of genes and genomes, KEGG pathway enrichment analysis. The Go analysis includes biological process, cellular component, and molecular function. Import the analysis results into R language for composition. Go analysis included biological process, cellular component, and molecular function. Finally, the analysis results were imported into R language for visualization.

GEO analysis

The platform annotation files of GSE76925 and GPL10558 - 50081 were obtained by retrieving "synchronous obstructive pulmonary disease" in GEO database. The chip contained 111 samples of COPD patients and 40 samples of healthy control group. Perl software was used to read the file, and the platform annotation file was used to annotate the probes, and the probes that did not match the genes were eliminated. When different probes were mapped to the same gene, the mean value of different probes was selected as the final expression value of this gene. The "limma" package in R language was used to analyze the gene matrix and screen differentially expressed genes. Absolute value of Lock > 1 and the P - value < 0.05 was set as cut - offs. DEGs were displayed using heat maps and volcano maps. The targets of DEGs and Feilike capsule in the treatment of COPD were mapped to each other.

Molecular Docking

The core targets screened by PPI network were imported into UniProt for retrieval, and the screening conditions were set as human and reviewed, so as to obtain the corresponding protein of target gene. The protein conformation with "X - ray" of method was selected and the corresponding PDB format file of the conformation was downloaded in the PDB database was used for molecular docking analysis of the core targets screened by PPI and their corresponding chemical components, and the total score value was obtained. Finally, the 3D display was performed.

RESULTS

The Active Ingredients of Feilike Capsules and Their Corresponding Targets

Through searching TCMSP and related literature, a total of 114 active ingredients in each single Chinese medicine of Feilike capsules meeting OB ≥ 30 % and DL ≥ 0.18 were obtained. The SDF format file of active ingredients was imported into openbabelgui software and converted into smiles number. After that, the smiles number was imported into Excel software to filter duplicate values. A total of 5 components of 7 traditional Chinese medicines of Feilike capsule were obtained, which were. Traditional Chinese medicines containing A1 included Scutellaria *baicalensis* George, *Stemona Stemona*, *Hedyotis diffusa* and *Peucedanum praeruptorum*. Traditional Chinese medicines containing A2 included *Scutellaria baicalensis* Georgi, *Stemona Stemona* and *Peucedanum praeruptorum*. Traditional Chinese medicines containing A3 components included *Scutellaria baicalensis* Georgi, *Stemona Stemona* and *Hedyotis diffusa.* Traditional Chinese medicines containing A4 included *Scutellaria baicalensis* Georgi and Chinese parasol root. Traditional Chinese medicines containing B1 included *Hedyotis diffusa*, *Peucedanum praeruptorum*, *Piper rubrum* and *Gentiana scabra*. The unique active ingredients of each traditional Chinese medicine were renamed by using the initials and Arabic numerals of the pinyin names of traditional Chinese medicines (Table 1).

