The mechanism of treating chronic bronchitis by Fritillaria thunbergii was discussed based on network pharmacology

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Abstract. Objective: The mechanism of treating chronic bronchitis by Fritillaria thunbergii was studied by network pharmacology. Methods: The targets of active chemical components in Fritillaria thunbergii were predicted, the component-target-disease network was constructed, and the topological parameters of the network were analyzed; meanwhile, protein interaction network (PPI) was constructed, and gene GO functional annotation and KEGG pathway enrichment were analyzed. Results: There are 6 active ingredients and 44 potential targets of Fritillaria thunbergii in the treatment of chronic bronchitis, the HRAS PIK3CA, CCND1, CDK2, AKT1, MTOR, known targets such as Fritillaria thunbergii may be important targets for the treatment of chronic bronchitis. The treatment of chronic bronchitis by Fritillaria thunbergii mainly involves the biological processes such as peptidyl serine phosphorylation, platelet activation, protein C terminal binding insulin binding, exogenous transport atpase activity, histone kinase activity and so on, major signaling pathways include prostate cancer, melanoma, estrogen signaling pathway, pi3k-akt signaling pathway, etc. Conclusions: This study preliminarily revealed the molecular mechanism of Fritillaria thunbergii in the treatment of chronic bronchitis, laying a foundation for further experimental study on the basis of pharmacodynamic substances and mechanism of action.

Key words: Fritillaria thunbergii, Active ingredient, Chronic bronchitis, Network pharmacology, Molecular mechanisms.

1. Introduction
Fritillaria thunbergii is the dry bulb of Fritillaria thunbergii Miq. in liliaceae, it has the effect of clearing heat, resolving phlegm, relieving cough and removing toxin, removing carbuncle, for wind heat cough, phlegm and fire cough, lung carbuncle, breast carbuncle, scrofula and sores[1]. It is well known that it is a common medicine in traditional Chinese medicine prescription. Modern studies have shown that it has antitussive and expectorant effects, analgesic and anti-inflammatory effects, anti-ulcer effects, antidiarrheal effects, antibacterial and anti-tumor effects, among which antitussive and expectorant effects, relaxation of tracheal smooth muscle anti-inflammatory effects and reversal of bacterial resistance and other effects constitute the pharmacological basis for the treatment of respiratory diseases[1]. It was found that these pharmacological effects were related to the content of alkaloids and other active components in Fritillaria thunbergii[2].
Chronic bronchitis is a chronic, nonspecific inflammation of the tracheal bronchial mucosa and surrounding tissues due to infection or non-infection (allergic oxidative stress, etc.) [3]. The patient has cough, phlegm, asthma and other clinical symptoms, repeated attacks on their quality of life caused serious impact. In recent years, the global prevalence of chronic bronchitis is increasing year by year, and the death rate is also increasing significantly. Infection is an important cause of acute exacerbation of chronic bronchitis, and inflammation is the core mechanism of the development of chronic bronchitis [4-5]. In the past, the treatment of chronic bronchitis was mostly treated with western medicine. Although the disease could be effectively controlled, the patients were prone to relapse, and the long-term effect was not ideal [6-7]. Moreover, the treatment based on antibiotics will increase the occurrence of bacterial resistance and adverse drug reactions [8] so that making treatment more difficult. Traditional Chinese medicine (TCM) has the characteristics of overall regulation and multi-target intervention in the treatment of chronic bronchitis with high therapeutic safety. In recent years, network pharmacology, based on system biology and multidirection pharmacology, integrates computer biology and network analysis to explain the integrity and systematicness of drug target disease interactions from the perspective of multi-component, multi-target and multi-pathway[9-10].

Network pharmacology can systematically and comprehensively reveal the pharmacodynamic basis and mechanism of Fritillaria thunbergii in the treatment of chronic bronchitis from the cellular and molecular level. Based on this, this paper adopts the method of network pharmacology to predict the target and signal pathway of effective components of Fritillaria thunbergii for the treatment of chronic bronchitis, so as to provide reference for the molecular mechanism and in-depth research of Fritillaria thunbergii for the treatment of chronic bronchitis.

