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Polysaccharides in Organ Fibrosis: Therapeutic and Preventive Effects Through Gut Microbiota Modulation

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Abstract

Fibrosis is characterized by the proliferation of fibrous tissue and decreased functional cells within the affected organs, ultimately resulting in organ damage or failure. The incidence of this pathological process is on the rise globally, necessitating the development of more efficient therapeutic interventions. Recent scientific investigations have put forth the idea that polysaccharides extracted from natural sources exhibit promising abilities in alleviating fibrotic conditions by mitigating inflammatory responses and influencing intestinal microbiota composition. This scholarly discourse delves into the intricate relationship between polysaccharides and organ fibrosis concerning the dynamics of the intestinal microbiota, offering profound insights that could significantly influence the direction of future endeavours in drug development and treatment modalities. The in-depth exploration of these interconnected factors holds immense potential in shaping innovative strategies to combat fibrosis-related disorders and enhance patient outcomes in a clinical setting. The potential impact of this research on future drug development and treatment modalities cannot be overstated, as it underscores the importance of the study and its potential to influence the direction of future research in the field.

Keywords*: Drug Development, Fibrosis, Inflammatory Responses, Intestinal Microbiota, Polysaccharides.*

Introduction

The development of fibrosis is driven by the abnormal proliferation of fibroblasts and the accumulation of extracellular matrix (ECM) due to various pathological stimuli [1]. It can affect almost all solid tissues and organs, leading to structural changes and loss of organ function. In developed nations, fibrosis is associated with high rates of morbidity and mortality, and searching for pharmaceutical

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interventions is a critical area of research. The human intestinal microbiota is a complex microbial community consisting of a variety of microorganisms. *Firmicutes, Bacteroidetes, Actinobacteria,* and *Proteobacteria* are the major phyla in the human intestinal microbiota, with Firmicutes and Bacteroidetes playing crucial roles [1]. The interactions between the intestinal microbiota and its metabolites significantly affect energy metabolism, immune function, defence mechanisms, and intestinal balance, leading to the recognition of the intestinal microbiota as a vital organ. Polysaccharides, complex macromolecules found in animals, plants, and microorganisms, are essential for maintaining life [2-4]. They possess immune-modulating, anti-tumor antiviral, antioxidant, hypoglycemic, and intestinal microbiota-regulating properties. Polysaccharides modulate the composition of the intestinal microbiota by promoting the growth of beneficial bacteria and inhibiting the growth of harmful bacteria [5]. This modulation enhances immunity, antioxidant capacity, and short-chain fatty acid (SCFA) production, thereby mitigating inflammatory responses and reducing the production of pro-inflammatory mediators, offering promise for combatting fibrosis. This review explores the aetiology of fibrosis and recent insights into the influence of polysaccharides on modulating the intestinal microbiota to alleviate hepatic, renal, and pulmonary fibrosis. The aim is to provide valuable information for future research and aid in developing polysaccharide-based anti-fibrotic therapies [6, 7].

Organ Fibrosis

Organ fibrosis can result from various chronic conditions and is characterized by excess connective tissue and decreased parenchymal cells in the affected organs [8]. Fibrosis, a pathological process characterized by excessive deposition of extracellular matrix (ECM), affects various organs, including the liver, kidney, heart, lung, skin, and muscle, often leading to organ dysfunction and high morbidity and mortality. The persistent activation of myofibroblasts, influenced by signals like transforming growth factor-β (TGF-β), platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF), is a crucial driver of this process. Inflammation, driven by cytokines from immune cells, is critical to stimulating myofibroblast activation and creating a cycle of inflammation and ECM production [9-11]. Over time, excessive ECM deposition leads to an increase in fibrous tissue and a decrease in parenchymal cells, culminating in the formation of permanent scar tissue. This process ultimately leads to the deterioration of the structure and function of the affected organ and can result in organ dysfunction or failure if left unaddressed [1]. The receptor for advanced glycation end products (RAGE) is a significant regulator in fibrosis, influencing inflammation, cell proliferation, apoptosis, and angiogenesis. Programmed cell deaths such as apoptosis, autophagy, ferroptosis, and necroptosis are closely linked to fibrosis, with necroptosis being a potential therapeutic target. Inter-organ crosstalk, particularly between the lung and liver, has been identified in idiopathic pulmonary fibrosis (IPF), involving molecules like kininogen 1 and bradykinin receptor B1, which activate pathways leading to fibrosis. While fibrosis has traditionally been viewed as irreversible, recent evidence suggests it can regress, especially in the liver, by removing dangerous factors, myofibroblast inactivation, and ECM degradation. Shared fibrotic signalling pathways across different organs, such as TGF-β, PDGF, WNT, and hedgehog signalling, offer the potential for developing general antifibrotic therapies effective across multiple fibrotic diseases [12]. However, the specific cellular and molecular mechanisms leading to fibrosis in human muscle remain less understood, underscoring the urgent need

