

Progress of Radix Astragali and Radix Angelicae Sinensis in the treatment of idiopathic pulmonary fibrosis

Hui-Zhe Zhang¹, Cong Wang², Yu-Feng Zhang^{2*}

¹Department of Respiratory Medicine, Yancheng Hospital Affiliated to Nanjing University of Chinese Medicine, Yancheng 224005, China. ²Department of Pulmonary and Critical Care Medicine, Jiangyin Hospital Affiliated to Nanjing University of Chinese Medicine, Jiangyin 214400, China.

*Corresponding to: Yu-Feng Zhang, Department of Pulmonary and Critical Care Medicine, Jiangyin Hospital Affiliated to Nanjing University of Chinese Medicine, No. 130, Middle Renmin Road, Jiangyin 214400, China. E-mail: yufengzhang@njucm.edu.cn.

Author contributions

Hui-Zhe Zhang and Yu-Feng Zhang conceived and designed the review. Hui-Zhe Zhang, Cong Wang and Yu-Feng Zhang wrote, revised and edited this article. Yu-Feng Zhang performed supervision and project administration. All authors read and approved the final manuscript.

Competing interests

The authors declare no conflicts of interest.

Acknowledgments

This work was supported by Research Grants of Jiangyin Hospital of Traditional Chinese Medicine (202014 to YF Zhang), Grants from the Wuxi Health Commission's Scientific Research Project (M202154 to YF Zhang).

Abbreviations

IPF, Idiopathic pulmonary fibrosis; RA, Radix Astragali; RAS, Radix Angelicae Sinensis; DGBXD, Danggui Buxue decoction; TCM, Traditional Chinese medicine; TGF- β 1, transforming growth factor- β 1; ECM, extracellular matrix; VEGF, vascular endothelial growth factor; Treg, regulatory T cell; FGF2, fibroblast growth factor 2; Th17, T helper cell 17; Foxp3, forkhead box P3; IL-6, interleukin 6; MMP, matrix metalloproteinase; TIMP-1, tissue inhibitor of metalloproteinases 1; COL I, collagen type I; HIF-1, hypoxia-inducible factor-1; PKD1, protein kinase D1; NF- κ B, nuclear factor- κ B; MnSOD, manganese superoxide dismutase; TLR4, Toll-like receptor 4; NLRP3, NOD-like receptor protein 3; PAI-1, plasminogen activator inhibitor-1; NOX4, NADPH oxidase 4; miRNA, miR/microRNA; mRNA, messenger RNA.

Peer review information

TMR Integrative Medicine thanks all anonymous reviewers for their contribution to the peer review of this paper.

Citation

Zhang HZ, Wang C, Zhang YF. Progress of Radix Astragali and Radix Angelicae Sinensis in the treatment of idiopathic pulmonary fibrosis. *TMR Integr Med*. 2022;6:e22024. doi: 10.53388/TMRIM202206024.

Executive editor: Chun Ling.

Received: 14 May 2022; Accepted: 29 August 2022; Available online: 31 August 2022.

© 2022 By Author(s). Published by TMR Publishing Group Limited. This is an open access article under the CC-BY license. (<https://creativecommons.org/licenses/by/4.0/>)

Abstract

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, fibrotic interstitial lung disease. Current treatment options for IPF are limited. Radix Astragali (RA) and Radix Angelicae Sinensis (RAS), according to 5:1 ratio composed of Danggui Buxue decoction (DGBXD), which have played an essential role in the treatment of IPF. This article reviewed the experimental research, clinical research, and progress of RA and RAS (DGBXD) treating IPF to provide a deeper scientific basis for the future experimental research and clinical research.

Keywords: idiopathic pulmonary fibrosis; Radix Astragali; Radix Angelicae Sinensis; Danggui Buxue decoction

Background

IPF is a chronic, progressive, fibrotic interstitial lung disease, with clinical manifestations of dyspnea, restrictive ventilation dysfunction and gas exchange dysfunction, hypoxemia, and even progressive aggravating respiratory failure [1]. Usual interstitial pneumonia is the characteristic manifestation of IPF [2, 3]. IPF is a rare disease that mostly occurs in the elderly [4]. The incidence of IPF in Europe and North America is about 2.8 to 9.3 per 100,000 people, with few epidemiological data in China, but the incidence has significantly increased in recent years [5–7]. The prognosis of IPF remains poor, with a median survival time after diagnosis of around 2 to 3 years [8].

Current treatment options for IPF are limited, and the aim of the treatment is still to delay the progression of the disease, improve the quality of life and prolong the survival [9]. Traditional Chinese medicine (TCM) compound prescriptions play a role in the treatment of IPF with the superiorities of multiple targets and multiple components, small side effects, and easy acceptance to patients. Many studies have shown that IPF patients can achieve certain clinical efficacy using TCM [10–13]. Radix Astragali (RA; huangqi in Chinese) and Radix Angelicae Sinensis (RAS; danggui in Chinese) have played a very important role in the treatment of IPF.