2. Materials and methods

2.1. The establishment of chemical constituents
Through the comprehensive database of traditional Chinese medicine (TCMID,http://www.megabionet.org/tcmid/search/) and Chinese medicine system pharmacology analysis platform (TCMSP,http://lsp.nwu.edu.cn/tcmsp.php), Search for all chemical constituents of Fritillaria thunbergii.

2.2. Screening of active ingredients
Through TCMSP database, ADME parameters (OB≥30% and DL≥0.18) as the standard, Screening the active chemical constituents of Fritillaria thunbergii; used the PubChem database to find the structural formula for the active chemical ingredients.

2.3. Screening and establishment of targets
The targets of active chemical constituents of Fritillaria thunbergii were found and the data set of active chemical constituents was established with The Database ClassesTCMSP SwissTargetPrediction (http://www.swisstargetprediction.ch/). Identify gene and protein targets associated with chronic bronchitis and establish their target data sets with OMIM (http://www.omim.org/), DrugBank (https://www.drugbank.ca/) and TTD (http://bidd.nus.edu.sg/group/tdt/tdt.asp). Finally, all the selected targets were transformed into UniProtID format by UniProt database query.

2.4. Network construction and analysis
The component - target - disease network was constructed by PPI (http://www.genome.jp/kegg/) network analysis. Using Cytoscape3.6.1 software, the above network is analyzed visually to obtain the value of each node Degree、Betweennesscentrality、Closenesscentrality three topology parameters. Targets whose values of the above three topological parameters are greater than the median values of all points are selected as a potential target for the treatment of chronic bronchitis.
2.5. Biological process analysis

KEGG pathway analysis and GO (GeneOntology) biological process analysis were performed on the screened potential targets using DAVID database (https://david.ncifcrf.gov/). Then, the selected potential targets were analyzed by using STRING database.

2.6. To construct the pathway diagram of *Fritillaria thunbergii* in the treatment of chronic bronchitis

The KEGGMapper function in KEGG signal pathway database is used to target potential targets, the biological effect of multi-target and multi-pathway therapy on chronic bronchitis was verified by labeling the signal pathway that is most closely related to chronic bronchitis.

3. Result

3.1. Screening of active ingredients of *Fritillaria thunbergii*

A total of 17 chemical constituents reported by *Fritillaria* thunbergii were obtained from PubMed TCMSP and other databases of CNKI, and 6 active constituents were screened according to ADME parameters (OB 30% and DL 0.18), and their structural formulae were downloaded, the results are shown in table 1.

| MolID       | name                               | OB(%) | DL    | Chemical structure  |
|-------------|------------------------------------|-------|-------|---------------------|
| MOL000358   | beta-sitosterol                    | 36.91 | 0.751 | ![beta-sitosterol](image) |
| MOL001004   | pelargonidin                       | 37.98 | 0.212 | ![pelargonidin](image) |
| MOL004440   | Peimisine                          | 57.40 | 0.805 | ![Peimisine](image)  |
| MOL004444   | Ziebeimine                         | 64.24 | 0.704 | ![Ziebeimine](image) |
| MOL004446   | 6-Methoxyl-2-acetyl-3-methyl-1,4-   | 33.30 | 0.572 | ![6-Methoxyl-2-acetyl-3-methyl-1,4-naphthoquinone-8-O-beta-D-glucopyranoside](image) |
| MOL004450   | Chaksine                           | 65.63 | 0.664 | ![Chaksine](image)   |
3.2. Target prediction of the effective components of *Fritillaria thunbergii*

The TCMSP SwissTargetPrediction database was used to retrieve all targets of the active compound, and the repeated targets were deleted. Finally, a total of 93 targets were obtained. A total of 1036 disease targets were identified by OMIM and GeneCards databases. Finally, all the selected targets were transformed into UniProtID format by UniProt database query.

3.3. Screening of potential targets of *fritillaria thunbergii* for the treatment of chronic bronchitis

The intersection of drug targets and disease targets was obtained, 124 intersection targets were obtained, and the Wayne diagram was drawn. The results are shown in figure 1. Input the intersection targets into the String database (https://string-db.org/) to build the PPI network, the PPI network was analyzed visually by cytoscape3.6.1 software. The median values of the three topology parameters of all nodes are obtained to be 20 (Degree), 0.0019 (Betweennesscentrality), 0.5236 (Closenesscentrality), nodes that meet the screening criteria are selected as potential targets, as shown in table 2; meanwhile, the potential target PPI network was constructed by using cytoscape3.6.1 software, as shown in figure 2.