Name	Component	Name	Component	Name	Component
HQ1	MOL000173	BB3	MOL005384	QH8	MOL013078
HQ2	MOL000228	BB4	MOL009361	QH9	MOL013079
HQ3	MOL000525	BB5	MOL009363	QH10	MOL013081
HQ4	MOL000552	BB6	MOL009374	QH11	MOL013083
HQ5	MOL001458	BB7	MOL009377	QH12	MOL013087
HQ6	MOL001490	BB8	MOL009379	QH13	MOL013098
HQ7	MOL001506	BB9	MOL009380	QH14	MOL013100
HQ8	MOL002714	BB10	MOL009382	QH15	MOL013103
HQ9	MOL002879	BB11	MOL009387	HGY1	Kaempferia galangal phenol
HQ10	MOL002897	BB12	MOL009388	HGY2	3,5,7,3 - tetrahydroxy - 4
HQ11	MOL002908	BB13	MOL009394	HGY3	Wheat flavin
HQ12	MOL002909	BB14	MOL009411	HGY4	Emodin methyl ether
HQ13	MOL002910	BB15	MOL009419	HGY5	Emodin
HQ14	MOL002911	BB16	MOL009422	HGY6	Mignonette,
HQ15	MOL002913	BB17	MOL009423	HGY7	Caffeic acid
HQ16	MOL002914	BB18	MOL009424	HGY8	Gallic acid
HQ17	MOL002915	BB19	MOL009430	HGY9	3',4' - dimethoxy flavone
HQ18	MOL002917	BB20	MOL009433	HGY10	Umbelliferolactone
HQ19	MOL002925	BB21	MOL009434	HGY11	16β, 17 - dihydroxy -
HQ20	MOL002926	BB22	MOL009436	HGY12	16β - hydroxy-17 - acetoxy - [- -] -
HQ21	MOL002927	BB23	MOL009441	HGY13	16β, 17 - dihydroxyl -
HQ22	MOL002928	BHSSC1	MOL001659	HHLD1	1, 3, 7, 8 - tetrahydroxy
HQ23	MOL002932	BHSSC2	MOL001663	HHLD2	Rhodanthenone D1, 3, 6, 7 -
HQ24	MOL002933	BHSSC3	MOL001670	HHLD3	Rhodanthenone D1, 3, 6, 7 -
HQ25	MOL002937	QH1	MOL001941	HHLD4	1, 3, 7 – trihydroxy - 4, 8 dimethylxanthon
HQ26	MOL008206	QH2	MOL001942	HHLD5	Ethyl gallate
HQ27	MOL010415	QH3	MOL002644	HHLD6	Salicylic acid
HQ28	MOL012245	QH4	MOL004653	HHLD7	2α - hydroxyursolic
HQ29	MOL012266	QH5	MOL005100	WTG1	A - lapachone
BB1	MOL000392	QH6	MOL007154	WTG2	9 – hydroxyl – α - lapachone
BB2	MOL001558	QH7	MOL013077	WTG3	3,4, 5 - trihydroxy

Table 1. Active Ingredients of Feilike Capsule.

The SDF format files of all active ingredients were imported into Swiss Target Prediction database to predict targets and 6144 pieces of target protein information were obtained, and 901 target proteins were obtained after eliminating duplicate values. The information of active ingredients and corresponding targets was imported into Cytoscape software to construct the network diagram of traditional Chinese Medicine - active ingredients - target protein, (Figure 1). The degree of freedom degree value of

the target was in the range of 1 - 50. The greater the value, the higher the importance of the target, indicating that it participates in more biological functions. Cytoscape analysis showed that 114 components of Feilike Capsule acted on human body through 901 targets, and there were 6144 connections between components and action targets. Due to the complexity of the network, only targets with a degree value of 10 - 50 were displayed. The size of each node was positively correlated with the degree value. Circular nodes represented traditional Chinese medicine, regular octagonal nodes represented chemical components, and rectangular nodes represented target proteins.

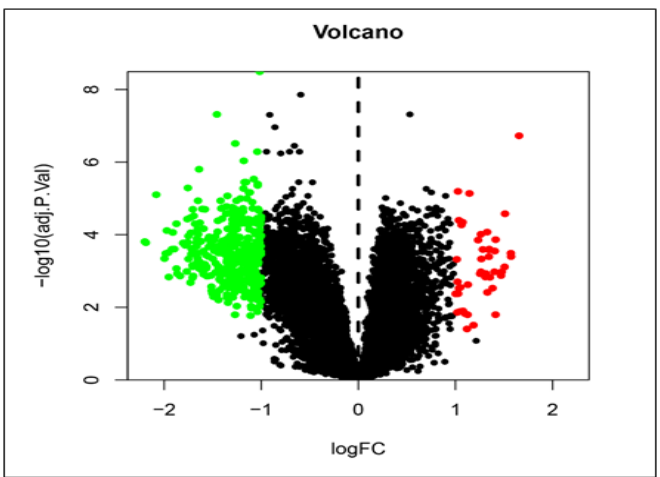

Figure 1. DEGs Volcano Map.