Cognition of IPF in TCM

IPF is a modern medical name, without definition in TCM. According to the symptoms of cough, asthma, shortness of breath, chest tightness, chest pain and fatigue in IPF patients, similar diseases such as “pulmonary arthralgia”, “pulmonary fistula”, “cough”, “dyspnea”, “shortness of breath”, “pulmonary distension” and “collateral disease” are widely recorded in the ancient medical literatures. Among them, IPF is more commonly belonged to the category of “pulmonary arthralgia” and “pulmonary fistula”. In the early phase, due to external evil invasion, lung qi deficiency and other pulmonary obstruction, the disease develops into “pulmonary arthralgia”. Later, due to long lung obstruction and lung nourishment loss, the disease finally develops into a “pulmonary fistula” [14, 15]. “Pulmonary arthralgia” often focuses on qi and blood, and lung collaterals obstruction; “pulmonary fistula” generally emphasizes the qi and blood deficiency and lung collaterals deficiency.

“Pulmonary arthralgia” refers to the external evil, internal injury of diet and mood, obstruction lung of evil qi, lung qi deficiency, affecting the operation of lung qi and blood, smooth of lung meridians in TCM. Patients often show symptoms such as cold, fever, cough and sputum, chest tightness, shortness of breath, chest pain and restlessness, qi and blood stagnation of the body and lung meridians, chronic delay, and finally form “pulmonary arthralgia”. For example, “Su Wen” records that “dyspnea and deficiency, called pulmonary arthralgia, cold and hot, drunk and make the inside”, “disease in the lung, called pulmonary arthralgia, cough on qi”. According to modern medical research, the heart and lung blood vessels are rich, and qi and blood exchange is completed through breathing. During IPF, lung qi and blood exchange function is disordered, while the number of local capillaries in lung tissue is reduced, and blood stasis is formed. These pathological changes are similar to the TCM “pulmonary arthralgia” of lung qi and blood deficiency, blood stasis and qi stagnation. At this time, IPF complies with the category of “pulmonary arthralgia” [16, 17].

“Pulmonary fistula” in TCM refers to the loss of lungs in caring, lung withered, lung qi deficiency, cough, shortness of breath, long-term cough, and vomiting white foam sputum as the main clinical characteristics, with modern medicine chronic bronchitis, chronic obstructive pulmonary disease, chronic cor pulmonale, and other chronic lung deficiency diseases. In Zhang Zhongjing’s *Medical Treasures of the Golden Chamber*, it is recorded that “fistula is also wilt, such as the wilt and failure of plants and trees”. In the course of IPF, cough and vomit white foam sputum, dyspnea and chest tightness recurrent attack, and the disease position is from lung and spleen kidney, lung spleen kidney deficiency. According to its clinical

syndrome and pulmonary pathological changes, IPF is in line with the category of “pulmonary fistula” [18–20].

Cognition of RA and RAS treating IPF

RA and RAS according to 5:1 ratio composed of DGBXD. DGBXD was first recorded in *Nei Wai Shang Bian Huo Lun (Internal and External Injuries)*, created by Li Dongyuan in the Jin and Yuan Dynasties, which has a history of about 800 years. It is the ancient classic and famous prescription of TCM [21–23]. DGBXD was included in the Catalogue of Ancient Classic and Famous Prescriptions (First Batch) formulated by the National Administration of TCM in 2018, which provides better opportunities for the research, inheritance, innovation, and high-quality development of DGBXD (RA and RAS) [24]. DGBXD is commonly used in the clinical treatment of leukopenia, dysfunctional uterine bleeding, diabetic nephropathy, nephrotic syndrome, liver fibrosis, and other diseases and has achieved a certain curative effect [25–29].

At present, RA and RAS also have some application in the treatment of pulmonary fibrosis. Some animal experiments have shown that RA and RAS can improve the degree of pulmonary fibrosis in animal models of bleomycin-induced IPF [30–32]. Based on literature, association studies show that RA and RAS are the most commonly used herbs for the treatment of pulmonary fibrosis [33, 34]. RA, slightly warm, belongs to spleen and lung meridian, has the function of supplementing qi and rising yang, benefiting health and consolidating exterior, benefiting yang but not hurting yin, and benefiting qi and regulating qi. RAS, warm, sweet and pungent, belongs to liver, heart and spleen, has the function of promoting blood circulation without hurting blood, replenishing qi and generating blood, removing blood stasis and passing collaterals, and relieving dyspnea. Comprehensive view of the whole prescription, the compatibility of RA and RAS complement each other, which can improve the IPF lung spleen kidney deficiency, and strengthen the blood stasis to remove blood stasis. Thus, RA and RAS in the treatment of IPF is accord with the important rule of TCM “benefiting qi and nourishing blood, promoting blood circulation and removing meridian obstruction” [35].