for further research in this area. The importance of this research cannot be overstated, as it is crucial for developing targeted therapies to treat fibrosis across different organs [11].

The Connection between Intestinal Microbiota and Organ Fibrosis

The intricate and significant study of the connection between intestinal microbiota and fibrosis is a fascinating area of research. It has been revealed that an imbalance of gut microbiota, known as dysbiosis, plays a pivotal role in the development and progression of various fibrotic diseases. For instance, in myocardial fibrosis (MF), gut microbiota influences the condition through the gut-heart axis. Metabolites such as trimethylamine-N-oxide (TMAO) and short-chain fatty acids (SCFAs) impact cardiac fibrosis by modulating inflammatory factors and immune cells [12, 13]. Similarly, gut microbiota dysbiosis is implicated in developing intestinal fibrosis in Crohn's disease (CD), where microbial ligands activate intestinal fibroblasts, leading to extracellular matrix production and fibrosis independent of inflammation. In cystic fibrosis (CF), significant changes in gut microbiota composition, such as increased Enterococcus and decreased *Bifidobacterium*, are linked to reduced microbial diversity and correlated with gastrointestinal complications and inflammation. Additionally, liver fibrosis demonstrates a strong connection with gut microbiota, where alterations in bile acid metabolism and microbial composition contribute to disease progression. This suggests the gut microbiota–bile acid axis as a potential therapeutic target [10, 14]

In idiopathic pulmonary fibrosis (IPF) and connective-tissue disease-associated interstitial lung diseases (CTD-ILDs), gut microbiota dysbiosis is associated with disease severity and prognosis. Studies have indicated that butyrate acid administration can reduce lung fibrosis in animal models [15, 16]. Furthermore, the influence of gut microbiota and diet on macrophages, critical players in inflammatory responses and wound healing, can alter macrophage profiles and contribute to a pro-fibrotic environment in the gut, highlighting the intricate relationship between diet, gut microbiota, and fibrogenesis. Overall, the role of gut microbiota in fibrosis extends across multiple organ systems, underscoring the pressing need for further research to explore microbiome-targeted therapies for managing fibrotic diseases [10, 14].

Therapeutic and Preventive Effects of Polysaccharides on Organ Fibrosis Mediated by Modulating the Intestinal Microbiota

Hepatic fibrosis is a complex condition involving the progressive accumulation of scar tissue in the liver. It can be caused by various factors such as alcohol consumption, nonalcoholic fatty liver disease, viral hepatitis, and autoimmune hepatitis. The communication between the intestines and the liver, known as the gut-liver axis, plays a crucial role in developing hepatic fibrosis [17-20]. Research has shown that specific polysaccharides, such as *Aronia melanocarpa* polysaccharide (AMP) from the *Aronia melanocarpa* plant, garlic polysaccharide (GP) from garlic, *Lycium barbarum* polysaccharides (LBP) from the *Lycium barbarum* plant, *Taraxacum mongolicum* polysaccharide (TMP) from the *Taraxacum mongolicum* plant, *Astragalus* polysaccharide (ASP) from the *Astragalus* plant, *Auricularia auricula* polysaccharides (AAPs) from the Auricularia auricula fungus, *Lonicerae flos* polysaccharides (LPs) from *the Lonicerae flos* plant, *Gardenia jasm*inoides Ellis polysaccharides (GPs) from the *Gardenia jasminoides* Ellis plant, and *Poria cocos* polysaccharides (PCP) from the *Poria cocos* fungus, have the potential to alleviate hepatic fibrosis by modulating the intestinal microbiota. For example, AMP has been