Coped Disease Targets

Using "chronic obstructive pulmonary disease" as the keyword, 1235 targets were retrieved in OMIM database, 856 targets in gene cards database and 114 targets in Drugbank database. 1987 disease targets were obtained by summarizing and de-duplicating the targets.

Drug - Disease Common Target and PPI Analysis

The targets of Feilike capsule and COPD disease targets were imported into R language. Using the "venn diagram" program package of the software, a total of 214 action targets of Feilike capsule in the treatment of COPD were obtained and visually displayed. The target of Feilike Capsule in treating COPD was imported into String database, and PPI network and data were obtained. The PPI data was imported into Cytoscape, and the CytoNCA plug - in of the software was used for calculation. The R language was used to analyze the results, and the PPI network targets were selected according to the median values of Betweenness, closeness, degree, eigenvector, lac, and network of the targets in the results. The targets screened by the R language were imported into Cytoscape to construct a sub - network, and the CytoNCA plugin was used again for calculation. Similarly, the operation results were imported into R language for analysis. After 3 repetitions, 14 core targets were finally obtained, namely AKT1, TNF, SRC, MMP9, PTGS2, CASP3, EGFR, TP53, STAT3, MAPK3, APDH, MAPK1, IL2 and STAT1. The results were visually displayed by Cytoscape.

Go Analysis and Kegg Analysis

The target of Feilike capsule in the treatment of COPD was imported into metascape database, and the species was set as *H. sapiens* for go function enrichment analysis and KEGG pathway enrichment analysis. The results showed that the target of Feilike capsule in the treatment of COPD involves 2486 biological processes, 148 cell components, 235 molecular functions and 177 signal pathways. The analysis results of BP, CC and MF are sorted according to the two values of Count Gene In GO and hit list, the number of genes involved in this biological process, cell composition or molecular function and FDR log Q – value , adjusted p - value. The higher the Count value, the more meaningful it was, and the smaller the FDR value, the more meaningful it was. The top 20 information were displayed in R language. The results showed that the biological process was related to cellular response to nitrogen compound and informational response, the cell composition was related to perinuclear region of cytoplast, membrane raft and membrane microdomain and the molecular function was related to protein kinase activity, phosphotransfer activity, alcohol group as acceptor, etc. The KEGG analysis results were sorted according to the three values of count, FDR and ratio % Ingo, ratio of the number of genes enriched in this pathway to the total number of genes. The top 30 signal pathways were displayed in R language. The results showed that the signal pathways involved in the action target of Feilike capsule in the treatment of COPD were PIK3 - Akt signal pathway, HIF - 1 signal pathway and MAPK signal pathway.

Geo Analysis

As mentioned in the Section Materials and Methods, the GSE76925 was analyzed using R language to obtain a total of 452 DEGs. Among them, 45 were up - regulated genes and 407 were down - regulated genes. The "ggpubr" package of R language was used to draw volcano map and the "pheatmap" package was used to draw heat map. Combining DEGs with finlike capsule in treating COPD, six common targets were obtained, which included BCHE, PLA2G7, MMP9, PLA2G4A, LGALS3 and HSPA1A. The genes with significant high expression were HTR2B, FGG, CD19, DPYS, TNFRSF17, COMP, COL10A1, HS3ST2, CHIT1, CCL19. The genes with significantly low expression were KLF5, SUMO1, LOC391359, LOC645231, ADI1, DNTTIP2, B3GNT5, ID4, LOC727962 and PPIB (Figure 2).

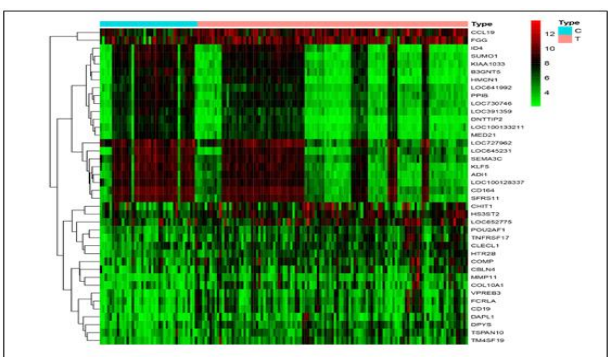

Figure 2. Degs Heat.