Experimental research of RA and RAS treating IPF

Peng YF established a bleomycin-induced rat IPF model to investigate the pharmacodynamic mechanism of RA and RAS on IPF [35]. It indicated that intervention to transforming growth factor- β 1 (TGF- β 1)/Smad signaling pathway by inhibiting microRNA-21 (miR-21) and improving the expression of miR-326 and miR-29b could reduce the extracellular matrix (ECM) deposit and improve pulmonary fibrosis in rats. Zhao HZ first proved the correlation of pulmonary fibrosis and “pulmonary fistula” to explore the treatment mechanism of lung fibrosis through literature research [30]. Experiment research showed that RA and RAS extract might promote macrophages to M1 macrophages differentiation and inhibit macrophages to M2 macrophages differentiation, reducing the degree of pulmonary fibrosis. Geng QX et al. replicated mouse pulmonary fibrosis model by endotracheal injection of bleomycin and showed that RA aqueous extract and RAS alcohol extract could reduce the content of hydroxyproline in the lung and inhibit the expression level of TGF- β and vascular endothelial growth factor (VEGF) to improve the degree of lung fibrosis in mice [36, 37]. Li LJ et al. intervened in an IPF mouse model and verified that high dose of RA and RAS with 5:1 ratio could inhibit the expression level of VEGF mRNA, promote the expression level of the c-kit proto-oncogene and fibroblast growth factor 2 (FGF2) mRNA, inhibit the expression level of key genes for T helper cell 17 (Th17) differentiation, such as TGF- β , interleukin 6 (IL-6), and ROR γ t mRNA, promote regulatory T cell (Treg) differentiation gene forkhead box P3 (Foxp3) mRNA expression and improve the quality of survival of the mice [31, 32, 38, 39]. Bao HY et al. used bleomycin airway injection method to replicate the experimental rat pulmonary fibrosis model [40]. By the dynamic evaluation of morphometric method and hydroxyproline content in lung tissue, it was pointed out that both RA and RAS alcohol extract

and aqueous extract could slow down the process of pulmonary interstitial fibrosis in rats and have some therapeutic effects on pulmonary interstitial fibrosis. Liu Y et al. replicated the rat lung interstitial fibrosis model using endotracheal intubation with pingyangmycin, and pointed out that total glycosides of DGBXD could regulate the free radical levels in lung fibrosis, reduce oxidative damage to lung tissue structure, reduce serum TGF- β 1 level, reduce the expression of TGF- β 1 mRNA, and prevent lung fibrosis in rats [41, 42]. Gao J et al. constructed experimental pulmonary fibrosis rat model [43]. Through experiment, it was concluded that DGBXD total glycosides could inhibit bleomycin-induced pulmonary fibrosis, and its mechanism of action was related to the ability of DGBXD total glycosides to inhibit ECM synthesis and balance matrix metalloproteinase (MMP)/tissue inhibitor of metalloproteinases 1 (TIMP-1) system. Gao Jian constructed a model of bleomycin-induced rat pulmonary fibrosis, and found that DGBXD total glycosides could reduce alveolar inflammatory edema, maintain alveolar structure, inhibit fibrosis formation and significantly reduce the generation of ECM in pulmonary fibrosis rats [44]. It was related to reduce the elevated TGF- β 1 levels in serum and promote collagen type I (COL I) degradation. The regulation of ECM remodeling realized by regulating the expression of MMP1 and MMP9/TIMP1. DGBXD total glycosides could downregulate Smad3 and P-Smad3 expression through the TGF- β 1, reduce the COL I expression, and reduce the ECM deposition to play an antifibrotic effect. Lu CX et al. observed the rat model of bleomycin replicating IPF, showed that DGBXD could regulate the angiogenic status of IPF rats by downregulating hypoxia-inducible factor-1 (HIF-1) expression and upregulating endostatin expression, and delay the course of IPF disease [45]. Liu Na et al. observed bleomycin induced pulmonary fibrosis model rats, found that DGBXD could improve the antioxidant capacity by regulating protein kinase D1 (PKD1)/nuclear factor- κ B (NF- κ B)/manganese superoxide dismutase (MnSOD) mitochondrial nuclear antioxidant pathway, and then alleviate lung fibrosis [46]. Wang JP et al. induced pulmonary fibrosis rat model by bleomycin endotracheal injection [47]. Experimental observation was that DGBXD could improve qi deficiency and blood stasis status in pulmonary fibrosis rats by regulating blood rheological indicators. Wang J et al. constructed a bleomycin-induced rat pulmonary fibrosis model, and observed that DGBXD improved pulmonary fibrosis by inhibiting Toll-like receptor 4 (TLR4)/NOD-like receptor protein 3 (NLRP3) signaling [48]. Wang J et al. showed that DGBXD could improve lung fibrosis, and the mechanism of action might involve the inhibition of lung inflammation, inhibiting lung inflammation and collagen deposition by inhibiting TGF- β 1/Smad3/plasminogen activator inhibitor-1 (PAI-1) signaling pathway [49]. Zhao P et al. observed the rat model of bleomycin-induced pulmonary fibrosis and showed that DGBXD total glycosides alleviated pulmonary fibrosis by regulating oxidative stress by inhibiting NADPH oxidase 4 (NOX4) [50]. Li SC et al. pointed out that the treatment of DGBXD total glycosides combined with hirudo in the rat model of bleomycin-induced pulmonary fibrosis could improve pulmonary fibrosis by reducing the expression level of TGF- β 1, PAI-1 and hydroxyproline content in lung tissue [51].

