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Review Article

Endocannabinoids Could be the Potential Therapeutic Target for Pulmonary Fibrosis

Kaustav Chakraborty*

Post Graduate Department of Zoology, Barasat Government College, India

***Corresponding author**
Kaustav Chakraborty, Assistant Professor (W.B.E.S.), Post Graduate Department of Zoology, Barasat Government College; 10, K.N.C. Road, Barasat, Kolkata – 700124, West Bengal, India

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Abstract

Pulmonary fibrosis (PF) is an irreversible, progressive, fatal lung disease where chronic inflammation triggers and initiates the development of a fibrotic condition in lung tissue. Abnormal repair of lung tissue is a serious pathological condition in the case of IPF. The FDA recently approved pirfenidone and nintedanib for the treatment of IPF. However, both compounds have tolerability problems; their efficacy is limited, with many patients progressing to end-stage disease. Therefore, it is important to explore novel therapeutic targets and develop potential drugs for IPF. The endocannabinoid system (ECS) consists of endocannabinoids, cannabinoid receptors, and related enzymes. The role of cannabinoid receptors in the nervous system is established, but a few recent studies suggest that the ECS with immunomodulatory functions serves as a target in treating inflammatory and fibrotic diseases. For example, in bleomycin (BLM)-induced experimental skin fibrosis, the CB2R agonist inhibited collagen synthesis and delayed ECM deposition as well as prevented fibrotic progression in vitro and in vivo. In this review article, we summarize several fruitful studies that account for the therapeutic targeting of the endocannabinoid system in the context of PF. Various cannabinoid type 2 receptor (CB2R) agonists such as AM1241, JWH133, WIN 55212–2, etc. show promising results in the case of fibrosis. Icariin (ICA), a natural compound, exerts a potential therapeutic effect in experimental PF. URB937, an inhibitor of fatty acid amide hydrolase, attenuates radiation-induced lung fibrosis. The hybrid CB1R/iNOS inhibitor has greater anti-fibrotic efficacy than inhibition of CB1R alone, thus making it a viable candidate for future translational studies in IPF.

INTRODUCTION

Pulmonary fibrosis is an irreversible, progressive, fatal lung disease where chronic inflammation triggers and initiates the development of a fibrotic condition in lung tissue. Abnormal repair of lung tissue is a serious pathological condition in the case of IPF [1,2]. It manifests as progressive dyspnea, with a median survival of 2–5 years from diagnosis [3]. Development of pulmonary fibrosis interrupts the normal gaseous exchange and causes severe breathing trouble [4]. The FDA recently approved pirfenidone and nintedanib for the treatment of IPF. However, both compounds have tolerability problems; their efficacy is limited, with many patients progressing to end-stage disease [3]. Therefore, developing effective antifibrotic drugs is warranted to impede the fibrotic response and improve survival in such patients. Apart from those above- mentioned drugs, there are few other compounds, such as N-acetyl cysteine (NAC) [4], or natural products or phytomedicine, e.g., black tea extract [5] that are found to be good candidates for experimental pulmonary fibrosis, but their acceptability in context of the IPF puts many unresolved questions forward. It is important to explore novel therapeutic targets and develop potential drugs for IPF.

According to the review research, cannabinoids are a class of medicines that should be considered for the treatment of respiratory conditions. Cannabinoids and inhibitors of endocannabinoid degradation have illustrated advantageous anti-inflammatory, asthma, pulmonary fibrosis, and pulmonary artery hypotension effects in numerous studies (*in vitro* and *in vivo*). Notably, CB2 and CB1 receptors play a major role in immune system modulation and anti-inflammatory activities [6]. The endocannabinoid system (ECS) consists of endocannabinoids, cannabinoid receptors, and related enzymes. The system includes the cannabinoid type 1 receptor (CB1R) and cannabinoid type 2 receptor (CB2R), which are engaged in signal transfer through cannabinoids [7]. The role of cannabinoid receptors in the nervous system is established, but a few recent studies suggest that the ECS with immunomodulatory functions serves as a target in treating inflammatory and fibrotic diseases.

