Mechanism prediction of *Astragalus mongholicus* Bunge and *Angelica sinensis* Diels in treating interstitial lung disease based on network pharmacology and molecular docking

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**Author contributions**

Di: manuscript conception, interpretation of data, molecular docking, manuscript writing. HJ: data acquisition and interpretation, manuscript review. WW: manuscript conception, manuscript review. All authors read and approved the final manuscript.

**Competing interests**

The authors declare no conflicts of interest.

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**Abbreviations**

AECl, Alveolar epithelial cell; AM; Alveolar macrophage; AM, Astragalus mongholicus Bunge; AS, Angelica sinensis Diels; CNKI, China National Knowledge Infrastructure; CTD, Comparative Toxicogenomics Database; CDX-2, Cyclooxygenase-2; DL, Drug likeness; EC, Endothelial cell; ECM, Extracellular matrix; EMT, Epithelial-to-mesenchymal transition; ETCM, The Encyclopedia of Traditional Chinese Medicine; FOX, Fork head box; GD, Gene Ontology; HIF-1α, Hypoxia-inducible factor-1α; IGF-1, Insulin-like growth factor-1; IGF-1 receptor, Insulin-like growth factor-1 receptor; ILD, Interstitial lung disease; KEGG, Kyoto Encyclopedia of Genes and Genomes; MMPs, Matrix metalloproteinases; mTOR, mammalian target of rapamycin; NCBI, National Center for Biotechnology Information; PDGFB, Platelet derived growth factor-β; PPARγ, Peroxisome proliferator-activated receptor gamma; TCMSP, The Traditional Chinese Medicine System Pharmacology Database; TGF-β, Transforming growth factor-β.

**Citation**


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**Abstract**

**Objective:** To investigate the mechanism by which *Astragalus mongholicus* Bunge (AM), and *Angelica sinensis* Diels (AS) act in interstitial lung disease (ILD) based on computational prediction. **Methods:** We screened the ingredients of AM and AS in PubMed, the Web of Science, China National Knowledge Infrastructure (CNKI) Databases, etc. Then obtained the potential effective components. By sharing the same molecular with ILD, we got the possible target genes for ILD treatment and constructed components–targets–disease network with Cytoscape software. The CTD (Comparative Toxicogenomics Database) database was used for GO and KEGG enrichment analysis of these target genes. **Results:** 59 active ingredients that can be druggable were chosen from AM, 67 active ingredients were chosen from AS. 77 overlapping target genes for AM and ILD and 36 overlapping target genes for AS and ILD were acquired. The hub targets of AM were PTGS2, PTGS1,CDK2, MAOA, ESR1, TOP2A, GSK3B, ESR2, PPARG, NOS2, The hub targets of AS were PTGS2, GABRA1, PTGS1, CHRM1, SLC6A2, ADRA1B, ADRAIA, ADRB2, CHRM3, GABRA2, CHRM2. 

Quercetin, kaempferol, daidzein, quercetin, 7-Hydroxycoumarin, and 5-Hydroxycoumarin were the main active ingredients which have more effective targets. Prediction of the protein-protein interaction network showed PTGS2, GSK3B, PPARG, etc., were the important predicted targets. The enriched KEGG pathways, including the Immune System, Metabolism of lipids and lipoproteins, Cytokine Signaling in the Immune System, Generic Transcription Pathway, the interleukin pathway, Metabolism of proteins, PI3K-Akt signaling pathway, Metabolic pathways, Innate Immune System, Neuroactive ligand-receptor interaction, Metabolism, GPCR downstream signaling, Amine ligand-binding receptors, Class A/1, Calcium signaling pathway. Molecular docking showed that quercetin, kaempferol, daidzein, quercetin, 7-Hydroxycoumarin, 5-Hydroxycoumarin had good binding activities with PTGS2 and GSK3B, which mainly mediated PI3K/Akt and other important signaling pathways in the pathogenesis of ILD. **Conclusion:** The components in AS and AM share some common targets, such as PTGS2. AM and AS may ameliorate ILD through the PI3K-Akt signaling pathway which is mediated by GSK3B. PTGS2, PPARG may also be vital target genes in the treatment of ILD with AM and AS.