Clinical research of RA and RAS treating IPF

Peng YF collected IPF patients with pulmonary qi deficiency and internal stasis [35]. IPF patients were randomly divided into control group and observation group. The control group was treated with conventional treatment and the observation group was treated with RA and RAS combined with conventional treatment. The total effective rate of the observation group was 84%, which was significantly higher than that of the control group. The improvement of TCM syndrome points and quality of life points in the observation group was significantly better than that in the control group. Six-minute walk test in the observation group was significantly better than that in the control group. Improvement of diffusion capacity of the lung for carbon monoxide was better than that of the control group. Tumor necrosis factor- α and TGF- β 1 in the observation group decreased better than that in the control group. It is suggested that the

addition of RA and RAS can treat IPF well, effectively improve clinical symptoms, improve exercise tolerance and quality of life, and reduce the level of inflammatory factors in patients. The curative effect is better than that of the control group, and has a positive effect on delaying the progression of the disease. There are few clinical studies on only RA and RAS treating IPF or DGBXD treating IPF. However, many clinical studies of Chinese herbal prescriptions, including RA and RAS for IPF patients have also achieved good results. Sun XS carried out a clinical observation study on Qihong decoction in the treatment of pulmonary interstitial fibrosis, which was divided into TCM group and hormone control group [52]. The TCM group applied Qihong decoction, including 30 g of RA, 15 g of RAS, 10 g of Flos Carthami (honghua), 15 g of Radix Curcumae (yujin), 15 g of Flos Inulae (xuanfuhua), 15 g of Semen Coicis (yiyiren), and 6 g of Radix Platycodi (jiegeng). It was found that the TCM group was significantly better than the control group in improving symptoms, improving pulmonary function, and arterial oxygen partial pressure. The number of pulmonary reinfections in the TCM group during the treatment was significantly lower than that in the control group. Wei GS et al. observed the clinical efficacy of promoting blood circulation, removing phlegm and opening the inhibited lung-energy of TCM prescription, including RA 30 g, RAS, Semen Lepidii (tinglizi), Fructus Aurantii (zhike) 12 g each, Flos Lonicerae (jinyinhua), Radix Salviae Miltiorrhizae (danshen), Poria (fuling), Semen Coicis (yiyiren) 15 g each, Semen Persicae (taoren), Flos Inulae (xuanfuhua), Flos Carthami (honghua) 10 g each for IPF [53]. It was found that significant improvements in clinical symptoms, arterial oxygen partial pressure and pulmonary function. Sun ZT et al. performed a clinical research [54]. Comparing with single western medicine control group, TCM prescription of tonifying qi, activating blood and dispersing accumulation, which included RA 20 g, RAS 15 g, Rhizoma Curcumae (ezhu) 10 g, Radix Salviae Miltiorrhizae (danshen) 20 g, Bulbus Fritillariae Cirrhosae (chuanbeimu) 10 g, Radix Scutellariae (huangqin) 10 g, Radix Curcumae (yujin) 10 g could significantly relieve clinical symptoms, improve lung function, reduce adverse drug reactions, improve the quality of life. Nowadays, there are many such clinical research reported. Obviously, the effect of other herbs will have a certain impact on the results, but RA and RAS as main components of benefiting qi and activating blood circulation are still of great significance, such clinical research is still worth further mining analysis, in order to find reliable evidence-based modern scientific basis. Recently, Zhang YF et al. have performed a meta-analysis and revealed that RA and RAS were effective and safe in the treatment of IPF, which was beneficial to pulmonary function and exercise tolerance of these patients [55].

Other progress of RA and RAS treating IPF

The existing basic research and clinical research provide a basis for the further research and development of the treatment of IPF, but there are still short comings. The components of TCM are diverse and complex. Currently, the basic research on RA and RAS mostly explains the action mechanism of a certain target gene and a certain pathway, and lacks the overall view and syndrome differentiation of TCM for the research on multi-component, multi-target and multi-pathway. Zhang YF et al. used the systems bioinformatic tactic of microarray dataset analysis and network pharmacology, found the characteristics of RA and RAS treating IPF were multi-component, multi-target and multi-pathway, revealed the relationships among the active compounds of RA and RAS and their target genes, proteins, and pathways in IPF, created gene-pathway network, achieved preliminary molecular docking, which could prove beneficial in future studies on their mechanisms of action for the treatment of IPF [56, 57]. Zhao C et al. used network pharmacology to explore the mechanism of DGBXD in the treatment of IPF, explained the role of DGBXD in the treatment of multi-component, multi-target and multi-channel pulmonary fibrosis, and carried out experimental verification of the active ingredients, which provided a research basis for further exploring the pharmacological mechanism of DGBXD [58]. Zhang H et al. revealed a potential mechanism of involvement of microRNA (miRNA) and

messenger RNA (mRNA) modulatory axes in the pathogenic mechanisms of IPF, which developed a putative IPF-related miRNA-mRNA regulatory network through which DGBXD ameliorated IPF [59].

The composition of RA and RAS is complex, and the modern scientific connotation of the action mechanism of RA and RAS on the treatment of IPF needs to be further deepened, making it a more modern scientific connotation in line with the internationalization of TCM research. It is urgent to carry out a comprehensive and systematic evaluation of the clinical efficacy of RA and RAS in the treatment of IPF, find preliminary evidence-based medical evidence, make the clinical application of RA and RAS in the treatment of IPF more modern scientific connotation, and provide a basis for further scientific research.

Conclusion

Therefore, we have reviewed the experimental research, clinical research and progress of RA and RAS (DGBXD) treating IPF. It is necessary to systematically study the modern scientific connotation of RA and RAS in the treatment of IPF from multiple angles. Exploring the modern scientific connotation of the curative effect and action mechanism of RA and RAS treating IPF from the overall perspective and making the basic mechanism research from surface to point more scientific connotation, will provide a deeper scientific basis for the future experimental research and clinical research.