For example, in bleomycin (BLM)-induced experimental skin fibrosis, CB2R agonist inhibited collagen synthesis and delayed ECM deposition, as well as prevented fibrotic progression in vitro and in vivo, without psychoactive side effects [8]. Treatment with the CB2R agonist AM1241 reduced oxidative stress and inflammation and improved myocardial fibrosis [9]. Moreover, CB2R agonist reduced nicotine-induced interstitial pulmonary fibrosis, indicating its anti-fibrotic action [10].

ENDOCANNABINOIDS AS THERAPEUTIC TARGET FOR PF

JWH133 is a potent CB2R-selective agonist that binds to CB2R with a 200-fold greater affinity than CB1R [3]. The study by Du et al., clarifies that treatment with Icariin (ICA) expressed outstanding therapeutic effects on bleomycin-induced pulmonary fibrosis, and targeting CB2 may be the main underlying mechanism. ICA is a promising drug candidate to cure pulmonary fibrosis and mediate antagonists of the CB2 receptor [11]. URB937, an inhibitor of fatty acid amide hydrolase, lessened radiation-induced lung injury and increased endocannabinoid concentration in lung tissue. URB937 causes decreased leukocyte migration and pro-inflammatory cytokines (e.g., interleukin-1β, interleukin-6, tumor necrosis factor-α) in bronchoalveolar lavage fluid and plasma as well as reduced levels of pro-fibrotic cytokine (e.g., TGF-β1). It could restore lung structure and restrain inflammatory cell and fibroblast accumulation caused by irradiation in lung tissue. More interestingly, URB937 could prolong animal survival in case of mice model [12].

WIN 55212–2 is a cannabinoid receptor agonist that acts on cannabinoid receptors, CB1R and CB2R. It has been documented that WIN 55212–2 could abrogate dermal fibrosis in scleroderma by expressing a strong inhibition of TGFβ, CTGF, and PDGF-BB expression [13]. There are several reports which indicate endocannabinoids are involved in the development of fibrosis of multiple organs, including the liver [14–17], kidney [18,19], heart [20], and skin [21]. CB2 receptor is highly expressed on immune cells, such as B and T cells, macrophages, neutrophils, and mast cells [22]. Findings from the study of He et al., account that WIN 55212–2 inhibits the paraquat (PQ)-induced mice model of lung fibrosis and regulates the polarization of M2 macrophages. This notion supports the therapeutic potential of targeting the CB2R system for PQ-induced pulmonary fibrosis. Their other study opens up the beneficial effects of WIN 55212– 2 on PQ-induced lung fibrosis, which were linked to increased M2 cell infiltration and higher expressions of IL-10, CD163, and CD206 markers [23].

The combination of the endocannabinoid system (ECS) and the type 2 cannabinoid receptor (CB2R) can stimulate various signaling pathways, leading to distinct pathophysiological roles. This interaction has gained significant attention in recent research on fibrosis diseases. Focal adhesion kinase (FAK) is involved in the transformation of fibroblasts into myofibroblasts. According to Wu et al., JWH133 yields a protective effect against pulmonary fibrosis by inhibiting the FAK/ERK/S100A4 pathway. Therefore, JWH133 could be a potential therapeutic target for pulmonary fibrosis [3].

It was reported that increased activity of the endocannabinoid/CB1R system results in disease progression in the lungs of IPF patients and in mice with bleomycin-induced PF and is associated with increased tissue levels of interferon regulatory factor-5. More surprisingly, it was observed that simultaneous engagement of the secondary target iNOS by the hybrid CB1R/iNOS inhibitor has greater antifibrotic efficacy than inhibition of CB1R alone. This hybrid antagonist also arrested the progression of established fibrosis in mice model, thus making it a viable candidate for future translational studies in IPF [24]. CB1R on alveolar macrophages (AMs) mediates the release of anandamide into the alveoli, which endorses pulmonary fibrosis by inducing pro-fibrotic macrophages that are accessible to locally delivered antifibrotic therapy. A multitargeted therapy may improve therapeutic efficacy in PF. A systems pharmacology approach revealed that zevaquenabant (dual CB1R/iNOS inhibitor) and nintedanib treatments reversed pathologic changes in both distinct and shared PF-related pathways, which are conserved in humans and mice. Moreover, zevaquenabant treatment also attenuated fibrosis and pro-fibrotic mediators in human precision- cut lung slices. These findings establish CB1R-expressing AMs as a therapeutic target and support local delivery of dual CB1R/iNOS inhibitor zevaquenabant by inhalation as an effective, well-tolerated, and safe strategy for PF [25]. Evidence from the study of Bronova et al., accounts for the key pathological role of CB1 signaling in radiation-induced pulmonary fibrogenesis and shows that peripherally restricted CB1 antagonists may represent a novel therapeutic approach against this devastating and untreatable complication of radiotherapy-induced pulmonary fibrosis [26].