**Keywords:** *Astragalus mongholicus* Bunge; *Angelica sinensis* Diels; computational prediction; interstitial lung disease; PI3K-Akt signaling pathways
Background

Interstitial lung disease (ILD), also known as diffuse parenchymal lung disease, is a group of diffuse lung diseases that mainly involve the interstitial lung and alveolar cavity, resulting in loss of alveolar-capillary function [1]. Epidemiological survey shows that ILD is diagnosed to 595000 people worldwide each year and the annual global incidence of the disease is between 10.7/100,000-27.14/100,000, the prevalence rate in China is about 2/100,000-5/100,000 [2]. ILD patients usually have progressive pulmonary fibrosis, which is characterized by deterioration of lung function and progressive dyspnea. ILD patients often do not respond well to treatment, have reduced quality of life, and have increased early mortality. Antifibrotic drugs or immunosuppressants are the most commonly used drugs. However, the patients often have a poor prognosis.

Western medicine now offers some therapeutic methods in the treatment of IPF, but these treatments are limited due to their high cost and potential adverse effects [3], traditional Chinese medicine has become increasingly significant in the therapy of IPF in recent years. Clinical research and meta-analyses have demonstrated that herbal treatments for IPF can improve clinical symptoms, postpone the loss of lung function, and enhance patient quality of life [4]. Astragalus mongholicus Bunge (AM), and Angelica sinensis (AS) are two commonly used Chinese herbal remedies. The combination of AM and AS has a history of nearly 800 years, which has the effects of boosting vital energy and enhancing blood circulation [5]. Mechanistic studies have shown that Astragalus saponins (the main ingredient of AM) have the function of regulating nitric oxide metabolism and influencing the balance of Th1/Th2 cytokines, enhancing antioxidant capacity, thereby protecting the lung tissue of rats with pulmonary fibrosis. Astragalus polysaccharides (the main ingredient of AM) play an antifibrotic role by regulating the balance of Th1/Th2 cytokines. Angelica volatile oil (the main ingredient of AS) can inhibit the proliferation and collagen synthesis of fibroblasts, Angelica polysaccharides (the main ingredient of AS) can significantly improve lung function, lung histopathological changes, and extracellular matrix metabolism in rats with pulmonary fibrosis [6-8]. It is important to further explore the interaction of these two herbs in the ILD treatment.

Methods

Active compounds and target genes of AM/AS

The PubMed, The CNKI Databases, and The web of Science were used to obtain the drug information(molecular name,molecular ID, oral bioavailability, drug similarity,etc) of AM & AS using the following terms: “Angelica sinensis”, “Chinese angelica”, “Angelica sinensis (Oliv.) Diels”, “Angelica sinensis Diels”, “AS”, “Astragalus”, “Astragalus membranaceus”, “Astragalus mongholicus Bunge” and “AM”. The Traditional Chinese Medicine System Pharmacology Database, also known as TCMSP, was used to collect information on drug ingredients (https://tcmp-e.com/index.php) [9], The Chinese Pharmacopoeia, The Encyclopedia of Traditional Chinese Medicine (ETCM) (http://www.tcmp.cn/ETCM/index.php/Home/Index/), relevant reviews, documents and textbooks, were also used to supplement the information of AM and AS. Drug likeness (DL) describes how closely a molecule resembles a well-known drug. All the databases were used to gather all the target genes for the active ingredients in AM and AS. The compounds containing DL 0.18 were chosen as candidate components for the following stage because they are thought to have stronger pharmacologic effects; also, the components were required to meet the five principles of generic drugs. There are four known methods to predict the targets: molecular docking method, the method based on chemical similarity, machine learning method and Integrated Prediction method [10], Chemmapper (http://www.lilab-ecust.cn/chemmapper/index.html), based on chemical similarity, was used to predict the target genes in our study [11, 12]. PubChem was used to obtain the SMILES codes of active ingredients, and then SMILES were submitted to the Chemmapper to predict the target genes based on the chemical similarity method.

Acquisition of interstitial lung disease target genes

We used “interstitial lung disease” as the keyword and then received the specific details of the target genes for ILD. The related target with the pathogenesis and progression of ILD were acquired from two databases: OMIM (https://omim.org), also known as the Online Mendelian Inheritance in Man database; The GeneCards database (www.genecards.org/) [13, 14].

