Pulmonary microecology is a key role of traditional Chinese medicine in improving pulmonary fibrosis

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Idiopathic pulmonary fibrosis (IPF) is a type of interstitial lung disease, characterized by an unknown etiology, chronicity, and progressive respiratory impairment. Following IPF diagnosis, patients exhibit a median survival of only 2 to 3 years, with a staggering 70% to 80% mortality rate within 5 years [1]. However, the corresponding therapeutic options remain severely limited. Presently, the efficacious treatment drugs are Pirfenidone and Nintedanib. Regrettably, these two drugs fail to substantially reverse pulmonary fibrosis, offering only a partial slowing of its progression. IPF predominantly afflicts the elderly [1], and with the aging population in China continuously increasing, there is a compelling need to explore novel and more effective treatment strategies. Interestingly, studies by David N. O'Dwyer and colleagues have demonstrated a significant correlation between pulmonary microbial load and the progression of lung fibrosis in IPF patients, underscoring the intimate connection between pulmonary microbiota and the advancement and prognosis of IPF [2].

In the realm of traditional Chinese medicine, IPF falls within the category of lung impediment and lung flaccidity, yet, a unified diagnostic criterion has been elusive [3]. The Diagnostic Criteria of Traditional Chinese Medicine Syndrome Differentiation for Idiopathic Pulmonary Fibrosis (2019 Edition) employed comprehensive statistical analysis, artificial neural networks, and the Delphi method to scrutinize the collected data. As a result, a standardized framework was established, and three major syndromes and two accompanying syndromes associated with IPF were identified, namely Yin deficiency (The consumption of Yin fluids or relative hyperactivity of Yang Qi) with lung dryness syndrome, lung Qi (The Qi stored in the lung. It is the driving force of physiological activities of the lung) deficiency syndrome, Qi (Qi refers to the basic substance that constitutes the human body and maintains life activities, and is the unity of substance and function) deficiency of the lung and kidney syndrome, phlegm-dampness syndrome (accompanying syndrome), and blood stasis syndrome (accompanying syndrome) [4]. Grounded in traditional Chinese medicine theory, experiments on bleomycin-mice have revealed varying degrees of improvement in pulmonary fibrosis through the administration of treatments such as Maimendong decoction for Yin deficiency, Astragali Radix, Qizhi Feixian decoction, YiFei Sanjie formula, and Buyang Huanwu decoction for lung Qi deficiency, Ophiocordyceps sinensis and Bushen Tongluo formula for Qi deficiency of the lung and kidney. Similarly, treatments addressing blood deficiency, such as Salviae Miltiorrhizae Radix et Rhizoma, Angelicae Sinensis Radix, Notoginseng Radix, Carthami Flos, and Rhe仁 Radix et Rhizoma, have demonstrated in mitigating pulmonary fibrosis [5].

Traditionally, the lung has been considered a sterile environment. However, recent research has revealed the presence of a distinct lung microbiota, which is associated with the onset and progression of various diseases [6]. The lung microbiota encompasses a diverse community of microorganisms, including bacteria, fungi, and viruses [7]. In healthy individuals, the lung microbiota serves as a natural biological barrier, exerting a protective role through mechanisms such as the neuraminidase expressed by Streptococcus pneumoniae, which inhibits the adhesion of influenza to host cells [8, 9]. Additionally, colonizing lung microbiota can influence host immune tolerance and inflammatory responses, providing protection against external pathogens. Studies by Sulaiman et al. suggest that the lung microbiota may be linked to local immunity [10].

Furthermore, research indicates that alterations in the lung microbiota significantly contribute to the development of pulmonary fibrosis [11]. Studies in mice induced with bleomycin have shown that dysbiosis in the lung microbiota is associated with increased production of interleukin-17B during pulmonary fibrosis, depletion of the lung microbiota or deficiency in interleukin-17B can ameliorate fibrotic progression [12]. Additionally, numerous pathogens possess corisin or corisin-like compounds, which promote apoptosis of alveolar epithelial cells. Administration of corisin to mice induced with bleomycin results in significant changes in the total number of lymphocytes in bronchoalveolar lavage fluid compared to the control group. Anti-corisin treatment leads to a notable improvement in alveolar epithelial cell apoptosis and a reduction in fibrotic severity [12]. Host responses to microbiota changes are evident, and the bacterial community in the lower respiratory tract may serve as a persistent stimulus for repetitive alveolar injury in IPF. Honeycombing is a prominent feature of pulmonary fibrosis, and it has been demonstrated to correlate with alterations in the lung microbiome [13]. A study reports minimal bacterial signals in ex vivo tissues of IPF patients, suggesting that the host-microbiota interface may more readily interact functionally through the airway mucosa rather than lung parenchyma [14]. Molyneaux et al. also provide evidence that higher bacterial loads in bronchoalveolar lavage fluid of IPF patients are associated with poorer lung function and higher mortality rates [15]. Traditional Chinese medicine, as a well-known immune homeostasis regulator, plays an important role in the microbiota during the development of IPF. For example, purified protein P2 from Rhizoma Bellean attributed inhibits pulmonary fibrosis progression by modulating the TGF-β1-Smad pathway [16]; Qingfei oral liquid might exert the anti-IPF effects through the regulation of inflammatory signaling pathways [17]; Qingyan decoction reduced the severe acute pancreatitis-induced lung injury partially by influencing the lung microbiota [18].

Studies have shown that the composition of the lung microbiota varies with some factors, such as dietary vitamin D intake, and serum 25 (OH) D levels are negatively correlated with Pseudomonas aeruginosa in animal models [19]. While it has been acknowledged that the pulmonary microbiota plays a pivotal role in the occurrence, progression, and treatment of pulmonary diseases, and traditional Chinese medicine holds promise in the realm of pulmonary fibrosis, numerous questions need further investigation. For instance, it is unclear which microbial communities play a primary role in the development of IPF, and can alleviate the degree of fibrosis by targeting them, and whether a single herbs or formulas of traditional Chinese medicine can suppress pulmonary fibrosis by acting on the key microbial communities. By utilizing metagenomic and sequencing technologies, elucidating the mechanisms by which traditional Chinese medicine influences lung microbiota in IPF can provide improved therapeutic strategies for treating pulmonary fibrosis.

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Author Contributions
Zhiheng Xue conceived the study, outlined the manuscript, and revised the initial draft. Zehua Wang collected the data and contributed to the drafting of the initial manuscript.

Competing interests
The authors declare no conflicts of interest.

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Abbreviations
IPF, idiopathic pulmonary fibrosis.

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