



Piceatannol supplementation: A promising therapeutic approach for Protection against Pulmonary Fibrosis

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Abstract

Idiopathic pulmonary fibrosis (IPF) is a degenerative pulmonary condition marked by progressive fibrosis of the lungs, leading to a fatal outcome. This disease predominantly affects individuals in the middle-aged and elderly populations. It represents a significant contributor to both morbidity and mortality rates. It serves as a significant and devastating complication arising from the global outbreak of Corona Virus Disease 2019 (COVID-19). Currently, the utilization of antifibrotic medications such as pirfenidone and nintedanib is associated with various undesirable adverse effects and may result in significant financial burdens for patients without exerting any discernible impact on the disease progression and elevated fatality rates observed within 3 to 5 years following diagnosis. The sole therapeutic intervention for IPF that has demonstrated a significant improvement in life expectancy is the surgical procedure of lung transplantation, which can be performed unilaterally or bilaterally. Consequently, there is an urgent and ongoing requirement for the advancement of more efficacious antifibrotic treatments that exhibit minimal adverse effects in the future. The objective of this review is to present a comprehensive assessment of the existing evidence concerning the effectiveness of piceatannol as a therapeutic intervention for pulmonary fibrosis.

Keywords: Idiopathic pulmonary fibrosis; COVID-19; Antifibrotic medication; Piceatannol.

1. Introduction

Idiopathic pulmonary fibrosis (IPF) is a fatal and degenerative pulmonary condition that is marked by inflammation, fibrosis, and the degradation of lung structure. Chronic and sustained inflammation of lung epithelial cells with abnormal wound healing, resulting in IPF development. IPF is currently an incurable disease, with the typical age of onset being approximately 65 years. Following diagnosis, the average survival rate ranges from 3 to 5 years.

The probability of survival for a period of five years following the initial diagnosis varies between 20% and 40% (**Raghu et al., 2014**). Annually, a global incidence of 30,000 to 40,000 new cases of IPF is reported, accompanied by an increasing prevalence rate ranging from 13 to 20 per 100,000 individuals. Additionally, IPF exhibits a higher incidence rate among males with a history of smoking compared to females (**Velagacherla et al., 2022**). It serves as a significant and devastating complication arising from the global pandemic of COVID-19

(**Mohammadi et al., 2022**). IPF exacerbations often present as acute episodes of respiratory function deterioration, thereby complicating the clinical course. Currently, there are no effective interventions for preventing and managing acute exacerbations in individuals with IPF (**Kottmann et al., 2009; Collard et al., 2016**). The prevailing complications associated with IPF encompass a spectrum of medical conditions, notably lung cancer, depressive disorders, pulmonary hypertension, muscular debility, cardiac insufficiency, thrombotic events, respiratory insufficiency, and acute respiratory distress syndrome (ARDS). The advent of two novel anti-fibrotic medications, namely pirfenidone and nintedanib, is expected to result in a notable deceleration in the deterioration of pulmonary function and a decrease in the occurrence and seriousness of related problems. Nevertheless, due to the limited curative properties of these agents, it is imperative to explore novel therapeutic strategies (**Somogyi et al., 2019**).

Piceatannol (PIC) is a naturally derived compound that serves as an analogue to resveratrol. It is present in several dietary sources, including grapes, white tea, and passion fruit. It exhibits a multitude of recognized health advantages, including its notable anti-cancer, anti-adipogenic, antioxidant, and anti-inflammatory properties (**Kukreja et al., 2014; Nayyab et al., 2020; Kershaw et al., 2022**). Additionally, piceatannol exhibits significant therapeutic potential in the treatment of respiratory diseases. In the context of sepsis-induced acute lung injury, the administration of piceatannol has been observed to effectively preserve the integrity of the air-blood barrier by inhibiting the TLR4/NF- κ B signaling pathway (**Peng et al., 2020**). Moreover, the administration or prior administration of piceatannol has been shown to ameliorate hepatic dysfunction and suppress collagen fiber expression in CCl₄-induced hepatic fibrosis, while also mitigating oxidative stress (**Hung et al., 2021**). The objective of this review is to present a comprehensive analysis of the existing evidence about the effectiveness of piceatannol as a therapeutic agent for pulmonary fibrosis.