![Venn diagram for the treatment of chronic bronchitis by Fritillaria thunbergii](image1)

**Figure 1.** Venn diagram for the treatment of chronic bronchitis by *Fritillaria thunbergii*

![Intercross protein interaction network of fritillaria thunbergii in the treatment of chronic bronchitis](image2)

**Figure 2.** Intercross protein interaction network of *fritillaria thunbergii* in the treatment of chronic bronchitis
Table 2. Topological parameters of potential targets of fritillaria thunbergii in the treatment of chronic bronchitis

| UniProt CID | name     | Degree | BetweennessCentrality | ClosenessCentrality |
|-------------|----------|--------|------------------------|---------------------|
| P01112      | HRAS     | 65     | 0.0239                 | 0.6740              |
| P42336      | PIK3CA   | 44     | 0.0170                 | 0.5894              |
| P24385      | CCND1    | 60     | 0.0166                 | 0.6359              |
| P24941      | CDK2     | 34     | 0.0082                 | 0.5674              |
| P31749      | AKT1     | 83     | 0.0696                 | 0.7578              |
| P42345      | MTOR     | 51     | 0.0117                 | 0.6224              |
| Q07817      | BCL2L1   | 47     | 0.0167                 | 0.6070              |
| O14757      | CHEK1    | 33     | 0.0027                 | 0.5596              |
| P27986      | PIK3R1   | 38     | 0.0123                 | 0.5782              |
| P24864      | CCNE1    | 25     | 0.0045                 | 0.5328              |
| P04637      | TP53     | 87     | 0.0746                 | 0.7722              |
| P00374      | DHFR     | 23     | 0.0063                 | 0.5259              |
| P04818      | TYMS     | 29     | 0.0106                 | 0.5422              |
| Q00987      | MDM2     | 48     | 0.0091                 | 0.6131              |
| P00533      | EGFR     | 77     | 0.0619                 | 0.7262              |
| P00734      | F2       | 30     | 0.0129                 | 0.5622              |
| P07900      | HSP90AA1 | 62     | 0.0296                 | 0.6630              |
| P11388      | TOP2A    | 25     | 0.0020                 | 0.5351              |
| P06493      | CDK1     | 31     | 0.0021                 | 0.5495              |
| P01375      | TNF      | 68     | 0.0733                 | 0.6932              |
| Q02750      | MAP2K1   | 36     | 0.0039                 | 0.5701              |
| P78527      | PRKDC    | 24     | 0.0034                 | 0.5328              |
| P14780      | MMP9     | 56     | 0.0288                 | 0.6455              |
| P28482      | MAPK1    | 64     | 0.0283                 | 0.6740              |
| P27361      | MAPK3    | 68     | 0.0357                 | 0.6893              |
| P12931      | SRC      | 62     | 0.0308                 | 0.6667              |
| Q16539      | MAPK14   | 40     | 0.0057                 | 0.5922              |
| Q16665      | HIF1A    | 37     | 0.0035                 | 0.5701              |
| P26358      | DNMT1    | 27     | 0.0022                 | 0.5398              |
| P08069      | IGF1R    | 32     | 0.0047                 | 0.5596              |
| P04150      | NR3C1    | 26     | 0.0101                 | 0.5571              |
| P31751      | AKT2     | 31     | 0.0021                 | 0.5495              |
| P37231      | PPARG    | 33     | 0.0075                 | 0.5674              |
| P10721      | KIT      | 28     | 0.0027                 | 0.5495              |
| P35968      | KDR      | 40     | 0.0125                 | 0.5894              |
| P09874      | PARP1    | 35     | 0.0041                 | 0.5701              |
| P78536      | ADAM17   | 23     | 0.0051                 | 0.5398              |
| P08183      | ABCB1    | 26     | 0.0091                 | 0.5495              |
| P08253      | MMP2     | 42     | 0.0098                 | 0.5980              |
| Q05655      | PRKCD    | 21     | 0.0027                 | 0.5281              |
| P04406      | GAPDH    | 83     | 0.0829                 | 0.7578              |
| P52333      | JAK3     | 23     | 0.0034                 | 0.5304              |
| P05164      | MPO      | 30     | 0.0148                 | 0.5571              |
| Q9UNQ0      | ABCG2    | 25     | 0.0051                 | 0.5398              |
3.4. Construction of a network of potential targets for the treatment of chronic bronchitis by *Fritillaria thunbergii*

The effective component - target network disease - target network was constructed by cytoscape3.6.1 software. The above networks were combined into one network, and the network of TCM - active ingredients - core target - disease was finally constructed. The results are shown in figure 4.