References

1. Raghu G, Remy-Jardin M, Myers JL, et al. Diagnosis of idiopathic pulmonary fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. *Am J Respir Crit Care Med* 2018;198:e44–e68. Available at: <http://dx.doi.org/10.1164/rccm.201807-1255ST>
2. Cao M-S, Sheng J, Wang T-Z, et al. Acute exacerbation of idiopathic pulmonary fibrosis. *Chin Med J* 2019;132:2177–2184. (Chinese) Available at: <http://dx.doi.org/10.1097/CM9.0000000000000422>
3. Interstitial Lung Disease Group of Respiratory Society of Chinese Medical Association. The Chinese expert consensus on the diagnosis and treatment of idiopathic pulmonary fibrosis. *Chin J Tuberculosis Resp Dis* 2016;39(6):427–432. (Chinese) Available at: <https://doi.org/10.3760/cma.j.issn.1001-0939.2016.06.005>
4. Sheng G, Chen P, Wei Y, et al. Viral infection increases the risk of idiopathic pulmonary fibrosis. *Chest* 2020;157:1175–1187. Available at: <http://dx.doi.org/10.1016/j.chest.2019.10.032>
5. Huang. Idiopathic pulmonary fibrosis: The current status of its epidemiology, diagnosis, and treatment in China. *Intractable Rare Dis Res* 2013. Available at: <http://dx.doi.org/10.5582/irdr.2013.v2.3.88>
6. Navaratnam V, Fleming KM, West J, et al. The rising incidence of idiopathic pulmonary fibrosis in the UK. *Thorax* 2011;66:462–467. Available at: <http://dx.doi.org/10.1136/thx.2010.148031>
7. Hutchinson J, Fogarty A, Hubbard R, et al. Global incidence and mortality of idiopathic pulmonary fibrosis: a systematic review. *Eur Respir J* 2015;46:795–806. Available at: <http://dx.doi.org/10.1183/09031936.00185114>
8. Kim HJ, Perlman D, Tomic R. Natural history of idiopathic pulmonary fibrosis. *Resp Med* 2015;109:661–670. Available at: <http://dx.doi.org/10.1016/j.rmed.2015.02.002>
9. Cerri S, Monari M, Guerrieri A, et al. Real-life comparison of pirfenidone and nintedanib in patients with idiopathic pulmonary fibrosis: a 24-month assessment. *Resp Med* 2019;159:105803. Available at: <http://dx.doi.org/10.1016/j.rmed.2019.105803>
10. Chen M-J, Yang G-L, Ding Y-X, et al. Efficacy of TCM therapy of tonifying lung-kidney's Qi-deficiency in a case of idiopathic pulmonary fibrosis. *Medicine* 2019;98:e15140. Available at: <http://dx.doi.org/10.1097/MD.00000000000015140>
11. Yang Y, Zengtao S, Liqing S, et al. Effects of Feiwei granules in the treatment of idiopathic pulmonary fibrosis: a randomized and placebo-controlled trial. *J Tradit Chin Med* 2016;36:427–433. (Chinese) Available at: [http://dx.doi.org/10.1016/S0254-6272\(16\)30058-9](http://dx.doi.org/10.1016/S0254-6272(16)30058-9)
12. Zhang Y, Lu P, Qin H, et al. Traditional Chinese medicine combined with pulmonary drug delivery system and idiopathic pulmonary fibrosis: rationale and therapeutic potential. *Biomedicine amp; Pharmacother* 2021;133:111072. Available at: <http://dx.doi.org/10.1016/j.biopha.2020.111072>
13. Zhang H-Y, Pang L-J, Lv X-D, et al. Multiple traditional Chinese medicine interventions for idiopathic pulmonary fibrosis. *Medicine* 2020;99:e22396. Available at: <http://dx.doi.org/10.1097/MD.00000000000022396>
14. Liu X, Gong JN. Overview of traditional Chinese medicine understanding and treatment of traditional Chinese and western medicine in pulmonary fibrosis. *Shandong J Tradit Chin Med* 2018;37(08):699–702. (Chinese) Available at: <https://doi.org/10.16295/j.cnki.0257-358x.2018.08.025>
15. Dai Y, Xiao SY, Qi FJ. Discussion on pathogenesis of idiopathic pulmonary fibrosis from the perspective of blood stasis and traditional Chinese medicine treatment methods. *J Tianjin Univ Tradit Chin Med* 2021;40(5):572–577. (Chinese) Available at: <https://doi.org/10.11656/j.issn.1673-9043.2021.05.08>
16. Meng LX, Wu C, Wen YL, et al. Experience in distinguishing between “fei bi” and “fei wei” in treating interstitial pulmonary disease. *Global Tradit Chin Med* 2021;14(11):2064–2066. Available at: <https://doi.org/10.3969/j.issn.1674-1749.2021.11.033>
17. Cheng JM, Wu X, Zhu JY, et al. To analyze connective tissue disease related pulmonary interstitial fibrosis based on “fei bi” and “fei wei” in TCM. *Lishizhen Med Materia Medica Res* 2020;31(3):668–669. (Chinese) Available at: <https://doi.org/10.3969/j.issn.1008-0805.2020.03.053>
18. Ma JD, Li JS, Li QL, et al. Study on the medication patterns of modern famous traditional Chinese medicine master' diagnosis and treatment of lung flaccidity based on traditional Chinese medicine inheritance support system. *Mod Tradit Chin Med Materia Medica-World Sci Technol* 2021;23(9):3126–3131. (Chinese) Available at: <https://doi.org/10.11842/wst.20200922002>
19. Li R, Zhao Y. Research and treatment of pulmonary fibrosis (fei wei) in the Japanese literature before the Meiji Restoration. *J Sichuan Tradit Chin Med* 2021;39(4):24–28. (Chinese) Available at: <https://kns.cnki.net/kcms/detail/detail.aspx?dbcode=CJFD&d bname=CJFDLAST2021&filename=SCZY202104009&uniplatf orm=NZKPT&v=xRZ4uQhNnB3AchG1NiPRgdWHgVKO7DGT LzagzxxGQZfPDBj5GW-3ido0VUfLZyUC>
20. Li R, Zhao Y. Research and treatment of pulmonary fibrosis (fei wei) in the Japanese literature after the Meiji Restoration. *J Sichuan Tradit Chin Med* 2021;39(5):22–26. (Chinese) Available at: <https://d.wanfangdata.com.cn/periodical/sczy202105009>
21. Hu J, Li K, Li AP, et al. Research progress on material basis of Danggui Buxue Decoction. *Chin Tradit Herb Drugs* 2020;51(21):5658–5663. (Chinese) Available at: <https://doi.org/10.7501/j.issn.0253-2670.2020.21.032>
22. Zhao M-M, Zhang Y, Li L-S, et al. Efficacy and safety of Danggui Buxue Decoction in combination with western medicine treatment of anemia for renal anemia: a systematic review and meta-analysis. *Ann Transl Med* 2017;5:136–136. Available at: <http://dx.doi.org/10.21037/atm.2017.01.17>
23. Lin HQ, Gong AGW, Wang HY, et al. Danggui Buxue Tang (Astragali Radix and Angelicae Sinensis Radix) for menopausal