Network construction for herbs, compounds, target genes and diseases

An intricate data network was constructed by Cytoscape 3.7.2 (https://cytoscape.org) [15]; Cytoscape 3.7.2 is an open-source bioinformatics software platform which can build a visual molecular interaction network that visually displays the interactions between Chinese medicines, drug ingredients, target genes, and diseases. The ILD/AM ingredients /AS ingredients /target genes are shown as nodes in the network figure, while their connections to one another are shown as edges.

Network construction of protein-protein interaction

STRING database, also known as Search Tool for the Retrieval of Interacting Genes/Proteins (https://string-db.org/), is a protein interaction network database based on public database and literature information. It gathers several public databases, including UniProt, KEGG (Kyoto Encyclopedia of Genes and Genomes), NCBI (National Center for Biotechnology Information), and GO (Gene Ontology), to integrate these data and generate a comprehensive protein interaction network database [16, 17]. In STRING, we selected the “Homo sapiens” option when searching for species-related common target proteins, and set the confidence score to greater than 0.4, then obtained the PPI results; finally, we used the results derived from STRING to make a network image with Cytoscape. Solid dots represent proteins, and straight lines represent protein-protein relationships.

Enrichment analysis

A global categorization method for gene function is called GO [18]. By defining and describing the roles of genes and proteins, it intends to create a standard of linguistic vocabulary that is appropriate to various species and can be updated when new research is done. The GO enrichment analyze method was used to analysis the biological function of target genes. We carried out the investigation using the online web page after the duplicated or disease-unrelated entries were deleted. A higher-order biological function is represented by a pathway or complex, which is linked to a cluster of genomic genes by molecular networks that interact within cells as part of the KEGG initiative. The duplicated or disease-unrelated entries were required to be deleted as well. We used the CTD database (https://ctdbase.org) to analyze the GO and KEGG enrichment functions of the key molecules.

Molecular docking of major target genes and major active ingredients

We screened the key genes in the PPI network. The 2D structure of the compound was searched in the PubChem database (https://pubchem.ncbi.nlm.nih.gov) as the ligand for molecular docking and saved in “.pdb” format; the crystal structure of the core gene was screened in the RSCB PDB database (https://www.pdb.org) as the protein receptor and saved in the “.pdb” format. After the protein was processed by CB-Dock2 (https://caddlabshare.cn/cb-dock2/php/index.php), the key genes were targeted to the main active components.

Results

Target prediction and active ingredients
After duplicate entries were removed, 59 active ingredients that can be druggability were chosen from the AM, then we acquired the duplicated target genes by searching the chemmapper with SMILES, finally 1002 target genes associated with the ingredients were acquired. Similarly, 67 effective ingredients were obtained from the AS, 401 target genes associated with the compounds were acquired. 2139 known genes associated with ILD were obtained using GeneCards and OMIM. The most relevant genes are listed as follows: TERT, ABCA3, COPA, SFTPC, ITGA3, LOC101806263, MUC5B, FARS1, ABCA3, SFTPA2, etc. 77 overlapping target genes for AM and ILD and 36 overlapping target genes for AS and ILD were acquired to further analysis the relationships between herbs, components, and disease.

**Network study of the relationships between herbs, components, and disease**

First, we identified potential targets between AM and ILD. Figure 1 showed the network between ingredients and target genes of AM (Fig. 1). Solid circles represented the putative targets or ingredients, with the darker the color, the higher the degree. 119 nodes were presented in the network of AM ingredients and their action targets. 77 proteins were chosen as assumed targets of AM, with the top ten were PTGS2, PTGS1, CDK2, MAOA, ESR1, TOP2A, GSK3B, ESR2, PPARG, NOS2. These proteins might be effective targets for the treatment of ILD. Quercetin, kaempferol, daidzein, isorhamnetin, formononetin, 7-O-methylisoyaconitine, hederaegenin, rhamnocitrin, calycosin, 13,9-di-O-methylisoscillarin were the main active ingredients which have more predictive targets. 36 proteins were chosen as assumed targets of AS, with the top ten were PTGS2, GABRA1, PTGS1, CHRM1, SLC6A2, ADRA1B, ADRA1A, ADRA2B, CHRM3, GABRA2, CHRM2. The major active compounds were Pavillion, 7-Hydroxycoumarin, 5-Hydroxycoumarin, isoeugenol, succinic acid, anisic acid, 2',4'-Dihydroxyacetophenone, vanillin, stigmasterol, carvacrol, dodecanol (Figure 2). To some extent, it reflects the difference in ingredients and targets between AM and AS in treating ILD.