![Network Diagram](image)

**Figure 3.** Traditional Chinese medicine for the treatment of chronic bronchitis by *Fritillaria thunbergii* - effective ingredient - core target - disease network

3.5. GO biological process enrichment analysis

Forty-four potential targets were imported into the database for GO bioprocess enrichment analysis, and the results of P 0.01 were retained. Results a total of 134 biological processes were obtained (biologicalprocess, BP) , 30 molecular function (molecularfunction, MF) and 25 Cellular Component (cellularcomponent, CC). According to the principle that the smaller the p-value is, the higher the significance is, the top 20 biological processes are listed. The results are shown in figure 3. The results showed that *Fritillaria thunbergii* was mainly involved in the treatment of chronic bronchitis Peptide serine phosphorylation, platelet activation, protein C terminal binding insulin binding, exogenous transport atpase activity, histone kinase activity, positive regulation of protein phosphorylation,ERBB2 signaling pathway, positive regulation of gene expression, negative regulation of apoptosis and other biological processes. The treatment of chronic bronchitis by *Fritillaria thunbergii* may play a therapeutic role by regulating these biological processes.
3.6. KEGG channel enrichment analysis

Forty-four potential targets were imported into DAVID database for KEGG pathway enrichment analysis, and the results of P 0.01 were retained. According to the principle that the smaller the P-value is, the higher the significance is, the top 20 signaling pathways are listed. The results are shown in Figure 4. Results a total of 85 signaling pathways were obtained, including prostate cancer, melanoma, estrogen signaling pathway, pi3k-akt signaling pathway, hepatitis b, thyroid hormone signaling pathway, chronic myelogenous leukemia, non-small cell lung cancer VEGF signaling pathway, pancreatic cancer hif-1 signaling pathway and so on, It is suggested that the treatment of chronic bronchitis by Fritillaria thunbergii may be the result of the above signaling pathways.

Figure 4. Biological process enrichment results of the top 20 in the treatment of chronic bronchitis by Fritillaria thunbergii (different colors represent different biological processes)
Figure 5. KEGG pathway enrichment results of the top 20 in the treatment of chronic bronchitis by *Fritillaria* thunbergii (different colors represent different biological processes)

Annotated diagram of the pathway of *Fritillaria* thunbergii for the treatment of chronic bronchitis

44 potential targets were input into the KEGGMapper function of KEGG database to mark the number of potential targets in each relevant signaling pathway. The results showed that 16 target proteins were involved in the regulation of MAPK signaling pathway, suggesting that the treatment of chronic bronchitis by *Fritillaria* thunbergii was associated with multiple targets and multiple pathways, as shown in figure 6.
Figure 6. Annotated map of potential targets in the treatment of chronic bronchitis by *Fritillaria thunbergii* on MAPK signaling pathway (genes marked in red represent potential targets, while genes marked in green represent original targets in the pathway)

4. Discussion

Chronic bronchitis is a kind of chronic non-specific inflammation of respiratory system, in traditional Chinese medicine, it belongs to the category of cough, wheeze and so on. Its pathogenic factors include lung qi unclear viscera function and so on abnormal, has repeatedly attack is difficult to cure and so on the characteristic\[11-12\]. In recent years, the incidence of chronic bronchitis continues to rise due to the frequent occurrence of severe air pollution, fog and haze, high smoking rate and other factors. Traditional Chinese medicine has unique advantages in the treatment of chronic recurrent diseases. *Fritillaria thunbergii* bulb is one of the eight authentic herbs of Zhejiang, it is effective in treating chronic bronchitis and other respiratory diseases. With the development of Internet big data, network pharmacology has adapted to the characteristics of multi-component and multi-target of traditional Chinese medicine, and its integrity and systematicness fit the overall concept of syndrome differentiation and treatment of traditional Chinese medicine. Therefore, using network pharmacology to explore the molecular mechanism of *Fritillaria thunbergii* in the treatment of chronic bronchitis is beneficial to explain the modern scientific basis of *Fritillaria thunbergii* in the treatment of chronic bronchitis.