shown to improve intestinal homeostasis and attenuate hepatic fibrosis in mice. GP has demonstrated the ability to modulate the intestinal microbiota in mice with alcoholic fibrosis. LBP reduced the content of specific bacteria and attenuated hepatic fibrosis, while TMP and ASP regulated the composition and abundance of the intestinal microbiota in mice with hepatic fibrosis [21-25].

Furthermore, polysaccharides from AAPs, LPs, GPs, and PCP have also been found to alleviate liver diseases such as nonalcoholic fatty liver disease and cholestatic liver injury by modulating the intestinal microbiota. These findings suggest that polysaccharides, by targeting the gut-liver axis, hold promise for the development of new therapeutic approaches for hepatic fibrosis and related liver diseases [6]. The excessive proliferation of fibroblasts within the renal interstitium, along with the formation of myofibroblasts and the excessive production and deposition of extracellular matrix (ECM), are key processes that contribute to a gradual decline in renal function, leading to interstitial fibrosis, glomerulosclerosis, and tubular necrosis [26]. Renal fibrosis represents the final pathway in most chronic and progressive kidney diseases, ultimately resulting in impaired renal function and organ failure [27]. The concept of the 'gut–kidney axis' (GKA) pertains to the intricate interaction between the intestinal tract and the kidneys, with various levels of connection between these organs. These connections involve exchanging information related to water and electrolyte regulation, inflammatory responses, toxin metabolism and clearance, nutrient metabolism, and neuromodulation [27, 28]. The maintenance of intestinal homeostasis is closely linked to the development of kidney disease [28]. This axis is particularly relevant to our discussion as it underscores the potential of polysaccharides in modulating the intestinal microbiota to prevent renal fibrosis [6].

In a study by Yang et al., it was discovered that Cordyceps cicadae polysaccharides (CCP) can enhance the relative abundance and proliferative capacity of probiotics in the intestinal tract of rats with diabetic nephropathy, thereby playing a role in regulating intestinal homeostasis. The mechanism through which these polysaccharides alleviate tubulointerstitial fibrosis in rats with diabetic nephropathy likely involves the suppression of the inflammatory response and the modulation of dysbiosis by interfering with the TLR4–NF-κB and TGF-β1–Smad signalling pathways. Furthermore, polysaccharides can prevent renal fibrosis by modulating the intestinal microbiota of individuals with diabetic nephropathy [6, 29]. In experimental settings, Moutan Cortex polysaccharide (MC-Pa) has been shown to lower hyperglycemia and reduce renal injury in rats with diabetic nephropathy. This polysaccharide also reshapes the intestinal microbiota and increases the content of short-chain fatty acids (SCFAs), indicating its potential as a prebiotic for enhancing outcomes in diabetic nephropathy. Several investigations have reported that Bupleurum polysaccharides (BCP, BPs) can improve the diversity of the intestinal microbiota, boost the levels of beneficial bacteria, strengthen the integrity of the intestinal barrier, and alleviate the renal inflammatory response, ultimately leading to improvements in diabetic nephropathy in mice [30, 31].