**GO enrichment analysis**

We used the CTD database for GO enrichment analysis of the selected core target genes and filter with P < 0.1. As shown in Figure 3, many biological processes may be responsible for the mechanism in the treatment of ILD with AM, the top 21 biological processes which were most closely related to AM, the metabolism process of nitrogen compounds, multicellular biological development, response to oxygen-containing compound, cell population proliferation, programmed cell death, cell differentiation, apoptotic process, RNA biosynthetic process, response to hormone, lipid metabolic process, tube development, etc. (Figure 3). Then we intercepted the top 18 terms related to AS. Relevant biological processes included protein binding, activity of molecular transducer, transmembrane signal transduction receptor activity, activity of G protein-coupled receptor, enzyme binding, receptor activity of neurotransmitter, transmembrane transporter activity, protein dimerization activity, oxidoreductase activity (Figure 4).

**KEGG enrichment analysis**

We used the CTD database for KEGG enrichment analysis of the selected core target genes of AM in treating ILD. The enriched KEGG pathways include Immune System, Metabolism of lipids and lipoproteins, cytokine signaling in the immune system, generic transcription pathway, Interleukin-mediated signaling, Metabolism of proteins, PI3K-Akt signaling pathway, Metabolic pathways, Innate Immune System and so on (Figure 5). Then, we used the CTD database for KEGG enrichment analysis of the selected core target genes of AS in treating ILD. The enriched KEGG pathways include metabolism, neuroactive ligand-receptor interaction, GPCR downstream signaling, amine ligand-binding receptors, Class A/1, calcium signaling pathway and so on (Figure 6).

**Construction of protein interaction network and analysis of core target genes**

Based on the STRING database, we constructed the PPI network with 99 common target genes (Figure 7). Solid red circles represent the target gene, the purple lines represent interactions between proteins. The following genes were the important predicted targets related to AM: PTGS2, PTGS1, CDK2, MAOA, ESR1, GSK3B, TOP2A, ESR2, PPARG, ACHE, etc. AS related targets were: PTGS2, GABRA1, PTGS1, CHRM1, LCE2A, ADRA1B, ADRA1A, ADRA2B, CHRM3, GABRA2, etc. Overlapping genes were: PTGS2, GABRA1, PTGS1, CHRM1, SLC6A2, ADRB2, CHRM2, NCOA2, SCNSA, RXRA, PGR, MAOA, NOS3, AR.

**Docking exercises of hub target genes and the major components**

In this study, quercetin, kaolin, daidzein, pavilion, 7-hydroxycoumarin, 5-hydroxycoumarin and other important components were selected for molecular docking with key targets PTGS2, PPARG and GSK3B. We conducted the docking exercises of hub target genes and the major components. Binding energy ~ -5.0 kcal/mol indicates that the target protein and the active component have good binding activity. The smaller the binding energy value, the more stable the binding of ligand and receptor, and the more likely the interaction will occur. The binding energies of quercetin, kaempferol, daidzein, pavilion, 7-hydroxycoumarin, 5-hydroxycoumarin and key targets are shown in Table 1 and Table 2. The binding energies ranged from ~4.7 to ~9.6 kcal/mol, indicating good binding activity. Figure 8 showed how the active ingredients interface with PTGS2, PPARG, and GSK3B.

**Discussion**

Intestinal lung disease (ILD) is a disease mainly manifested as infiltration, diffuse exudation and fibrosis of the lung interstitium. Studies on the pathological process of pulmonary fibrosis have found that the early pathological manifestations were diffuse damage of vascular endothelial cells and alveolar epithelial cells, resulting in alveolar inflammation. Due to the persistence of immune-mediated pulmonary inflammation, a series of immune factors cause tissue damage through signal transduction pathways, and a large number of fibroblasts aggregate, leading to abnormal deposition of extracellular matrix (ECM). Normal alveolar tissue is damaged and abnormally repaired, eventually contributing to structural dysfunction and abnormalities [19]. Many cells are involved in the above pathogenesis. The destruction of the damaged epithelial cell layer of alveolar epithelial cells (AECs) is regarded as the initial event in the pathogenesis of ILD, the proliferation and differentiation dysfunction of AECs leads to abnormal repair of the lung tissue. AECs can also differentiate into fibroblasts through epithelial-to-mesenchymal transition (EMT). Endothelial cells (EC) proliferation promotes the formation of new capillaries, which aggregate a large number of AECs, leading to fibrin proliferation and collagen deposition. In the inflammatory stage of pulmonary fibrosis, alveolar macrophage (AM) can further differentiate and lead to excessive proliferation of fibroblasts. Neutrophils will also be recruited to the injured site and participate in the inflammatory stage of pulmonary fibrosis.