Molecular Docking

The core targets and protein conformations of Feilike Capsule in treating COPD are as follows: AKT1 (1UNQ), TNF (4Y6O), SRC (1FMK), MMP9 (6ESM), PTGS2 (5F19), CASP (2J32), EGFR (3POZ), TP53 (1YC5), STAT3 (5AX3), MAPK3 (4QTB), GAPDH (3GPD), MAPK1 (2Y9Q), IL2 (1M48) and STAT1 (1BF5). Sybyl - X docking software was used for molecular docking and obtaining the total score. The total score value ≥ 5.0 was taken as the screening standard (Table 2).

Target	Component	Total Score	Target	Component	Total Score
SRC	BB10	7.6908	CASP3	HQ6	6.7719
	BB11	7.5824		QH9	6.1955
	BB7	7.2591		BB7	5.3183
	QH8	6.6503	EGFR	HGY3	8.2818
	BB20	6.4169		HQ14	8.0102
	HHLD1	6.1848		HQ17	7.3409
	QH7	5.9861		QH14	7.327
	HQ3	5.812		HQ21	7.3
	HQ21	5.5018		QH9	7.1171
	HHLD4	5.4286		QH8	6.8472
	QH4	5.3982		QH12	6.7382
	HQ12	5.3031		HQ12	6.7342
	BB23	5.2341		HQ24	6.6825
	HQ18	5.0985		QH4	6.5923
MMP9	HQ12	9.2547		BB1	6.4479
	HQ11	7.0878		HQ23	6.3694
	HQ14	7.0584		HQ18	6.2392
	HQ22	6.955		BB14	6.0699
	HQ17	6.8438		HQ26	6.0184
	HQ28	6.7786		BB23	5.9881
	HGY6	6.7753		HQ1	5.9209
	A4	6.6452		BB12	5.8602
	HQ8	6.5135		HQ11	5.7496
	QH5	6.5107		HGY2	5.7333
	HGY2	6.4497		B1	5.6921
	HGY3	6.3837		HGY6	5.6364
	HQ19	6.3725		HQ3	5.5448
	B1	6.3115		BB20	5.5127
	HQ3	6.1776		HQ8	5.4289
	HQ23	5.9793		BHSSC3	5.2828
	HQ24	5.9637		HHLD1	5.2038
	HQ18	5.8799		HGY5	5.1943
	HGY9	5.8531		HGY1	5.1749
	HGY1	5.6126		WTG2	5.1263
	QH7	5.3912	TP53	BB10	9.6084
	HQ26	5.3823		HGY11	6.9591
	QH13	5.3654	STAT3	HQ2	5.6215
	HGY7	5.3386		BB15	5.1715
	QH14	5.0634	MAPK3	HQ8	6.7673
	HQ21	5.0131		BB20	6.2972
PTGS2	HQ6	9.9616	GAPDH	QH14	6.4064
	HQ27	9.767		QH11	6.0008
	HQ18	7.0022		HQ2	5.3058
	HQ21	6.7999	MAPK1	QH8	8.1604
	HQ23	6.3723		QH11	6.9913
	HQ29	6.3189		QH5	6.7059
	HQ14	6.2996		QH9	6.6179
	HQ17	6.2142		BB11	6.566
	HQ4	5.8638		BB9	6.081
	QH1	5.8438		HGY9	5.1633
	QH13	5.7906		BB20	5.1633
	HQ26	5.6942	IL2	QH11	5.5476
	WTG3	5.2891	STAT1	QH5	5.1596
	HQ12	5.196	AKT1	BB20	5.9738
	HQ19	5.1692		HGY3	5.947
	HQ2	5.1399		HGY2	5.1328
	HQ1	5.1314		HQ12	5.0757

HGY6	5.0635	TNF	BB10	6.6188
HQ24	5.0242		QH11	6.2558

Table 2. Docking Scores of Core Targets and Active Ingredients.