In this study, the effective components of *Fritillaria thunbergii* were found by network pharmacology, and six active components, mainly alkaloid sterol flavonoids, were obtained. Results alkaloids were found to be the main components of cough antiseptis and antiphlogistic in *Fritillaria thunbergii*\[13\]. By acting on the M receptor excitin receptor and antagonizing the release of internal calcium, Peimisine can promote the production and release of NO, thus achieving the smooth muscle
of the diastolic trachea and the antiasthmatic effect[14]. Cui yanru et al. [15] found that Peimisine can reduce the expression of MUC5AC in mice with high mucus secretion induced by LPS, and the mechanism may be related to the down-regulation of EGFR expression. Studies have shown that a variety of stimuli in upstream signaling pathways leading to EGFR activation can induce EGFR activation in airway epithelial cells, and TGF-α binds to EGFR to regulate MUC expression[16]. β-Sitosterol also has anti-allergic asthma activity, increasing tidal volume, decreasing respiratory frequency and inhibiting TNF-α, IL-4 and IL-5, protect lung tissue against airway inflammation[17]. At present, studies have found that inflammation is the main mechanism for the development of chronic bronchitis, and its central link is oxidative stress, which eventually leads to pulmonary hypertension respiratory dysfunction and even respiratory failure in emphysema.

GO biological process enrichment analysis showed that the Fritillaria thunbergii mainly relates to the treatment of chronic bronchitis peptidyl serine phosphorylation, platelet activation, group of protein kinase activity and protein phosphorylation of positive regulate biological processes, and gene expression regulation, negative regulation of apoptosis process, double-stranded DNA binding reaction, etc. The biosynthesis of nitric oxide, MAPK cascade, lipopolysaccharide mediated signaling pathways for the main process of occurrence and development of chronic bronchitis. NO plays an important role in maintaining the airway microenvironment, and NO is synthesized by nitric oxide synthase, which is present in the airway and alveolar epithelial cells of vascular endothelial cells and some inflammatory cells. The decreased expression of cNOS in lung tissues leads to the limitation of the biological role of NO, the decreased function of adhesion and release of active substances, the release of inflammatory factors, and the promotion and aggravation of the development process of chronic bronchitis[18-19].

KEGG pathway enrichment analysis, the results show that the Fritillaria thunbergii mainly by regulating the main signaling pathways including prostate cancer, melanoma, estrogen signaling pathways, PI3K - Akt signaling pathways, hepatitis b, thyroid hormone signaling pathways, chronic granulocyte leukemia, non-small cell lung cancer with VEGF signaling pathways, pancreatic HIF - 1 signaling pathways such as the treatment of chronic bronchitis.

The occurrence and development of inflammatory response is not only related to common inflammatory factors such as interleukin tumor necrosis factor, but also the result of extensive involvement of various cytokines[20]. In the process of inflammatory response, the up-regulation of prostaglandins can mediate the migration of inflammatory cells, apoptosis, proliferation, vascular tension and the production of downstream cytokines, promoting the development of inflammation[21]. Threonine protein kinase is involved in a variety of intracellular biological responses, including the regulation of stress of cell transformation and apoptosis, which is closely related to the occurrence and development of inflammatory response[22].

In summary, this study used network pharmacology to predict the potential targets of Fritillaria thunbergii for the treatment of chronic bronchitis. Through mutual analysis of proteins, it was found that these target proteins were correlated and regulated with each other. Through the establishment of traditional Chinese medicine (TCM) -active component -core target-disease target-pathway network and mapping pathway, it was found that the mechanism of treating chronic bronchitis by Fritillaria thunbergii involves multiple biological processes and multiple pathways, reflecting the functional characteristics of traditional Chinese medicine (ethnic medicine) with multiple components, multiple targets and multiple pathways. At the same time, it was also found that one signaling pathway may be regulated by multiple targets, thus affecting the biological response in vivo and participating in the occurrence and development of chronic bronchitis, suggesting that the mechanism of treating chronic bronchitis by Fritillaria thunbergii may be the result of multiple signaling pathways acting on multiple targets. Further experiments are needed to confirm the results.
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