AM is the root of the legume Astragalus mongholicus or Astragalus membranaceus. Its chemical components mainly include saponins, flavonoids, vitamins, amino acids and polysaccharides. AS is the dry root of Angelica sinensis. AM and AS have been common clinical medication pairs in Chinese medicine in past generations. The complex components and numerous targets of compound Chinese medicine have been the focus of research in the past several years. AM and AS is a representative drug pair, it has a certain anti-fibrosis effect and has been widely used in the traditional Chinese medicine treatment of liver, kidney and pulmonary fibrosis. It has been confirmed that the herbs AM and AS can mediate the therapy of pulmonary fibrosis from the mechanism point of view. Astragaloside IV can significantly slow down the excessive phosphorylation and downregulation of FOXO 3a induced by TGF-β1/PI3K/Akt, thereby reversing the fibrosis process [20]. AM injection inhibited bleomycin (BLM)-induced pulmonary fibrosis by significantly reducing the
Whereas the underlying mechanisms remain unknown. Therefore, we used a network pharmacology approach to further study the pathogenesis of AS and AM in the therapy of pulmonary fibrosis.

In this study, we explored the ingredients and mechanisms of AM and AS in the treatment of ILD by network pharmacology. 59 active ingredients of AM and 1002 target genes were obtained from different databases, 77 genes were related to ILD. 67 active ingredients of AS and 401 target genes were acquired, of which 36 genes were related to ILD, indicating that AM and AS were involved in the treatment of ILD with multiple components and targets. The results of topological analysis of the AM active ingredients-ILD disease targets network showed that the components with higher degree values were quercetin, kaempis, daidzein, Pavillon, etc. Quercetin, as one of the important flavonoids in AM, has a wide range of physiological activities. It has been reported that oral administration of quercetin...
Figure 3 Gene ontology enrichment analysis of AM ingredient targets and ILD-related

Figure 4 Gene ontology enrichment analysis of AS ingredient targets and ILD-related

Figure 5 KEGG enrichment analysis of AM target genes and ILD-related target genes
can effectively reduce collagen deposition and oxidation-antioxidant imbalance in lung tissue of ILD rats induced by bleomycin, and reduce the concentrations of pro-fibrotic mediators IL-13, PDGF-β and TNF-α in bronchoalveolar lavage fluid [22].

We screened out the important target genes of AM and AS in the treatment of ILD: PTGS2, CDK2, MAOA, ESR1, GSK3B, ESR2, PPARG, NOS2, GABRA1, PTGS1, CHRM1, SLC6A2, ADRA1B, ADRA1A, ADRB2, CHRM3, GABRA2, CHRM2, etc. Among these target genes, PTGS2 is the core gene of the network, which means this target is very important in the treatment of pulmonary fibrosis. PTGS2 is the coding gene of COX-2 (cyclooxygenase-2), COX-2 is an inducible enzyme involved in prostaglandin synthesis during inflammatory responses and pain. PTGS2 is regulated by a variety of factors in vivo, including cytokines, inflammatory mediators, hormones, etc. Overexpression of PTGS2 is associated with the occurrence and development of many diseases, such as tumors, inflammatory diseases, and cardiovascular diseases [23]. Studies have shown that COX-2 is highly expressed in bleomycin-induced ILD tissues [24], and COX-2 is a microcosm type, which plays an important part in the up-regulation of PGE2. PGE2 can stimulate the production of Th2 cytokines IL-13, IL-10, and inhibit the synthesis of Th1 cytokines IL-12, IFN-γ, which leads to the imbalance of Th1/Th2 cytokine secretion, resulting in further expansion of alveolar inflammation and ultimately ILD.