The greater the value, the better the binding degree between the ligand molecule of the active component of Feilike capsule and its receptor protein. The results showed that the total score of 117 chemical components, including BB20, HGY3, HGY2 and HQ12, docking with 14 target protein molecules, including AKT1, TNF, SRC and MMP9, was ≥ 5.0. The docking mode of representative active component molecules combined by each core target protein molecule was displayed (Figure 3).

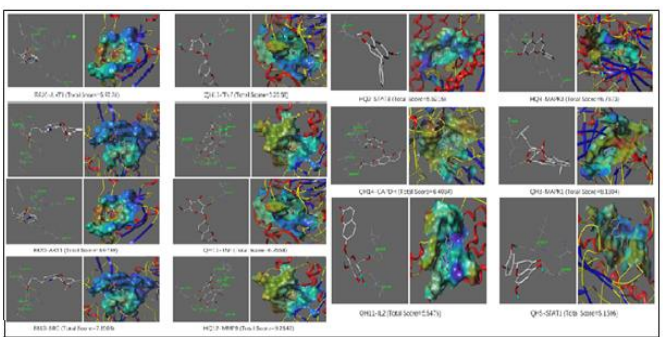

Figure 3. Represents the docking mode of core active ingredients and target protein molecules

DISCUSSION

Based on the method of network pharmacology, we found that multiple active ingredients of Feilike Capsule can act on the same target at the same time, and a single active ingredient can also act on multiple targets at the same time. According to the results of molecular docking, the main active ingredients of Feilike Capsule include Skimmin, (2R) – 7 – hydroxyl - 5 – methoxy – 2 – phenylchroman - 4 - one, Baicalein, Praeruptorin E, and so on. According to the topological analysis of PPI network, the therapeutic effect of Feilike Capsule on COPD may be more closely related to AKT1, TNF, SRC, MMP9, PTGS2, CASP3, EGFR, TP53, STAT3, MAPK3, GAPDH, MAPK1, IL2, STAT1 and other targets. Each target will be analyzed below.

AKT1: Many pathological processes of COPD are mediated by cigarette smoke, including apoptosis and proliferation of steady - state cells, degradation of Extra Cellular Matrix (ECM), production of protease and oxidative stress, and telomere dysfunction, which lead to the activation of DNA damage reaction pathway and finally lead to cell aging.[9] Aging cells can produce and secrete many harmful inflammatory and degradation mediators. AKT can regulate the survival and proliferation of lung cells by phosphorylating several anti - apoptotic proteins, and can also stimulate cell proliferation by promoting the accumulation of cyclin D.[10,11] Studies have shown that the lungs of transgenic mice with p16 gene deficiency have structural and functional resistance to emphysema induced by cigarette smoke, which is due to AKT regeneration and activation of protective signals.[12] found that TNF - α can promote the release of inflammatory factors such as IL - 6 and IL - 8 by activating NF κ B. The activation of NF - κB can be detected in sputum, macrophages and airway epithelial cells of COPD patients, which is related to the production of various inflammatory factors including IL - 1, IL - 6 and IL – 8 and chemokines.[13] found that tumor necrosis factor - α can induce airway epithelial cells to synthesize MUC5AC by activating NF - κB, thus promoting the development of COPD.

SRC: The hypertrophy and proliferation of airway smooth muscle may lead to irreversible airflow restriction. SRC is a non - receptor tyrosine kinase proto - oncogene. It is reported that SRC can regulate cell proliferation response to growth factors, contraction agonists and inflammatory mediators. Studies have proved that, the activation of SRC is necessary for mitosis and movement of human ASM cells. SRC regulates the proliferation and migration of human ASM cells, suggesting that SRC may play an important role in airway remodeling in patients with asthma and COPD. SRC is a potential therapeutic target, which can eliminate the proliferation and migration of ASM cells peculiar to airway of chronic severe asthma and COPD patients.