CONCLUSION

Various cannabinoid type 2 receptor (CB2R) agonists such as AM1241, JWH133, WIN 55212–2, etc. show promising result in case of fibrosis. Icariin (ICA), a natural compound, exerts a potential therapeutic effect in

experimental PF. URB937, an inhibitor of fatty acid amide hydrolase, attenuates radiation-induced lung fibrosis. The hybrid CB1R/iNOS inhibitor has greater anti-fibrotic efficacy than inhibition of CB1R alone, thus making it a viable candidate for future translational studies in IPF.

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REFERENCES

1. Chakraborty K, Chatterjee S, Bhattacharyya A. Modulation of CD11c+ lung dendritic cells in respect to TGF-β in experimental pulmonary fibrosis. Cell Biol Int. 2017; 41: 991- 1000.
2. Chakraborty K, Chatterjee S, Bhattacharyya A. Impact of Treg on other T cell subsets in progression of fibrosis in experimental lung fibrosis. Tissue Cell. 2018; 53: 87-92.
3. Wu X, Chen L, Cheng Y, Zhang Y, Yang W, Pan L, et al. A selective CB2R agonist (JWH133) protects against pulmonary fibrosis through inhibiting FAK/ERK/S100A4 signaling pathways. BMC Pulm Med 2023; 23: 440.
4. Chakraborty K, Chatterjee S, Bhattacharyya A. ROS scavenger mediated modulation of TGF- β/Smad signaling through Nrf2 activation which alters the fibrotic phenotype in experimental pulmonary fibrosis. Proceedings of the Zoological Society. 2025; 78: 200-208.
5. Chakraborty K, Dey A, Bhattacharyya A, Dasgupta SC. Anti-fibrotic effect of black tea (Camellia sinensis) extract in experimental pulmonary fibrosis. Tissue Cell. 2019; 56: 14-22.
6. Das S, Ghosh A, Karmakar V, Khawas S, Vatsha P, Roy KK, et al. Cannabis effectiveness on immunologic potency of pulmonary contagion. J Basic Clin Physiol Pharmacol. 2024; 35: 129-142.
7. Pacher P, Kunos G. Modulating the endocannabinoid system in human health and Disease– successes and failures. FEBS J. 2013; 280: 1918-1943.
8. Gonzalez EG, Selvi E, Balistreri E, Palumbo K, Lorenzini S, Montilli C, et al. Synthetic cannabinoid ajulemic acid exerts potent antifibrotic effects in experimental models of systemic sclerosis. Ann Rheum Dis. 2012; 71: 1545-1551.
9. Li X, Han D, Tian Z, Gao B, Fan M, Li C, et al. Activation of cannabinoid receptor type II by AM1241 ameliorates myocardial fibrosis via Nrf2-Mediated inhibition of TGF-β1/Smad3 pathway in Myocardial Infarction mice. Cell Physiol Biochem 2016; 39: 1521-1536.
10. Wawryk-Gawda E, Chłapek K, Zarobkiewicz MK, Franczak A, Biala G, Zarobkiewicz MK, et al. CB2R agonist prevents nicotine induced lung fibrosis. Exp Lung Res. 2018; 44: 344-351.
11. Du W, Zhang T, Yang F, Gul A, Tang Z, Zhang H, et al. Endocannabinoid signalling/cannabinoid receptor 2 is involved in icariin-mediated protective effects against bleomycin-induced pulmonary fibrosis. Phytomed. 2022; 103: 154187.
12. Li R, Chen G, Zhou L, Xu H, Tang F, Lan J, et al. The Fatty Acid Amide Hydrolase Inhibitor URB937 Ameliorates Radiation-Induced Lung Injury in a Mouse Model. Inflammation. 2017; 40: 1254-1263.