PPARG is the coding gene of PPARγ (Peroxisome proliferator-activated receptor gamma), PPARγ is a ligand-activated receptor in the nuclear hormone receptor family, which can regulate many metabolic processes in cells, and then participate in glucose metabolism, lipid metabolism, immune regulation, etc. Numerous studies have revealed that PPARγ has a strong anti-pulmonary fibrosis effect. PPARγ is widely expressed in lung tissues, such as alveolar epithelial cells, endothelial cells, smooth muscle cells, and dendritic cells. PPARγ can inhibit the expression of PDGF-β (platelet derived growth factor-β) mediated by STAT6 [25], and can also attenuate inflammatory cell infiltration and fibroblast proliferation by inhibiting
Figure 8 Docking exercises of hub targets and the major components. A: The three components of AM docking with PTGS2, PPARG, GSK3B; B: The three components of AS docking with PTGS2, PPARG, GSK3B.

the MAPK signal transduction pathway. In addition, activation of PPARγ can inhibit the activity of NF-κB and reduce pulmonary inflammation and fibrosis [26]. Previous studies have confirmed that metformin can reduce bleomycin-induced pulmonary fibrosis and αSMA expression by partly activating PPARγ signaling pathway [27-29].

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Results of GO and KEGG's enrichment analysis revealed that AS and AM were implicated in a variety of targets in the treatment of ILD, combined with the analysis results and literature research findings, we found that AM and AS may have a targeted therapeutic effect on ILD through PI3K/Akt. The PI3K/Akt signal transduction pathway, involving the downstream regulators, plays an important part in the pathogenesis of ILD. Under pathological conditions, alveolar epithelial cells release TGF-β, which activates the IGF-1 receptor (IGF-1R) on the surface of adjacent normal alveolar epithelial cells, further activating intracellular downstream PI3K and Akt [30–32]. Activated PI3K/Akt participates in alveolar epithelial cell senescence and IPF progression through the release of connective tissue growth factor (CTGF), transforming growth factor-β (TGF-β), and matrix metalloproteinases (MMPs) [33–35]. Additionally, activation of PI3K/Akt can be involved in pulmonary fibrosis by regulating its downstream pathways, such as the mammalian target of rapamycin (mTOR), hypoxia-inducible factor-1α (HIF-1α), and fork head box (FOX) family. As mentioned above, quercetin has antioxidant and anti-inflammatory effects, and it has been shown to attenuate oxidative stress in pulmonary fibrotic tissues and reduce levels of inflammatory markers [36, 37]. Boots and his colleagues have demonstrated that quercetin had antifibrotic and anti-inflammatory properties in mice with pulmonary fibrosis induced by bleomycin [38]. Protein kinases including PI3K and Akt have a role in quercetin's mechanism of action [39, 40]. According to Hohmann et al., quercetin reduces bleomycin-induced lung fibrosis in mice by activating Akt and restoring the susceptibility of senescent fibroblasts to pro-apoptotic stimuli [41]. As mentioned above, in this study, GSK3β is also an important common target of AM in treating ILD which encodes the protein glycogen synthase kinase-3 beta. GSK3β is an important effector molecule in the PI3K signal transduction system which can affect the stability, intracellular distribution and functional activity of proteins through the recognition and phosphorylation of target proteins. Studies have shown that GSK3β can be activated when cells are in starvation culture [42, 43]. Guarriera et al. found that GSK3β was highly expressed in the lung tissue of mouse in the mouse model of pulmonary fibrosis, blocking GSK3β could inhibit the production of inflammation and the occurrence of fibrosis in the lung tissue [44].

Conclusions

In this paper, the complex network relationship of AM and AS in the intervention of ILD with multi-components, multi-targets and multi-pathways was explored through network pharmacology, and the main active substances, target genes and pathways of AM combined with AS in the treatment of ILD were preliminarily clarified, so as to lay the foundation for future study on the pathogenesis of the combination of AS and AM in the therapy of ILD. Our preliminary study came to the conclusion that the components in AS and AM share some common targets, such as PTGS2, AM and AS may ameliorate ILD through PI3K-Akt signaling pathway which is mediated by GSK3β. PTGS2, PPARG may also be vital target genes in the treatment of ILD with AM and AS.

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