Potential Therapeutic Agents in Pulmonary Fibrosis via the Gut-Lung Axis

Pulmonary fibrosis is a progressive and often fatal lung disease characterized by the accumulation of fibroblasts and extracellular matrix in the lung tissues, leading to inflammation and tissue damage. The "gut-lung axis" refers to the complex interplay between the intestines and lungs, involving

interactions such as immune regulation and changes in the gut microbiota. Research has shown that polysaccharides can have a therapeutic effect on pulmonary fibrosis by regulating intestinal balance. For example, *Astragalus* polysaccharides have been found to reduce lung tissue damage and inflammation in mice with pulmonary fibrosis and modulate intestinal equilibrium by regulating metabolic pathways and promoting beneficial probiotic bacteria (Figure 1). Similarly, *Ephedra sinica* polysaccharides and *Houttuynia cordata* polysaccharides have demonstrated the ability to modulate the intestinal microbiota and exert a therapeutic influence on lung injury in mice. These findings highlight the potential of polysaccharides in addressing chronic lung conditions and preventing the onset of pulmonary fibrosis through their interactions with the intestinal microbiota [32, 33].

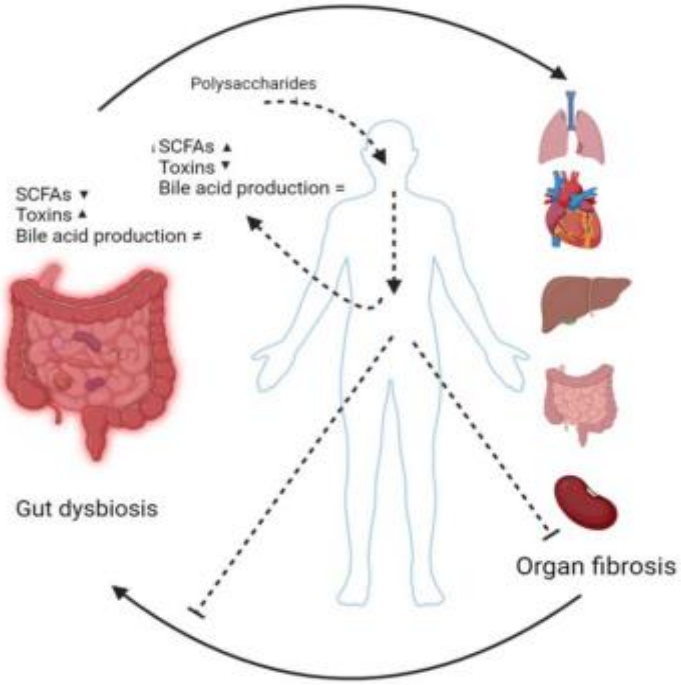

Figure 1. Therapeutic and Preventive Effects of Polysaccharides on Organ Fibrosis Mediated by Modulating the Intestinal Microbiota

Conclusion

The complex interplay between the gut microbiota and various organs through the circulatory, immune, and nervous systems still needs to be fully understood and further investigated. Additionally, there is a need to elucidate the precise mechanism by which the gut microbiota influences organ fibrosis. It has been observed that polysaccharides can attenuate fibrosis in different organs by reducing inflammation and modulating immune function in conjunction with the gut microbiota. However, most recent research on polysaccharides, the gut microbiota, and fibrosis has been primarily limited to animal models, thus limiting the generalizability of the findings. These studies have highlighted the potential of polysaccharides as prebiotics for ameliorating fibrosis and as promising candidates for developing therapeutic agents against fibrosis. The scarcity of substantial data in this field underscores the necessity for further studies to establish foundational evidence upon which future reviews can be based. Future research should focus on unravelling the intricate relationship between polysaccharides and the gut microbiota and the communication networks between the

intestines and organs, including the gut–liver, gut–kidney, gut-lung, and gut–cardiac axes. Furthermore, upcoming studies should aim to provide more precise insights into the mechanistic involvement of the gut microbiota in fibrosis. This comprehensive understanding will be crucial for formulating innovative treatment approaches for fibrosis and advancing the development of anti-fibrotic drugs based on polysaccharides.

Conflict of Interest

None.

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Credit Authorship Contribution Statement

Malairaj Sathuvan: Conceptualization, Writing-original draft, Writing- review and editing.

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