MMP9: Proteases are particularly related to the pathophysiological processes of many inflammatory pathways and mediators involved in the development of COPD. Inflammation changes protease / antiprotease balance, leading to progressive airway destruction and remodeling. Matrix metalloproteinase affect the occurrence and development of emphysema through direct and indirect mechanisms.[15] MMP - 9 mediates lung inflammation by degrading extracellular matrix, neutrophil chemotaxis and aggravating inflammation.[16] Studies have proved that, the increase of MMP - 9 is related to the obvious clinical features and the increased risk of exacerbation of COPD, and may be used as an accurate drug treatment target.

PTGS2: PTGS2 also known as cyclooxygenase - 2 is a key enzyme in prostaglandin biosynthesis. Under normal circumstances, this enzyme is not expressed in most cells. The PTGS2 of the body is up - regulated after exposure to cigarette smoke extract, and the level of PTGS2 is also increased during inflammation.[17] The activation of PTGS2 promotes the transcription and expression of prostaglandin E2 and inflammatory cytokines such as IL - 6, IL - 8 and IL - 1β, and mediates long - term and chronic inflammatory reactions in COPD patients[18].

CASP3: This target plays a central role in the process of apoptosis. Carcinogenic studies have found that the interaction between CASP3 gene polymorphism and smoking is associated with the high risk of lung cancer, while the low expression of CASP3 is associated with the high risk of NSCLC.[19]

EGFR: Airway inflammation is one of the main characteristics of COPD. Airway epithelial cells [AEC] respond to various stimuli including cigarette smoke by producing cytokines and chemokines, thus significantly promoting inflammatory response. This, in turn, causes inflammatory cells to regroup in the airway. Under normal conditions, the expression of cytokines is strictly regulated by negative regulatory molecules, thus limiting the inflow of inflammatory cells and restoring the dynamic balance of tissues. Therefore, inactivation or decreased expression of negative regulatory molecules may lead to sustained

cytokine expression and the development of airway inflammation. FOXO3a is a negative regulator of NF - k - mediated chemokine expression, and its decrease in activity is related to this mechanism. FOXO3a deficiency has been shown to increase the susceptibility to lung inflammation in mice that induced by CS.[20] In COPD airway, abnormal EGFR activity increased PI3 / Akt - mediated FOXO3a phosphorylation, thereby reducing nuclear FOXO3a and increasing chemokine expression.

TP53: This target can induce cell cycle arrest, apoptosis, aging, DNA repair or metabolic changes to cope with oxidative stress and DNA damage. Studies have confirmed that TP53 is overexpressed in lung tissues of patients with emphysema.[21] A genome - wide association studies of 365 patients with emphysema confirmed that the single nucleotide polymorphism of TP53 gene is related to the apoptosis signal in the lungs of smokers and the changes of smoking - related emphysema.[22] Aging is related to the pathogenesis of COPD, and the role of TP53 in aging may also reveal its role in COPD. STAT3, also known as signal transduction and transcription activator 3, is an intracellular signal transduction molecule, which can be activated by various extracellular stimuli, thus playing an important role in signal transduction in inflammatory reaction. In the signal transduction of IL - 6, IL - 6ST promotes phosphorylation of JAK2 and phosphorylation of STAT3, and homodimerization of STAT3. They transport to the nucleus to bind DNA and activate transcription of STAT3 target gene, thus promoting the occurrence and development of inflammatory reaction. Blocking STAT3 signal with p - STAT3 inhibitor or siRNA targeting STAT3 can inhibit the expression and secretion of MMP - 2 and MMP - 9 induced by IL - 33, and significantly delay the pathological changes of lung tissue in model rats, such as alveolar wall thickening, alveolar collapse and inflammatory cell infiltration.[23]