- symptoms: a review. *J Ethnopharmacol* 2017;199:205–210. Available at: <http://dx.doi.org/10.1016/j.jep.2017.01.044>
24. Chen H, Song J, Yang P, et al. Introduction of Guidance on CMC of traditional Chinese medicine compound preparations developed from catalogued ancient classical prescriptions (Interim). *Chin Food Drug Administr Magazine* 2021(9):78–87. (Chinese) Available at: <https://doi.org/10.3969/j.issn.1673-5390.2021.09.012>
 25. Zhang MZ, Guan LC, Chen YJ, et al. Research progress of Danggui Buxue Decoction. *Hunan J Tradit Chin Med* 2018;34(8):241–243. (Chinese) Available at: <https://doi.org/10.16808/j.cnki.issn1003-7705.2018.08.101>
 26. Wang WK, Zhang L, Sun Y, et al. Research progress of treatment of Danggui Buxue decoction on diabetes mellitus with depression. *Mod Tradit Chin Med Materia Medica-World Sci Technol* 2018;20(12):2191–2195. (Chinese) Available at: <https://doi.org/10.11842/wst.2018.12.016>
 27. Zhou YX. Research progress on mechanism of Danggui Buxue Decoction in hematologic disease. *Chin Manipulation Rehabilitation Med* 2019;10(11):64–65. (Chinese) Available at: <https://doi.org/10.3969/j.issn.1008-1879.2019.11.029>
 28. Wu X, Zhou X. Mechanism of action and application of Danggui Buxue decoction in the treatment of cardiovascular diseases. *Sci Technical Inform Gansu* 2019;48(3):81–83. (Chinese) Available at: <https://doi.org/10.3969/j.issn.1672-6375.2019.03.023>
 29. Yang FX, Wang Y, Xia PF, et al. Review of chemical constituents, pharmacological effects and clinical applications of Danggui Buxue decoction and prediction and analysis of its Q-markers. *Chin J Chin Materia Medica* 2021;46(11):2677–2685. (Chinese) Available at: <https://doi.org/10.19540/j.cnki.cjcm.20200828.201>
 30. Zhao HZ. Effect of Astragalus and Angelica sinensis extract on pulmonary fibrosis based on macrophage polarization. *Beijing Univ Chin Med* 2018. (Chinese) Available at: <https://kns.cnki.net/kcms/detail/detail.aspx?dbcode=CMFD&dbname=CMFD201802&filename=1018192243.nh&uniplatform=NZKPT&v=HLigGqHhVeuMj2bYO7LFA7krm61jkY-zTgEjsluLF4MJtznvqB9Be8k3Q6oGVQOQ>
 31. Li LJ, Fan AR, Ge DY, et al. Influence of the pair drugs of astragalus and angelica on the IPF living conditions and tissue repair related gene expression level in mice. *Global Tradit Chin Med* 2015;8(12):1441–1445. (Chinese) Available at: <https://doi.org/10.3969/j.issn.1674-1749.2015.12.005>
 32. Li LJ, Li LN, Li GM, et al. Different ratio and dosage of Huangqi (Astragalus) and Danggui (Angelica) for pulmonary fibrosis in mice lung morphology and hydroxyproline content. *J Liaoning Univ Tradit Chin Med* 2015;17(3):30–33. (Chinese) Available at: <https://doi.org/10.13194/j.issn.1673-842x.2015.03.010>
 33. Ren BY. The rule of treatment of pulmonary fibrosis with traditional Chinese medicine based on the literature study. *Liaoning Univ Tradit Chin Med* 2017. (Chinese) Available at: https://kns.cnki.net/kcms/detail/detail.aspx?dbcode=CMFD&dbname=CMFD201801&filename=1017865417.nh&uniplatform=NZKPT&v=a0O_HYqVPeQ5JY2Uk6d6cl0o7X7mxSQpzDxpARoB8Hhq0k02jAJ4LTJhrqd8aE
 34. Zhang YY. Clinical analysis and literature study on the law of drug use in treating idiopathic pulmonary fibrosis by nourishing yin and activating blood circulation. *Liaoning Univ Tradit Chin Med* 2016. (Chinese) Available at: <https://xuewen.cnki.net/CMFD-1016194295.nh.html>
 35. Peng YF. Clinical and experimental study of Qi Gui Recipe on idiopathic pulmonary fibrosis based on TGF- β /Smad/miRNA signaling pathway. *Hebei Univ Chin Med* 2019. (Chinese) Available at: <https://kns.cnki.net/kcms/detail/detail.aspx?dbcode=CDFD&dbname=CDFDLAST2019&filename=1019111399.nh&uniplatform=NZKPT&v=SS0zPr7RACUyRNAMDYhgQ6FoQTMd2ElVwbsi0-yoPqaLGYgInf0JdLE0VXiB6lB>