2. Idiopathic pulmonary fibrosis (IPF)

Idiopathic pulmonary fibrosis (IPF) is a degenerative pulmonary condition marked by progressive lung fibrosis, leading to a fatal outcome. It is hypothesized that continuous micro-injuries to the aging alveolar epithelium result in a

disturbance of communication between the epithelial cells and fibroblasts. This disruption ultimately leads to the recruitment and activation of myofibroblasts, which are responsible for producing an extracellular matrix abundant in alpha smooth muscle actin (α -SMA) and collagen type I (**Tsukui et al., 2020**). The excessive accumulation of this matrix leads to the irreversible collapse and dysfunction of the alveoli, resulting in diminished gas exchange and respiratory distress (**Heukels et al., 2019**).

The pathological processes underlying idiopathic pulmonary fibrosis (IPF) are distinguished by the proliferation of fibroblasts into myofibroblasts and the remodeling of the ECM. These mechanisms create a conducive environment for the formation of fibrotic scars. Selman et al. said that it should be noted that not all inflammatory injuries have the capacity to elicit a fibrotic reaction in lung tissue (**Selman et al., 2001**). Notwithstanding this assertion, the recent study conducted by Zhou et al. has indicated a notably elevated prevalence of pulmonary fibrosis in individuals diagnosed with severe cases of COVID-19 pneumonia, as compared to those with moderate COVID-19 (**Zou et al., 2021**).

3. Piceatannol

Plant-based products offer numerous advantages compared to synthesized compounds. These advantages encompass more favorable pharmacological actions, reduced costs, abundant sources, and diminished toxicity levels (**Susanti et al., 2022**). In contemporary times, individuals have the potential to derive advantages from a diverse array of nutritional components found in natural products that are commonly consumed as part of their daily dietary intake. Therefore, scientists are emphasizing the significance and efficacy of plant-based products in the management of metabolic and chronic disorders (**Jardine et al., 2021; Rahman et al., 2022**).

Piceatannol is a natural phenolic molecule and the hydroxylated form of resveratrol. It was initially isolated in 1984 from the plant *Euphorbia lagascae* Spreng. (**da Costa et al., 2019**), and it is present in several dietary sources, including grapes, white tea, and passion fruit (**Banik et al., 2020**). Based on current understanding, resveratrol exhibits a diverse array of advantageous impacts, encompassing anti-inflammatory and antioxidant properties in addition to anti-aging and

hypoglycemic effects (**Pannu and Bhatnagar, 2019**). Piceatannol, a resveratrol analogue, has been shown to have many of the same biological effects as resveratrol. These include protecting the heart and brain, preventing cancer, hypoglycemic effects, and depigmentation (**Cao et al., 2020**). It is worth mentioning that piceatannol has the potential to mitigate organ fibrosis through various mechanisms, encompassing the liver (**Hung et al., 2021**), kidney (**Choi et al., 2016**), and heart (**Li et al., 2019**).

3.1. Antiproliferative activity of piceatannol

Prior research has documented the suppressive effects of piceatannol on a range of human cancer cell types with relatively low levels of cytotoxicity, such as prostate cancer, colon cancer, breast cancer, and hepatocellular carcinoma (**Ko et al., 2012; Kwon et al., 2012; Banik et al., 2020; Kido et al., 2020; Salama et al., 2022**). In addition to its antitumor properties, it is worth noting that piceatannol also demonstrates the potential to provide hepatocyte protection and prevent hepatic fibrosis caused by thioacetamide (TAA) intoxication (**Torres-Hernandez et al., 2019**).

3.2. Antifibrotic and anti-inflammatory activities of piceatannol

A previous study provided evidence that the administration of piceatannol attenuated pulmonary fibrosis by demonstrating a substantial reduction in collagen deposition and myofibroblast accumulation induced by bleomycin. In addition, piceatannol played a notable role in the induction of autophagy during the process of anti-fibroblast activation, as observed in both in vitro and in vivo investigations. Moreover, the activation of autophagy was accomplished through the inhibition of the TGF- β 1-Smad3/ERK/P38 signaling pathway, leading to a reduction in the proportion of activated myofibroblasts (**Sheng et al., 2022**). Moreover, piceatannol exhibits the ability to mitigate anaphylactic bronchial contraction in an in vitro setting through the selective inhibition of spleen tyrosine kinase (Syk) (**Seow et al., 2002; Kita et al., 2012**).