MAPK1 and MAPK3: MAPKs are a kind of serine / threonine protein kinases, which are the signal messengers of cells, responsible for carrying signals from the cell surface to the nucleus, and participating in the transmission of various inflammatory cytokines and stress signals. It was found that the expression of MAPK was increased in sputum induced in COPD patients, and the increase of MAPK expression was positively correlated with the increase of IL - 8 and neutrophils in sputum supernatant. Studies have shown that MAPK activation is closely related to airway remodeling in COPD patients. Reducing VEGFA expression level in COPD model rats can inhibit airway remodeling and improve COPD.[24] Therefore, MAPK signal transduction pathway may be one of the important mechanisms for the occurrence and development of COPD.

GADPH: In the development of COPD, the intracellular antioxidant defense of red blood cells must maintain the integrity of plasma membrane through the production of NADPH + in order to obtain a sufficient number of non - protein SH groups. 3 - GAPDH is a highly conservative protein, which plays a key role in glycolytic pathway. [25] The research data showed that, when healthy volunteers were compared with COPD patients, GAPDH activity in all study groups was significantly improved, and the increase was even greater after adding fine particles. The results showed that PM2.5 in cities could induce red blood cell damage in COPD patients by activating GAPDH. IL - 2 is a T cell growth factor, which can mediate the activation, proliferation and differentiation of T and B cells, play an important role in inflammatory reaction, and have immunoregulatory function. Autoimmune response is considered to play a role in the pathogenesis of COPD. It is found that the IL - 2 level of COPD and asthma patients infected by gram - positive bacteria is obviously decreased, which may mean that the immune system will be affected to a certain extent when the body is infected.[26,27]

STAT1: Studies have found that, COPD is related to the increase of pulmonary macrophages, but there are bacteria in the lower respiratory tract, such as *Haemophilus influenzae* and *Streptococcus pneumoniae.* This is related to the decrease of phagocytosis of COPD macrophages to these bacteria. The level of interferon - γ is increased in the airway of COPD patients, which is related to the decrease of phagocytosis. Interferon γ can activate JAK / STAT pathway through phosphorylation of STAT1, thus initiating signal transduction. Therefore, the deficiency of macrophage phagocytosis in COPD patients may be related to the decrease of STAT1 phosphorylation. The results of KEGG enrichment showed that the core targets of Feilike Capsule in treating COPD mainly involved PIK3 - Akt signal pathway, HIF - 1 signal pathway and MAPK signal pathway.

PIK3 – Akt: Oxidative stress can activate PIK3 - Akt signaling pathway, which is an important factor in the pathogenesis of COPD.[28] It is found that, PIK3 - Akt signaling pathway is involved in regulating the release of inflammatory mediators, activation of inflammatory cells and airway remodeling, thus playing a key role in the inflammatory response of COPD. Excessive inflammatory mediators can cause tracheal contraction and airway reconstruction, and at the same time produce elastase, MMPs and other enzymes, resulting in destruction of lung parenchyma and formation of emphysema. The poor effect of glucocorticoid on COPD is considered to be related to glucocorticoid resistance, and PIK3 - Akt signaling pathway plays an important role in regulating glucocorticoid resistance. Up - regulation of PIK3 - Akt signal may lead to the decrease of HDAC2 activity, which will damage the ability of glucocorticoid receptor α to inhibit the expression of proinflammatory factors, and lead to the increase of proinflammatory factors expression.[29] PI3K inhibitor can protect lung tissue from chronic lung injury induced by trypsin, inhibit inflammatory reaction and edema, and reduce emphysema and airway remodeling. This study predicts that Feilike Capsule may inhibit the activity of PI3K and AKT1 kinases by inhibiting the stimulation of cytokines upstream of this pathway, thus inhibiting the abnormal proliferation and delaying the survival of cells. HIF – 1 hypoxia inducible factor - 1 are a transcriptional activator of hypoxia induction and a regulator of oxygen homeostasis and physiological response.[30] HIF - 1 signaling pathway can regulate oxygen transport by influencing vascular remodeling and angiogenesis, and regulate oxygen utilization by participating in redox homeostasis and glucose metabolism.[31] Vascular endothelial growth factor is an important regulator of angiogenesis and vascular permeability, and its expression is induced by HIF - 1α. Studies have confirmed that HIF - 1 signaling pathway is activated in COPD patients with a history of smoking, and the overexpression of related proteins such as HIF - 1α, vascular endothelial growth factor and vascular endothelial growth factor 2 is related to the decline of lung function, quality of life and disease