 36. Geng QX, Zhao HZ, Zong CZ, et al. Effects of optimized formulas of Radix Astragali and Radix Angelicae Sinensis extracts on survival status of idiopathic pulmonary fibrosis mice and on expression of cytogenesis-related factors in lung tissues. *J Guangzhou Univ Tradit Chin Med* 2017;34(3):408–412. (Chinese) Available at: <https://doi.org/10.13359/j.cnki.gzxbtcm.2017.03.027>
 37. Geng QX. Effect of optimized formula of effective components of Astragali Angelica on the number of bronchoalveolar stem cells in IPF mice. *Beijing Univ Chin Med* 2017. (Chinese) Available at: <https://kns.cnki.net/kcms/detail/detail.aspx?dbcode=CMFD&dbname=CMFD201702&filename=1017201468.nh&uniplatform=NZKPT&v=LaQwqf49fCYzzvmCeqnwUgMgdF0gj-RQV9Q8Sx9GBvfzKueTvBK3WcTy5yFuL7S>
 38. Li LJ, Fan AR, Ge DY, et al. Astragali Angelica ratio of drugs doses and on IPF mice survival condition and TGF- β , IL-6, foxp3 and roryt influence of the level of gene expression. *J Liaoning Univ Tradit Chin Med* 2015;17(7):42–46. (Chinese) Available at: <https://doi.org/10.13194/j.issn.1673-842x.2015.07.015>
 39. Li LJ. Changes of immune environment in IPF mouse model and protective mechanism of Astragalus and Angelica. *Beijing Univ Chin Med* 2015;83. (Chinese) Available at: https://kns.cnki.net/kcms/detail/detail.aspx?dbcode=CMFD&dbname=CMFD201502&filename=1015385724.nh&uniplatform=NZKPT&v=Lu-JaOGVj0Lz3otJlJ5sq_IdOhRIWd4JnAUUYzVHRIG8mHT1kejFxPPR8xOue15R
 40. Bao HY, Wang YK, Wu GT, et al. Effect of alcohol extract and water extract from Radix Angelicae and Sinensis Radix Astragali on pulmonary fibrosis in rats. *Chin J New Drugs* 2010;19(12):1064–1067. (Chinese) Available at: <https://chem.ckcest.cn/Journal/Details?id=1838889>
 41. Liu Y, Li J, Gao J, et al. Experimental study of total glycosides of Danggui Buxue decoction against pulmonary fibrosis in rats. *Acta Univ Med Anhui* 2009;44(5):594–598. (Chinese) Available at: <https://doi.org/10.3969/j.issn.1000-1492.2009.05.017>
 42. Liu Y. Experimental study on pulmonary fibrosis treat with total glycosides of Danggui Buxue decoction in rats. *Anhui Med Univ* 2009. (Chinese) Available at: <https://kns.cnki.net/kcms/detail/detail.aspx?dbcode=CMFD&dbname=CMFD2010&filename=2009200141.nh&uniplatform=NZKPT&v=W3nuL4ZLH5dGLP4c2fzY3swOtUyQPerznff6FhgIARJyaXGXU3Er7Whv9kN0Ms2>
 43. Gao J, Feng L, Huang Y, et al. Total glucosides of Danggui Buxue Tang attenuates bleomycin-induced pulmonary fibrosis via inhibition of extracellular matrix remodelling. *J Pharmacy Pharmacol* 2012;64:811–820. Available at: <http://dx.doi.org/10.1111/j.2042-7158.2012.01490.x>
 44. Gao J. Preparation of total glycosides of DangGui BuXue decoction and its intervention in the experimental idiopathic pulmonary fibrosis and underlying molecular mechanisms. *Anhui Med Univ* 2009. (Chinese) Available at: https://kns.cnki.net/kcms/detail/detail.aspx?dbcode=CDFD&dbname=CDFD0911&filename=2009130987.nh&uniplatform=NZKPT&v=hCZyRhbX06ohJ2PKwtvHhYsUtBuhH5_4h39YOL3iU_GQrcoz-2kyWR3ggqMceH5
 45. Lu CX, Wang JP, Liu N, et al. Effects of Danggui Buxue decoction on HIF-1 α and endostatin of angiogenesis factors in experimental idiopathic pulmonary fibrosis rats. *Chin J Tradit Chin Med Pharmacy* 2021;36(3):1683–1687. (Chinese) Available at: https://kns.cnki.net/kcms/detail/detail.aspx?dbcode=CJFD&dbname=CJFDLAST2021&filename=BXYY202103126&uniplatform=NZKPT&v=WYr8yPIp9_T67vM8YiBDojWY_-f9DNih2XVKZKodgh6wT5zTXRrkGsEK93txy9rj
 46. Liu N, Wang JP, Lu CX, et al. Effect of Danggui Buxuetang on PKD1/NF-kB/MnSOD signal pathway in Bleomycin-induced pulmonary fibrosis in rats. *Chin J Exp Tradit Med Formulae*