13. Balistreri E, Garcia-Gonzalez E, Selvi E, Akhmetshina A, Palumbo K, Lorenzini S, et al. The cannabinoid WIN 55, 212–2 abrogates dermal fibrosis in scleroderma bleomycin model. Ann Rheum Dis. 2011; 70: 695-699.
14. Teixeira-Clerc F, Julien B, Grenard P, Tran Van Nhieu J, Deveaux V, Li L, et al. CB1 cannabinoid receptor antagonism: A new strategy for the treatment of liver fibrosis. Nat Med. 2006; 12: 671-676.
15. Patsenker E, Stoll M, Millonig G, Agaimy A, Wissniowski T, Schneider V, et al. Cannabinoid receptor type I modulates alcohol-induced liver fibrosis. Mol Med. 2011; 17: 1285-1294.
16. Trebicka J, Racz I, Siegmund SV, Cara E, Granzow M, Schierwagen R, et al. Role of cannabinoid receptors in alcoholic hepatic injury: Steatosis and fibrogenesis are increased in CB2 receptor deficient mice and decreased in CB1 receptor knockouts. Liver Int. 2011; 31: 860-870.
17. Cinar R, Iyer MR, Liu Z, Cao Z, Jourdan T, Erdelyi K, et al. Hybrid inhibitor of peripheral cannabinoid-1 receptors and inducible nitric oxide synthase mitigates liver fibrosis. JCI Insight. 2016; 1.
18. Lin CL, Hsu YC, Lee PH, Lei CC, Wang JY, Huang YT, et al. Cannabinoid receptor 1 distur bance of PPARgamma2 augments hyperglycemia induction of mesangial inflammation and fibrosis in renal glomeruli. J Molecular Med. 2014; 92: 779-792.
19. Lecru L, Desterke C, Grassin-Delyle S, Chatziantoniou C, Vandermeersch S, Devocelle A, et al. Cannabinoid receptor 1 is a major mediator of renal fibrosis. Kidney Int. 2015; 88: 72-84.
20. Slavic S, Lauer D, Sommerfeld M, Kemnitz UR, Grzesiak A, Trappiel M, et al. Cannabinoid receptor 1 inhibition improves cardiac function and remodelling after myocardial infarction and in experimental metabolic syndrome. J Mol Med. 2013; 91: 811-823.
21. Lazzerini PE, Natale M, Gianchecchi E, Capecchi PL, Montilli C, Zimbone S, et al. Adenosine A2A receptor activation stimulates collagen production in sclerodermic dermal fibroblasts either directly and through a cross-talk with the cannabinoid system. J Mol Med. 2012; 90: 331-342.
22. Sipe JC, Arbour N, Gerber A, and Beutler E. Reduced endocannabinoid immune modulation by a common cannabinoid 2 (CB2) receptor gene polymorphism: Possible risk for autoim mune disorders. J Leukocyte Biol. 2005; 78: 231-238.
23. He Q, Zhang W, Zhang J, Deng Y. Cannabinoid Analogue WIN 55212–2 Protects Paraquat-Induced Lung Injury and Enhances Macrophage M2 Polarization. Inflammation. 2022; 45: 2256-2267.
24. Cinar R, Gochuico BR, Iyer MR, Jourdan T, Yokoyama T, Park JK, et al. Cannabinoid CB1 receptor overactivity contributes to the pathogenesis of idiopathic pulmonary fibrosis. JCI Insight. 2017; 2: e92281.
25. Basu A, Arif M, Wolf KM, Behee M, Johnson N, Pommerolle L, et al. Targeting cannabinoid receptor 1 for antagonism in pro- fibrotic alveolar macrophages mitigates pulmonary fibrosis. JCI Insight. 2025; 10: e187967.
26. Bronova I, Smith B, Aydogan B, Weichselbaum RR, Vemuri K, Erdelyi K, et al. Protection from Radiation-Induced Pulmonary Fibrosis by Peripheral Targeting of Cannabinoid Receptor-1. Am J Respir Cell Mol Biol. 2015; 53: 555-562.