progression of COPD patients.[32] Feilike capsule may improve the tolerance of organism to hypoxia environment through the regulation of HIF - 1 signal pathway, thus stabilizing COPD. MAPK is a group of serine / threonine protein kinases in cells, mainly including ERK, JNK, p38 and so on. Among MAPK family members, p38MAPK subgroup is most involved in airway inflammation and lung inflammation in patients with asthma and COPD. In particular, several environmental factors, including air allergens, cigarette smoke, air pollutants, virus and bacterial pathogens, activated the p38α subtype, and then up - regulated the expression of many pro-inflammatory cytokines and chemokine's, as well as the production of some fibrosis factors. Therefore, inflammation and remodeling of bronchus induced by p38MAPK signaling pathway play an important role in the formation, persistence and expansion of airflow restriction. Pathogens that often cause COPD deterioration, such as bacterial pathogens, can act synergistically with pro-inflammatory cytokines such as tumor necrosis factor - α, thus enhancing the signal transduction function of p38MAPK.[33] Tumor necrosis factor - α and Haemophilus influenzae trigger apoptosis by stimulating caspase - 3 activity mediated by p38 - MAPK. Apoptosis of human bronchial epithelial cells is also caused by p38 - MAPK signal through hydrogen peroxide which is usually used as an experimental inducer of oxidative stress. Due to the toxic effects of cytokines, bacterial pathogens and oxidative stress, p38MAPK signal transduction module is significantly involved in the induction of harmful damage to airway primitive cells.[34] P38MAPK, as a convergent signal synapse of several causes of COPD aggravation, can damage bronchial epithelium and its barrier function by continuously amplifying harmful pathogenic pathways. The increased epithelial permeability makes the airway more susceptible to bacterial infection. P38MAPK also plays a central role in the cellular mechanism of accelerated lung aging caused by COPD, especially in the small airway and lung parenchyma level of COPD patients. Activated p38MAPK upregulates microRNA miR - 570, thus inhibiting the expression of anti - aging protein sirtuin – 1.35 Feilike capsule may inhibit p38MAPK signaling pathway, thus improving airway mucus secretion and repairing airway inflammation injury in COPD patients. To further explore and verify the accuracy of target prediction, we downloaded the gene chip data set related to COPD from GEO database, screened DEGs between COPD patients and healthy control group, and compared with the results of network pharmacology research,. We obtained six common targets, namely BCHE, PLA2G7, MMP9, PLA2G4A, LGALS3 and HSPA1A. These potential targets may be the potential key target proteins of the main active ingredients of Feilike capsule for treating COPD. Overall, based on network pharmacology, transcriptomics and molecular docking technology, the mechanism of Feilike capsule in treating COPD is predicted. The results showed that Feilike capsule can play a therapeutic role in resisting oxidative stress, regulating inflammatory reaction, inhibiting pulmonary vascular smooth muscle contraction and resisting apoptosis through multiple components, multiple targets and multiple channels. This study has certain reference significance, but the results of network pharmacology are only obtained by computer virtual prediction.[35]

CONCLUSION

The conclusions of this study can only provide clues and ideas for the next experimental verification. The mechanism of Feilike capsule on COPD needs further animal and cell experiments to confirm.

AVAILABILITY of DATA and MATERIALS

The datasets analyzed in this study are available from the corresponding author on request.

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