- 2020;26(13):66–72. (Chinese) Available at: <https://doi.org/10.13422/j.cnki.syfjx.20201303>
47. Wang JP, Wang SX, Fang CY, et al. Preliminary study on the mechanism of Danggui Buxue decoction interfering with Qi deficiency and blood stasis in rats with pulmonary fibrosis. *Med Pharmac J Chin People's Liber Army* 2020;32(3):24–28. (Chinese) Available at: <https://doi.org/10.3969/j.issn.2095-140X.2020.03.006>
 48. Wang J, Wang H, Fang F, et al. Danggui Buxue Tang ameliorates bleomycin-induced pulmonary fibrosis by suppressing the TLR4/NLRP3 signaling pathway in rats. *Evid Based Complement Altern Med* 2021;2021:1–13. Available at: <http://dx.doi.org/10.1155/2021/8030143>
 49. Wang J, Fang C, Wang S, et al. Danggui Buxue Tang ameliorates bleomycin-induced pulmonary fibrosis in rats through inhibiting transforming growth factor-beta1/Smad3/ plasminogen activator inhibitor-1 signaling pathway. *J Tradit Chin Med* 2020;40(2):236–244. (Chinese) Available at: <https://doi.org/10.19852/j.cnki.jtcm.2020.02.007>
 50. Zhao P, Zhou W-C, Li D-L, et al. Total glucosides of Danggui Buxue Tang attenuate BLM-Induced pulmonary fibrosis via regulating oxidative stress by inhibiting NOX4. *Oxid Med Cell Longev* 2015;2015:1–10. Available at: <http://dx.doi.org/10.1155/2015/645814>
 51. Li SC, Yang NX, Xia ZY, et al. Danggui Buxue decoction total glycosides combined with Hirudo in the treatment of pulmonary fibrosis in rats. *Chin Tradit Patent Med* 2017;39(11):2243–2248. (Chinese) Available at: <https://doi.org/10.3969/j.issn.1001-1528.2017.11.004>
 52. Sun XS. A preliminary study on the clinical observation and mechanism of Qihong prescription in the treatment of idiopathic pulmonary fibrosis. *Beijing Univ Chin Med* 2005. (Chinese) Available at: <https://xuewen.cnki.net/CMFD-2005077270.nh.html>
 53. Wei GS, Qiang NX. Thirty six cases of Tongfeihuoxue decoction in the treatment of idiopathic pulmonary fibrosis. *Shaanxi J Tradit Chin Med* 2007(4):389–390. (Chinese) Available at: <https://doi.org/10.3969/j.issn.1000-7369.2007.04.003>
 54. Sun ZT, Feng JH, Li XJ, et al. Interference of tonifying qi, activating blood and dispersing accumulation on pulmonary fibrosis and the mechanism research. *J Tianjin Univ Tradit Chin Med* 2008(3):209–212. (Chinese) Available at: <https://doi.org/10.11656/j.issn.1673-9043.2008.03.23>
 55. Zhang Y, Gu L, Xia Q, et al. Radix Astragali and Radix Angelicae Sinensis in the treatment of idiopathic pulmonary fibrosis: a systematic review and meta-analysis. *Front Pharmacol* 2020;11. Available at: <http://dx.doi.org/10.3389/fphar.2020.00415>
 56. Zhang Y, Gu L, PuYang J, et al. Systems bioinformatic approach to determine the pharmacological mechanisms of radix astragali and radix angelicae sinensis in idiopathic pulmonary fibrosis. *Phcog Mag* 2021;17:708. Available at: http://dx.doi.org/10.4103/pm.pm_9_21
 57. Zhang Y, Jiang W, Xia Q, et al. Pharmacological mechanism of Astragalus and Angelica in the treatment of idiopathic pulmonary fibrosis based on network pharmacology. *Eur J Integr Med* 2019;32:101003. Available at: <http://dx.doi.org/10.1016/j.eujim.2019.101003>
 58. Zhao C, Li H, Liu X, et al. Dissecting the underlying pharmaceutical mechanism of Danggui Buxue decoction acting on idiopathic pulmonary fibrosis with network pharmacology. *Tradit Med Res* 2020;5:238–251. (Chinese) Available at: <http://dx.doi.org/10.53388/TMR20191102146>
 59. Zhang H, Wang X, Shi Y, et al. Danggui Buxue decoction ameliorates idiopathic pulmonary fibrosis through microRNA and messenger RNA regulatory network. *Evid-Based Complement Altern Med* 2022;2022:1–19. Available at: <http://dx.doi.org/10.1155/2022/3439656>