Moreover, piceatannol exhibited cardioprotective effects in mice with sepsis by reducing apoptosis and inflammation through direct inhibition of the JAK2/STAT3 pathway activation (**Xie et al., 2021**). In addition, the protective effect of piceatannol was observed in a murine model of bleomycin-induced

lung fibrosis. This effect was achieved by reducing collagen synthesis and oxidative injury, which were mediated by the inhibition of the JAK2/STAT3 pathway (**Sheng et al., 2022**).

Epigenetic modification, such as histone acetylation, plays a key role in the development of IPF. The process of histone acetylation is controlled by two different enzymes: histone acetyltransferases (HATs) and histone deacetylases (HDACs). HDACs are a class of enzymes responsible for the removal of acetyl groups from both histone and nonhistone proteins. This enzymatic activity leads to the formation of transcriptionally repressed chromatin, thereby suppressing the expression of genes involved in cell cycle regulation, apoptosis, DNA repair, and metabolism. Consequently, HDACs are widely recognized as pivotal epigenetic factors (**Asawa et al., 2020**).

Dysregulated HDAC activities have been shown in pulmonary fibrosis. The upregulation of HDACs has been demonstrated to induce the activation of lung fibroblasts, leading to the synthesis of ECM components such as α -SMA and collagen type I. This process ultimately promotes the development of lung fibrosis (**Seto and Yoshida, 2014**).

A previous study demonstrated a potential association between the anti-fibrotic impacts of piceatannol and the downregulation of HDAC4 and HDAC5 in the context of kidney fibrosis (**Choi et al., 2016**). In addition, assessments were conducted to determine the HDAC inhibitory activity of piceatannol. The findings indicated that piceatannol exhibits HDAC inhibitory activity, specifically targeting HDAC2 and HDAC6 (**Blackwell et al., 2008; Zhang et al., 2017; Beetch et al., 2019**).

3.3. Antioxidant activity of piceatannol

It has been reported that piceatannol possesses the ability to prevent neurodegeneration caused by excessive glutamate exposure by maintaining the functionality of mitochondria, inhibiting glutamate-induced apoptosis, safeguarding dopaminergic neurons against degradation, and maintaining the functionality of neural responses regulated by these neurons. It maintained the functionality of mitochondria by reducing the accumulation of reactive oxygen species (ROS) in mitochondria by stimulating the antioxidant response through the activation of Nrf2/HO-1 and super oxide dismutase (SOD) and enhancing the process of mitochondrial biogenesis through the activation of the

PGC1 α /NRF1/TRAM/SIRT3 pathway, leading to the upregulation of genes associated with mitochondrial fusion, such as Mfn1, Mfn2, and Opa1 (Koh et al., 2023).

Additionally, piceatannol exhibited a protective effect on brain endothelial cells against inflammation and oxidative stress induced by lipopolysaccharide. This effect was achieved through the suppression of the mitogen-activated protein kinase (MAPK) and the nuclear factor kappa B (NF- κ B) signaling pathways on cerebral endothelial cells in an in vitro setting (Zhou et al., 2022).

4. Conclusion

Considering the previously mentioned studies, it is plausible to suggest that piceatannol may exhibit potential in the mitigation and treatment of pulmonary fibrosis by virtue of its antiproliferative, antifibrotic, anti-inflammatory, and antioxidant properties. In addition, the advancement and evolution of piceatannol holds the potential to offer a heightened level of efficacy in the clinical management of the consequences arising from COVID-19-induced pulmonary fibrosis. This is accomplished through the inhibition of TGF- β -mediated pathways, the selective inhibition of Syk, the direct suppression of the JAK2/STAT3 pathway activation, the preservation of mitochondrial functionality, the suppression of the mitogen-activated protein kinase (MAPK) and the nuclear factor kappa B (NF- κ B) signaling pathways, the reduction of oxidative stress, and the improvement of antioxidant defense mechanisms and epigenetic regulation of DNA expression via the downregulation of HDACs.

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